A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease

Protocol Number: AST-ADP2-US01

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Clinical Study Sponsor: Nature Cell Co., Ltd.
5F, 10 Gukhoe-daero 76-gil
Yeongdeungpo-gu, Seoul 150-870, Korea
Phone: +82-2-545-4137

US Representative: KCRN Research, LLC
20251 Century Blvd. Suite 325
Germantown, MD 20874
Phone: 301-540-2600

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Protocol Signature Page

I have carefully read the attached protocol (v 6.0) entitled "A Phase 1/2, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease" dated Mar 4, 2019 and agree to its terms including principles of disclosure and confidentiality.

I agree to obtain the approval for this protocol from the Institutional Review Board prior to initiation of the study.

I also agree to comply with the International Conference of Harmonization (ICH) Tripartite Guidelines on good Clinical Practice, and applicable regulations/guidelines set forth in the Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of NC.

Signature

Name of Principal Investigator

Date (DD/MMM/YYYY)

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PROTOCOL SYNOPSIS

Name of Sponsor/Company: Nature Cell Co., Ltd. 5F, 10 Gukhoe-daero 76-gil, Yeongdeungpo-gu, Seoul 150-870, Korea	
Investigational Product: AstroStem	
Protocol Number	**AST-ADP2-US01**
Indication	**Alzheimer's Disease (AD)**
Protocol Title	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease
Study Phase	**Phase 1 and 2**
Planned Number of Subjects	**Total up to 22 subjects** - Treatment group: AstroStem ($2x10^8$ cells/220 mL), N=11 - Control group: Saline 220 ml, N=11
Objectives	To evaluate the safety and efficacy of AstroStem (autologous adipose tissue derived mesenchymal stem cells, AdMSCs) in patients with Alzheimer's disease
Study Design	This is a randomized, double-blind, placebo-controlled, parallel-group comparison study in subjects with Alzheimer's Disease. Following first screening period, subjects will be randomly assigned into one of the following treatment arms: AstroStem and placebo. At Week -4, 30 mL of abdominal adipose tissue will be taken by liposuction from subjects. The adipose tissue samples will be sent to Biostar Stem Cell Research Institute to isolate AdMSCs. The isolated AdMSCs or saline will be sent to the clinical sites with identical syringes to preserve double-blinding of the study. A total $2x10^8$ AdMSCs in 220 mL of saline or the same volume of saline will be administered via I.V. at Week 0. This procedure will be repeated 9 times at 2-week interval. Subjects will be scheduled for two follow-up visits at Weeks 30 and 52 to evaluate primary and secondary outcome endpoints.
Drug Administration	A total $2x10^8$ AdMSCs in 220 mL of saline or the same volume of saline will be administered via I.V. for 2-6 hours to patients in the treatment group and the placebo group, respectively.
Study Visits	Visit 1 (Week -8) – Screening Visit 2 (Week -4) – Liposuction Visit 3 (Week 0) – 1^{st} injection of AstroStem or Placebo Visit 4 (Week 2) – 2^{nd} injection of AstroStem or Placebo Visit 5 (Week 4) – 3^{rd} injection of AstroStem or Placebo Visit 6 (Week 6) – 4^{th} injection of AstroStem or Placebo Visit 7 (Week 8) – 5^{th} injection of AstroStem or Placebo Visit 8 (Week 10) – 6^{th} injection of AstroStem or Placebo Visit 9 (Week 12) – 7^{th} injection of AstroStem or Placebo Visit 10 (Week 14) – 8^{th} injection of AstroStem or Placebo Visit 11 (Week 16) – 9^{th} injection of AstroStem or Placebo Visit 12 (Week 18) – 10^{th} injection of AstroStem or Placebo Visit 13 (Week 30) – 1^{st} follow-up Visit 14 (Week 52) – Final follow-up
Study Hypothesis	AstroStem treatment group has improvement on neurological/neurocognitive assessment from baseline at Week 30 compared to the placebo group.

Name of Sponsor/Company: Nature Cell Co., Ltd. 5F, 10 Gukhoe-daero 76-gil, Yeongdeungpo-gu, Seoul 150-870, Korea	
Investigational Product: AstroStem	
Protocol Number	**AST-ADP2-US01**
Indication	**Alzheimer's Disease (AD)**
Clinical Endpoints	**The primary endpoint** used to determine the safety and efficacy of AstroStem is the following: • Number of subjects with treatment related adverse events as assessed by analysis of adverse events including symptoms, and abnormal findings on physical examination, vital signs, ECG, and standard laboratory examination results • Change of ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale) from baseline at Week 30 The **secondary endpoints** used to determine the efficacy and safety of AstroStem are: • Change of MMSE (Mini-mental status examination) from baseline at Week 30 • Changes of CDR-SOB (Clinical Dementia Rating-Sum of Boxes) from baseline at Week 30 • Changes of NPI (Neuropsychiatric Inventory) from baseline at Week 30 • Changes of GDS (Geriatric Depression Scale) from baseline at Week 30 • Change of ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living) from baseline at Week 30 • Changes of C-SSRS (Columbia Suicide Severity Rating Scale) from baseline at Week 30 • Change of MRI imaging results from baseline at Week 30 • Biomarkers in blood: Amyloid beta 40, Amyloid beta 42, Amyloid precursor protein intracellular domain (AICD), soluble neuregulin-1 (sNRG-1)
Inclusion/ Exclusion Criteria	**Inclusion Criteria** 1. Male or female subjects aged 50 and above at the time of signing the Informed Consent form 2. Subjects who can understand and provide written informed consent (assent) 3. Subjects who have diagnosis of probable mild-to-moderate Alzheimer disease according to NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association) criteria 4. Subjects who have MMSE Score of 16 to 26 at screening 5. Subjects who are taking FDA-approved AD medications (donepezil, galantamine, memantine, rivastigmine or their combinations) treatment on a stable dosage for at least 3 months prior to screening. 6. Subjects who have one (or more) identified adult caregiver (study partner) who is able to read, understand, and speak the designated language at the study site; either lives with the subject or sees the subject for ≥2 hours/day ≥4 days/week; and agrees to accompany the subject to each study visit and to participate in the subject's clinical assessments. **Exclusion Criteria** 1. Subjects who are females who are pregnant, nursing, or of childbearing potential while not practicing effective contraception 2. Subjects who have signs of delirium 3. Subjects who have had cortical stroke within the preceding 2 years 4. Subjects who have a prolonged QTc interval; >450 msec in male or >470 msec in female at screening

Name of Sponsor/Company: Nature Cell Co., Ltd. 5F, 10 Gukhoe-daero 76-gil, Yeongdeungpo-gu, Seoul 150-870, Korea	
Investigational Product: AstroStem	
Protocol Number	**AST-ADP2-US01**
Indication	**Alzheimer's Disease (AD)**
	5. Subjects who have diagnosis of severe white matter hyperintensity (WMH), which is defined as ≥ 25mm of the deep white matter and ≥ 10mm of the periventricular capping/banding in lengths 6. Subjects who have diagnosis of dementia or cause of cognitive impairment other than Alzheimer's disease 7. Subjects who have a significant abnormal result in laboratory tests, in the opinion of the investigator 8. Subjects who have participated in any investigational drug, stem cell therapy, or device trial within the previous 3 months at screening 9. Subjects with any current psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessments, or affect the subject´s ability to complete the study 10. Subjects who are known to have autosomal dominant mutation-associated presenile AD 11. Subjects who show signs of AIDS (Acquired Immunodeficiency Syndrome), HBV (Hepatitis B Virus), HCV (Hepatitis C), VDRL (Venereal Disease Research Laboratory) 12. Subjects who have any conditions that would contraindicate an MRI, such as the presence metallic objects in the eyes, skin, or heart 13. Subjects who have > 4 cerebral microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"), a single area of superficial siderosis, or evidence of a prior microhemorrhage as assessed by MRI 14. Subjects who have history of malignant cancer within the last 5 years (The following is a partial list of conditions that are permissible for study entry: non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical, or non-progressive prostate cancer) 15. Subjects who have suspected active lung disease based on chest X-ray 16. Subjects who are hypersensitive to fetal bovine serum or penicillin 17. Subjects who are currently using immunosuppressants, cytotoxic drug, corticosteroids or similar steroidal anti-inflammatory medication (e.g., Prednisone) on a regular basis (exceptions allowed include; regular use of steroidal nasal sprays, topical steroids, and estrogen-replacement therapy) 18. Subjects for whom the investigator judges the liposuction can cause any problems 19. Subjects who have history of local anesthetic allergy
Statistical Analysis	The primary variable, score change of ADAS-Cog from baseline at Week 30 will be analyzed using T-test or Kruskal-Wallis test depending on the violation of normality assumption. The secondary efficacy variables include the percentage of subjects who show improvement along with several change scores from baseline. The percentage of subjects who show improvement will be compared between groups using chi-square test or Fisher's exact test. The change scores will be analyzed using T-test or Kruskal-Wallis tests, as appropriate. Safety variables will be summarized descriptively, by treatment group and visit. When the first 4 subjects complete Visit 4 at Week 2, one unblinded interim safety analysis of the subjects can be performed by an independent safety monitor to evaluate the safety of AstroStem without the suspension of subject enrollment. Change of vital signs and AEs will be evaluated.

SCHEDULE OF ASSESSMENTS

Procedure	Screen		Treatment										Follow-up		Early Termination
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	
Tested Group	-W8	-W4	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W30	W52	
Informed Consent[1]	V														
Inclusion/Exclusion Criteria	V														
Demographic information	V														
Medical/medication history	V														
Physical examination	V		V			V			V			V	V	V	V
Vital signs	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V
Hematology, serum chemistry, and urinalysis [2]	V		V			V			V			V	V	V	V
Pregnancy test [3]	V		V									V	V	V	V
Electrocardiogram	V		V			V			V			V	V	V	V
Chest X-ray	V														
Liposuction		V													
Serum for IP		V	V		V		V		V						
ADAS-Cog			V			V			V			V	V	V	V
MMSE	V		V			V			V			V	V	V	V
CDR-SOB			V			V			V			V	V	V	V
NPI			V			V			V			V	V	V	V
GDS			V			V			V			V	V	V	V
C-SSRS			V			V			V			V	V	V	V
ADCS-ADL			V			V			V			V	V	V	V
MRI Scan	V								V				V	V	V
Biomarker [4]			V										V	V	V
Drug administration			V	V	V	V	V	V	V	V	V	V			
Concomitant medications		V	V	V	V	V	V	V	V	V	V	V	V	V	V
Adverse events		V	V	V	V	V	V	V	V	V	V	V	V	V	V

[1] Informed Consent Form should be signed prior to any clinical trial related activities

[2] See Appendix 1 for the complete list of laboratory tests

[3] Serum pregnancy test is performed for all females of childbearing potential.

[4] Amyloid beta 40, Amyloid beta 42, Amyloid precursor protein intracellular domain (AICD), soluble neuregulin-1 (sNRG-1)

GLOSSARY AND ABBREVIATIONS

Aβ	Amyloid beta
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living
AdMSC	Adipose Tissue Derived Mesenchymal Stem Cell
AE	Adverse Event
AICD	Amyloid precursor protein Intracellular Domain
AIDS	Acquired Immunodeficiency Syndrome
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
APP	Amyloid Precursor Protein
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BUN	Blood Urea Nitrogen
CDR-SOB	Clinical Dementia Rating-Sum of Boxes
CFR	Code of Federal Regulations
C-SSRS	Columbia Suicide Severity Rating Scale
CREDOS	Clinical Research Center for Dementia of South Korea
ECG	Electrocardiography
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GDNF	Glial cell-derived Neurotrophic Factor
GDS	Geriatric Depression Scale
hASCs	Human Adipose-derived Stem Cells
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
ICH	International Conference of Harmonization
IRB	Institutional Review Board
ITT	Intent-to-Treat
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MMSE	Mini-mental status examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
NT3	Neurotrophin 3
PP	Per Protocol
PT-INR	Prothrombin Time - International Normalized Ratio
RBC	Red Blood Cell Count
SAE	Serious Adverse Event
SD	Standard Deviation
sNRG-1	Soluble Neuregulin-1
VDRL	Venereal Disease Research Laboratory
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell Count
WMH	White Matter Hyperintensity

1. PURPOSE OF STUDY

The purpose of this study is to evaluate the safety and efficacy of AstroStem (autologous adipose tissue derived mesenchymal stem cells, AdMSCs) in patients with Alzheimer's disease.

2. INTRODUCTION

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder in The United States affecting approximately 5.4 million Americans [1]. AD is characterized by progressive loss in memory and as well as a decline in the ability to learn that is associated with neuronal death. Well known hallmarks of AD are neuritic plaques and neurofibrillary tangles [2, 3] and extensive inflammation [4]. Currently, no treatment has been developed to fully cure or prevent the progression of dementia that is associated with AD.

In addition to neuritic plaques and neurofibrillary tangles, oxidative stress, mitochondrial dysfunction, hormone dysregulation, inflammation, mitotic dysfunction, calcium imbalance, and genetic risk factors are all involved in AD processes [5]. The disease is now recognized as multifactorial and consequently strongly demands more effective treatments.

Therapeutic potentials of stem cells in several brain disorders are enticing researchers to apply stem cell based therapies [6–9]. Among stem cells, adipose tissue-derived mesenchymal stem cells (AMSCs), mesenchymal stem cells isolated from adipose tissue, are well known for their pluripotency and ability to differentiate into mesenchymal and non-mesenchymal lineages [10]. AMSCs are readily accessible and show high proliferation rates in vitro with lower senescence ratios than bone marrow derived mesenchymal stem cells [11]. Considering clinical applications, AMSCs are the most suitable source of stem cells due to the possibility of intravenous transplantation of autologous AMSCs with no immune rejections, ethical problems or tumorigenesis [12] and intravenous injection is the most convenient, simple and safest method of administration.

The paracrine effects of stem cells, including the production of growth factors and anti-inflammatory cytokines and anti-apoptotic regulation, are strongly exerted and induce neural regeneration, remyelination and immunomodulation [13]. In a preclinical study, we demonstrated that intravenously injected stem cells could enter the brain through blood brain barrier and hASCs could have beneficial effects in a murine model of Alzheimer's disease [14]. Compared to placebo group, memory impairments, the number of amyloid plaques, protein level of Amyloid beta (Aβ) and Amyloid Precursor Protein (APP) were reduced after intravenous injection of hASCs in Tg2567 mouse brain. Furthermore, analysis of Tg2576 mouse brain revealed that anti-inflammatory cytokine, IL-10 and neurotrophic factors including vascular endothelial growth factor (VEGF), Glial cell-derived neurotrophic factor (GDNF), and Neurotrophin 3 (NT3) were significantly increased after the injection of hASCs. These findings suggest that a convenient and safe intravenous injection of hASCs might be very useful for the treatment of AD.

The clinical study of AstroStem aims to evaluate the safety and efficacy of AstroStem as a potential treatment for AD. Based on the preclinical results, AstroStem could be an effective treatment option with a mechanism of action that has not been explored for AD indication.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AstroStem for the treatment of Alzheimer's Disease. Three investigational centers in the United Statesmay be utilized so that a total of approximately 22 subjects will be randomized.

3.2 Selection of Study Population

The study population will be males or females, aged 50 and above, who have who have diagnosis of probable Alzheimer disease according to NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association) criteria with 16-26 MMSE score.

3.2.1 Inclusion Criteria

1) Subjects who are males or females of any race, aged 50 and above at the time of signing the Informed Consent Form

2) Subjects who can understand and provide written informed consent (assent).

3) Subjects who have diagnosis of probable mild-to-moderate Alzheimer disease according to NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke; Alzheimer's Disease and Related Disorders Association) criteria

4) Subjects who have MMSE Score of 16 to 26

5) Subjects who are taking FDA-approved AD medications (donepezil, galantamine, memantine, rivastigmine or their combinations) treatment on a stable dosage for at least 3 months prior to screening.

6) Subjects who have one (or more) identified adult caregiver (study partner) who is able to read, understand, and speak the designated language at the study site; either lives with the subject or sees the subject for ≥2 hours/day ≥4 days/week; and agrees to accompany the subject to each study visit and to participate in the subject's clinical assessments.

3.2.2 Exclusion Criteria

1) Subjects who are female who are pregnant, nursing, or childbearing potential while not practicing effective contraception

2) Subjects who have signs of delirium

3) Subjects who have had cortical stroke within the preceding 2 years

4) Subjects who have a prolonged QTc interval; >450 msec in male or >470 msec in female at screening

5) Subjects who have diagnosis of severe white matter hyperintensity (WMH), which is defined as ≥ 25mm of the deep white matter and ≥ 10mm of the periventricular capping/banding in lengths

6) Subjects who have diagnosis of dementia or cause of cognitive impairment other than Alzheimer's disease

7) Subjects who have a significant abnormal result in laboratory tests, in the opinion of the investigator

8) Subjects who have participated in any investigational drug, stem cell therapy, or device trial within the previous 3 months at screening

9) Subjects with any current psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessments, or affect the subject´s ability to complete the study

10) Subjects who are known to have autosomal dominant mutation-associated presenile AD

11) Subjects who show signs of AIDS (Acquired Immunodeficiency Syndrome), HBV (Hepatitis B Virus), HCV (Hepatitis C), VDRL (Venereal Disease Research Laboratory)

12) Subjects who have any conditions that would contraindicate an MRI, such as the presence metallic objects in the eyes, skin, or heart

13) Subjects who have > 4 cerebral microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"), a single area of superficial siderosis, or evidence of a prior microhemorrhage as assessed by MRI

14) Subjects who have history of malignant cancer within the last 5 years (The following is a partial list of conditions that are permissible for study entry: non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical, or non-progressive prostate cancer)

15) Subjects who have suspected active lung disease based on chest X-ray

16) Subjects who are hypersensitive to fetal bovine serum or penicillin

17) Subjects who are currently using immunosuppressants, cytotoxic drug, corticosteroids or similar steroidal anti-inflammatory medication (e.g., Prednisone) on a regular basis (exceptions allowed include; regular use of steroidal nasal sprays, topical steroids, and estrogen-replacement therapy)

18) Subjects for whom the investigator judges the liposuction can cause any problems

19) Subjects who have history of local anesthetic allergy

3.3 Removal of Subjects from Study

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

- At their own request or at the request of their legally acceptable representative
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the sponsor

Also, subjects must be withdrawn for the following reasons:

- A significant violation of the protocol, as determined by the sponsor or the investigator
- Highly significant abnormalities in the laboratory results (Highly significant abnormalities generally follow lab related exclusion criteria, but a PI can determine the high significance on any abnormalities for the safety of subject)
- Use of any other investigational drugs
- Subjects enrolled in the current trial but taking any prohibited medication/therapy stated in the inclusion/exclusion criteria
- Subject enrolled in the current trial but having a baby

If a subject prematurely withdraws from the study, the subject must return to the clinical site for the early termination visit. In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) and in the subject's medical records.

Contact will be maintained with subjects who are removed due to an adverse event (AE) until it has been resolved or stabilized, and the information will be documented in the eCRF and in the subject's medical records.

3.4 Premature Termination of Study / Closure of Center

The sponsor has the right to terminate this study, and the investigator/sponsor has the right to close a clinical site, at any time, although this should occur only after consultation between involved parties; the IRB must be informed in any case. Should the clinical site be closed prematurely, all study materials (equipment, study medication, etc.) must be returned to the sponsor.

This study will discontinue due to medical or administrative reasons such as:

- Serious adverse events probably related to study drug administration so that the use of study drug may no longer be justifiable
- 2 or more deaths are observed during any point in the trial
- Significant change of benefit-risk ratio for the subjects
- Sponsor discontinues the investigation of AstroStem for the treatment of Alzheimer's Disease or determines that the doses being studied are no longer justifiable

Possible reasons for closing of a clinical site include the following:

- The investigator feels that the number or severity of adverse events is excessive
- A change of technical, administrative, or personal circumstances occurs and the conduct of the study no longer meets ICH-GCP guidelines
- In case of evident, significant non-compliance to protocol or poor data quality

3.5 Treatment

3.5.1 Treatment to be Administered

At Visit 2 (Week -4), a subject, who is qualified for this study, will be randomized to one of two study groups and the adipose tissue will be harvested via liposuction. At Visits 3 through 12, the randomized subject will receive a single intravenous injection per visit.

3.5.2 Identity of Investigational Product

AstroStem is in a 20 ml syringe including AdMSCs as $1x10^8$ cells/10mL of saline with 30% auto-serum and is stable at refrigerated condition (+2 to +8 °C) up to 1 week. A negative control syringe including saline with 30% auto-serum will be packed by the aluminum foil pack to be matched with AstroStem syringe in appearance to be indistinguishable.

3.5.3 End of Study

The efficacy results will be analyzed when the last subject completes Visit 13 (Week 30 follow-up) and this study is finished when the last subject completes Visit 14 (Week 52 follow-up).

3.5.4 Selection of Dose in Study

The dosage of AstroStem was chosen through pre-clinical study published in PLOS One [14].

3.5.5 Choice of Control/Comparator

This study uses saline with 30% auto-serum as a control.

3.5.6 Randomization and Blinding

As this is a double-blinded study, blinding of the drug contents from the subjects, investigators, and other study personnel at each clinical site is necessary. Because two syringes of AstroStem and control are different, one physician must be only assigned to the role of syringe injection in order to maintain the double-blinding against other site physicians and staffs.

After the eligibility is confirmed, a subject will be assigned with one randomization code using the electronic data capture (EDC) system on Visit 2 (Week -4). A randomization code is assigned into one of two groups.

A code-break envelope for each subject including the randomization code information will be retained by each site and can be opened, revealing the randomization information, for emergency purposes only. Investigator should note that the occurrence of a SAE should not routinely precipitate immediate unblinding. An attempt to contact the sponsor must be made prior to unblinding. If unblinding occurs, the subject must be early terminated; a written explanation must be prepared immediately.

3.5.7 Prior and Concomitant Treatments

If the use of any concomitant treatment(s) becomes necessary, the treatment(s) must be recorded in the eCRF, including the name of the drug or treatment, dose, route of administration, date and time of the treatment, and indication. In the event that concomitant medication is administered, the principal investigator or qualified sub-investigator must assess the subject's eligibility of continuing the participation in the study.

The following medications/therapies are not allowed to be taken/used by subjects enrolled in this study during the trial (up to Week 52, a final follow-up visit):

- Any investigational drug
- Any therapy that may affect Alzheimer's disease, in the judgment of the investigator
- Immunosuppressant
- Cytotoxic drug
- Corticosteroids or similar steroidal anti-inflammatory medication (e.g., Prednisone) on a regular basis (exceptions allowed include; regular use of steroidal nasal sprays, topical steroids, and estrogen-replacement therapy)

3.5.8 Treatment Compliance

All subjects will return on Visits 4, 5, 6, 7, 8, 9, 10, 11 and 12 (Weeks 2, 4, 6, 8, 10, 12, 14, 16 and 18) for subsequent injections and Visits 13 and 14 (Weeks 30 and 52) for follow-ups.

3.6 Study Endpoints and Variables

3.6.1 Study Endpoints

Primary endpoints used to determine the safety and efficacy of AstroStem is the following:

- Number of subjects with treatment related adverse events as assessed by analysis of adverse events including symptoms, and abnormal findings on physical examination, vital signs, ECG, and standard laboratory examination results
- Change of ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale) from baseline at Week 30

The **secondary endpoints** used to determine the efficacy and safety of AstroStem are the following:

- Change of MMSE (Mini-mental status examination) from baseline at Week 30
- Changes of CDR-SOB (Clinical Dementia Rating-Sum of Boxes) from baseline at Week 30
- Changes of NPI (Neuropsychiatric Inventory) from baseline at Week 30
- Changes of GDS (Geriatric Depression Scale) from baseline at Week 30
- Change of ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living) from baseline at Week 30
- Changes of C-SSRS (Columbia Suicide Severity Rating Scale) from baseline at Week 30
- Change of MRI imaging results from baseline at Week 30
- Biomarkers in blood: Amyloid beta 40, Amyloid beta 42, Amyloid precursor protein intracellular domain (AICD), soluble neuregulin-1 (sNRG-1)

3.6.2 Efficacy Variables

- ADAS-Cog at Visits 3, 6, 9, 12, 13 and 14 or Early Termination

- MMSE at Visits 1, 3, 6, 9, 12, 13 and 14 or Early Termination
- CDR-Box at Visits 3, 6, 9, 12, 13 and 14 or Early Termination
- NPI at Visits 3, 6, 9, 12, 13 and 14 or Early Termination
- GDS at Visits 3, 6, 9, 12, 13 and 14 or Early Termination
- ADCS-ADL at Visits 3, 6, 9, 12, 13 and 14 or Early Termination
- Biomarkers in blood [Amyloid beta 40, Amyloid beta 42, Amyloid precursor protein intracellular domain (AICD), soluble neuregulin-1 (sNRG-1)] at Visits 3, 13 and 14 or Early Termination

The rating scales used in this study are ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale), MMSE (Mini-mental status examination), CDR-SOB (Clinical Dementia Rating-Sum of Box), NPI (Neuropsychiatric Inventory), GDS (Geriatric Depression Scale) and ADCS-ADL (Alzheimer's Disease Cooperative Study Activities). All questionnaires that are subject-administered should be completed by the subjects alone or along with caregiver at the beginning of each visit to minimize influences from other procedures to be performed at that visit. A short explanation should be given to each subject about the purpose and the necessity of these questionnaires.

3.6.3 Safety Variables

- Hematology, blood chemistry and urinalysis at Visits 1, 3, 6, 9, 12, 13 and 14 or Early Termination. See Section Appendix 1 for a complete list of laboratory tests to be done.
- ECG evaluation at Visits 1, 3, 6, 9, 12, 13 and 14 or Early Termination
- Complete physical examination at Visits 1, 3, 6, 9, 12, 13 and 14 or Early Termination
- Vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight will be measured at all visits.
- MRI Scan of the brain at Visit 1, 9, 13 and 14 or Early Termination.
- C-SSRS at Visit 3, 6, 9, 12, 13, and 14 or Early Termination
- Data regarding AEs and concomitant medications will be collected at all visits

4. STUDY PROCEDURES

4.1 Screening Period

A signed and dated Institutional Review Board (IRB) approved informed consent must be obtained before any study-specific procedures are performed. Once written informed consent has been obtained, the subject will be screened to determine eligibility and document adherence to the preliminary inclusion/exclusion criteria.

4.1.1 Visit 1: Screening (Week -8)

The following screening assessments/procedures must be performed and the results documented within 2 weeks before Visit 2 unless otherwise indicated:

- Administer informed consent
- Review the inclusion and exclusion criteria (See Section 3.2)
- Record demographic data (i.e., date of birth, race and height).
- Record medical and medication history.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.
- Complete MMSE assessment
- Perform chest X-ray.
- Perform MRI scan including fluid-attenuation inversion recovery (FLAIR) and T2*-weighted gradient-recalled-echo (GRE) sequences.

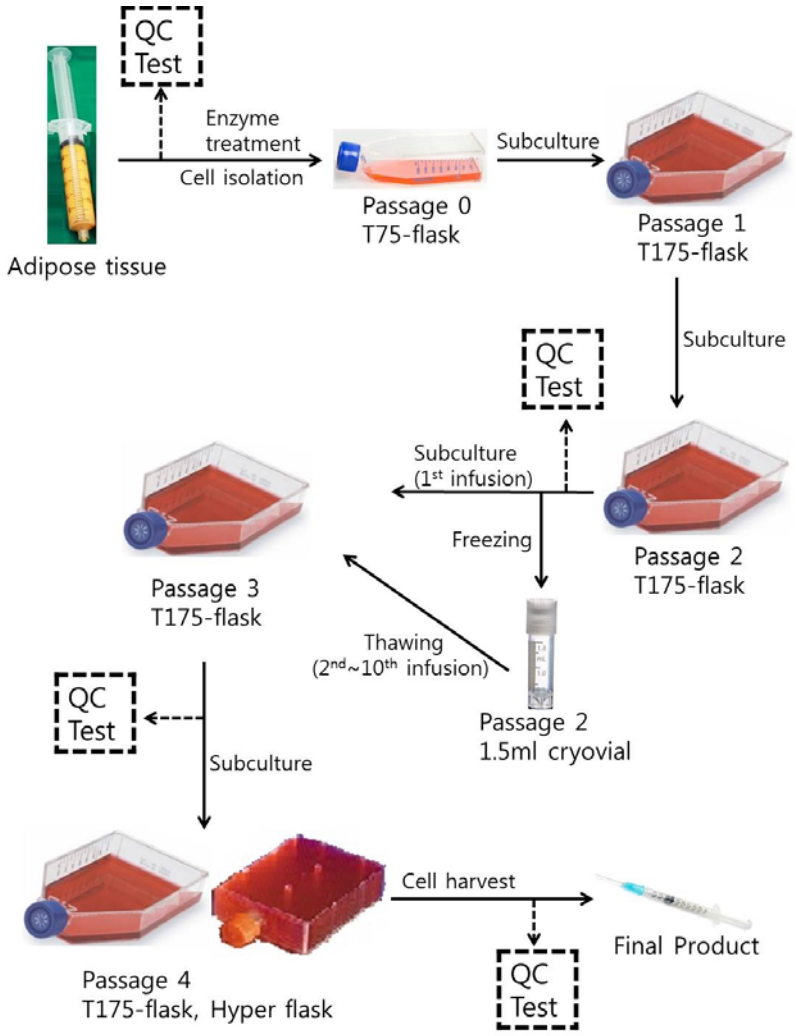
4.1.2 Visit 2 (Week -4)

Visit 2 will occur approximately 4 weeks (± 1 week) after Visit 1. During this visit, the following assessments/procedures should be performed:

- Confirm eligibility and perform randomization instructed in Section 3.5.6.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- In sterile conditions, collect blood and harvest approximately 30 mL of fat using the syringe liposuction technique with Tumescent (or super-wet) local anesthesia (Please see the detail procedures in Appendix 9).
- Ship the packaging box containing the harvested syringes and serum tubes to the lab designated by the sponsor (pre-labeled).

4.1.3 Preparation of Final Drug Product at Lab

The following procedures for the preparation of final drug product will be performed by well-trained lab technicians at the lab designated by the sponsor. The official package containing the final drug product (syringes) will be shipped to the clinical site.



4.2 Treatment Period

4.2.1 Visit 3: Baseline (Week 0)

Visit 3 will occur approximately 4 weeks after Visit 2. During this visit, the following assessments/procedures should be performed:

- The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7) and C-SSRS (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential), biomarker analysis and urinalysis.
- Collect blood for IP and ship the packaging box containing the serum tubes to the lab designated by the sponsor (Please follow the serum for IP handling instruction separately provided by the sponsor).
- Administer the AstroStem in 220 mL of saline (two times of 10 ml AstroStem in 100 mL of saline) or the same volume of saline via I.V. for 2-6 hours to patients in the treatment group and the placebo group, respectively (Please see the detail procedures in Appendix 10).

4.2.2 Visits 4, 8, 10 and 11 (Weeks 2, 10, 14 and 16)

Visits 4, 8, 10 and 11 will occur approximately 2 weeks (± 3 days) after the previous visit. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Verify if subjects are eligible to have a repeated injection by confirming subjects has not experienced infusion reaction, allergic reaction or anaphylaxis in associated with the previous study drug administration.
- Administer the AstroStem in 220 mL of saline or the same volume of saline via I.V. for 2-6 hours to patients in the treatment group and the placebo group, respectively.

4.2.3 Visits 5 and 7 (Weeks 4 and 8)

Visits 5 and 7 will occur approximately 2 weeks (± 3 days) after the previous visit. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Collect blood for IP and ship the packaging box containing the serum tubes to the lab designated by the sponsor (Please follow the serum for IP handling instruction separately provided by the sponsor).

- Verify if subjects are eligible to have a repeated injection by confirming subjects has not experienced infusion reaction, allergic reaction or anaphylaxis in associated with the previous study drug administration.
- Administer the AstroStem in 220 mL of saline or the same volume of saline via I.V. for 2-6 hours to patients in the treatment group and the placebo group, respectively.

4.2.4 Visit 6 (Week 6)

Visit 6 will occur approximately 2 weeks (± 3 days) after Visit 5. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Verify if subjects are eligible to have a repeated injection by confirming subjects has not experienced infusion reaction, allergic reaction or anaphylaxis in associated with the previous study drug administration.
- The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7) and C-SSRS (see Appendix 8).
- Collect blood and urine samples for hematology, serum chemistry and urinalysis.
- Administer the AstroStem in 220 mL of saline or the same volume of saline via I.V. for 2-6 hours to patients in treatment group and placebo group, respectively.

4.2.5 Visit 9 (Week 12)

Visit 9 will occur approximately 2 weeks (± 3 days) after Visit 8. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Verify if subjects are eligible to have a repeated injection by confirming subjects has not experienced infusion reaction, allergic reaction or anaphylaxis in associated with the previous study drug administration.
- The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7), and C-SSRS (see Appendix 8).
- Perform MRI scan including FLAIR and T2- weighted gradient-echo sequences.

- Collect blood and urine samples for hematology, serum chemistry and urinalysis.
- Collect blood for IP and ship the packaging box containing the serum tubes to the lab designated by the sponsor (Please follow the serum for IP handling instruction separately provided by the sponsor).
- Administer the AstroStem in 220 mL of saline or the same volume of saline via I.V. for 2-6 hours to patients in treatment group and placebo group, respectively.

4.2.6 Visit 12 (Week 18)

Visit 12 will occur approximately 2 weeks (± 3 days) after Visit 11. During this visit, the following assessments/procedures should be performed:

- The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7) and C-SSRS (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Verify if subjects are eligible to have a repeated injection by confirming subjects has not experienced infusion reaction, allergic reaction or anaphylaxis in associated with the previous study drug administration.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential) and urinalysis.
- Administer the AstroStem in 220 mL of saline or the same volume of saline via I.V. for 2-6 hours to patients in treatment group and placebo group, respectively.

4.3 Follow-up Period

4.3.1 Visit 13: 1st Follow-up Visit (Week 30)

The first follow-up visit, Visit 13, will occur approximately 12 weeks (± 7 days) after Visit 12. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7) and C-SSRS (see Appendix 8).

- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential), biomarker analysis and urinalysis.
- Perform MRI scan including FLAIR and T2- weighted gradient-echo sequences.

4.3.2 Visit 14: Final Follow-up Visit (Week 52)

The final follow-up visit, Visit 14, will occur approximately 22 weeks (± 7 days) after Visit 13. During this visit, the following assessments/procedures should be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Perform The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7), and C-SSRS (see Appendix 8).
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential), biomarker analysis and urinalysis.
- Perform MRI scan including FLAIR and T2- weighted gradient-echo sequences.

4.4 Early Termination Visit

If a subject will drop-out the study before Visit 14 (Week 52), the clinical site will try to schedule an early termination visit. During this visit, the following assessments and procedures should be performed:

- The following questionnaires will be completed: ADAS-Cog (see Appendix 2), MMSE (see Appendix 3), CDR-SOB (see Appendix 4). NPI (see Appendix 5), GDS (see Appendix 6), ADCS-ADL (see Appendix 7) and C-SSRS (see Appendix 8).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a complete physical examination.
- Measure 12-lead ECG.
- Record any changes in concomitant medications.
- Record any adverse events, if applicable.
- Collect blood and urine samples for hematology, serum chemistry, pregnancy test (only for women of childbearing potential), biomarker analysis and urinalysis.
- Perform MRI scan including FLAIR and T2- weighted gradient-echo sequences.

4.5 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed in compliance with current GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP guideline, and other regulatory aspects. This will include

on-site review of the eCRF for completeness and clarity, consistency with source documents, and clarification of administrative matters.

4.6 Documentation

Entries made in the eCRF must be either verifiable against source documents or have been directly entered into the eCRF, in which case the entry in the eCRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained/archived until notification by the sponsor for change of archive site or destruction.

5. ETHICAL AND LEGAL ASPECTS

5.1 Institutional Review Board (IRB)

Documented approval from the IRB will be obtained for all participating trial center(s)/clinic(s) prior to study start, according to GCP and applicable laws and regulations. When necessary, an extension, amendment, or renewal of the IRB approval must be obtained and also forwarded to the sponsor. The IRB must supply to the sponsor, upon request, a list of the IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

5.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will be implemented by the investigator only after sponsor's approval. However, the investigator may implement a deviation form, or change of the protocol to eliminate any immediate hazard(s) to the trial subjects without prior IRB/sponsor approval. The implemented deviation or change, the reasons for it and, if appropriate, the proposed amendment should be submitted to the IRB/sponsor as soon as possible. Any deviations from the protocol must be fully explained and documented by the investigator.

5.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, will be in place and fully documented prior to the study's start.

5.4 Subject Information Consent

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the IRB written approval of the Informed Consent Form and any other written information that will be provided to the subjects. The written approval of the IRB with the approved Informed Consent Form must be in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

5.5 Insurance

All subjects participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

5.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Even if the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects' records to be identified.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical and Analytical Plans

6.1.1 Analytical Populations

6.1.1.1 Intent-to-Treat Population

An intent-to-treat (ITT) population will include subjects who received at least one intravenous injection and have post-injection efficacy measurements. This population will be evaluated for all efficacy variables.

6.1.1.2 Per-Protocol Population

All subjects valid for ITT who complete Visit 13 (Week 30) will be 'valid per protocol' (also called 'valid for efficacy'). Additional criteria may be added prior to unblinding the study database. As with the ITT population, this per-protocol (PP) cohort will also be evaluated for all efficacy variables.

6.1.1.3 Safety Population

A safety population will include subjects who received at least one intravenous injection and have post-injection safety measurements. This population will be evaluated for all safety variables.

6.1.2 Treatment Group Comparability

Demographic variables, medical history, treatment duration, and efficacy variables at baseline will be summarized by treatment group for the subjects valid for potential safety analysis. Because, in theory, the goal of randomization is to balance out the patient characteristics, statistical tests are not planned for these variables.

6.1.3 Significance Level

The primary efficacy hypothesis test will be performed using a 5% significance level. For the secondary efficacy endpoints, hypothesis tests will be performed individually at the 5% significance level. All hypothesis tests will be performed with two-sided alternative hypotheses. No adjustments on the significance level for multiple comparisons are planned, as this is a phase 1/2 study.

6.1.4 Primary Efficacy Analyses

The primary efficacy variable is the change from Baseline on the ADAS-Cog score at Week 30. The primary efficacy variable will be summarized with means, standard deviations, medians and ranges, overall and by group. The change from Baseline ADAS-Cog score will be analyzed with Student's t-test or Kruskal-Wallis test depending on the violation of normality assumption.

6.1.5 Secondary Efficacy Analyses

The secondary efficacy analyses are described below. They will be summarized with means, standard deviations, medians and ranges for continuous variables and with counts and percentages for categorical variables.

The percentage of subjects who show improvement will be compared between groups using chi-square test or Fisher's exact test, as appropriate. Fisher's exact test will be used if the expected frequency in any of the cells of the crosstabulation is less than 5.

Change from baseline at Week 30 in MMSE, CDR-SOB, NPI, GDS and ADCS-ADL will be compared between groups using t-test or Kruskal-Wallis tests, as appropriate. If the change is approximately normally distributed, t-test will be used. If the change is markedly non-normally distributed, Kruskal-Wallis test will be used.

6.1.6 Exploratory Efficacy Analyses

Change from baseline scores at Visits 6, 9, 12, 13 and 14 or Early Termination for: ADAS-Cog, MMSE, CDR-Box, NPI, GDS, and ADCS-ADL will be summarized with means, standard deviations, medians and ranges by treatment group and visit. Biomarkers in blood [Amyloid beta 40, Amyloid beta 42, Amyloid precursor protein intracellular domain (AICD), soluble neuregulin-1 (sNRG-1)] will be summarized at all visits with means, standard deviations, medians and ranges for continuous variables and with counts and percentages for categorical variables.

6.1.7 Safety Analyses

AE rates will be summarized by treatment group and overall, and will be broken down by severity, seriousness and relation to study drug. Change of MRI, C-SSRS, physical examinations, vital signs, ECG and standard laboratory results will be summarized with means, standard deviations, medians and ranges for continuous variables and with counts and percentages for categorical variables. Statistical tests are not planned for safety variables.

6.1.7.1 Interim Safety Analyses

When the first 4 subjects complete Visit 4 at Week 2, one unblinded interim safety analysis can be performed by an independent safety monitor contracted by the sponsor to evaluate the safety of

AstroStem without the suspension of subject enrollment. Change of vital signs and AEs will be evaluated.

6.1.8 Missing Data

No adjustments for missing data and no imputation methods are planned for this phase 1/2 study.

6.2 Determination of Sample Size

There was no formal sample size calculation since this is a phase 1/2 study and is not a hypothesis-driven study. The number of enrolled subjects is predefined at n=22, for 11 subjects per group.

7. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

7.1 Definitions

7.1.1 Adverse Events

An adverse event is defined in the 21 CFR 312.32(a) as "Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose. Worsening of a pre-existing medical condition (e.g., diabetes, migraine headaches, and gout) after the drug administration should be considered an adverse event if there is either an increase in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from baseline values. Abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

Adverse events will be reviewed continuously throughout the study.

7.1.2 Serious Adverse Events

A serious adverse event (SAE) is any AE or suspected adverse reaction that in the view of either the investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE: it is defined as an AE or suspected adverse reaction that in the view of the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
  A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function.
- A congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of outcomes listed in the above definition

Life threatening: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as 'serious', UNLESS at least one of the following exceptions is met:

- the admission results in a hospital stay of less than 24 hours OR
- the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment.

Disability means a substantial disruption of a person's ability to conduct normal life functions.

Important medical event: As guidance for determination of important medical events see the 'WHO Adverse Reaction Terminology – Critical Terms List'. These terms either see or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

7.2 Reporting Procedures for All Adverse Events

The investigator is responsible for ensuring that all adverse events (as defined in Section 7.1) observed by the investigator or reported by subjects after the first dose of each subject are properly captured in the subject's medical records and reported on the eCRF.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with subject identification, relationship to investigational product, start and stop dates, severity, action taken, and outcome.

7.2.1 Relationship of Adverse Event to Study Drug

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to study drug and action taken. The investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

If applicable, the relationship of the adverse event to the study drug will be assessed by means of the question: "Is there a reasonable possibility that the event may have been caused by the study drug?" The investigator should respond to this question with either Yes or No.

7.2.2 Adverse Event Severity

The severity of adverse events should be graded as follows:

- Mild – Usually transient in nature and generally not interfering with normal activities
- Moderate – Sufficiently discomforting to interfere with normal activities
- Severe – Prevents normal activities

Medically significant adverse events considered related to the study drug by the investigator or Sponsor will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

7.3 Serious Adverse Event Reporting Procedures

Serious Adverse Events, including laboratory test abnormalities fulfilling the definition of serious, after the first dose, and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person/parties as detailed in the study file. A Serious Adverse Event form must also be completed within 1 day of the investigator's awareness and forwarded to the designated person/parties as detailed in the study file. Each Serious Adverse Event must be followed up until resolution or stabilization by submission of updated reports to the designated person/parties.

Reporting of SAEs begins from the first administration of the study drug through within 30 days after the last dose of study drug. Events assessed by the Investigator as related to study drug (or

having an unknown relationship at the time of reporting) should be reported within 24 hours regardless of the number of days since the last dose.

For all deaths, available autopsy reports and relevant medical reports should be faxed to Sponsor or their designee. For this reporting process, subject assessments must be made 30 days after administration of the last dose of study drug. Deaths assessed by the Investigator as related to study drug (or having an unknown relationship at the time of reporting) should be reported within 24 hours regardless of the number of days since the last dose.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Study Case Report Form.

When required, and according to local law and regulations, serious adverse events must be reported to the institutional review board and Regulatory Authorities.

7.4 Procedures for Managing Microhemorrhages and Cerebral Vasogenic Edema

MRI scan will be performed at screening, Visit 9 (Week 12), Visit 13 (Week 30), Visit 14 (Week 52), and/or Early Termination Visit. The protocols for MRI scans should include fluid-attenuation inversion recovery (FLAIR) and T2-weighted gradient-recalled-echo (GRE) sequences. Standards for the detection of cerebral microhemorrhage or superficial siderosis will include: 2D T2 GRE; field strength of 1.5 Tesla or greater; slice thickness of 5mm or less; Echo Time (TE) of 20 ms or greater. Standard FLAIR sequences are generally appropriate for the detection of cerebral vasogenic edema.

Subjects who are found to have new clinically asymptomatic microhemorrhages will be followed up closely, and a follow-up MRI will be done to evaluate the stability of those lesions.

All Principal Investigators will be notified of the possible occurrence of cerebral vasogenic edema, its imaging manifestations, and the clinical signs and symptoms that may accompany this phenomenon. They will also be told of the measures to be taken if cerebral vasogenic edema occurs. Those measures will include more frequent serial MRI scans until the imaging abnormalities resolve, and consideration of treatment with high-dose dexamethasone if symptoms are severe.

8. USE OF DATA AND PUBLICATION

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies both parties.

The investigator is encouraged to participate in the evaluation of the data for scientific purposes but is expected to work with the sponsor in the development of any scientific presentation or publication. Since the sponsor authors will be included, it is expected that all co-authors of the manuscripts will have an opportunity for feedback in the content and conclusions. The technical and editorial resources of the sponsor will be available to assist in the development of abstracts, presentations, and publications regarding this study and it is expected that drafts will be sent to the sponsor with adequate time for input and revisions prior to submission.

9. REFERENCES

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10. APPENDICES

Appendix 1. Laboratory Parameters

Appendix 2. ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale)

Appendix 3. MMSE (Mini-mental status examination)

Appendix 4. CDR-SOB (Clinical Dementia Rating-Sum of Box)

Appendix 5. NPI (Neuropsychiatric Inventory)

Appendix 6. GDS (Geriatric Depression Scale)

Appendix 7. ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living)

Appendix 8. C-SSRS (Columbia Suicide Severity Rating Scale)

Appendix 9. Instruction for Liposuction Procedure

Appendix 10. IP Administration Instruction for Clinical Sites

Appendix 1. Laboratory Parameters

Blood and urine samples for complete laboratory evaluation (hematology, serum chemistry, biomarker analysis and urinalysis) at Visits 1, 3, 6, 9, 12, 13 and 14 or Early Termination.

HEMATOLOGY	CHEMISTRY	URINALYSIS	BIOMARKER***
Hemoglobin Hematocrit RBC WBC MCV MCH MCHC Neutrophils (absolute) Lymphocytes (absolute) Monocytes (absolute) Eosinophils (absolute) Basophils (absolute) Platelets PT-INR	Total bilirubin Alkaline phosphatase ALT (SGPT) AST (SGOT) Blood urea nitrogen (BUN) Creatinine Glucose Albumin Total protein Sodium Potassium Chloride Bicarbonate Calcium HCG * HIV ** HBV** HCV** VDRL**	Color Appearance Specific gravity pH Protein Glucose Ketones Bilirubin Blood Leukocyte esterase WBC RBC Epithelial cell Bacteria Hyaline casts	Amyloid beta 40 Amyloid beta 42 Amyloid precursor protein intracellular domain (AICD) soluble neuregulin-1 (sNRG-1)

* HCG (pregnancy test) only for all females of childbearing potential at Visits 1, 3, 12, 13 and 14 or Early Termination

** Visit 1 only

*** Visits 3 and 13, 14 or Early Termination

Appendix 2. ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale)

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Alzheimer's Disease Assessment Scale – Cognitive Behavior (ADAS-Cog)

ADAS Initial Conversation Notes

Instructions:

For Specific instructions for all tasks, refer to the Administration Manual. The first several minutes are spent in open-ended conversation in order to assess various aspects of expressive and receptive speech. Then the remaining cognitive tests are administered. Language abilities are evaluated throughout the interview and on specific tests. Questions eliciting "yes" and "no" answers assess comprehension on a very basic level. Other questions should require specific information and well-developed communication skills.

Engage the subject in a short conversation about neutral topics (for example: weather, the subject's trip to the clinic, or what the subject had for breakfast). This conversation will help to put the subject at ease before the testing begins and will give the examiner an opportunity to observe how well the subject can use and understand language. There are three clinical ratings of language ability on the cognitive part of the ADAS. Use this page to record your interview notes. Documentation should be evident on this form to support rating of Spoken Language Ability, Word Finding Difficulty and Comprehension. Any rating of impairment should be supported by notes documented on this page.

Possible Topics	Weather	Breakfast	Clinic trip	Other
1) Comprehension				
2) Word Finding				
3) Spoken Language				

Testing Comments: _____

_____

_____

_____

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1. Word-recall (Word List 1)

To begin testing, say: **"I am going to show you some words printed on these white cards. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. Ready, read the word and try to remember it."**

Present each word to the subject and ask him/her to say it aloud. After all 10 words have been presented, say: **"Good, now tell me all the words you can remember that were on that list."** Prompt with **"Any others?"** as necessary. For trials 2 and 3 say: **"Now I am going to show you that same list again. Read each word out loud and try to remember it."** *Examiner should check a response (yes/no) for every word.*

	Word recalled correctly?	
Trial 1	**Yes**	**No**
BUTTER		
ARM		
SHORE		
LETTER		
QUEEN		
CABIN		
POLE		
TICKET		
GRASS		
ENGINE		

Total Not Recalled ☐

	Word recalled correctly?	
Trial 2	**Yes**	**No**
POLE		
LETTER		
BUTTER		
QUEEN		
ARM		
SHORE		
GRASS		
CABIN		
TICKET		
ENGINE		

Total Not Recalled ☐

	Word recalled correctly?	
Trial 3	**Yes**	**No**
SHORE		
LETTER		
ARM		
CABIN		
POLE		
TICKET		
ENGINE		
GRASS		
BUTTER		
QUEEN		

Total Not Recalled ☐

If any trial not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, enter a score of "10" in eCRF)**

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2. Commands

This task is designed to assess receptive speech. The subject is asked to carry out five separate commands with 1 to 5 steps per command. Each command should be read once. If the subject does not respond or looks confused, or asks for a repetition, the examiner should give the entire command one more time. Then go on to the next command. All commands should be given to every subject. *Examiner should check a response (yes/no) for every command.*

To begin testing, say: **"Now I am going to ask you to do a few things. First…"**

Command performed correctly?

Command	Yes	No
a. "Make a ***fist***." (say "*Relax it*" if needed upon completion).		
b. "Point to the ***ceiling***, and then to the ***floor***."		
Line up a pencil, watch and card (left to right from subject's point of view) on the table.		
c. "Put the ***pencil on top of the card*** and then ***put it back***."		
d. "Put the ***watch on the other side of the pencil*** and ***turn over the card***."		
e. "Tap ***each shoulder twice*** with ***two fingers***, keeping your ***eyes shut***."		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= all commands correct
1	= 1 command incorrect
2	= 2 commands incorrect
3	= 3 commands incorrect
4	= 4 commands incorrect
5	= 5 commands incorrect

3. Constructional Praxis

This test assesses the subject's ability to copy 4 geometric forms. The forms should be presented one at a time. If the subject looks confused or dissatisfied with the drawing, or asks to try again, the subject should be allowed **a second attempt** for each shape. If a second attempt is made, ask the subject to indicate which one is better, and score only that attempt. *Examiner should check a response (yes/no) for every form.*

To begin testing, say: **"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page."**

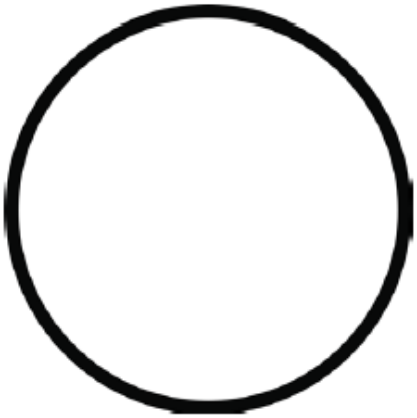
Figure	Figure drawn correctly? Yes	No
a. **Circle** A closed curved figure. Small gaps do not count as errors. Size is not critical.		
b. **Two overlapping rectangles** Figure must be four-sided, and overlap must be similar to presented form. Changes in size are not scored.		
c. **Diamond (Rhombus)** Figure must be four-sided, oriented so that the points are at the top and bottom, and the sides approximately equal in length (e.g., longest side is not > 1.5 times the length of the shortest side).		
d. **Cube** The figure is 3-demensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.		
e. No figures drawn; scribbles; parts of forms; words instead of form		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= all 4 drawings correct
1	= 1 form drawn incorrectly
2	= 2 forms drawn incorrectly
3	= 3 forms drawn incorrectly
4	= 4 forms drawn incorrectly
5	= no figures drawn; scribbles; parts of forms; words instead of forms



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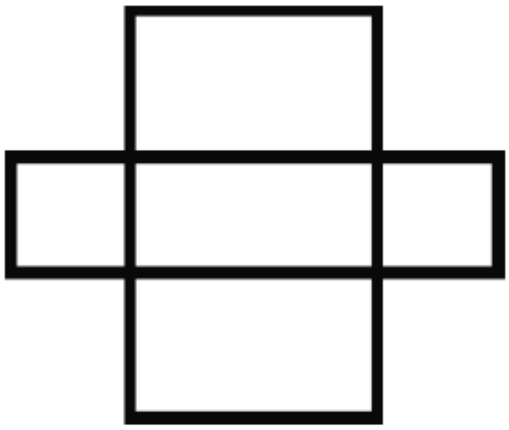

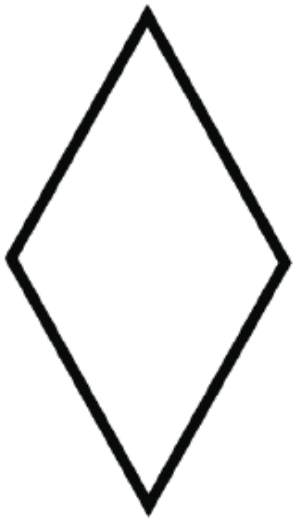

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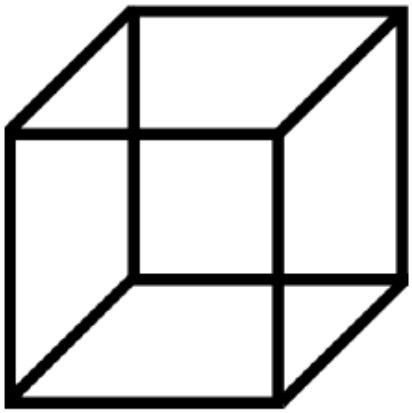

4. Naming Objects/Fingers

For this task, the subject is asked to name 12 randomly presented real objects. Objects should be presented in random order. Give the subject instructions similar to the following: **"Now I am going to show you some objects. I want you to tell me what their names are. What is this called?"** (present object). If the subject responds with the object's function say: **"Yes, that's what it does, but what is its name?"** If the subject does not respond, the examiner should give the semantic cue for that item (provided below). If the subject still does not respond or makes an error, proceed to the next object. *Examiner should check a response (yes/no) for every object/finger.*

		Response correct?	
Item	**Acceptable Clue**	**Yes**	**No**
Flower	grows in garden		
Bed	used for sleeping		
Whistle	makes a sound when you blow on it		
Pencil	used for writing		
Rattle	a baby's toy		
Mask	hides your face		
Scissors	cuts paper		
Comb	used on hair		
Wallet	holds your money		
Harmonica	a musical instrument		
Stethoscope	doctor uses it to listen to your heart		
Tongs	picks up food		

4. Naming Objects/Fingers (cont'd)

The subject is also asked to name the fingers on his/her dominant hand. Say: **"Please place your right (or left) hand on the table. Now I am going to point to a part of your hand and I want you to tell me what it's called. What is this?"** If a query is necessary say: **"What is another name for this finger?"**

Fingers	Response correct? Yes	No
Thumb		
Index/Pointer/Forefinger		
Middle		
Ring		
Pinky/Little/Baby		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= 0-2 items (objects and fingers) named incorrectly
1	= 3-5 items (objects and fingers) named incorrectly
2	= 6-8 items (objects and fingers) named incorrectly
3	= 9-11 items (objects and fingers) named incorrectly
4	= 12-14 items (objects and fingers) named incorrectly
5	= 15-17 items (objects and fingers) named incorrectly

5. Ideational Praxis

This task is designed to determine whether the subject can perform a familiar but complex sequence of actions. There are 5 components to this task. Place a blank long envelope, an 8 ½ x 11" sheet of paper and a pencil in front of the subject.

Read the following instruction to the subject exactly as written:
"I want you to pretend you have written yourself a letter. Take this piece of paper, fold it so that it will fit into the envelope, and then put it into the envelope. Then seal the envelope, address the envelope to yourself, and show me where the stamp goes."

If the subject forgets part of the task, or is having difficulty, the tester should repeat the instruction for the component of the task where the subject is having difficulty. After the first complete instruction, only one additional reminder should be given for each component. *Examiner should check a response (yes/no) for every component.*

	Action correct?	
Component	**Yes**	**No**
a. Folds paper		
b. Put paper in envelope		
c. Seal envelope		
d. Address envelope		
e. Indicate where stamp goes		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "5" on the scoring table below)**

Scoring: (circle one)

0	= all components performed correctly
1	= failure to perform 1 component
2	= failure to perform 2 components
3	= failure to perform 3 components
4	= failure to perform 4 components
5	= failure to perform 5 components

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6. Orientation

This task is designed to determine how well oriented the subject is with regard to time and place. Ask the subject for each of these pieces of information **one at a time**. One restatement of each question is allowed (e.g. if subject confuses day and date.) Questions must not be restated based on an incorrect response but only if the subject does not understand the initial question or asks for a repetition. *Examiner should check a response (yes/no) for every question.*

Question	Response correct? Yes	No
Full name: (must be exact)		
Month: (must be exact)		
Date: (± 1 day)		
Year: (must be exact)		
Day of the week: (must be exact)		
Season: (within 1 week of upcoming season or within 2 weeks of previous season)		
Place: (Partial names are acceptable, but generic terms are not) Say: **"Where are we now?"** or **"What is the name of this place?"**		
Time: (± 1 hour) Say: **"Without looking at your watch, tell me approximately what time it is."**		

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons **(if selected, circle "8" on the scoring table below)**

Scoring: (circle one)

0	= all responses correct
1	= 1 response incorrect
2	= 2 responses incorrect
3	= 3 responses incorrect
4	= 4 responses incorrect
5	= 5 responses incorrect
6	= 6 responses incorrect
7	= 7 responses incorrect
8	= 8 responses incorrect

7. Word Recognition (Word List 1)

In the learning portion of this test, the subject is given one trial to learn a list of 12 words. Say: **"I am going to show you some words printed on these white cards. I want you to read each word out loud and try to remember it."**

In the recognition portion of this test, the examiner should say: **"Now I'm going to show you another set of words. Some of the words were on the list I just showed you and others are new. For each word I want you to tell me whether it is one of the words I just showed you."**

The examiner shows that first word and says either **"Is this one of the words I showed you before, yes or no?"**, or **"Did I show you this word before?"** The same instruction is given before the second test word. For the remaining test words the examiner should say **"How about this one?"**

Check the **subject's response** to each word **Yes** or **No**. If the subject needs to be reminded of the task during the exam, the examiner should repeat the question and place a check in the reminder column.

***R = Reminder given**

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reason
- ☐ Subject unable for cognitive reasons

(Enter Max Score or "12")

Check Subject Response

Word	Yes	No	*R
NURSE			
MAGAZINE			
WIZARD			
VAN			
LEOPARD			
SALE			
SEA			
TRAIN			
COIN			
SHIP			
INSTITUTION			
MAP			
AXE			
BOARD			
CARROT			
MILK			
VOLUME			
FOREST			
ANCHOR			
GEM			
CAT			
FUND			
EDGE			
CAKE			

Total Not Recalled (Max Score=12) ☐ ***Reminder Given**

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8. Remembering Test Instructions

This item evaluates the subject's ability to remember the requirements of the **Word Recognition** task. The number of reminders given on the Word Recognition task are counted to rate this item. If the Word Recognition task was not completed or not attempted, then this item must not be scored.

Each instance of memory failure for the test instructions after the first two items is scored.

Scoring: (circle one)

0	**None**	=	subject never needs extra reminders of instructions
1	**Very mild**	=	forgets once
2	**Mild**	=	must be reminded 2 times
3	**Moderate**	=	must be reminded 3 or 4 times
4	**Moderately severe**	=	must be reminded 5 or 6 times
5	**Severe**	=	must be reminded 7 or more times

9. Comprehension

This item evaluates the subject's ability to understand speech. To rate this item consider how well the subject was able to understand the examiner's speech during the opening discussion and during the test session. **Do not count performance on Commands subtest when rating this item.**

Scoring: (circle one)

0	**None**	=	subject understands
1	**Very mild**	=	one or two instance of misunderstanding
2	**Mild**	=	3-5 instances of misunderstanding
3	**Moderate**	=	requires several repetitions and rephrasing
4	**Moderately severe**	=	subject only occasionally responds correctly; i.e. yes/no questions
5	**Severe**	=	subject rarely responds to questions appropriately, not due to poverty of speech

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10. Word Finding Difficulty

To rate this item, the examiner must determine whether the subject has difficulty in finding the desired word in spontaneous speech during the interview and test session. **Do not count performance on Naming Objects and Fingers subtest when rating this item.** Documentation should be evident on page 1 to support any rating above zero.

Scoring: (circle one)

0	**None**	=	no evidence of word finding difficulty in spontaneous speech
1	**Very mild**	=	1 or 2 instances, not clinically significant
2	**Mild**	=	noticeable circumlocution or synonym substitution
3	**Moderate**	=	loss of words without compensation on occasion
4	**Moderately severe**	=	frequent loss of words without compensation
5	**Severe**	=	nearly total loss of contest of words; speech sounds empty; 1-2 word utterances

11. Spoken Language Ability

This item is a global rating of the quality of speech, *i.e.*, clarity, difficulty in making oneself understood. In rating this item the examiner should consider all of the speech produced by the subject in the initial interview and the test session. Documentation should be evident on Page 1 to support any rating above zero. (Refer to the procedures manual for guidelines)

Scoring: (circle one)

0	**None**	=	no instances where it is difficult to understand the subject
1	**Very mild**	=	one instance of lack of understandability
2	**Mild**	=	subject has difficulty less than 25 % of the time
3	**Moderate**	=	subject has difficulty 25-50% of the time
4	**Moderately severe**	=	subject has difficulty more than 50% of the time
5	**Severe**	=	one or two word utterance; fluent, but empty speech; mute

12. Delayed Word Recall

Say to the subject, **"Now I want you to try to remember the words that I showed you earlier on printed cards. Can you tell me any of those words?"** Allow a maximum of two minutes for recall.

Check *each* word correctly recalled. Total equals words *not correctly* recalled.

Word	Word recalled correctly? Yes	No
BLOOD		
CAMP		
COTTON		
FIRE		
HALL		
LAD		
PLANT		
RIVER		
STEAM		
TOY		

Total Not Recalled ☐

If any trial not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive).
- ☐ Subject refused.
- ☐ Subject unable for physical reasons.
- ☐ Subject unable for cognitive reasons. (If selected, enter a score of "10" in eCRF)

13. Executive Function (Maze)

Present the practice maze in the correct orientation in front of the participant. Indicate where to begin and where to exit the maze. Say to the subject, **"I want you to find the route from the start to the exit of this maze. Put your pencil here (point to the start) at the start. Here (point to the exit) is the exit of the maze. Try not to run into dead ends or cross solid lines. Please keep your pencil on the paper at all times."** If the participant lift his or her pencil, remind him or her to keep the pencil on the page.

Once the participant has completed the Mandatory Practice Maze, proceed to the Scored Maze.

Check *each* word correctly recalled. Total equals words *not correctly* recalled.

a. Number of errors (range = 0-2) ☐

b. Time at completion or second error (maximum = 240 seconds total) ☐☐☐

If task not administered, please specify reason (check one):

- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons (If selected, enter a score of "5" in eCRF)

Scoring: (circle one)

0	= 0-30 seconds at completion or second error
1	= 31-60 seconds at completion or second error
2	= 61-90 seconds at completion or second error
3	= 91-120 seconds at completion or second error
4	= 121 - 239 seconds at completion or second error
5	= 240 seconds at completion or second error

14. Number Cancellation

Place the **practice** form face up in front of the participant. Say the following instructions word-for-word:
"On the top of this page are two numbers. In this row of numbers you will find these numbers mixed in with other numbers. I'd like you to begin here" (point to the beginning of the line) and cross off each number that matches either of the two numbers at the top of the page. Please work as quickly as you can."
Correct any errors and re-explain as necessary to ensure understanding of the task. Discontinue the example after 30 seconds or when the participant finishes the line, whichever is first.

Place the **test** form face up in front of the participant. Say the following instructions word-for-word:
"On the top of this page are two numbers. Throughout this page you will find these numbers mixed in with other numbers. I'd like you to begin here" (point to the beginning of the line) and going across off each number that matches either of the two numbers at the top of the page. Please work as quickly as you can."

If the participant stops at the end of a line, before the last line, and there is still time left, ask him or her to "keep going." Discontinue the task after 45 seconds or when the participant finishes the last line, whichever is first.

a. Number of targets hit (range = 0-49) | | |

b. Number of errors | | |

c. Number of times reminded of task | | |

If task not administered, please specify reason (check one):
- ☐ Not done (for reasons other than physical/cognitive impairment)
- ☐ Subject refused
- ☐ Subject unable for physical reasons
- ☐ Subject unable for cognitive reasons

Scoring: (circle one)

0	= >/= 30 total score
1	= 24-29 total score
2	= 18-23 total score
3	= 12-17 total score
4	= 6-11 total score
5	= 0-5 total score

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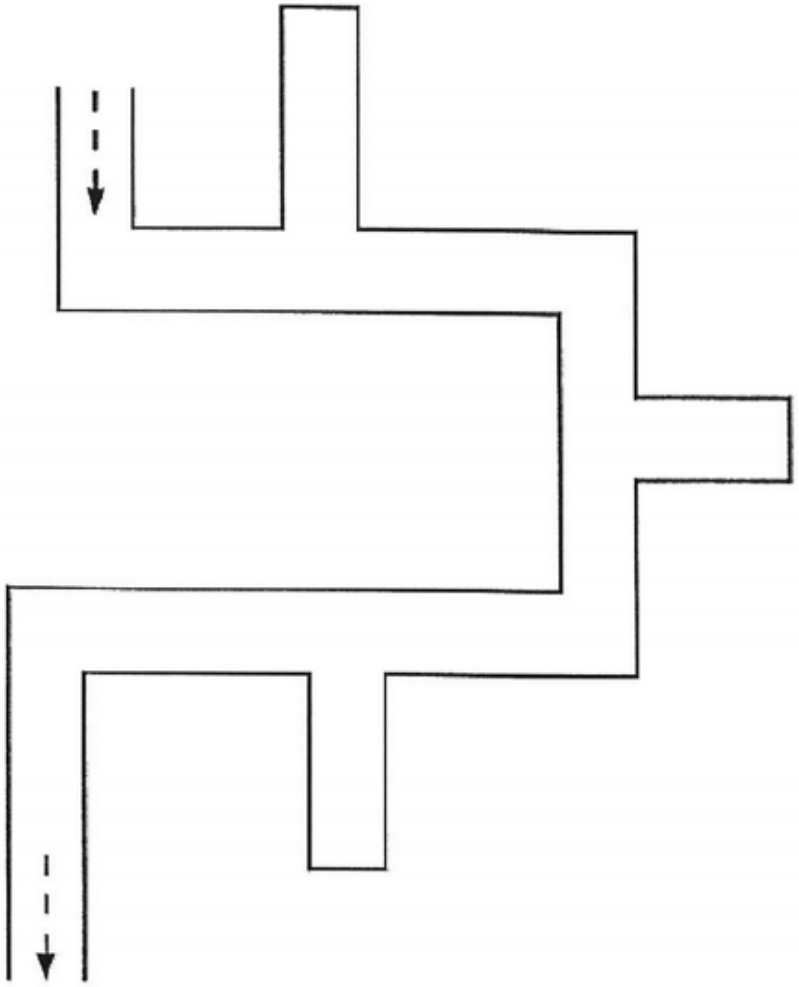
(Example)



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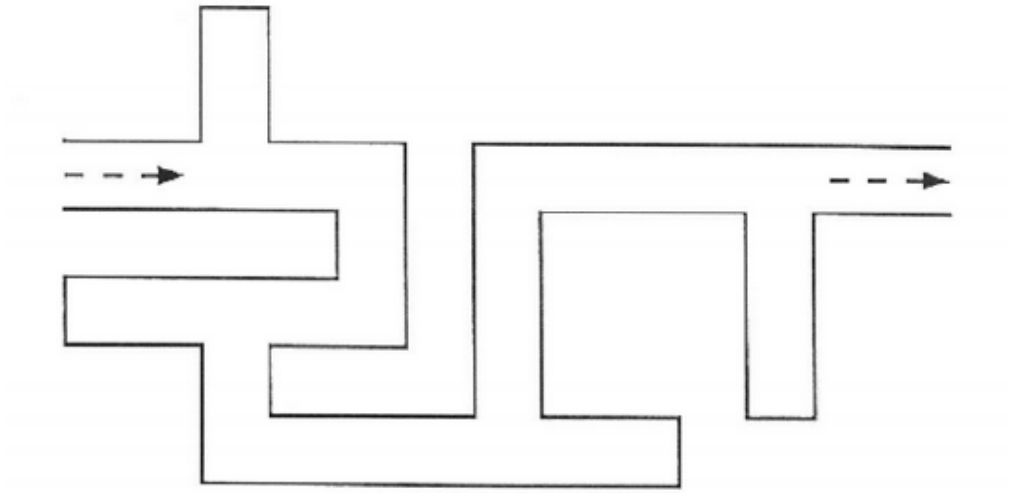
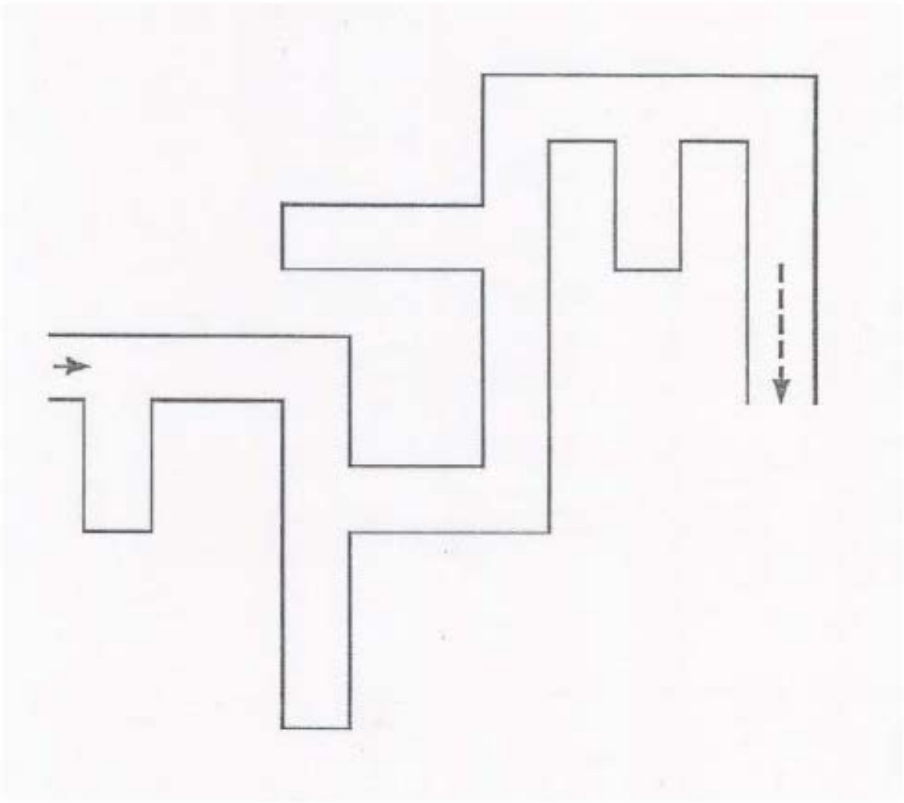
(Test 1)



(Test 2)



(Example)

"6" and "1"

1 2 2 4 5 9 5 6 6 9 1 9 6 7 8 3 2 4 3 7 2 1 4 2 2 1 2 6 6 3

Example for use with versions A, B, and C

(Test)

"2" and "8"

6 2 6 7 2 3 1 3 8 5 5 5 8 1 7 9 1 7 2 7 4 5 7 6 1 3 9 6 2 1

9 4 6 9 5 7 1 8 9 5 6 5 4 2 7 1 5 2 7 9 1 7 1 1 1 4 2 8 5 8

1 9 7 9 7 1 6 7 8 6 5 5 7 2 9 6 5 9 5 4 7 3 2 4 5 6 1 4 3 4

4 6 8 4 1 4 1 7 2 4 7 1 7 6 7 5 4 9 8 7 5 6 2 1 6 9 3 1 4 8

7 8 6 7 1 7 1 3 4 3 9 8 6 5 1 8 3 4 2 6 9 9 6 1 6 4 3 9 3 4

4 9 3 8 7 2 5 4 4 8 7 6 4 1 4 7 2 6 8 7 5 6 3 2 6 4 4 6 8 4

4 8 3 4 7 5 4 4 7 9 7 3 6 8 6 5 4 7 4 3 4 9 2 5 3 5 4 7 3 5

4 9 3 3 8 1 8 4 2 6 5 6 6 1 7 2 4 2 9 7 9 7 6 1 5 1 4 1 9 8

A

Appendix 3. MMSE (Mini-mental status examination)

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Mini-Mental State Examination (MMSE)

PAR Psychological Assessment Resources, Inc. •16204 N. Florida Avenue • Lutz, FL 33549 • 1.800.331.8378 • www.parinc.com

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? May I ask you some questions about your memory?

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)	
What is the...	year?	_____	0	1
	season?	_____	0	1
	month of the year?	_____	0	1
	day of the week?	_____	0	1
	date?	_____	0	1

ORIENTATION TO PLACE*

Where are you now? What is the...			
state (province)?	_____	0	1
county (or city/town)?	_____	0	1
city/town (or part of city/ neighborhood)?	_____	0	1
building (name of type)?	_____	0	1
floor of the building (room number or address)?	_____	0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready?
Here they are...APPLE [*pause*], PENNY [*pause*], TABLE [*pause*]. Now repeat those words back to me.
[*Repeat up to 5 times, but score only the first trial.*]

APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.
*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [*Serial* 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0	1
If needed, say: Keep going.	[86]	_____	0	1
If needed, say: Keep going.	[79]	_____	0	1
If needed, say: Keep going.	[72]	_____	0	1
If needed, say: Keep going.	[65]	_____	0	1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task →

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Substitute and score this item only if the examinee refuses to perform the Serial 7s task.
Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
But score only the backward spelling.

(D = 1)	(L = 1)	(R = 1)	(O = 1)	(W = 1)	(0 to 5)

RECALL	RESPONSE	SCORE (circle one)	
What were those three words I asked you to remember? [*Do not offer any hints.*]			
APPLE		0	1
PENNY		0	1
TABLE		0	1
NAMING*			
What is this? [*Point to a pencil or pen.*]		0	1
What is this? [*Point to a watch.*]		0	1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS.		0	1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [*pause], fold it in half* [pause], and put it on the floor (*or* table).

TAKE IN RIGHT HAND	_____	0	1
FOLD IN HALF	_____	0	1
PUT ON FLOOR (*or* TABLE)	_____	0	1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES	_____	0	1

WRITING

Please write a sentence. [*If examinee does not respond, say:* ***Write about the weather.***] 0 1
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Assessment of level of consciousness.

Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive

Total Score = _____ (30 points max.)
(sum all item scores.)

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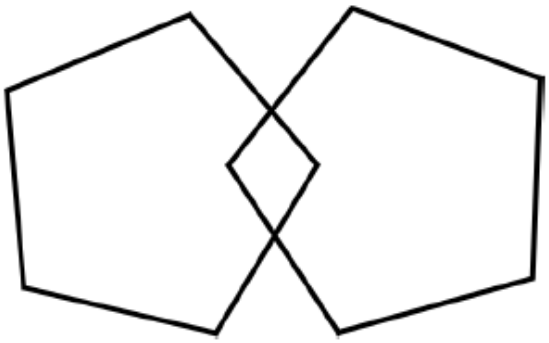
CLOSE YOUR EYES



Appendix 4. CDR-SOB (Clinical Dementia Rating-Sum of Box)

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number	Subject Number	Subject Initials	Caregiver Initials

Clinical Dementia Rating Worksheet

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

Memory Questions for Informant:

1.	Does he/she have a problem with his/her memory or thinking?		☐Yes ☐No	
1a.	If yes, is this a consistent problem (as opposed to inconsistent)?		☐Yes ☐No	
2.	Can he/she recall recent events?	☐ Usually	☐ Sometimes	☐ Rarely
3.	Can he/she remember a short list of items (shopping)?	☐ Usually	☐ Sometimes	☐ Rarely
4.	Has there been some decline in memory during the past year?		☐Yes ☐No	
5.	Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion)		☐Yes ☐No	
6.	Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event?	☐ Usually	☐ Sometimes	☐ Rarely
7.	Does he/she forget pertinent details of the major event?	☐ Usually	☐ Sometimes	☐ Rarely
8.	Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)?	☐ Usually	☐ Sometimes	☐ Rarely

9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).
   Within 1 week : _____
   _____
   Within 1 month: _____
   _____
10. When was he/she born? _____
11. Where was he/she born? _____
12. What was the last school he/she attended? _____
    Name _____
    Place _____
    Grade _____
13. What was his/her main occupation/job (or spouse's job if subject was not employed)? _____
14. What was his/her last major job (or spouse's job if subject was not employed?) _____
15. When did he/she (or spouse) retire and why? _____

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Clinical Dementia Rating Worksheet

Orientation Questions for Informant:

How often does he/she know of the exact:

1. Date of the Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way about familiar streets?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way about indoors?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

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Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

☐ As good as they have ever been
☐ Good, but not as good as before
☐ Fair
☐ Poor
☐ No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):

☐ No loss
☐ Some loss
☐ Severe loss

3. Rate his/her ability to handle complicated financial or business transaction (e.g., balance check-book, pay bills):

☐ No loss
☐ Some loss
☐ Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

☐ As well as before
☐ Worse than before because of trouble thinking
☐ Worse than before, another reason (why) _____

_____

_____

5. Can he/she understand situations or explanations?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

*This item rates behavior, not appearance.

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Clinical Dementia Rating Worksheet

Community Affairs Questions for Informant:
Occupational

1. Is the subject still working? ☐ Yes ☐ No ☐ N/A
   If not applicable, proceed to item 4
   If yes, proceed to item3
   If no, proceed to item 2
2. Did memory or thinking problem contribute to the subject's decision to retire? (Question 4 is next) ☐ Yes ☐ No ☐ D/K
3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?
   ☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

Social

4. Did he/she ever drive a car? ☐ Yes ☐ No
   Does the subject drive a car now? ☐ Yes ☐ No
   If no, is this because of memory or thinking problems? ☐ Yes ☐ No
5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No
*6. Is he/she able to independently shop for needs?
   ☐ Rarely or Never (Needs to be accompanied on any shopping trip) ☐ Sometimes (Shops for limited number of items: buys duplicate items or forgets needed items) ☐ Usually ☐ Don't Know
7. Is he/she able to independently carry out activities outside the home?
   ☐ Rarely or Never (Generally unable to perform activities without help) ☐ Sometimes (Limited and/or routine, e.g., superficial participation in church or meetings: trips to beauty parlor) ☐ Usually (Meaningful participation in activities, e.g., voting) ☐ Don't Know
8. Is he/she taken to social functions outside a family home? ☐ Yes ☐ No
   If no, why not? _____
9. Would a casual observer of the subject's behavior think the subject was ill? ☐ Yes ☐ No
10. If in nursing home, does he/she participate well in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in community affairs?
If not, please probe further.

Community Affairs: Such as going to church, visiting with friends or family, political activities, professional organizations such as bar association, other professional groups social clubs, service organization, educational programs.

***Please add notes if needed to clarify subject's level of functioning in this area.**

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Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household chores? _____

_____

_____

1b. What can he/she still do well? _____

_____

2a. What changes have occurred in his/her abilities to perform hobbies? _____

_____

2b. What can he/she still do well? _____

_____

3. If in nursing home, what can he/she no longer do well (H and H)?

_____

Everyday Activities (Blessed):

4. Ability to perform household tasks

No Loss		Severe Loss
0	0.5	1

Please describe: _____

_____

_____

5. Is he/she able to perform household chores at the level of:
(Pick one. Informant does not need to be asked directly).

☐ No meaningful function.
(Performs simple activities, such as making a bed, only with much supervision)

☐ Functions in limited activities only.
(With some supervision, washes dishes with acceptable cleanliness; sets table)

☐ Functions independently in some activities.
(Operates appliances, such as a vacuum cleaner; prepares simple meals)

☐ Functions in usual activities but not at usual level.

☐ Normal function in usual activities.

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?
If not, please probe further.

Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple care maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading entertaining photography, gardening, going to theater or symphony, woodworking, participation in sports.

Clinical Dementia Rating Worksheet

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

	Unaided	Occasionally misplaced buttons, etc.	Wrong sequence commonly forgotten items	Unable to dress
A. Dressing (Blessed)	0	1	2	3

	Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B. Washing, grooming	0	1	2	3

	Cleanly: proper utensils	Messily: spoon	Simple solids	Has to be fed completely
C. Eating habits	0	1	2	3

	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D. Sphincter control (Blessed)	0	1	2	3

*A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

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Clinical Dementia Rating Worksheet

Memory Questions for Subject:

1. Do you have problems with memory or thinking? ☐ Yes ☐ No
2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week
1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

Within 1 month
1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

4. When were you born? _____
5. Where were you born? _____
6. What was the last school you attended?
   Name _____
   Place _____ Grade _____
7. What was your main occupation job (or spouse if not employed)? _____
8. What was your last major job (or spouse if not employed)? _____
9. When did you (or spouse) retire and why? _____
10. Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly).

Clinical Dementia Rating Worksheet

Orientation Question for Subject:

Record the subject's answer verbatim for each question

1. What is the date today? ☐ Correct ☐ Incorrect

   _____

2. What day of the week is it? ☐ Correct ☐ Incorrect

   _____

3. What is the month? ☐ Correct ☐ Incorrect

   _____

4. What is the year? ☐ Correct ☐ Incorrect

   _____

5. What is the name of this place? ☐ Correct ☐ Incorrect

   _____

6. What town or city are we in? ☐ Correct ☐ Incorrect

   _____

7. What time is it? ☐ Correct ☐ Incorrect

   _____

8. Does the subject know who the informant is (in your judgment)? ☐ Correct ☐ Incorrect

   _____

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Clinical Dementia Rating Worksheet

Judgment and Problem Solving Question for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing instruments)

How are these things alike?" Subject's Response

1. turnip . . . . . cauliflower _____
   (0 = vegetables)
   (1 = edible food, living things, can be cooked, etc.)
   (2 = answers not pertinent; differences; buy them)

2. desk . . . . . bookcase _____
   (0 = furniture, office furniture; both hold books)
   (1 = wooden, legs)
   (2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)

What is the difference between these things?"

3. lie . . . . . mistake _____
   (0 = one deliberate, one unintentional)
   (1 = one bad the other good – or explains only one)
   (2 = anything else, similarities)

4. river . . . . . canal _____
   (0 = natural – artificial)
   (2 = anything else)

Calculations:

5. How many nickels in a dollar? ☐ Correct ☐ Incorrect
6. How many quarters in $6.75? ☐ Correct ☐ Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?
   (0 = try the telephone book, go to the courthouse for a directory; call a mutual friend)
   (1 = call the police, call operator (usually will not give address)
   (2 = no clear response)

9 Subject's assessment of disability and station in life and understanding of why he/she is present at the examination (may have covered, but rate here):

☐ Good Insight ☐ Partial Insight ☐ Little Insight

Clinical Dementia Rating (CDR)

CLINICAL DEMENTIA RATING (CDR)	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragment remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

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Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Clinical Dementia Rating

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Categories	Score
Memory	
Orientation	
Judgement & Problem Solving	
Community Affairs	
Home & Hobbies	
Personal Care	
CDR Sum of Boxes Score	

ASP1N2 / CDR v2.0 2Nov2017

Appendix 5. NPI (Neuropsychiatric Inventory)

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Caregiver Initials

Neuropsychiatric Inventory (NPI)

Comprehensive Assessment of Psychopathology in Patients with Dementia

by Jeffrey L. Cummings, MD

ASP1N2 / NPI 11Jan2017 Version

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Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Caregiver Initials

A. Delusions **(NA)**

Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient believe that he/she is in danger – that others are planning to hurt him/her? _____
2. Does the patient believe that others are stealing from him/her? _____
3. Does the patient believe that his/her spouse is having an affair? _____
4. Does the patient believe that unwelcome guests are living in his/her house? _____
5. Does the patient believe that his/her spouse or others are not who they claim to be? _____
6. Does the patient believe that his/her house is not his/her home? _____
7. Does the patient believe that family members plan to abandon him/her? _____
8. Does the patient believe that television or magazine figures are actually present in the home? _____
   [Does he/she try to talk or interact with them?]
9. Does the patient believe any other unusual things that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:
1. Occasionally – less than once per week.
2. Often – about once per week
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:
1. Mild – delusions present but seem harmless and produce little distress in the patient.
2. Moderate -delusions are distressing and disruptive.
3. Marked – delusions are very disruptive and are a major source of behavioral disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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B. Hallucinations **(NA)**

Does the patient have hallucinations such as seeing false visions or hearing imaginary voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken belief such as stating that someone who has died is still alive; rather we are asking if the patient actually has abnormal experiences of sounds or visions.

No (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient describe hearing voices or act as if he/she hears voices? _____
2. Does the patient talk to people who are not there? _____
3. Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)? _____
4. Does the patient report smelling odors not smelled by others? _____
5. Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? _____
6. Does the patient describe tastes that are without any known cause? _____
7. Does the patient describe any other unusual sensory experiences? _____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:
1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:
1. Mild – hallucinations are present but harmless and cause little distress for the patient.
2. Moderate – hallucinations are distressing and are disruptive to the patient.
3. Marked – hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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C. Agitation/Aggression (NA)

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes? _____
2. Is the patient stubborn, having to have things his/her way? _____
3. Is the patient uncooperative, resistive to help from others? _____
4. Does the patient have any other behaviors that make him hard to handle? _____
5. Does the patient shout or curse angrily? _____
6. Does the patient slam doors, kick furniture, throw things? _____
7. Does the patient attempt to hurt or hit others? _____
8. Does the patient have any other aggressive or agitated behaviors? _____

If the screening question is confirmed, determine the frequency and severity of the agitation.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week
3. Frequently – several times per week but less than daily.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – behavior is disruptive but can be managed with redirection or reassurance.
2. Moderate – behaviors are disruptive and difficult to redirect or control.
3. Marked – agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. moderately
4. Severely
5. Very severely or extremely

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D. Depression/Dysphoria **(NA)**

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have periods of tearfulness or sobbing that seem to indicate sadness? _____
2. Does the patient say or act as if he/she is sad or in low spirits? _____
3. Does the patient put him/herself down or say that he/she feels like a failure? _____
4. Does the patient say that he/she is a bad person or deserves to be punished? _____
5. Does the patient seem very discouraged or say that he/she has no future? _____
6. Does the patient say he/she is a burden to the family or that the family would be better off without him/her? _____
7. Does the patient express a wish for death or talk about killing him/herself? _____
8. Does the patient show any other signs of depression or sadness? _____

If the screening question is confirmed, determine the frequency and severity of the depression.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – depression is distressing but usually responds to redirection or reassurance.
2. Moderate – depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
3. Marked – depression is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

E. Anxiety **(NA)**

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient say that he/she is worried about planned events? _____
2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense? _____
3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness? _____
4. Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health] _____
5. Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds? _____
6. Does the patient become nervous and upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?] _____
7. Does the patient show any other signs of anxiety? _____

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – anxiety is distressing but usually responds to redirection or reassurance.
2. Moderate – anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
3. Marked – anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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F. Elation/Euphoria **(NA)**

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self? _____
2. Does the patient find humor and laugh at things that others do not find funny? _____
3. Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? _____
4. Does the patient tell jokes or make remarks that have little humor for others but seem funny to him/her? _____
5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it? _____
6. Does the patient "talk big" or claim to have more abilities or wealth than is true? _____
7. Does the patient show any other signs of feeling too good or being too happy? _____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – elation is notable to friends and family but is not disruptive.
2. Moderate – elation is notably abnormal.
3. Marked – elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

G. Apathy/Indifference **(NA)**

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient seem less spontaneous and less active than usual? _____
2. Is the patient less likely to initiate a conversation? _____
3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self? _____
4. Does the patient contribute less to household chores? _____
5. Does the patient seem less interested in the activities and plans of others? _____
6. Has the patient lost interest in friends and family members? _____
7. Is the patient less enthusiastic about his/her usual interests? _____
8. Does the patient show any other signs that he/she doesn't care about doing new things? _____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – nearly always present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
2. Moderate – apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
3. Marked – apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

H. Disinhibition **(NA)**

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient act impulsively without appearing to consider the consequences? _____
2. Does the patient talk to total strangers as if he/she knew them? _____
3. Does the patient say things to people that are insensitive or hurt their feelings? _____
4. Does the patient say crude things or make sexual remarks that he/she would not usually have said? _____
5. Does the patient talk openly about very personal or private matters not usually discussed in public? _____
6. Does the patient take liberties or touch or hug others in way that is out of character for him/her? _____
7. Does the patient show any other signs of loss of control of his/her impulses? _____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than one per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – disinhibition is notable but usually responds to redirection and guidance.
2. Moderate – disinhibition is very evident and difficult to overcome by the caregiver.
3. Marked – disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

I. Irritability/Lability (NA)

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have a bad temper, flying "off the handle" easily over little things? _____
2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next? _____
3. Does the patient have sudden flashes of anger? _____
4. Is the patient impatient, having trouble coping with delay or waiting for planned activities? _____
5. Is the patient cranky and irritable? _____
6. Is the patient argumentative and difficult to get along with? _____
7. Does the patient show any other signs of irritability? _____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than one per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – irritability or lability is notable but usually responds to redirection and reassurance.
2. Moderate – irritability and lability are very evident and difficult to overcome by the caregiver.
3. Marked – irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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J. Aberrant Motor Behavior **(NA)**

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient pace around the house without apparent purpose? _____
2. Does the patient rummage around opening and unpacking drawers or closets? _____
3. Does the patient repeatedly put on and take off clothing? _____
4. Does the patient have repetitive activities or "habits" that he/she performs over and over? _____
5. Does the patient engage in repetitive activities such as handling buttons, picking wrapping string, etc? _____
6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? _____
7. Does the patient do any other activities over and over? _____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – essentially continuously present.

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – abnormal motor activity is notable but produces little interference with daily routines.
2. Moderate – abnormal motor activity is very evident; can be overcome by the caregiver.
3. Marked – abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver, and is a major source of distress.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

K. Sleep (NA)

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have difficulty falling asleep? _____
2. Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? _____
3. Does the patient wander, pace, or get involved in inappropriate activities at night? _____
4. Does the patient awaken you during the night? _____
5. Does the patient awaken at night, dress, and plan to go out thinking that it is morning and time to start the day? _____
6. Does the patient awaken too early in the morning (earlier than was his/her habit)? _____
7. Does the patient sleep excessively during the day? _____
8. Does the patient have any other nighttime behaviors that bother you that we haven't talked about? _____

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior disturbance.

Frequency: Now I want to find out how often these things [define using the description of behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day (every night)

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – nighttime behaviors occur but they are not particularly disruptive.
2. Moderate – nighttime behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of nighttime behavior may be present.
3. Marked – nighttime behaviors occur; several types of nighttime behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

L. Appetite and eating disorders **(NA)**

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Has he/she had a loss of appetite? _____
2. Has he/she had an increase in appetite? _____
3. Has he/she had a loss of weight? _____
4. Has he/she gained weight? _____
5. Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once? _____
6. Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food? _____
7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order? _____
8. Have there been any other changes in appetite or eating that I haven't asked about?

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency: Now I want to find out how often these things [define using the description of the behaviors noted as most problematic on the subquestions] occur. Would you say that they occur:

1. Occasionally – less than once per week.
2. Often – about once per week.
3. Frequently – several times per week but less than every day.
4. Very frequently – once or more per day or continuously

Severity: Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the patient. Would you say that [the behaviors] are:

1. Mild – changes in appetite or eating are present but have not led to changes in weight and are not disturbing
2. Moderate – changes in appetite or eating are present and cause minor fluctuations in weight.
3. Marked – obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress: How emotionally distressing do you find this behavior?

0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

Appendix 6. GDS (Geriatric Depression Scale)

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Geriatric Depression Scale (GDS) (Short Form)

Instructions read to the Subject: Choose the best answer for how you felt over the past week.

Evaluation		Yes	No
1	Are you basically satisfied with your life?	☐ 0	☐ 1
2	Have you dropped many of your activities and interests?	☐ 1	☐ 0
3	Do you feel that your life is empty?	☐ 1	☐ 0
4	Do you often get bored?	☐ 1	☐ 0
5	Are you in good spirits most of the time?	☐ 0	☐ 1
6	Are you afraid that something bad is going to happen to you?	☐ 1	☐ 0
7	Do you feel happy most of the time?	☐ 0	☐ 1
8	Do you often feel helpless?	☐ 1	☐ 0
9	Do you prefer to stay at home, rather than going out and doing new things?	☐ 1	☐ 0
10	Do you feel you have more problems with memory than most?	☐ 1	☐ 0
11	Do you think it is wonderful to be alive now?	☐ 0	☐ 1
12	Do you feel pretty worthless the way you are now?	☐ 1	☐ 0
13	Do you feel full of energy?	☐ 0	☐ 1
14	Do you feel that your situation is hopeless?	☐ 1	☐ 0
15	Do you think that most people are better off than you are?	☐ 1	☐ 0
		Total GDS Score:	

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol.* 1986 June; 5(1/2): 165-173.

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Appendix 7. ADCS-ADL (Alzheimer's Disease Cooperative Study- Activities of Daily Living

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Caregiver Initials

ADCS – ACTIVITIES OF DAILY LIVING (ADL) INVENTORY

NOTES: (1) {S} refers to the participant and should be replaced by the participant's name or relationship to the study partner each time an ADL question is asked of the study partner.

(2) This ADL inventory must be given in the format of an interview of the study partner, either directly or by telephone. The form should NOT be given to a study partner to complete on his/her own.

READ THE FOLLOWING INSTRUCTIONS TO THE STUDY PARTNER:

I am going to ask you about a number of daily activities that {S} may have performed during the past 4 weeks. Please tell me about {S}'s actual performance, not about what he/she could have done if an opportunity had arisen. For each activity that {S} attempted, I'm going to ask you to choose one out of a number of descriptions that best fits his/her most usual performance.

For some activities, I'll ask about whether {S} performed independently, or with supervision or help. Let me explain how we are defining these words:

Independently means that {S} completed the activity without being helped. We still consider it independent if {S} was reminded or prompted to get started, or received a little prompting while performing the activity.

With supervision means that {S} required verbal reminders and instructions while doing the activity.

With help means that {S} was given some degree of physical assistance by another person to perform the activity.

INSTRUCTIONS FOR THE RATER:

If the study partner states that {S} had no opportunity to perform the task during the past four weeks (e.g., {S} did not have access to a telephone, therefore could not possibly make phone calls), the response should be recorded as 'no.'

If either the study partner's answer or the questionnaire are unclear, please make notes on the case report form detailing the problem.

For questions regarding specific ADL items, please refer to the ADL response Card.

Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.;and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39.

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Caregiver Initials

Information obtained through: ☐ Informant visit

Instructions: For each question, use the subject's name where {S} appears.
Before beginning, read the questionnaire guidelines to the informant.

1. Regarding **eating**:
Which best describes {S} usual performance during the past 4 weeks?

3 ☐ ate without physical help, and used a knife

2 ☐ used a fork or spoon, but not a knife, to eat

1 ☐ used fingers to eat

0 ☐ {S} usually or always was fed by someone else

2. Regarding **walking** (or getting around in a wheelchair), in the past 4 weeks, which best describes his/her **optimal** performance:

3 ☐ mobile outside of home without physical help

2 ☐ mobile across a room without physical help

1 ☐ transferred from bed to chair without help

0 ☐ required physical help to walk or transfer

3. Regarding bowel and bladder function **at the toilet**, which best describes his/her **usual** performance in the past 4 weeks:

3 ☐ did everything necessary without supervision or help

2 ☐ needed supervision, but no physical help

1 ☐ needed physical help, and was usually continent

0 ☐ needed physical help, and was usually incontinent

"Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)".
Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.;and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39.

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ADCS – Activities of Daily Living Inventory

4. Regarding **bathing,** in the past 4 weeks, which best describes his/her **usual** performance:

3 ☐ bathed without reminding or physical help

2 ☐ no physical help, but needed supervision/reminders to bathe completely

1 ☐ needed minor physical help (e.g., with washing hair) to bathe completely

0 ☐ needed to be bathed completely

5. Regarding **grooming,** in the past 4 weeks, which best describes his/her **optimal** performance:

3 ☐ cleaned and cut fingernails without physical help

2 ☐ brushed or combed hair without physical help

1 ☐ kept face and hands clean without physical help

0 ☐ needed help for grooming of hair, face, hands, and fingernails

Yes	No	Don't know
☐	☐	☐
	0	0

6. Regarding **dressing, in the past 4 weeks:**

A) Did {S} select his/her first set of clothes for the day?
If yes, which best describes his/her usual performance:

3 ☐ without supervision or help

2 ☐ with supervision

1 ☐ with physical help

B) Regarding physically getting dressed, which best describes his/her usual performance in the past 4 weeks:

4 ☐ dressed completely without supervision or physical help

3 ☐ dressed completely with supervision, but without help

2 ☐ needed physical help only for buttons, clasps, or shoelaces

1 ☐ dressed without help if clothes needed no fastening or buttoning

0 ☐ always needed help, regardless of the type of clothing

ADCS – Activities of Daily Living Inventory

Yes	No	Don't know
☐	☐	☐
	0	0

7. In the past 4 weeks, did {S} use a telephone?
If yes, which best describes his/her highest level of performance:

- 5 ☐ made calls after looking up numbers in white or yellow pages, or by dialing directory assistance
- 4 ☐ made calls only to well-known numbers, without referring to a directory or list
- 3 ☐ made calls only to well-known numbers, by using a directory or list
- 2 ☐ answered the phone; did not make calls
- 1 ☐ did not answer the phone, but spoke when put on the line

Yes	No	Don't know
☐	☐	☐
	0	0

8. In the past 4 weeks, did {S} watch television?
If yes, ask all questions:
Did {S}:

☐	☐	☐	a) usually select or ask for different programs or his/her favorite show?
1	0	0	
☐	☐	☐	b) usually talk about the content of a program while watching it?
1	0	0	
☐	☐	☐	c) talk about the content of a program with in a day (24hours) after watching it?
1	0	0	

Yes	No	Don't know
☐	☐	☐
	0	0

9. In the past 4 weeks, did {S} ever appear to pay attention to conversation or small talk for at least 5 minutes?
Note: *{S} did not need to initiate the conversation.*
If yes, which best describes his/her usual degree of participation:

- 3 ☐ usually said things that were related to the topic
- 2 ☐ usually said things that were not related to the topic
- 1 ☐ rarely or never spoke

Yes	No	Don't Know
☐	☐	☐
	0	0

10. Did {S} clear the dishes from the table after a meal or snack?
If yes, which best describes how he/she usually performed:

- 3 ☐ without supervision or help
- 2 ☐ with supervision
- 1 ☐ with physical help

ADCS – Activities of Daily Living Inventory

Yes	No	Don't know
☐	☐	☐
	0	0

11. In the past 4 weeks, did {S} usually manage to find his/her personal belongings at home?
If yes, which best describes how he/she usually performed:

- 3 ☐ without supervision or help
- 2 ☐ with supervision
- 1 ☐ with physical help

Yes	No	Don't know
☐	☐	☐
	0	0

12. In the past 4 weeks, did {S} obtain a hot or cold beverage for him/herself?
(A cold beverage includes a glass of water.)
If yes, which describes his/her highest level of performance

- 3 ☐ made a hot beverage, usually without physical help
- 2 ☐ made a hot beverage, usually if someone else heated the water
- 1 ☐ obtained a cold beverage, usually without physical help

Yes	No	Don't know
☐	☐	☐
	0	0

13. In the past 4 weeks, did {S} make him/her self a meal or snack at home?
If Yes, which best describes his/her highest level of food preparation:

- 4 ☐ cooked or microwaved food, with little or no help
- 3 ☐ cooked or microwaved food, with extensive help
- 2 ☐ mixed or combined food items for a meal or snack, without cooking or microwaving (e.g., made a sandwich)
- 1 ☐ Obtained food on his/her own, without mixing or cooking it

Yes	No	Don't Know
☐	☐	☐
	0	0

14. In the past 4 weeks, did {S} dispose of garbage or litter in an appropriate place or container at home?
If yes, which best describes how he/she usually performed

- 3 ☐ without supervision or help
- 2 ☐ with supervision
- 1 ☐ with physical help

ADCS – Activities of Daily Living Inventory

Yes	No	Don't know
☐	☐	☐
	0	0

15. In the past 4 weeks, did {S} get around (or travel) outside of his/her home?
If yes, which best describes his/her **optimal** performance:

- 4 ☐ alone, went at least 1 mile away from home
- 3 ☐ alone, but remained within 1 mile of home
- 2 ☐ only when accompanied and supervised, regardless of the trip
- 1 ☐ only with physical help, regardless of the trip

Yes	No	Don't know
☐	☐	☐
	0	0

16. In the past 4 weeks, did {S} ever go shopping?
If yes, ask A and B:
A) Which one best describes how {S} usually selects items:

- 3 ☐ without supervision or physical help?
- 2 ☐ with some supervision or physical help?
- 1 ☐ not at all, or selected mainly random or inappropriate items?

☐	☐	☐
1	0	0

B) Did {S} usually pay for items without supervision or physical help?

Yes	No	Don't know
☐	☐	☐
	0	0

17. In the past 4 weeks, did {S} keep appointments or meetings with other people, such as relatives, a doctor, the hairdresser, etc.?
If yes, which best describes his/her awareness of the meeting ahead of time:

- 3 ☐ usually remembered, may have needed written reminders e.g. notes, a diary, or calendar
- 2 ☐ only remembered the appointment after verbal reminders on the day
- 1 ☐ usually did not remember, in spite of verbal reminders on the day

"Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)".
Galasko, D.; Bennett, D.; Sano, M.; Ernesto, C.; Thomas, R.; Grundman, M.; Ferris, S.;and the ADCS. "An Inventory to Assess Activities of Daily Living for Clinical Trials in Alzheimer's Disease." Alzheimer's Disease and Associated Disorders, 1997. Volume 11(2): S33-S39.

ASP1N2 / ADCS-ADL 11Jan2017 Version

Page 6 of 9

Note:	1.	Do not ask Q18 if the {S} is institutionalized; check here ☐
	2.	Being taken to day care or having a sitter at home does not constitute being left alone.

Yes	No	Don't know		
☐	☐	☐	18.	In the past 4 weeks, was {S} ever left on his/her own? ***If yes, ask all questions:*** Was {S} left:
	0	0		
☐ 1	☐ 0	☐ 0		a) away from home, for 15 minutes or longer, during the day?
☐ 1	☐ 0	☐ 0		b) at home, for an hour or longer, during the day?
☐ 1	☐ 0	☐ 0		c) at home, for less than 1 hour, during the day?

Yes	No	Don't know		
☐	☐	☐	19.	In the past 4 weeks, did {S} talk about **current** event? (This means events or incidents that occurred during the past month.) ***If yes, ask all questions:*** Did {S} talk about events that…:
	0	0		
☐ 1	☐ 0	☐ 0		a) he/she heard or read about or saw on TV but did not take part in?
☐ 1	☐ 0	☐ 0		b) he/she took part in outside home involving family, friends, or neighbors?
☐ 1	☐ 0	☐ 0		c) events that occurred at home that he/she took part in or watched?

Yes	No	Don't know		
☐	☐	☐	20.	In the past 4 weeks, did {S} read a magazine, newspaper or book for more than 5 minutes at a time? ***If yes, ask all questions:*** DID {S} usually:
	0	0		
☐ 1	☐ 0	☐ 0		a) talk about details of what he/she read while or shortly (<than 1 hour) after reading?
☐ 1	☐ 0	☐ 0		b) talk about what he/she read 1 hour or longer after reading?

ADCS – Activities of Daily Living Inventory

Yes	No	Don't know
☐	☐	☐
	0	0

21. In the past 4 weeks, did {S} ever write things down?
Note: *If {S} wrote things only after encouragement or with help, the response should still be 'yes'.*
If yes, which best describes the most complicated things that he/she wrote:

3 ☐ letters or long notes that other people understood
2 ☐ short notes or messages that other people understood
1 ☐ his/her signature or name

Yes	No	Don't know
☐	☐	☐
	0	0

22. In the past 4 weeks, did {S} perform a pastime, hobby or game?
If yes, which pastimes did he/she perform:

Ask about all of the following, check all that apply:

☐ card or board games (including bridge, chess, checkers)

☐ bingo	☐ crosswords	☐ art
☐ musical instrument	☐ knitting	☐ sewing
☐ reading	☐ gardening	☐ golf
☐ tennis	☐ workshop	☐ fishing

☐ other _____

Note: Walking does NOT count as a hobby/pastime for this scale.

☐ **If {S} performs hobbies/pastimes only at day care, check here.**

If yes, how did {S} usually perform his/her most common pastimes:

3 ☐ without supervision or help
2 ☐ with supervision
1 ☐ with help

ADCS – Activities of Daily Living Inventory

Yes	No	Don't know	
☐	☐	☐	**23.** In the past 4 weeks, did {S} use a household appliance to do chores?
	0	0	

→ *Ask about all of the following,* and check those that were used:

☐ washer	☐ dryer	☐ vacuum
☐ dishwasher	☐ toaster	☐ toaster oven
☐ range	☐ microwave	☐ food processor
☐ other _____		

If yes, for the most commonly used appliances, which best describes how {S} usually used them:

4	☐	without help, operating more than on-off controls if needed
3	☐	without help, but operated only on/off controls
2	☐	with supervision, but no physical help
1	☐	with physical help

	Total Score (0-78)
	Number of "Don't Know" Responses

Appendix 8. C-SSRS (Columbia-Suicide Severity Rating Scale)

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

COLUMBIA-SUICIDE SEVERITY RATING SCALE

(C-SSRS)

Baseline/Screening Version

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

Disclaimer:

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

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

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

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal		Past 2 Months	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it"* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐

Intensity of Ideation		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - **Most severe Ideation:** _____ *Type # (1-5)* _____ *Description of Ideation* Past 2 Months - **Most severe Ideation:** _____ Type # (1-5) _____ *Description of Ideation*	Most Severe (Lifetime)	Most severe (Past 2 Months)
Frequency **How many times have you had these thoughts?** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____	_____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting – few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____	_____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____	_____
Deterrents ***Are there things – anyone or anything (e.g., family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____	_____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equality to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling.) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	_____	_____

SUICIDAL BEHAVIOR *(Check All that apply, so long as these are separate events; must ask about all types)*	Lifetime		Past 6 Months	
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury result, this is considered an attempt. Inferring Intent: Event if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?***(Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ Total # of Attempts _____ Yes ☐	No ☐ No ☐	Yes ☐ Total # of Attempts _____ Yes ☐	No ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ Total # of Attempts _____	No ☐ 	Yes ☐ Total # of Attempts _____	No ☐
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ Total # of Attempts _____	No ☐ 	Yes ☐ Total # of Attempts _____	No ☐
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐	No ☐	Yes ☐	No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second- degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code	Enter Code	Enter Code
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code	Enter Code	Enter Code

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

COLUMBIA-SUICIDE SEVERITY RATING SCALE

(C-SSRS)

Since Last Visit

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

Disclaimer:

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

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

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask question 3,4, and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation " section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it"* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Intensity of Ideation	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. **Most severe Ideation:** _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe
Frequency **How many times have you had these thoughts?** (1)Less than once a week (2)Once a week (3)2-5 times in week (4)Daily or almost daily (5)Many times each day	_____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting – few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____
Deterrents ***Are there things – anyone or anything (e.g., family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equality to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling.) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	_____

Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem			AST-ADP2-US01
	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury result, this is considered an attempt. Inferring Intent: Event if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from _____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐

 C-SSRS-Since Last Visit (Version 1/14/09)
ASP1N2 / CSSRS for Treatment and Follow-Up Visits 11Jan2017 Version

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Study	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of AstroStem, Autologous Adipose Tissue Derived Mesenchymal Stem Cells, in Patients with Alzheimer's Disease		Protocol
ASP1N2 AstroStem	Date of Assessment DD-MMM-YYYY	Time of Assessment (24-hour clock)	Assessor's Initials
		:	
Visit Number		Subject Number	Subject Initials

Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second- degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____

Appendix 9. Instruction for Liposuction Procedure

Instruction for Liposuction Procedure

1. Pre-procedure for Liposuction

Sterilize operation room with 70% ethanol spray 20-30 min before liposuction procedure.

2. Liposuction Kits (Provided by Biostar, manufacturer)

One kit (plastic bag) includes 20ml-syringes, syringe tip caps, vacuette tubes, labels and sterilization envelopes, as shown in the following:

Syringe 20ml (BD302830)	
Syringe Tip Cap (BD305819)	
Vacuette tube (BD367955)	
Sterilization Envelope	
Label	Label for fat tissues (Syringe) **Tissue Samples from Liposuction (AST-ADP2-US01)** Subject ID / Initials: Randomization No: Label for fat tissues (sterilization envelope) **Tissue Samples from Liposuction (AST-ADP2-US01)** Subject ID / Initials: Randomization No: Tissue Collection Date & Time: Label for blood sampling (Vacuette tube) **Blood Samples from Liposuction (AST-ADP2-US01)** Subject ID / Initials: Randomization No: Label for blood sampling (sterilization envelope) **Blood Samples from Liposuction (AST-ADP2-US01)** Subject ID / Initials: Randomization No: Blood Collection Date & Time:

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3. Preparation for Liposuction

- Saline set, gauze, sterile pad, idodine solution, ring forcep
- 2% lidocaine, No 11 blade
- Tumescent solution (prepare right before the procedure and discard after 1 hour)
  - Hartmann Solution 1L + Lidocane 1000mg (2% Lidocane 50ml) + Epinephrine 1mg (= 1mg/ml Epinephrine 1ml)
  - (using 100ml normal saline) normal saline 100ml + Lidocane 100mg (2% Lidocane 5ml) + Epinephrine 0.1mg
- 5x Antibiotic-Antimycotic
  - Dilute 100x antiboitic-antimycotic (Thermofisher/Cat NO.15240-096) using sterile saline solution to 5x (sterlie saline solution 380ml + 100x antibiotic-antimycotic 20ml) and aliquot 5x antibiotic-antimycotic 400ml into 4ml
  - Freeze aliquots and thaw before use
- 10 cc syringe (Lock syringe; BD 10 ml syringe Luer-Lok Tip; syringe connected to cannula)
- 3-way cock
- Cannula for injection
- Cannula for suction
- 2.5 cc syringe (for anesthesia), 50 cc syringe (for collection of tissues)
- Surgical drape with hole, cotton ball, surgical instrument tray
- Needle Holder, suture (blue nylon 5.0)
- Sharp Scissors
- Towel Clip
- Syringe holder

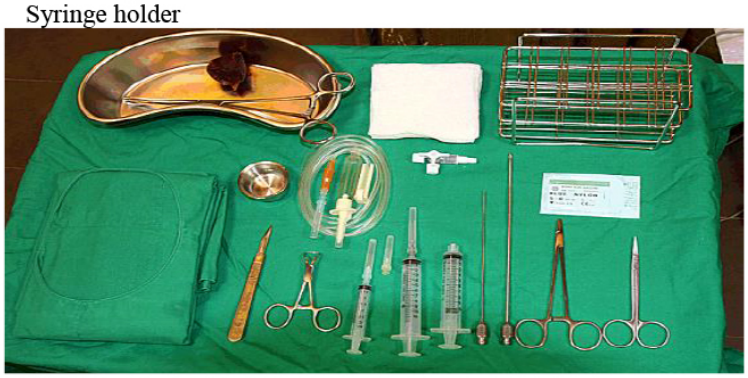

Figure 1. Liposuction Set-up

4. Cautions for Use

- Before liposuction
  - Stop taking thrombolytic agents such as Aspirin within 5-7 days of liposuction
- After liposuction
  - Your belly be covered in bruises.
  - Your belly may be squeezed.
  - You can take shower, but avoid going and soaking in the bath.
  - You can take pain medicine if necessary.

5. Intraoperative and postoperative monitoring recommendation

Baseline vital signs including blood pressure and heart rate are recorded pre- and postoperatively. Pulse oximeter monitoring is essential in all cases and may be continued after surgery until the patient has fully recovered and is ready for discharge. Although serious complications are rare and any physician

should be able to handle such complications should they arise, it is recommended that a physician trained in resuscitation and emergency care such as a trained anesthetist be available on the premises.

6. Liposuction Procedures

Liposuction procedures can be summarized as three steps: injection of tumescent solution, waiting time, and collection of fat tissues. The detail procedures are instructed below.

1) Confirm the subject ID and randomization number before liposuction procedure and write them on each label.
2) Collect 60 ml blood (13 of 5 ml Vacuettes serum tubes) before the collection of fat tissues.
3) Insert the blood sample bottle into the sterilization envelope and place it in a refrigerator.
4) Sterilize skin with iodine solution and cover it with sterile pad.
5) Inject small amount (2-3 cc) of 2% Lidocaine, solution for local anesthesia.
6) Connect injection cannula, 10 cc lock syringe and solution sets connected to tumescent solution into 3-way cock (Refer to Figure 2).

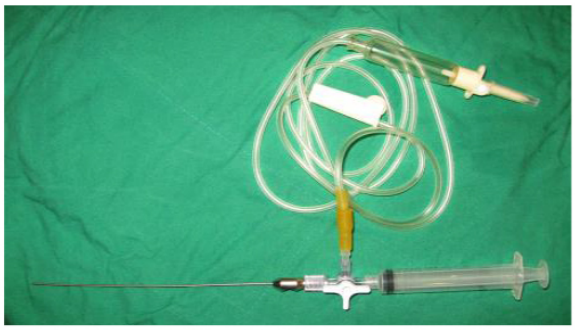

Figure 2. 3-way Connection

7) Make an incision about 2-4mm long with No 11 blade, at around umbilicus (if possible, place where scar is not seen easily).
8) Insert slowly the injection cannula into subcutaneous fatty layer (Insert it into right site of belly in case of right-handed subjects).
9) Inject the tumescent solution evenly around the liposuction area (Refer to Figure 3).
; the amount of tumescent solution injected is 90-150 cc, which is about 3-5 times of the amount of adipose tissues

Figure 3. Method for using 3-way Stopcock
(Left) Put the solution in the syringe like left figure.
(Right) Inject after spinning 3-way cock like right figure.

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10) After the injection of tumescent solution, wait for about 15-30 minutes.
11) Remove the lock syringe from the 3-way cock and connect to the cannula for suction.
12) After the injection of suctioning cannula, collect the adipose tissue by suctioning with about 1~2cm of negative pressure.
13) Place the collected adipose tissue into a 50 cc syringe closed with a needle.
14) The adipose tissues will float and the tumescent solution will sink to the bottom. Discard the sunken solution and continue the tissue collection until the amount of pure adipose tissue is 30 cc.
15) After the sufficient amount of adipose tissues is suctioned, stop the suction.
16) Insert 15 cc fat tissues into each 20 ml syringe sealed with tip cap, discard the tip cap, and suck 3ml of 5x antibiotics.
17) Close syringe with tip cap, confirm the subject ID and randomization number, insert the syringe into the sterilization envelope, and place it in a refrigerator.
18) After completing the fat tissue collection, dress the incision area with #5 blue nylon.
19) After completing dressing, inject 1 ampule of lincomycin or gentamycin intramuscularly in order to prevent infection
20) Take out stitches after 1 week.

7. Blood Collection Procedures

1) Attach corresponding labels to 13 of 5 ml serum tubes.
2) Draw 60 ml blood into the tubes.
3) Mix gently by inverting the tube eight (8) times. Do not shake.
4) Allow blood to clot upright at room temperature for 60 minutes.
5) Centrifuge the specimen at room at 3000 rpm, room temperature for 5 minutes

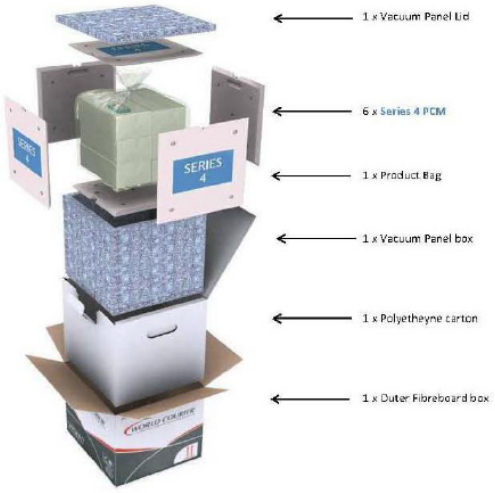
8. Transportation Methods of Collected Fat Tissues and Blood

1) Prepare 'Adipose Tissue and/or Serum Collection Form'.
2) Insert the serum tubes into the sterilization envelope, and place in a refrigerator until the shipment.
3) Close syringe with tip cap, attach the label on syringe, insert into the sterilization envelope, and place in a refrigerator until the shipment.
4) Insert serum tubes, syringe(s) and the original copy of 'Adipose Tissue and/or Serum Collection Form' into the shipping package provided by the World Courier. (Please find detail instruction on next page)
5) Confirm the refrigerated transportation with the World Courier before pick-up.

** Collected fat tissue and blood shall be delivered to the manufacturing lab as soon as possible. Therefore, please in advance arrange the pick-up of shipping package with the World Courier.*

Shipment of a package with the World Courier

- In advance the pick-up of adipose tissues and/or serum tubes will be arranged with the World Courier.
- At the date when adipose tissues and/or serum tubes are collected the World Courier will bring all materials for packing and shipping the serum tubes.
- The adipose tissues and/or serum tubes and collection form placed in a refrigerator will be inserted into the shipping package provided by the World Courier.



- The product temperature will be monitored using a TempTale 4 Bio Monitor in the package. Temperature should be maintained at (+2 to +8 °C).

- The package will be sent to a manufacturing facility on the same day.

Once the package is arrived to Korea and cleared at the Korea Customs, the World Courier will deliver the package to a manufacturing facility, take back the temperature monitor, and provide shipment temperature record to the sponsor.

Adipose Tissue and/or Serum Collection Form

Prepared by Site (Time zone: PST)

Item	Information	Remarks
Subject ID / Initials	/	
Gender / Age	/	
Randomization No		
Site No / PI Name	**Site / Dr.**	
Name of Facility		
Date of Collection	(DD/MMM/YYYY)	
Time of Collection	Blood: _____ (HH:MM) Tissue: _____ (HH:MM)	
Volume of Collection	Blood: _____ ml / Tissue: _____ ml	
Collected by	Name: Signature: Date:	
Date and Time of Shipment Pick-up	(DD/MM/YYYY, HH:MM, 24-hr clock)	
Shipment Condition	☐ Refrigerated	
Tracking No		
Confirmed by	Signature: Date:	

- Please insert the original copy into the shipment package, and please file the photocopy into the ISF binder and send the photocopy to KCRN by email (yealimkim@kcrnresearch.com)

Prepared by Biostar Stem Cell Research Institute (Time zone: KST)

Item	Information	Remarks
Temp. Records from Temp. Monitor	□ No excursion □ Yes (Please describe excursion in remarks)	
Date and Time of Package Receipt	(DD/MM/YYYY, HH:MM, 24-hr clock)	
Person who Received Package	Name: Signature: Date:	

- Please send the photo copy to KCRN by email (yealimkim@kcrnresearch.com). KCRN will forward the copy to Site for filing into the ISF binder.

Appendix 10. IP Administration Instruction for Clinical Sites

IP Administration Instructions for Clinical Sites

Only unblinded designee (physician or study coordinator) will open the aluminum bag, dilute IP into saline bags and mask the saline bag and IV tubing with the brown IV bag cover and tubing cover.

Pre-procedure for IP administration

At least 2 hours before the infusion provide 500 mg Aspirin to subjects who are 75 years and older, have had cardiovascular disease, or may need the regimen at investigator's discretion.

Supplies

- Study drug in 20 cc syringe, Qty 2
- 100 cc fluid normal saline, Qty 2
- 18G needle, Qty 2
- Colored standard blood filter tubing set with a 170 to 260 micron filter, Qty 2
- 22G catheter needle, Qty 2
- A labeling with subject information, Qty 4
- Alcohols pads
- Gloves
- IV bag cover, Qty 2

Preparation of IV saline bags with study drug

1. Use aseptic technique when preparing saline bags with the study drug

2. Gather supplies and the study drug
   - Bring out the study drug stored in a refrigerator and open the aluminum foil pack.
   - Confirm the subject ID and randomization number of the study drug.
   - Sign the IP and Label Verification Form once you confirm that the subject ID and randomization number is correct.
   - Only take out one syringe from the aluminum foil pack and bring the pack back to the refrigerator.
   - Confirm all supplies are ready for the procedure.
   - Verify that a subject is not allergic to alcohol. In case a subject has alcohol allergies, alcohol swab can be replaced with 0.2 % Chlorhexidine Gluconate

3. Confirm the subject ID and randomization on the study drug is same with one on the label for a saline bag.

4. Sign the IP and Label Verification Form.

5. Inspect the saline bag. If visibly opaque particles, discoloration, or other foreign particulates are observed, the bag should not be used.

6. Attach the label on the top of the saline bag.

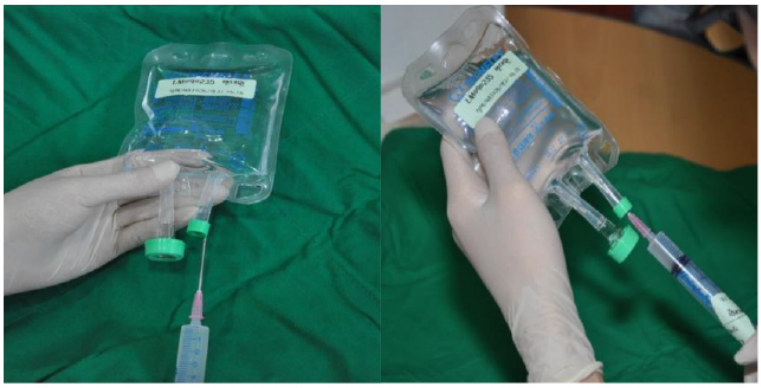
7. Confirm the subject ID and randomization of the study drug is the same with the label attached to the saline bag.

8. Gently invert syringes 15-20 times. Do not mix vigorously or vortex.

9. Connect 18G needle to a 20cc syringe.

10. Disinfect the saline bag access port with alcohol swab.

11. Insert needle and inject the contents into a saline bag with rate of 1 cc /20-25 secs.



12. After injection, mix the saline bag gently. Don't shake the bag.

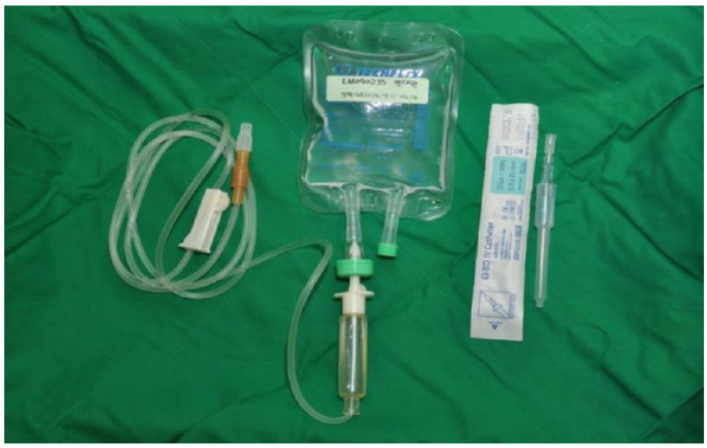
13. Cover the IV bag with the brown IV bag cover in order to maintain the blind to other study staffs and subjects prior to sending dose to be infused

14. Attach the label on the top of the brown IV bag cover and confirm the subject ID and randomization of the study drug is the same with the label attached to the IV bag cover.

15. The study drug infusion should begin within 20 minutes of mixing.

Infusion Procedures

1. Use aseptic technique when preparing and administering fluids and medications



2. Insert the spike of the colored IV tubing into the saline bag mixed with the study drug.

3. Select a vein that is well-dilated. The selection priority of vein will be the following; Dorsal venous plexus, metacarpal plexus, basilica vein, cephalic vein, median cubital vein.

4. Perform the venipuncture.

5. Hang the saline bag on an IV pole.

6. Adjust to the desired flow rate. The infusion time for one saline bag is 1-3 hours. The infusion rate will be determined by PI's discretion but maximum infusion rate will be 25 gtt/min (100cc/ hr).

7. Gently squeeze the saline bag every 30 min to prevent cell settling.

8. Document the relevant data regarding infusion.
   - Record the start time of the infusion on the client's chart.
   - Include the date and time of the venipuncture
   - Specific name and location of the accessed vein
   - Flow rate
   - Type, length and gauge of the needle or catheter
   - The client's general response
   - Your signature

9. Another saline bag should be mixed with the study drug stored in the refrigerator before the infusion of the first saline bag is finished. Follow the same procedure to prepare the second saline bag.

10. Once the infusion of the first saline bag is finished, close the roller clamp.

11. Take out the spike of the colored IV tubing from the first saline bag and insert into the second saline bag mixed with the study drug.

12. Hang the saline bag on an IV pole.

13. Adjust to the desired flow rate again. The infusion time for one saline bag is 1-3 hours. The infusion rate will be determined by PI's discretion but maximum infusion rate will be 25 gtt/min (100cc/ hr).

14. Gently squeeze the saline bag every 30 min to prevent cell settling.

15. Document the relevant data regarding infusion.
    - Record the start time of the infusion on the client's chart.
    - Include the date and time of the venipuncture
    - Specific name and location of the accessed vein
    - Flow rate
    - Type, length and gauge of the needle or catheter
    - The client's general response
    - Your signature

16. Once the infusion of the second saline bag is finished, perform saline flush with approximate 20 cc of saline to make sure entire IP is administered.

17. Once the saline flush is finished, close the flow regulator of IV tubing. Apply gentle pressure over the insertion site with sterile gauze. Withdraw the needle. Hold pressure on the insertion site until bleeding stops. Cover the insertion site with an adhesive bandage.

18. Enclose empty two syringes of study drug and two IV bags into a pre-labeled bag and seal with tamper tale. Store at the secure place until a close-out visit.

19. A subject should stay in the infusion bed/chair at least 1 hour after infusion.

20. A subject will be discharged by PI's discharge order.

Monitoring Plan during and after the IV infusion of the study drug

1. Document the relevant data regarding infusion.
    - Record the start time of the infusion on the client's chart.
    - Include the date and time of the venipuncture
    - Specific name and location of the accessed vein
    - Flow rate
    - Type, length and gauge of the needle or catheter
    - The client's general response
    - Your signature

2. Check tubing for anything that might interfere with flow. Be sure clamps are in the open position.

3. Inspect the site for swelling, leakage at the site, coolness, or pallor, which may indicate infiltration. Ask if subject is experiencing any pain or discomfort. If any of these symptoms are present, the IV will need to be removed and restarted at another site.

4. Inspect the site for redness, swelling, and heat. Ask if patient is experiencing pain. The findings may indicate phlebitis. Notify principle investigator (PI) if phlebitis is suspected. IV will need to be discontinued and restarted at another site.

5. Check for local manifestations (redness, pus, warmth, induration, and pain) that may indicate an infection is present at the site or systemic manifestations (chills, fever, tachycardia, and hypotension) that may accompany local infection at the site. If signs of infection are present, discontinue the IV and notify PI.

6. If subject is experiencing shortness of breath and chest pain, discontinue the IV and notify PI. With PI's discretion, IV infusion will be terminated.