A Randomized, Double-Blind, Vehicle-Controlled, Parallel, Phase II Study to Evaluate Efficacy and Safety of BAC in Patient with Alzheimer's Disease or Vascular Dementia

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PROTOCOL SUMMARY

Full Title	A Randomized, Double-Blind, Vehicle-Controlled, Parallel, Phase II Study to Evaluate Efficacy and Safety of BAC in Patient with Alzheimer's Disease or Vascular Dementia
Short Title	BAC for Alzheimer's Disease or Vascular Dementia Phase II Study
Project No	BAC-02
Study Phase	Phase II
Sponsor	Charsire Biotechnology Corp.
Objectives	To evaluate the efficacy and safety of BAC in patients with Alzheimer's disease or vascular dementia
Study Design	Randomized, double-blind, vehicle-controlled, parallel study
Study Population	Patient aged at least 40 years old in United States diagnosed with Alzheimer's disease or vascular dementia
Number of Patients	The sample size is determined to be 45 versus 15 patients (3:1 ratio) for Treatment versus Control groups, 60 patients in total. To ensure the completion of 60 evaluable (per-protocol population) patients, around 75 patients will be recruited.
Study Product, Dose, Route, Regimen	BAC (vapor fraction from seeds of *Glycine max (L.) Merr*. and composition thereof), topical application on external nasal skin, scalp, and neck, 2 times daily, 30g/day During the treatment period, patients may continue to receive routinely used medications or treatments for Alzheimer's disease or vascular dementia.
Duration of Administration	Twelve weeks
Study Visits	Screening, Randomization (Baseline) Treatment (Weeks 2, 4, and 8 compared to Baseline), Final (Week 12)
Patient Assignment	In each study site, patients who meet all eligible requirements for entry into the study will be randomized and stratified into 1 of 2 dementia types (Alzheimer's disease and non- Alzheimer's disease) into treatment group or vehicle control group in 3:1 ratio as shown below:

	Treatment Group: BAC Control Group: Matched vehicle Note: Dementia types (Alzheimer's disease and non- Alzheimer's disease) are classified as follows: 1. Alzheimer's disease: Alzheimer's disease according to the NIAAA criteria + "Mixed" dementia (possible Alzheimer's disease with cerebrovascular disease) according to the NIAAA criteria 2. Non- Alzheimer's disease: Vascular dementia according to the NINDS-AIREN International Workshop criteria
Patients Inclusion Criteria	A patient is eligible for the study if all of the following apply: 1. With either gender aged at least 40 years old 2. With a diagnosis of one of the following disease i. Vascular dementia according to the NINDS-AIREN International Workshop criteria or ii. Alzheimer's disease according to the NIAAA criteria iii. "Mixed" dementia (possible Alzheimer's disease with cerebrovascular disease) according to the NIAAA criteria Note: a. NINDS-AIREN: National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences b. NIAAA: National Institute on Aging-Alzheimer's Association 3. With mild-to-moderate dementia (score of the Mini-Mental State Examination (MMSE) defined as between 10 to 24 and score of ADAS-Cog as at least 12) 4. Able to communicate and understand cognitive testing instructions 5. Having a responsible caregiver who spends at least 4 hours daily with the patient. The caregiver will accompany the patient to all study visits, supervise administration of study drug, and be able to assess the patient's condition

	6. Patients and the responsible caregiver willing and able to provide written informed consent form. Patients who lack capacity to consent must be in agreement with entering into the study and have a personal legally authorized representative giving written informed consent to their participation.
Patients Exclusion Criteria	Any patient meeting any of the exclusion criteria will be excluded from study participation. 1. With large vessel thrombosis (thrombotic stroke occurring in large arteries) 2. With radiological evidence of other brain disorders (subdural hematoma, post-traumatic / post-surgery) 3. With dementia caused by other brain diseases except Alzheimer's disease and vascular dementia (e.g. Parkinson's disease, demyelinated disease of the central nervous system, tumor, hydrocephalus, head injury, central nervous system infection including syphilis, acquired immune deficiency syndrome, etc.) 4. With clinical evidence of pulmonary, hepatic, gastrointestinal, metabolic, endocrine or other life threatening diseases judged by investigators not suitable to enter the study 5. With clinically unstable hypertension, diabetes mellitus, and cardiac disease for the last 3 months 6. Ever hospitalized for stroke or with acute coronary syndrome in the previous 3 months prior to screening 7. Drug or alcohol abuse within the previous 12 months of screening. 8. With one of the following abnormal laboratory parameters: hemoglobin < 10 mg/dL or platelet < $100*10^9$/L; creatinine or total bilirubin more than 1.5 times the upper limit value; alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphates (ALP), γ-glutamyl transferase (γ-GT) more than 2 times the upper limit of normal, or thyroid-stimulating hormone (TSH) more than 2.5 times the upper limit value or less than the lower limit value of normal

9. With severe depression graded by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and Cornell Scale for Depression in Dementia (CSDD)
10. With any uncontrolled illness (including, but not limited to, any of the following: ongoing or active infection including hepatitis B, C, and HIV, active bleeding, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris or, cardiac arrhythmia) judged by the investigator that entering the trial may be detrimental to the patient
11. With known or suspected hypersensitivity to any ingredients of study product and vehicle
12. Pregnant or lactating or premenopausal with childbearing potential but not taking reliable contraceptive method(s) during the study period

    Note: Reliable contraceptive methods will consider as below:

    a. Established use of oral, injected or implanted hormonal methods of contraception > 3 months prior to baseline.

    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) > 3 months prior to baseline.

    c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

    d. Partner male sterilization (i.e., vasectomy) > 1 month of screening
13. Enrollment in any investigational drug trial within 4 weeks of screening visit
14. Experienced dosage increment of routinely use in drugs listed as follows within past three months before Screening visit
    a. medications/treatments for Alzheimer's disease or vascular dementia
    b. antipsychotic medications including but not limited to selective serotonin reuptake inhibitors (SSRIs), benzodiazepine (BZD)
    c. Vitamin B12
    d. drugs for thyroid disease

	15. Current antiplatelet drug (antiaggregant) except dosage including but not limited to aspirin ≤ 100mg/day, clopidogrel ≤ 75mg/day, ticagrelor ≤ 180mg/day, dipyridamole ≤ 400mg/day 16. Caregivers who have psychotic symptoms, are imminently suicidal, have an unstable medical condition (e.g. recent heart attack, recent stroke, episodes of dizziness, fainting attacks) or significant orthopaedic problems.
Primary Endpoint	***Efficacy***: Change in Alzheimer Disease Assessment Scale-cognitive (ADAS-cog) score at Week 12 visit compared to baseline
Secondary Endpoints	***Efficacy***: 1. Change in ADAS-cog score at all post treatment visits (except Week 12 visit) compared to baseline 2. Clinician's Interview Based Impression of Change-Plus Caregiver Input (CIBIC-plus) score at all post treatment visits 3. Change in Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) score at all post treatment visits compared to baseline 4. Change in MMSE score at all post treatment visits compared to baseline 5. Change in Neuropsychiatric Inventory (NPI) score at all post treatment visits compared to baseline ***Safety***: 1. Adverse event incidence 2. Change in physical examination results 3. Net change from baseline in laboratory test results 4. Net change from baseline in vital signs
Statistical Analysis	**Analysis Population** Two data sets will be introduced for statistical analysis. Intent-to-treat (ITT) population: – All randomized patients who have received at least one dose study medication. Per-protocol (PP) population:

- A subset of ITT population
- Fulfill all inclusion and exclusion criteria
- Accumulatively dosed with at least 63 days of study drug and with at least 75% of dosing compliance during treatment period
- With ADAS-cog score evaluation at or after Week 8 visit
- Did not receive any prohibited treatment during the study

Efficacy endpoints will be analyzed on ITT and PP population. Demographics, baseline characteristics, and safety endpoints will be analyzed on ITT population. The conclusion of efficacy will be made according to the results of ITT population analysis.

Analyses

Demographics and baseline characteristics will be summarized for each group by using descriptive statistics.

The efficacy endpoints will be compared between the BAC group and vehicle group. The primary endpoint of this study is change in ADAS-cog score at Week 12 visit compared to baseline. The test will be performed by ANCOVA with treatment group and center as factor and with baseline score as covariate. Test treatment group will be declared superiority if the null hypothesis is rejected and improvement in ADAS-cog of test product group is greater than that of matched vehicle group.

As for secondary endpoints, change in ADAS-cog score at all post-treatment visits (except Week 12 visit) compared to baseline will be analyzed by ANCOVA with treatment group and center as factor and with baseline score as covariate. Same statistical analysis methods will be applied for other secondary endpoints such as changes in ADCS-ADL score, MMSE score, and NPI score at all post treatment visits compared to baseline. The CIBIC-plus score at all post treatment visits will be presented by transition table.

All treatment group comparisons will be conducted with significance level of 0.05, using 2-tailed tests.

For safety analyses, adverse events will be reported by treatment groups and by physiological systems as appropriate. Incidence of adverse events between treatments will be analyzed by CMH test.

	Changes in physical examinations will be displayed for each individual system. Net changes from pre-treatment laboratory test results and vital signs will be analyzed by descriptive statistics. All treatment group comparisons will be conducted with significance level of 0.05, using 2-tailed tests. Additionally, descriptive statistics will be provided for all of the endpoints. Frequency table will be provided for categorical data, while mean, standard deviation, maximum, minimum, median, inter-quartile range (IQR), and 95% two-sided confidence interval will be calculated for continuous measurements.

SCHEDULE OF ASSESSMENTS

Visit	Screening	Randomization[1] (Baseline)	Treatment			Final
Visit No.	1	2	3	4	5	6
Weeks relative to Baseline visit	-2~0	0	2	4	8	12
Visit Window (days)	NA	NA	±4	±4	±4	±4
Informed consent signed and given	X					
Screening number assignment	X					
Randomization		X				
Demographic data & medical history	X					
Inclusion and exclusion criteria	X	X				
Pregnancy test for applicable patients	X					
Imaging (CT/MRI)	X[5]					
ADAS-cog	X	X		X	X	X
CIBIS/CIBIC-plus[2]		X		X	X	X
ADCS-ADL		X		X	X	X
MMSE	X	X		X	X	X
NPI		X		X	X	X
Vital signs	X	X	X	X	X	X
Physical examinations	X	X	X	X	X	X
Laboratory test	X[3]	X[4]				X
Record concomitant medication(s)	X	X	X	X	X	X
Record AE		X	X	X	X	X
Dispense trial medication		X	X	X	X	
Dispense Subject Diary		X	X	X	X	
Return trial medication			X	X	X	X
Return Subject Diary			X	X	X	X
Complete exit form						X
Dismiss patient						X

1. Can be on the same day of Screening visit if patient meets entry criteria
2. Randomization visit: CIBIS; Other Visits: CIBIC-plus
3. Laboratory test results within 7 days before Screening visit are acceptable.
4. Laboratory test results within 21 days before Randomization visit are acceptable and can be used as baseline measurement. If laboratory test results within past 21 days are not available, the laboratory test has to be performed.
5. Results of CT/MRI (computed tomography/ magnetic resonance imaging) obtained within 12 months before Screening visit are acceptable