Effects of Liraglutide, Empagliflozin and Linagliptin on Mild Cognitive Impairment Reversion in Type 2 Diabetes (LIGHT-MCI TRIAL) PROTOCOL

Version 5.0 November 17, 2025

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Investigator Signature Page

Research Title:	Effects of Liraglutide, Empagliflozin and Linagliptin on Mild Cognitive Impairment Reversion in Type 2 Diabetes (LIGHT-MCI TRIAL)
Investigational Medical Product:	Liraglutide, Empagliflozin and Linagliptin
Protocol Number:	2022-092-24
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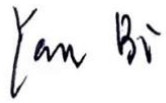
I have read the current research protocol, including all appendices and the Investigator's Brochure, and agree to conduct the study accordingly. I will provide protocol-related materials and offer appropriate guidance and assistance to all personnel under my supervision participating in the study, ensuring they are fully informed of the drug and research-related matters.

I will conduct the trial in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, International Council for Harmonization (ICH) E6 GCP (including necessary document archiving), and all applicable health and regulatory authorities, and Ethics Committee (EC) requirements. Acceptance of this document signifies my agreement that no unpublished information contained within this document will be disclosed or published without the prior written approval of the sponsor.

Research Center of the Principal Investigator:	Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University
Name of Investigator:	Yan Bi
Signature of Investigator:	
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LIST OF ABBREVIATIONS

Abbreviation	Term
AD	Alzheimer's disease
ADA	American Diabetes Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
APOE	Apolipoprotein E
BMI	Body mass index
CAP	controlled attenuation parameter
EASD	European Association of Diabetes
eGFR	estimated glomerular filtration rate
eCRF	electronic case report form
MCI	mild cognitive impairment
GCP	Good Clinical Practice
GLP-1 RAs	glucagon-like peptide-1 receptor agonists
GGT	gamma-glutamyltranspeptidase
SGLT-2	sodium–glucose cotransporter 2
DPP-4	dipeptidyl peptidases 4
IQR	interquartile range
LSM	Liver stiffness measurement
MRI	magnetic resonance imaging
TEAEs	treatment-emergent adverse events
SAEs	treatment-emergent serious adverse events
MD	mean diffusivity
MoCA	Montreal Cognitive Assessment
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
IADL	instrumental activity of daily living
ICV	intracranial volume
FAQ	Functional Activities Questionnaire
MMSE	Mini-Mental State Examination
HADS	Hospital Anxiety Depression Scale
TMT	Trail Making Test
BADL	Basic activities of daily living
FA	fractional anisotropy
FSL	FMRIB Software Library
DTI	diffusion tensor imaging
FW-WM	fractional volume of free water in white matter
DTI-ALPS	diffusion tensor image analysis along the perivascular space
PVSVF-WM	perivascular space volume fraction in white matter
HbA_{1c}	glycated haemoglobin
AESI	TEAEs of Special Interest
Aβ	amyloid beta
p-tau	phosphorylated tau
NfL	neurofilament light chain

GFAP	glial fibrillary acidic protein
NIA-AA	National Institute on Aging-Alzheimer's Association
ITT	Intent-to-Treat
PBF	percent body fat
PP	Per-protocol
T2D	Type 2 diabetes
GEE	generalized estimating equation
GLM	generalized linear model
CI	confidence intervals
VFA	visceral fat area
SD	standard deviation
SPM	Statistical Parametric Mapping
SAP	Statistical Analysis Plan
SIMOA	single-molecule array
TBV	Total brain volume
MAR	Missing at random
MICE	multiple imputation by chained equations
DSMB	data and safety monitoring board
EDC	Electronic Data Capture
CRA	Clinical Research Associate

1. PROTOCOL SUMMARY

SPONSOR	Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University
PRINCIPAL INVESTIGATOR	Prof. Yan Bi, MD, PhD Department of Endocrinology, Endocrine and Metabolic Disease Medical Center, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University Phone: (86)25-83686109 E-mail: biyan@nju.edu.cn
TITLE	Effects of Liraglutide, Empagliflozin and Linagliptin on Mild Cognitive Impairment Reversion in Type 2 Diabetes: A Multicenter, Randomized Controlled Trial with An Extension Phase
OBJECTIVES	The primary objective of the study is to evaluate the effects of liraglutide and empagliflozin, each compared separately to linagliptin, as add-on therapies to metformin monotherapy, on mild cognitive impairment (MCI) reversion in adults with type 2 diabetes (T2D). Secondary objectives are to evaluate the effects of liraglutide and empagliflozin, each compared separately to linagliptin, on: • general cognition • cognitive subdomains • basic and instrumental activities of daily living • magnetic resonance imaging (MRI)-derived brain structure and function • blood-based biomarkers for neurodegeneration • olfactory function • glucose and lipid metabolism, anthropometrics, liver fibrosis and fatty liver levels. The pre-specified safety objectives are to assess the effects of liraglutide, empagliflozin, and linagliptin, as add-on therapy with the metformin monotherapy, on the incidence of treatment-emergent adverse events (TEAEs), adverse events leading to study drug discontinuation, serious adverse events (SAEs),

	and adverse events of interest.
DESIGN OF THE STUDY	The LIGHT-MCI study is an investigator-initiated, multicenter, randomized, open-label, blinded-endpoint trial designed to evaluate the efficacy of three add-on therapies to metformin monotherapy for MCI reversion in T2D patients. Using a 1:1:1 allocation ratio, participants will be randomly assigned to receive either liraglutide, empagliflozin, or linagliptin for the 48-week core study period. Those completing the core study may opt for an additional 28-week extension phase after providing informed consent, resulting in a total possible intervention duration of 76 weeks.
NUMBER OF CENTERS	5 centers
SIZE OF THE STUDY	396 patients (132 patients per arm)
INCLUSION CRITERIA	• Participants aged ≥40 years and ≤75 years, of any gender. • T2D diagnosed according to the American Diabetes Association criteria. • MCI diagnosed according to the established criteria: a. Subjective cognitive concern reported by the patient or an informant. b. Objective cognitive impairment, defined as a Montreal Cognitive Assessment (MoCA) score between 18 and 25, or a score of 1 standard deviation (SD) or more below age- and education-adjusted norms in any assessed cognitive domain. c. Preserved independence in basic activities of daily living, indicated by a Barthel Index score of 60 or higher. d. Absence of dementia. • Treatment with a stable glucose lowering regimen of metformin monotherapy (≥ 1000 mg daily) or combination with sulfonylureas/glinides/glycosidase inhibitors/basal insulin over the previous 3 months. • Glycosylated haemoglobin during screening between ≥ 7.0% and ≤ 10.0%. • Body mass index (BMI) of ≥ 19 kg/m^2. • Education duration of ≥ 6 years.

	• Right-handed participants. • Understanding of the research procedures and methods, potential benefits and risks of the trial and sign written informed consent.
EXCLUSION CRITERIA	Participants will be excluded from the study if they meet any of the following criteria: • History of other neurological diseases associated with dementia, major depressive disorders, developmental disorders, bipolar disorder, schizophrenia, or related conditions within the past 2 years. • Significant sinonasal conditions (e.g., chronic sinusitis, nasal polyps), cranial or nasopharyngeal tumors or other space-occupying lesions, or congenital/traumatic disorders of the nose, sinuses, or skull base that may affect olfactory function. Participants presenting with symptoms of an upper respiratory tract infection (e.g., nasal congestion, rhinorrhea, fever) on the day of the MRI scan will also be excluded. • A history of acute diabetic metabolic complications (e.g., diabetic ketoacidosis, hyperosmolar hyperglycemic state, or hypoglycemic coma) within the previous 6 months. • Significant Organ Dysfunction: a. Cardiac: Unstable angina, acute myocardial infarction, or cardiac insufficiency (Class II or above per NYHA classification) within 3 months prior to screening. b. Renal: Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m² (calculated using the CKD-EPI formula). c. Hepatic: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 2 times the upper limit of normal. d. Thyroid: Uncontrolled thyroid dysfunction.

	• History of medullary thyroid carcinoma (MTC), multiple endocrine neoplasia syndrome type 2 (MEN 2), pancreatitis, recurrent urinary tract infections, severe gastrointestinal diseases, major gastrointestinal surgery, or any active malignancy. • Standard MRI contraindications apply, including but not limited to incompatible metallic implants or severe claustrophobia. • Female participants who are pregnant, lactating, or of childbearing potential not using highly effective contraception. • Participation in an investigational drug or device trial within the 6 months prior to screening. • Known or suspected allergy to the investigational product(s) or their excipients. • Treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dual agonists of the glucagon-like peptide-1 receptor and glucagon receptor (GLP-1R/GCGR), dual agonists of the glucagon-like peptide-1 receptor and glucose-dependent insulinotropic polypeptide receptor (GLP-1R/GIPR), sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors), or dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) within the 3 months preceding the baseline visit. • Known history of drug or alcohol abuse within the past 6 months.
STUDY TREATMENT/ STRATEGIES/ PROCEDURES	Following a 1-week guided discontinuation of all antidiabetic medications except metformin, eligible participants will be randomized to receive one of three add-on therapies: liraglutide, empagliflozin, or linagliptin. The core treatment period will last for 48 weeks. Participants who enter the extension study will continue on the same medication assigned during the core study for an additional 28 weeks. Patients with prior exposure to SGLT-2 inhibitors, GLP-1RAs, or DPP-4 inhibitors for

	less than six months will undergo a 3-month wash-out period using gliclazide or basal insulin before randomization. Participants will be randomly assigned to one of the following three groups: - Liraglutide Group: Treatment will be initiated at a dose of 0.6 mg administered once daily via subcutaneous injection in the abdomen. Based on the investigator's assessment of individual tolerance, the dose will be up-titrated over 8 weeks: first to 1.2 mg, and then to the target maintenance dose of 1.8 mg. - Empagliflozin Group: Participants will take one 10 mg tablet orally once daily, before breakfast. - Linagliptin Group: Participants will take one 5 mg tablet orally once daily, before breakfast.
STUDY OUTCOMES	The primary outcome of this study is MCI reversion at 48 weeks of treatment. MCI reversion is defined by meeting three criteria: an education-adjusted score of the Montreal Cognitive Assessment (MoCA) ≥26, no cognitive deficits in any explored subdomain, and preservation of ability to perform instrumental activity of daily living (IADL) with a Functional Activities Questionnaire (FAQ) score <5. Secondary outcomes are: 1) MCI reversion at 76 weeks of treatment. 2) The effects on general cognition will be evaluated by: - The change from baseline to 48 and 76 weeks in Mini-Mental State Examination (MMSE) score. - The change from baseline to 24, 48 and 76 weeks in MoCA score. - The change from baseline to 48 and 76 weeks in repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score. 3) The effects on cognitive subdomains will

	be evaluated by: - The change from baseline to 48 and 76 weeks in RBANS index score of immediate memory. - The change from baseline to 48 and 76 weeks in RBANS index score of visuospatial/constructional. - The change from baseline to 48 and 76 weeks in RBANS index score of language. - The change from baseline to 48 and 76 weeks in RBANS index score of attention. - The change from baseline to 48 and 76 weeks in RBANS index score of delayed memory. - The change from baseline to 48 and 76 weeks in Trail Making Test (TMT) completion time. - The change from baseline to 48 and 76 weeks in Victoria Stroop Color-Word Test completion time. 4) The effects on basic and instrumental activities of daily living will be evaluated by: - The change from baseline to 48 and 76 weeks in Barthel index score. - The change from baseline to 48 and 76 weeks in FAQ score. 5) The effects on MRI-derived brain structure and function will be evaluated by: - The change from baseline to 48 and 76 weeks in total brain volume. - The change from baseline to 48 and 76 weeks in total gray matter volume. - The change from baseline to 48 and 76 weeks in total white matter volume. - The change from baseline to 48 and 76 weeks in cerebrospinal fluid volume. - The change from baseline to 48 and 76 weeks in frontal cortical gray matter volume. - The change from baseline to 48 and 76 weeks in parietal cortical gray matter volume. - The change from baseline to 48 and 76

	weeks in temporal cortical gray matter volume. - The change from baseline to 48 and 76 weeks in occipital cortical gray matter volume. - The change from baseline to 48 and 76 weeks in insula cortical gray matter volume. - The change from baseline to 48 and 76 weeks in hippocampal volume. - The change from baseline to 48 and 76 weeks in parahippocampal volume. - The change from baseline to 48 and 76 weeks in entorhinal cortex volume. - The change from baseline to 48 and 76 weeks in inferior parietal lobule volume. - The change from baseline to 48 and 76 weeks in precuneus volume. - The change from baseline to 48 and 76 weeks in cuneus volume. - The change from baseline to 48 and 76 weeks in thalamus volume. - The change from baseline to 48 and 76 weeks in caudate nucleus volume. - The change from baseline to 48 and 76 weeks in putamen volume. - The change from baseline to 48 and 76 weeks in pallidum volume. - The change from baseline to 48 and 76 weeks in amygdala volume. - The change from baseline to 48 and 76 weeks in accumbens volume. - The change from baseline to 48 and 76 weeks in white matter hyperintensity volume. - The change from baseline to 48 and 76 weeks in mean fractional anisotropy (FA) in white matter derived from diffusion tensor imaging (DTI). - The change from baseline to 48 and 76 weeks in mean diffusivity (MD) in white matter derived from DTI. - The change from baseline to 48 and 76 weeks in fractional volume of free water in

	white matter (FW-WM). - The change from baseline to 48 and 76 weeks in diffusion tensor image analysis along the perivascular space (DTI-ALPS) index. - The change from baseline to 48 and 76 weeks in perivascular space volume fraction in white matter (PVSVF-WM). - The change from baseline to 48 weeks in functional MRI-derived odor-induced brain activation. - The change from baseline to 48 and 76 weeks in resting-state functional MRI-derived brain network connectivity. 6) The effects on blood-based biomarkers for neurodegeneration will be evaluated by: - The change from baseline to 48 weeks in plasma amyloid beta (Aβ)42/Aβ40 ratio. - The change from baseline to 48 weeks in plasma phosphorylated tau (p-tau)181concentration. - The change from baseline to 48 weeks in plasma p-tau 217 concentration. - The change from baseline to 48 weeks in plasma neurofilament light chain (NfL) concentration. - The change from baseline to 48 weeks in plasma glial fibrillary acidic protein (GFAP) concentration. 7) The effects on olfactory function will be evaluated by: - The change from baseline to 48 and 76 weeks in olfactory threshold score (as measured by OLFACT®, Osmic Enterprises, Inc.). - The change from baseline to 48 and 76 weeks in olfactory identification score (as measured by OLFACT®, Osmic Enterprises, Inc.). - The change from baseline to 48 and 76 weeks in olfactory memory score (as measured by OLFACT®, Osmic Enterprises, Inc.).

	- The change from baseline to 48 and 76 weeks in olfactory assessment total score (as measured by OLFACT®, Osmic Enterprises, Inc.). 8) The effects on glucose and lipid metabolism, anthropometrics, liver fibrosis and fatty liver levels will be evaluated by: - The change from baseline to 24, 48 and 76 weeks in glycated haemoglobin (HbA_{1c}). - The change from baseline to 24, 48 and 76 weeks in fasting plasma glucose. - The change from baseline to 48 and 76 weeks in 2-hour postprandial plasma glucose. - The change from baseline to 48 and 76 weeks in fasting insulin. - The change from baseline to 48 and 76 weeks in 2-hour postprandial insulin. - The change from baseline to 48 and 76 weeks in fasting C-peptide. - The change from baseline to 48 and 76 weeks in 2-hour postprandial C-peptide. - The change from baseline to 48 and 76 weeks in pancreatic islet function (HOMA2-β) estimated from fasting C-peptide via HOMA2 Calculator (v2.2.3, http://www.dtu.ox.ac.uk/homacalculator/). - The change from baseline to 48 and 76 weeks in insulin sensitivity (HOMA2-S) estimated from fasting C-peptide via HOMA2 Calculator (v2.2.3, http://www.dtu.ox.ac.uk/homacalculator/). - The change from baseline to 48 and 76 weeks in insulin resistance indexes (HOMA2-IR) estimated from fasting C-peptide via HOMA2 Calculator (v2.2.3, http://www.dtu.ox.ac.uk/homacalculator/). - The change from baseline to 24, 48 and 76 weeks in fasting serum triglyceride. - The change from baseline to 24, 48 and 76 weeks in fasting total cholesterol. - The change from baseline to 24, 48 and 76 weeks in fasting high-density lipoprotein-cholesterol.

	- The change from baseline to 24, 48 and 76 weeks in fasting low-density lipoprotein-cholesterol. - The change from baseline to 24, 48 and 76 weeks in visceral fat area measured by Inbody 720 analyser. - The change from baseline to 24, 48 and 76 weeks in percent body fat measured by Inbody 720 analyser. - The change from baseline to 24, 48 and 76 weeks in liver stiffness measurement quantified by FibroTouch® system. - The change from baseline to 24, 48 and 76 weeks in liver fat controlled attenuation parameter quantified by FibroTouch® system. - The change from baseline to 48 and 76 weeks in blood pressure as measured every 8 weeks. - The change from baseline to 48 and 76 weeks in body weight as measured every 8 weeks. - The change from baseline to 48 and 76 weeks in body mass index as measured every 8 weeks. - The change from baseline to 48 and 76 weeks in waist circumference as measured every 8 weeks. - The change from baseline to 48 and 76 weeks in hip circumference as measured every 8 weeks. - The change from baseline to 48 and 76 weeks in waist to hip circumference ratio as measured every 8 weeks. The safety and tolerability of the three drugs will be assessed using the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events leading to study drug discontinuation, and adverse events of interest.

STATISTICAL ANALYSIS OF THE DATA	Statistical analyses will be performed using SAS software (version 9.4 or higher). Detailed analytical procedures will be specified in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock. Unless otherwise stated, all statistical tests and confidence intervals will be two-sided. Continuous variables will be summarized using mean, standard deviation, median, maximum, and minimum values; categorical variables will be summarized using counts and percentages. Efficacy analyses will be based on the Intent-to-Treat (ITT) population. The primary outcome (MCI reversion rate at Week 48) will be analyzed using a generalized estimating equations (GEE) model to estimate the risk ratio (RR) and risk difference (RD) of liraglutide and empagliflozin versus linagliptin. Pre-specified alternative models will be used if the primary model fails to converge. All secondary outcomes will be tested for superiority (without adjustment for multiplicity), with results presented as point estimates (e.g., RR, mean difference) along with their 95% confidence intervals. Binary and continuous outcomes will be analyzed using GEE models, while repeated measures data will be analyzed using linear mixed models. Safety analyses will be performed on the Safety Population. Adverse events will be summarized by actual treatment group and reported using descriptive statistics (counts and percentages).
DURATION OF THE STUDY	Duration of the inclusion period: 26 months Duration of participation for each patient: 76 weeks (48-week core study period and additional 28-week extension phase) Total duration of the study: 46 months

2. BACKGROUND

Currently, there are approximately 537 million adults with diabetes worldwide, projected to rise to 783 million by 2045 [1]. Likewise, global dementia cases stand at around 55 million, with estimates indicating a surge to 151 million by 2050 [2,3]. Notably, diabetes significantly increases the risk of dementia by 1.5 to 2.5 times, and cognitive dysfunction is increasingly acknowledged as an emerging complication of diabetes [4,5].

Regrettably, the currently available pharmacological therapies for delaying or reversing the progression of dementia have limited efficacy and undesirable side effects. Mild cognitive impairment (MCI) is deemed as the prodromal stage of dementia, and constitute a high-risk group for progression to dementia [6,7]. Therefore, early identification and intervention of individuals with MCI is likely essential for successful disease prevention and progression mitigation. Although routine screening for the early detection of cognitive impairment in diabetes is widely recommended, current clinical guidelines have not offered strategies to combat cognitive dysfunction [8].

There is growing evidence that certain anti-diabetes medications hold promise in improving cognitive function. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown potential in restoring brain glucose metabolism in Alzheimer's disease, offering a putative repurposed candidate against cognitive dysfunction [9,10]. Exploratory or post-hoc analyses of randomized trials suggest GLP-1 RAs versus placebo may protect against cognitive decline [11-14]. Also, the role of sodium–glucose cotransporter-2 (SGLT-2) inhibitors in cognitive function has emerged as another focal point. Population-based cohort studies point to a significantly reduced risk of dementia associated with SGLT-2 inhibitors usage, yet clear neuroprotective effects from prospective randomized controlled trials remains lacking [15-18]. Linagliptin, a dipeptidyl peptidases-4 (DPP-4) inhibitor, showed neutral effects on cognition in the CARMELINA and CAROLINA-COGNITION trials [19,20]. Accumulating studies have explored the cognitive benefits of specific class of antidiabetic agents, yet there is limited evidence informs their head-to-head comparisons of cognitive effects. Our preliminary 16-week randomized trial comparing liraglutide, dapagliflozin, and acarbose, demonstrated liraglutide's superior effects on restoring odor-induced brain activation and cognitive domains in type 2 diabetes (T2D) [21]. However, these findings should be interpreted in light of methodological limitations including a modest sample size, short intervention period, and reliance on neuroimaging surrogate endpoints.

Therefore, we have further designed a multicenter, randomized, superiority trial on

head-to-head comparison of efficacy of liraglutide, empagliflozin, and linagliptin on MCI reversion in T2D. The results are expected to address knowledge gaps and inform clinical decision-making by providing robust evidence.

3. OBJECTIVES OF THE STUDY

3.1. PRINCIPLE OBJECTIVE

The primary objective of the study is to evaluate the effects of liraglutide and empagliflozin, each compared separately to linagliptin, as add-on therapies to metformin monotherapy, on MCI reversion in adults with T2D to assess their potential neuroprotection effects.

3.2. SECONDARY OBJECTIVES

Secondary objectives are to evaluate the effects of liraglutide and empagliflozin, each compared separately to linagliptin, on:

- general cognition
- cognitive subdomains
- basic and instrumental activities of daily living
- magnetic resonance imaging (MRI)-derived brain structure and function
- blood-based biomarkers for neurodegeneration
- olfactory function
- glucose and lipid metabolism, anthropometrics, liver fibrosis and fatty liver levels.

3.3. PRE-SPECIFIED SAFETY OBJECTIVE

The pre-specified safety objectives are to assess the effects of liraglutide, empagliflozin, and linagliptin, as add-on therapy with the metformin monotherapy, on the incidence of treatment-emergent adverse events (TEAEs), adverse events leading to study drug discontinuation, serious adverse events (SAEs), and adverse events of interest.

4. CONCEPTION OF THE STUDY

4.1. STUDY DESIGN

The LIGHT-MCI study is an investigator-initiated, multicenter, randomized, open-label, blinded-endpoint trial designed to evaluate the efficacy of three add-on therapies to metformin monotherapy for MCI reversion in T2D patients. Using a 1:1:1 allocation ratio, participants will be randomly assigned to receive either liraglutide, empagliflozin, or linagliptin for the 48-week core study period. Those completing the core study may

opt for an additional 28-week extension phase after providing informed consent, resulting in a total possible intervention duration of 76 weeks. The trial design is shown in Appendix 1.

4.2. TRIAL SITES

The trial will be conducted in five hospitals, including Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing First Hospital, Wuxi People's Hospital, Changzhou Second People's Hospital, and Nanjing Jiangning Hospital.

4.3. RANDOMIZATION AND BLINDING

This trial will adopt a block randomization method with a block size of 6, with each center competing for enrollment. The randomization list will be centrally generated by the statistician of the LIGHT-MCI trial platform before the start of the trial. This randomization list and a document describing the randomization procedure will be kept confidential by the LIGHT-MCI statistician who are not involved in participant screening or treatment. Participants meeting the eligibility criteria will be assigned a random number by a web-based system (JianDaoYun, Fanruan Software Co., Ltd.) and will be allocated to the "liraglutide," "empagliflozin," or "linagliptin" group by randomization in a 1:1:1 ratio after all baseline assessments are completed. When it is confirmed that the subjects are successfully enrolled, the researcher applies for the randomization allocation process, fills in the date and subject label, and the randomization process manager matches the random number and returns it to the applicant to complete the single randomization allocation process.

Given the inherent challenges of complete blinding due to differing drug administration routes (oral vs. injectable), this study will implement a rigorous evaluator blinding approach to uphold research integrity. The study will involve four independent teams with strictly segregated workflows, including intervention, evaluation, statistical and monitoring team. The intervention team will be dedicated to participant enrollment and clinical management. The evaluation team will conduct all participant assessments and collects anonymized data while remaining blinded to group allocation. All assessors will undergo standardized blinding protocol training and work in controlled environments free of treatment identifiers. The statistical team, unaware of study cohorts, will perform data cleaning and verification according to standard procedures. Finally, the statistical team will lock the database once declared complete and accurate, and will perform statistical analysis based on the pre - specified plan.

If accidental unblinding occurs, it will be immediately documented (time, cause, personnel) and reported to the independent data and safety monitoring committee. The unblinded assessor will be replaced, and affected data will be flagged for sensitivity

analysis. Preventive measures include enhanced staff training on blinding protocols, regular environmental audits, and ongoing process monitoring by the study coordinator. All unblinding events and corrective actions will be transparently reported in the final publication. Statistical analyses will also include pre - and post - unblinding comparisons to assess potential outcome impacts.

5. ELIGIBILITY CRITERIA

5.1. INCLUSION CRITERIA

Subjects are eligible for the study if all following criteria are met:

- Participants aged ≥40 years and ≤75 years, of any gender.
- T2D diagnosed according to the American Diabetes Association criteria.
- MCI diagnosed according to the established criteria:

a. Subjective cognitive concern reported by the patient or an informant.
b. Objective cognitive impairment, defined as a Montreal Cognitive Assessment (MoCA) score between 18 and 25, or a score of 1 standard deviation (SD) or more below age- and education-adjusted norms in any assessed cognitive domain.
c. Preserved independence in basic activities of daily living, indicated by a Barthel Index score of 60 or higher.
d. Absence of dementia.

- Treatment with a stable glucose lowering regimen of metformin monotherapy (≥ 1000 mg daily) or combination with sulfonylureas/glinides/glycosidase inhibitors/basal insulin over the previous 3 months.
- Glycosylated haemoglobin (HbA_{1c}) during screening between ≥ 7.0% and ≤ 10.0%.
- Body mass index (BMI) of ≥ 19 kg/m^2.
- Education duration of ≥ 6 years.
- Right-handed participants.
- Understanding of the research procedures and methods, potential benefits and risks of the trial and sign written informed consent.

5.2. EXCLUSION CRITERIA

Participants will be excluded from the study if they meet any of the following criteria:

- History of other neurological diseases associated with dementia, major depressive disorders, developmental disorders, bipolar disorder, schizophrenia, or related conditions within the past 2 years.
- Significant sinonasal conditions (e.g., chronic sinusitis, nasal polyps), cranial or nasopharyngeal tumors or other space-occupying lesions, or congenital/traumatic disorders of the nose, sinuses, or skull base that may affect olfactory function. Participants presenting with symptoms of an upper respiratory tract infection (e.g., nasal congestion, rhinorrhea, fever) on the day of the MRI scan will also be excluded.

- A history of acute diabetic metabolic complications (e.g., diabetic ketoacidosis, hyperosmolar hyperglycemic state, or hypoglycemic coma) within the previous 6 months.
- Significant Organ Dysfunction:

a. Cardiac: Unstable angina, acute myocardial infarction, or cardiac insufficiency (Class II or above per NYHA classification) within 3 months prior to screening.
b. Renal: Estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m² (calculated using the CKD-EPI formula).
c. Hepatic: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels > 2 times the upper limit of normal.
d. Thyroid: Uncontrolled thyroid dysfunction.

- History of medullary thyroid carcinoma (MTC), multiple endocrine neoplasia syndrome type 2 (MEN 2), pancreatitis, recurrent urinary tract infections, severe gastrointestinal diseases, major gastrointestinal surgery, or any active malignancy.
- Standard MRI contraindications apply, including but not limited to incompatible metallic implants or severe claustrophobia.
- Female participants who are pregnant, lactating, or of childbearing potential not using highly effective contraception.
- Participation in an investigational drug or device trial within the 6 months prior to screening.
- Known or suspected allergy to the investigational product(s) or their excipients.
- Treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dual agonists of the glucagon-like peptide-1 receptor and glucagon receptor (GLP-1R/GCGR), dual agonists of the glucagon-like peptide-1 receptor and glucose-dependent insulinotropic polypeptide receptor (GLP-1R/GIPR), sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors), or dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) within the 3 months preceding the baseline visit.
- Known history of drug or alcohol abuse within the past 6 months.

5.3. CASE ASCERTAINMENT AND CASE DEFINITIONS

- **Type 2 diabetes**

  Type 2 diabetes will be defined per American Diabetes Association criteria [22]: HbA_{1c} ≥ 6.5%, fasting glucose ≥ 126 mg/dL (≥ 7.0mmol/L), two-hour oral glucose tolerance test ≥ 200 mg/dL (≥11.1mmol/L), random glucose≥ 200 mg/dL (≥11.1mmol/L), or use of anti-diabetes medications.

- **Mild cognitive impairment**

  MCI diagnosis followed the Petersen criteria [23,24]: cognitive concern from the patient or an informant; objective evidence of cognitive impairment; preservation of independence in daily living abilities; and absence of dementia.

  In this trial, we predefine objective cognitive impairment as follows: an education-adjusted MoCA score ≤ 25 and ≥ 18; or ≥ 1.0 standard deviation (SD) below age- and education-adjusted norms in any assessed cognitive domain, including processing speed, executive function, immediate memory, visuospatial construction ability, language, attention and delayed memory, evaluated by Trail-Making Test,

Stroop Color-Word Test and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), respectively (the cut-off scores in all tests as detailed in Appendix 2).

5.4. METHODS OF RECRUITMENT

Patients will be recruited during routine follow-up consultations by endocrinologists experienced in the interdisciplinary field of metabolic and cognitive health. Participating centers are selected based on the following essential criteria: (a) membership in the Diabetes-Cognitive Dysfunction Consortium; (b) formal written agreements to ensure protocol adherence and compliance monitoring, supported by institutional ethical approvals and Good Clinical Practice (GCP) certification; (c) designation as tertiary hospitals with certified diabetes and neurology clinics, enabling comprehensive clinical and cognitive assessments; (d) multidisciplinary teams with documented research experience in endocrinology and cognitive health; and (e) capacity to implement the required data collection and management systems for accurate data handling.

These criteria ensure that all participating centers possess the necessary infrastructure, expertise, and commitment to facilitate the successful recruitment of eligible patients.

6. STUDY TREATMENTS

Following a 1-week guided discontinuation of all antidiabetic medications except metformin, eligible participants will be randomized to receive one of three add-on therapies: liraglutide, empagliflozin, or linagliptin. The core treatment period will last for 48 weeks. Participants who enter the extension study will continue on the same medication assigned during the core study for an additional 28 weeks. Patients with prior exposure to SGLT-2 inhibitors, GLP-1RAs, or DPP-4 inhibitors for less than six months will undergo a 3-month wash-out period using gliclazide or basal insulin before randomization.

6.1. TREATMENT BEING STUDIED AND COMPARATIVE TREATMENT

- Tested drug 1: Liraglutide

  Liraglutide (Victoza®) is supplied as a disposable pre-filled pen with the dosage of 18mg for 3ml per vial, which is manufactured by Novo Nordisk A/S (Bagsvaerd, Denmark) and packaged by Novo Nordisk A/S Pharmaceuticals (China) Co., Ltd. Participants will initiate treatment with liraglutide at a starting dose of 0.6 mg administered via daily subcutaneous abdominal injection. The dose will be escalated in a stepwise manner over an 8-week titration period, with incremental increases to 1.2 mg and subsequently to the target maintenance dose of 1.8 mg,

based on individual tolerance as assessed by the investigator. The protocol incorporates a flexible dose adjustment strategy: (a) individualized adjustment of dose-escalation intervals within the 8-week period, (b) dose reduction to 1.2 mg as the maximum tolerated dose when necessary, and (c) protocol-permitted treatment pauses of variable duration for managing persistent adverse events.

- Tested drug 2: Empagliflozin
  Empagliflozin tablets (Jardiance®) are available in a specification of 10mg per tablet and are taken orally. The medication is manufactured by Boehringer Ingelheim Pharma GmbH & Co.KG (Germany) and packaged by Boehringer Ingelheim Pharmaceuticals (Shanghai) Co., Ltd. Patients are instructed to take one 10mg tablet daily, orally before breakfast.
- Active control drug: Linagliptin
  Linagliptin tablets (Tradjenta®) are available in a specification of 5mg per tablet and are taken orally. This medication is manufactured by Boehringer Ingelheim Pharmaceuticals Inc. Patients are instructed to take one 5mg tablet daily, orally before breakfast.

All investigational drugs are purchased by the research team at fair market value using dedicated study funds. The respective pharmaceutical companies have no financial or scientific involvement in the trial.

6.2. ADDITIONAL TREATMENT CRITERIA

If glucose control does not meet standard during follow-up (fasting blood glucose ≥11.1 mmol/L more than twice or HbA_{1c}≥8.5%), additional intervention with gliclazide modified release tablets (starting from 30 mg once daily and maximum dose not exceeding 120 mg) or basal insulin (insulin glargine injection) will be given. The actual glycemic control target and additional treatment therapy will be determined by the investigators according to the individual conditions of participants.

6.3. DISPENSING THE MEDICAL PRODUCT

At each scheduled study visit (Week 0, 4, 8, 16, 24, 32, 40, 48, 56, and 64), the designated study drug manager of each investigating site will dispense the study medication upon verification of a valid study prescription. The quantity dispensed at each visit will be calculated to provide a sufficient supply, ensuring coverage until the next scheduled visit (for a maximum of 8 weeks).

6.4. STORAGE OF THE MEDICAL PRODUCT

- Liraglutide
  Prior to initiation, the investigational product must be stored under continuous refrigeration (2°C to 8°C), must not be frozen. The unopened product has a shelf

life of 30 months.

Following the first use, the pen may be stored either at room temperature (not exceeding 30°C) or under refrigeration (2°C to 8°C). The product retains stability for 1 month after initiation or until the expiration date of the unopened pen, whichever comes first. Freezing is prohibited. The pen cap should be kept on when not in use to protect from light.

- Empagliflozin
  The tablets should be stored in a cool, dark place and kept sealed (not exceeding 25 °C), with a shelf life of 24 months.
- Linagliptin
  The tablets should be stored in a cool, dark place and kept sealed (not exceeding 25 °C), with a shelf life of 24 months.
- Insulin glargine injection
  Prior to initiation, Insulin glargine injection (LANTUS® SOlOSTAR®, Sanofi) must be stored under continuous refrigeration (2°C to 8°C), must not be frozen. The unopened product has a shelf life of 36 months.
  Following the first use, the pen may be stored at room temperature (not exceeding 30°C). The product retains stability for 28 days after initiation or until the expiration date of the unopened pen, whichever comes first. After each injection, the needle must be properly discarded, and the pen cap should be kept on to protect from light.
- Gliclazide modified release tablets
  The tablets should be stored in a cool, dark place and kept sealed (not exceeding 30 °C), with a shelf life of 36 months.

6.5. TREATMENT COMPLIANCE MONITORING AND MANAGEMENT

All participants will receive standardized training on daily self-monitoring strategies and lifestyle modifications (including diet and exercise) focused on glycemic management to enhance adherence to the assigned treatment. This training and subsequent support will be delivered through regular follow-up visits or telephone contacts.

Treatment compliance will be assessed by the investigator based on patient diaries and the quantity of returned unused investigational drugs. The compliance rate (%) for each participant will be calculated as follows:

Compliance Rate = (Number of doses actually taken / Number of doses prescribed) × 100%.

Compliance rates will be categorized into the following levels: <50%, 50% to <75%, 75% to 100%, and >100%. A compliance rate of <50% will be considered a major protocol deviation. Participants meeting this criterion will be excluded from the Per-

Protocol (PP) population.

7. CONCOMITANT THERAPIES

All medications (including prescription, over-the-counter drugs, vaccines, vitamins, and herbal supplements) administered at enrollment or initiated during the study period must be documented in the electronic case report form (eCRF) with their dosage and any adjustments. Participants and their caregivers are required to consult the site investigator or designated study personnel prior to initiating any new medication or altering the dose of an existing one. The Medical Monitor should be consulted for any questions regarding concomitant or prior therapies.

7.1. PROHIBITED CONCOMITANT THERAPIES

The following medications are prohibited during the study period due to their potential to interfere with the study drug's mechanism of action, confound efficacy assessments, or pose unacceptable safety risks.

Generic Name	Trade Name
Alzheimer's disease-Modifying Therapy (Anti-amyloid Monoclonal Antibody)	
Lecanemab	Leqembi
Donanemab	Kisunla
Other anti-amyloid immunotherapies	
Cognitive Enhancers	
Acetylcholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine)	Aricept, Exelon, Reminyl, Razadyne and Razadyne ER
Memantine	Namenda
Donepezil and Memantine combination	Donamem, Namzaric
Any other drug approved for treatment of cognitive impairment	
Psychoactive Substances	
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem

Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Methylphenidate	Ritalin, Concerta, Ritalin LA, Focalin
Amphetamine	Adderall, Dexedrine, Dextrostat
Other benzodiazepines, tricyclic antidepressants, anti-psychotics, and psychostimulants	
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists	
Potent CYP3A4 & P-glycoprotein inducers	
Rifampin	Rifadin, Rimactane
Other potent CYP3A4 & P-glycoprotein inducers	
Any glucose-lowering medications beyond those explicitly permitted by the study protocol	
Medications that significantly affect glucose metabolism	
Oral, intravenous, intramuscular, intra-articular corticosteroids	Dexamethasone, Medrol, Solu-Medrol, Deltasone, Prednisone Intensol, Cortef, Hydrocortone
Growth hormone	Saizen, Yipaisen, Ansumeng, Jintropin
Other medications that significantly affect glucose metabolism	

7.2. PERMITTED CONCOMITANT THERAPIES

Concomitant medications commonly required for the management of T2D and its comorbidities, such as antihypertensives, lipid-lowering agents, and antiplatelet agents, are permitted.

Short-term insulin therapy is allowed for the management of acute medical conditions (e.g., infection, perioperative care). However, initiation of long-term insulin therapy (exceeding 2 weeks) for chronic conditions is prohibited and constitutes a protocol deviation. The final decision rests with the investigator based on the specific clinical

scenario.

8. STUDY OUTCOMES

8.1. PRIMARY OUTCOME

The primary outcome is MCI Reversion at 48 weeks of treatment.
MCI reversion is defined by meeting three criteria: an education-adjusted MoCA score ≥26, no cognitive deficits in any explored subdomain (with scores above the cut-off scores in all tests as detailed in Appendix 2), including processing speed, executive function, immediate memory, visuospatial construction ability, language, attention and delayed memory, evaluated by Trail-Making Test (TMT), Stroop Color-Word Test and RBANS, respectively, and preservation of ability to perform instrumental activity of daily living (IADL) with a FAQ score <5.

8.2. SECONDARY OUTCOMES

Secondary outcomes are:
1) MCI reversion at 76 weeks of treatment.
2) The effects on general cognition will be evaluated by:
- The change from baseline to 48 and 76 weeks in Mini-Mental State Examination (MMSE) score.
- The change from baseline to 24, 48 and 76 weeks in MoCA score.
- The change from baseline to 48 and 76 weeks in RBANS total score.

3) The effects on cognitive subdomains will be evaluated by:
- The change from baseline to 48 and 76 weeks in RBANS index score of immediate memory.
- The change from baseline to 48 and 76 weeks in RBANS index score of visuospatial/constructional.
- The change from baseline to 48 and 76 weeks in RBANS index score of language.
- The change from baseline to 48 and 76 weeks in RBANS index score of attention.
- The change from baseline to 48 and 76 weeks in RBANS index score of delayed memory.
- The change from baseline to 48 and 76 weeks in TMT completion time.
- The change from baseline to 48 and 76 weeks in Victoria Stroop Color-Word Test completion time.

4) The effects on basic and instrumental activities of daily living will be evaluated by:
- The change from baseline to 48 and 76 weeks in Barthel index score.
- The change from baseline to 48 and 76 weeks in FAQ score.

5) The effects on MRI-derived brain structure and function will be evaluated by:
- The change from baseline to 48 and 76 weeks in total brain volume.
- The change from baseline to 48 and 76 weeks in total gray matter volume.

- The change from baseline to 48 and 76 weeks in total white matter volume.
- The change from baseline to 48 and 76 weeks in cerebrospinal fluid volume.
- The change from baseline to 48 and 76 weeks in frontal cortical gray matter volume.
- The change from baseline to 48 and 76 weeks in parietal cortical gray matter volume.
- The change from baseline to 48 and 76 weeks in temporal cortical gray matter volume.
- The change from baseline to 48 and 76 weeks in occipital cortical gray matter volume.
- The change from baseline to 48 and 76 weeks in insula cortical gray matter volume.
- The change from baseline to 48 and 76 weeks in hippocampal volume.
- The change from baseline to 48 and 76 weeks in parahippocampal volume.
- The change from baseline to 48 and 76 weeks in entorhinal cortex volume.
- The change from baseline to 48 and 76 weeks in inferior parietal lobule volume.
- The change from baseline to 48 and 76 weeks in precuneus volume.
- The change from baseline to 48 and 76 weeks in cuneus volume.
- The change from baseline to 48 and 76 weeks in thalamus volume.
- The change from baseline to 48 and 76 weeks in caudate nucleus volume.
- The change from baseline to 48 and 76 weeks in putamen volume.
- The change from baseline to 48 and 76 weeks in pallidum volume.
- The change from baseline to 48 and 76 weeks in amygdala volume.
- The change from baseline to 48 and 76 weeks in accumbens volume.
- The change from baseline to 48 and 76 weeks in white matter hyperintensity volume.
- The change from baseline to 48 and 76 weeks in mean fractional anisotropy (FA) in white matter derived from diffusion tensor imaging (DTI).
- The change from baseline to 48 and 76 weeks in mean diffusivity (MD) in white matter derived from DTI.
- The change from baseline to 48 and 76 weeks in fractional volume of free water in white matter (FW-WM).
- The change from baseline to 48 and 76 weeks in diffusion tensor image analysis along the perivascular space (DTI-ALPS) index.
- The change from baseline to 48 and 76 weeks in perivascular space volume fraction in white matter (PVSVF-WM).
- The change from baseline to 48 weeks in functional MRI-derived odor-induced brain activation.
- The change from baseline to 48 and 76 weeks in resting-state functional MRI-derived brain network connectivity.

6) The effects on blood-based biomarkers for neurodegeneration will be evaluated by:

- The change from baseline to 48 weeks in plasma amyloid beta (Aβ)42/Aβ40 ratio.
- The change from baseline to 48 weeks in plasma phosphorylated tau (p-tau)181concentration.
- The change from baseline to 48 weeks in plasma p-tau 217 concentration.

- The change from baseline to 48 weeks in plasma neurofilament light chain (NfL) concentration.
- The change from baseline to 48 weeks in plasma glial fibrillary acidic protein (GFAP) concentration.

7) The effects on olfactory function will be evaluated by:

- The change from baseline to 48 and 76 weeks in olfactory threshold score (as measured by OLFACT®, Osmic Enterprises, Inc.).
- The change from baseline to 48 and 76 weeks in olfactory identification score (as measured by OLFACT®, Osmic Enterprises, Inc.).
- The change from baseline to 48 and 76 weeks in olfactory memory score (as measured by OLFACT®, Osmic Enterprises, Inc.).
- The change from baseline to 48 and 76 weeks in olfactory assessment total score (as measured by OLFACT®, Osmic Enterprises, Inc.).

8) The effects on glucose and lipid metabolism, anthropometrics, liver fibrosis and fatty liver levels will be evaluated by:

- The change from baseline to 24, 48 and 76 weeks in glycated haemoglobin (HbA_{1c}).
- The change from baseline to 24, 48 and 76 weeks in fasting plasma glucose.
- The change from baseline to 48 and 76 weeks in 2-hour postprandial plasma glucose.
- The change from baseline to 48 and 76 weeks in fasting insulin.
- The change from baseline to 48 and 76 weeks in 2-hour postprandial insulin.
- The change from baseline to 48 and 76 weeks in fasting C-peptide.
- The change from baseline to 48 and 76 weeks in 2-hour postprandial C-peptide.
- The change from baseline to 48 and 76 weeks in pancreatic islet function (HOMA2-β) estimated from fasting C-peptide via HOMA2 Calculator (v2.2.3, http://www.dtu.ox.ac.uk/homacalculator/).
- The change from baseline to 48 and 76 weeks in insulin sensitivity (HOMA2-S) estimated from fasting C-peptide via HOMA2 Calculator (v2.2.3, http://www.dtu.ox.ac.uk/homacalculator/).
- The change from baseline to 48 and 76 weeks in insulin resistance indexes (HOMA2-IR) estimated from fasting C-peptide via HOMA2 Calculator (v2.2.3, http://www.dtu.ox.ac.uk/homacalculator/).
- The change from baseline to 24, 48 and 76 weeks in fasting serum triglyceride.
- The change from baseline to 24, 48 and 76 weeks in fasting total cholesterol.
- The change from baseline to 24, 48 and 76 weeks in fasting high-density lipoprotein-cholesterol.
- The change from baseline to 24, 48 and 76 weeks in fasting low-density lipoprotein-cholesterol.
- The change from baseline to 24, 48 and 76 weeks in visceral fat area measured by Inbody 720 analyser.
- The change from baseline to 24, 48 and 76 weeks in percent body fat measured by Inbody 720 analyser.
- The change from baseline to 24, 48 and 76 weeks in liver stiffness measurement quantified by FibroTouch® system.

- The change from baseline to 24, 48 and 76 weeks in liver fat controlled attenuation parameter quantified by FibroTouch® system.
- The change from baseline to 48 and 76 weeks in blood pressure as measured every 8 weeks.
- The change from baseline to 48 and 76 weeks in body weight as measured every 8 weeks.
- The change from baseline to 48 and 76 weeks in body mass index as measured every 8 weeks.
- The change from baseline to 48 and 76 weeks in waist circumference as measured every 8 weeks.
- The change from baseline to 48 and 76 weeks in hip circumference as measured every 8 weeks.
- The change from baseline to 48 and 76 weeks in waist to hip circumference ratio as measured every 8 weeks.

8.3. SAFETY OUTCOMES

The safety outcomes will include the occurrence of the following adverse events (AEs):

- Treatment-emergent adverse events (TEAEs)

A TEAE is defined as an event that first occurred or worsened in severity after baseline.

- Serious adverse events (SAEs)

A SAE is any AEs from this study that results in one of the following outcomes: death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, considered significant by the investigator for any other reason.

- AEs leading to study drug discontinuation
- AEs of interest
  - Allergic reaction
  - Injection site reaction
  - Gastrointestinal adverse events (abdominal pain, bloating, constipation, diarrhoea, nausea, vomiting, etc.)
  - Hypoglycemic events
  - Acute coronary syndrome
  - Stroke events
  - Urinary tract infection
  - Fractures

Hypoglycemic events

According to the classification criteria for hypoglycemia of the American Diabetes Association (ADA)/European Association of Diabetes (EASD) 2017 version, hypoglycemia is defined as follows:

- Warning level (Grade 1) of hypoglycemia with a plasma glucose concentration no higher than 70 mg/dL (3.9 mmol/L)

  - Symptomatic hypoglycemia: plasma glucose concentration not greater than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) with symptoms associated with hypoglycemia.
  - Asymptomatic hypoglycemia: a plasma glucose concentration no greater than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) without symptoms associated with hypoglycemia.
  - Unclassified hypoglycemia: plasma glucose concentration no higher than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) with no documented information on hypoglycemic symptoms.
- Clinically significant hypoglycemia (Grade 2) with a plasma glucose concentration no greater than 54 mg/dL (3.0 mmol/L)
  - Symptomatic hypoglycemia: a plasma glucose concentration of less than 54 mg/dL (3.0 mmol/L) accompanied by symptoms associated with hypoglycemia.
  - Asymptomatic hypoglycemia: plasma glucose concentration not greater than 54 mg/dL (3.0 mmol/L) without symptoms associated with hypoglycemia.
  - Unclassified hypoglycemia: plasma glucose concentration no higher than 54 mg/dL (3.0 mmol/L) with no documented information on hypoglycemic symptoms.
- Severe hypoglycemia (Grade 3).

9. STUDY ASSESSMENTS

9.1. SCREENING ASSESSMENTS

- **Demography**

  Subject demography information will be collected at the Screening Visit. Demography information includes age and date of birth, sex, education attainment, ethnicity, and history of tobacco and alcohol use.
- **Medical history**

  At the Screening Visit, assessments will be conducted to ensure that subjects do not have medical conditions which may interfere with study participation. Medical and surgical history, current antidiabetes medications and concomitant medications, medical conditions will be recorded at this Visit.
- **Physical examinations**

A complete physical examination will be performed at the Screening Visit. This physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. The following measurements will also be obtained and recorded: height, body weight, waist circumference, hip circumference, and blood

pressure. Weight and height will be used to calculate BMI according to the standard formula: BMI= weight/height^2 (kg/m^2).

- **Neuropsychological assessments for eligibility**

At the Screening and Baseline Visit, all subjects will be assessed for eligibility, using neuropsychological assessments to confirm that subjects meet the diagnostic criteria for MCI. These assessments will include the MoCA, MMSE, RBANS, TMT, Victoria Stroop Color-Word Test, Barthel index and FAQ. Subjects will also be evaluated on the Hospital Anxiety Depression Scale for eligibility. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for this visit.

Hospital Anxiety Depression Scale (HADS)

Anxiety and depression will be measured using the HADS (Chinese version). The HADS is a 14-item self-report questionnaire with seven questions assessing severity of each disorder-related symptom over the past week. Higher scores indicate more severe symptomology with a maximum possible score of 21 and a cut-off score of 8. Participants of whose score ≥8 on either subscale will be excluded [25,26].

Barthel Index

Barthel index will be measured to assess the Basic activities of daily living (BADL), which includes ten items assessing basic self-care abilities (transfer, bathing, toileting, dressing, feeding). The score ranges from 0 to 100, with higher scores indicating better function, and ≤ 60 points indicating a severe degree of dependence [27].

9.2. EFFICACY ASSESSMENTS

9.2.1. NEUROPSYCHOLOGICAL ASSESSMENTS

- **Mini-Mental State Examination (MMSE)**

The MMSE (Chinese version) (Zhang, 2003) is a cognitive instrument commonly used for dementia screening, but also often measured longitudinally in clinical studies. It is a 30-point scale with higher scores indicating less impairment and lower scores indicating more impairment. Seven items measuring orientation to time and place, registration, recall, attention, language and drawing will be assessed. Due to the significant association of education level with performance on the MMSE test, validated education-based cutoff scores are used for the MMSE test to define cognitive deficit: ≤20 for those with ≤6 years of formal education, and ≤24 for those with more than 6 years of education [28].

- **Montreal Cognitive Assessment (MoCA)**

The MoCA (Chinese version) is a screening instrument for MCI comprised of 30 items to assess multiple cognitive domains (memory recall, visuospatial abilities, executive

functions, attention, language, and orientation to time and place; scores range from 0 to 30, with higher scores indicating better cognitive function). Participants received one additional point if they had a MoCA score < 30 and 12 years or less of formal school education. Education-adjusted MoCA scores of ≥26 are taken to indicate normal cognition, whereas scores of 19-25 indicate MCI [29].

- **Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)**

The RBANS (Chinese version) is a brief neuropsychological screening battery with established test-retest reliability and age-appropriate normative data. The RBANS includes 12 sub-tests that generate five age-adjusted index scores and a total score. The five indices include immediate memory (consisting of list learning and story memory tests), visuospatial/constructional domain (consisting of figure copying and line orientation tests), language (consisting of picture naming and semantic fluency tests), attention (consisting of digit span and coding tests) and delayed memory (consisting of list recall, story recall, figure recall and list recognition tests). The total scores range from 40 to 160, with higher scores indicating better global cognitive function. Similarly, higher index scores reflect better cognitive subdomain function [30].

- **Trail Making Test (TMT)**

The TMT (Chinese version) is a validated timed measure of processing speed, which consists of part A and part B (TMT-A and TMT-B) [31]. The tests are conducted according to the standard administration procedure as described. Briefly, the TMT-A requires the patient to alternately switch between a set of Arabic digits (1-4) and a set of Chinese numerals (‘一’ through ‘四’), again linking them in ascending order (1/一/2/二…). The TMT-B is similar to the TMT-A, while TMT-B involves connecting an alternating sequence of 25 Arabic digits and Chinese numerals. During the tests, the subject is asked to connect the array of circles as fast as possible without lifting the pencil. The time limits for performing the TMT-A and TMT-B are 180 and 300 seconds, respectively. Processing speed is estimated by the sum of the consuming time to complete TMT-A and TMT-B such that less time indicate faster processing speed.

- **Victoria Stroop Color-Word**

The Victoria Stroop Color-Word Test is a well-known measure of executive function [32]. There are three indices including Stroop-dot, Stroop-word and Stroop-color word in the test. The color task consists of colored dots; the word task comprises ordinary words that are unrelated to the meaning of color; the color–word task consists of words written in color that indicate the meaning of the color, but the color of these words differs from the meaning of the word itself. The participants will be asked to quickly read the color of the dots or Chinese words on the cards. The sum of consuming time taken to read the three cards is used as an index of executive function performance.

Less time indicates better executive function.

- **Functional Activities Questionnaire (FAQ)**

The FAQ (Chinese version) is a standardized instrument for evaluating instrumental activities of daily living (IADL). It assesses a range of activities, such as meal preparation and financial management. The total score ranges from 0 to 30, with a higher score indicating greater functional impairment. A score of ≥5 is conventionally used as the cut-off point for defining functional dependence [33].

To ensure maximal data reliability and minimize assessment bias, all cognitive and functional evaluations, comprising the MMSE, MoCA, RBANS, Trail Making Test (Parts A and B), Victoria Stroop Color-Word Test, and FAQ, will be administered in a strictly predefined, fixed sequence to eliminate variability arising from task-order effects. Evaluations should be performed at approximately the same time of day (preferably in the morning) for each participant across all study visits. To mitigate performance degradation due to stress or fatigue, these assessments must be conducted prior to any invasive or stressful medical procedures (e.g., venipuncture). The Principal Investigator is responsible for ensuring that all raters have completed standardized training and certification. To minimize inter-rater variance, the same primary rater will evaluate the same participant throughout the study. Raters shall remain strictly blinded to treatment allocation, clinical management, and any reported Adverse Events (AEs) to prevent investigative bias. To guarantee source data integrity, a dual-verification scoring protocol will be implemented, wherein a second qualified investigator independently reviews and cross-checks every completed scale to confirm scoring accuracy prior to final data entry.

9.2.2. BRAIN MAGNETIC RESONANCE IMAGING SCAN

- **Magnetic resonance imaging (MRI) acquisition**

Participants will undergo MRI scanning using a Philips 3.0T scanner (Ingenia 3.0T, Philips Medical Systems, Eindhoven, The Netherlands) with a 32-channel head coil at the Department of Radiology, Nanjing Drum Tower Hospital. T1-weighted high-resolution anatomical data are collected with a 3D magnetization-prepared rapid acquisition gradient echo sequence and the following parameters: echo time (TE) = 3. 7 ms, repetition time (TR) = 8.1 ms, flip angle 8°, field of view (FOV) = 256 × 256 mm^2, voxel size = 1.0 × 1.0 × 1.0 mm^3. T2-weighted echo planar images (EPI) sequence is employed, employing the following precise parameters: TR = 2500 ms, TE = 330 ms, flip angle = 8°, FOV = 256× 256 mm^2, voxel size = 1 ×1 × 1 mm^3. T2-weighted fluid-attenuated inversion recovery (FLAIR) data are collected with a 20 fast spin-echo (FSE) sequence and the following parameters: TE = 247 ms, TR = 4800 ms, FOV = 240× 240 mm^2, voxel size = 1 ×1 × 1 mm^3. Diffusion tensor imaging data are

collected with a 20 spin-echo echo-planar diffusion-weighted sequence and the following parameters: TE=75 ms, TR= 3517 ms, 64 axial slices, acquired voxel-size of 8 mm^3, parallel imaging acceleration factor of 2, b = 1,000 s/mm^2 for 45 diffusion directions uniformly distributed in 3D space, 7 b=Os/mm^2 volumes. The fMRI data are collected by gradient-echo planar imaging sequence scans (TR = 2,000 ms; TE = 30 ms; FOV=192 mm × 192 mm; flip angle, 90°; voxel size, 3 mm × 3 mm × 4mm).

- **Odor-Induced fMRI Paradigm**

The odor-induced task fMRI and the olfactory function testing will be conducted on 2 consecutive days to reduce the interactions of these two measurements in olfactory-related brain regions. The entire paradigm (Fig. 1) consisted of 12 trials, and each trial included 30 s of odorless fresh air and 6 s of lavender odor stimulation. Four gradually increased concentrations of lavender odor, including weakest (0.032%), weak (0.10%), medium (0.32%), and strong (1.0%) concentrations, are provided to counteract brain habituation. Each concentration is repeated three times. The visual cues with a symbol "+" and the word "smell" are used during baseline and odor stimulation. Gray words on black background are set to minimize the effects of visual stimulation. Throughout the scan, the participants are required to maintain normal breathing and press a button using the right-hand thumb once the lavender scent was smelt. All respiratory amplitude and keystrokes are monitored and recorded.

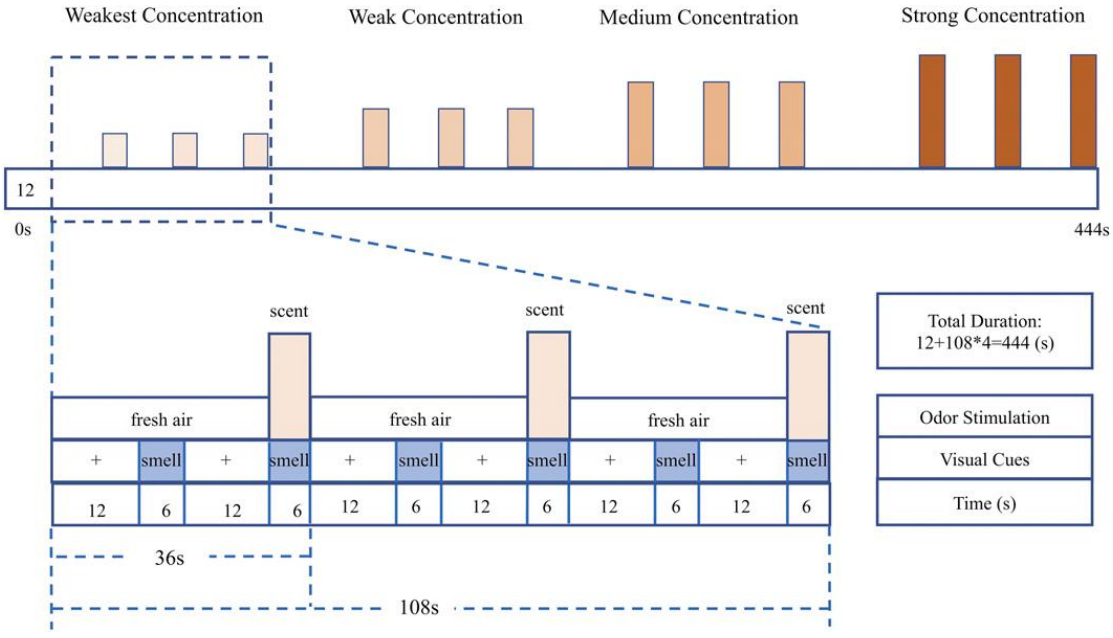

Figure 1—Odor-induced fMRI stimulation paradigm

- **MRI data Preprocessing**

All image analysts will be blinded to treatment group. An automated pipeline will be applied for preprocessing structural MRI scans, including correction of inhomogeneity

and extraction of the intracranial tissues using multiatlas skull stripping. Structural T1-weighted images will be processed using FreeSurfer software (version 8.1.0) to obtain comprehensive volumetric measures. The software will be used to calculate the intracranial volume (ICV), total gray matter volume, total white matter volume, and cerebrospinal fluid volume. Additionally, it will perform cortical parcellation and subcortical segmentation according to the Desikan-Killiany atlas to extract the volumes of 68 cortical and 14 subcortical regions [34]. Total brain volume (TBV) will be calculated as the sum of the total gray matter and white matter volumes.

The quantification of white matter lesions will be performed separately. WMH volume will be quantified using the Lesion Segmentation Toolbox (LST) within the Statistical Parametric Mapping software package (SPM 12.0, www.fil.ion.ucl.ac.uk/spm) [35]. This method will provide the total WMH volume for each subject.

DTI processing was performed in FSL 6.0 (https://fsl.fmrib.ox.ac.uk/fsl). The preprocessing steps included skull stripping, denoising, removing Gibbs artifact, EPI distortion correction, and eddy current correction. The b0 and b1000 images fit an ellipsoid model using DTIFIT in FSL. Then, all the generated results, including the fractional anisotropy (FA) map and mean diffusivity (MD) map, were normalized to the MNI space using linear registration. Color-coded FA maps in directions of the x-axis (right-left; Dxx), y-axis (anterior-posterior; Dyy), and z-axis (inferior-superior; Dzz) were generated, and spherical ROIs measuring 5 mm in diameter were placed in the projection and association areas at the level of the bilateral lateral ventricle body. The ALPS index is analyzed on DTI images using a method developed and validated by Taoka et al [36]. ALPS index = (mean (Dxxproj, Dxxassoc)) / (mean (Dyyproj, Dzzassoc)). The ALPS indices in the bilateral hemispheres were calculated, respectively, and the mean was used in further analyses. FW maps were constructed from preprocessed diffusion-weighted images using a regularized bi-tensor model and the open-source software package Diffusion Imaging in Python (also known as Dipy) algorithm (https://dipy.org/). PVSs were mapped from T2W images using an automated and highly reliable quantification method, following the pipeline of previous studies [37]. WM lesions (WMLs), which lead to a mis-segmented PVS mask, were excluded from the PVS mask to eliminate PVS mis-segmentation caused by WM hyperintensity. The PVS volume was measured in the WM, basal ganglia, hippocampus, and the sum of these structures (ALL). The PVS volume fraction (PVSVF) = PVS volume/TIV volume.

The preprocessing of task fMRI data was performed using Statistical Parametric Mapping 12.0, with the following stages: 1) The first six time points of each scan were excluded from the analysis to remove the initial transit signal fluctuations. 2) The

functional images were corrected for head movement. Six realignment parameters of head motion were also regressed out to control motion effects. 3) The T1-weighted high-resolution anatomical images were corecorded to themean functional image, segmented by using a unified segmentation algorithm, and spatially normalized to the Montreal Neurological Institute space template, in a spatial resolution of 1 mm × 1 mm × 1 mm. The time-course images were spatially normalized using the same normalization parameters with a spatial resolution of 3 mm × 3 mm × 3 mm. 4) Spatial smoothing was conducted with a Gaussian kernel of 8-mm full-width at half-maximum. 5) Low-frequency (0.01–0.08 Hz) fluctuations of the task fMRI signals were assessed to reflect spontaneous neuronal activity.

The preprocessing of resting-state fMRI was performed using Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI_V6.1), with the following stages: 1) the first 10 time points were automatically deleted to make the signal steady state; 2) slice-timing correction and motion correction were performed; 3) resting-state fMRI was registered to the Montreal Neurological Institute space template via each participant's T1-weighted high-resolution anatomical images and spatially normalized using the same normalization parameters with a spatial resolution of 3 mm × 3 mm × 3 mm; 4) spatial smoothing was conducted with fullwidth at half-maximum; 5) linear detrending and temporal band-pass filtering (0.01–0.08 Hz) were performed to eliminate high-frequency noise and low-frequency drift; and 6) simple regression with the residual head motions, white matter signal, and cerebrospinal fluid signal were used as the covariant for temporal nuisance correction.

9.2.3. BLOOD-BASED BIOMARKERS FOR NEURODEGENERATION

Plasma concentrations of neurodegenerative biomarkers will be measured using the following single-molecule array (SIMOA) kits from Quanterix in the central laboratory:

- Neurology 4-plex E Kit: for Aβ40, Aβ42, NfL and GFAP.
- p-Tau181 Advantage PLUS Kit: for p-tau181.
- ALZpath p-Tau217 Advantage PLUS Kit: for p-tau217.

9.2.4. APOLIPOPROTEIN E (APOE) GENOTYPING

APOE genotypes (ε2/ε3/ε4) will be determined by amplicon sequencing of two single-nucleotide polymorphisms in exon 4 (rs429358and rs7412). Briefly, genomic DNA will be extracted from whole blood using the DNA Extraction Kit for Blood (MyGenostics, Beijing, China). Libraries will be prepared via a two-step PCR, with purification steps using Pure Beads (MyGenostics, Beijing, China). The final libraries will be sequenced on an Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA). Sequencing reads will be aligned to the reference genome (hg19) using BWA, and genotypes at the two key sites will be called to assign the APOE alleles.

9.2.5. OLFACTORY FUNCTION TESTING

Olfactory Function Assessment by Computerized Testing (OLFACT®, Osmic Enterprises, Inc.) will be administered to assess olfactory threshold, identification, and memory. The olfactory threshold test (score range, 1-14) will be a forced-choice paradigm based on serial dilutions of N-butanol solutions. The olfactory identification (score 0–30) and memory (score 0–20) subtests consisted of two sequential phases will be separated by a 10-min interval. During task A, participants will be performed forced-choice identification of 10 distinct odors. In task B, they will be presented with 20 odors (10 from task A and 10 novel distractors) and required to complete two tasks per odor: identify the odor, then classify it as 'old' or 'new' (relative to task A).
The olfactory identification score is defined as the sum of the scores from Task A and the identification component of Task B (score range: 0–30). The olfactory memory score is derived solely from the memory component of Task B (score range: 0–20). The global olfactory function is represented by the total score, calculated as the sum of the olfactory threshold, identification, and memory scores (score range: 0–64), with higher scores indicating better performance [38,39].

9.2.6. BODY COMPOSITION ANALYSIS AND LIVER TRANSIENT ELASTOGRAPHY MEASUREMENT

Body composition, which includes PBF and VFA, will be assessed using bioelectrical impedance analysis with InBody 720 Body Composition analyzer (InBody Co., Ltd., Seoul, Korea). It will be evaluated in the morning before eating or drinking by trained and certified physicians. Participants will be asked to stand with their feet touching and both hands grabbing the electrodes. When they stand with their legs slightly apart and both arms raised 45° away from the body, InBody will perform multi-frequency measurements and check the impedance of each segment, including the trunk and four limbs. The results provided appendicular skeletal muscle mass, body fat mass, and VFA.

Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) will be obtained from transient elastography (FibroTouch®, Hisky Medical Technology, Wuxi, China) by trained and certified physicians according to the operations manual. LSM analyses are expressed in kilopascals (kPa) and CAP is expressed in decibels per meter (dB/m). Only if 10 successful measurements are obtained, an IQR/M ratio of LSM and FAP <30% and a success rate of > 60% will be considered reliable and then used for analysis.

9.2.7. LABORATORY TEST

HbA_{1c}, fasting plasma glucose, insulin, C-peptide, serum triglyceride, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol will be analyzed in the local laboratory using fasting blood samples after a 12-hour overnight fast. Blood samples will be also collected after a standard 100g steamed-bread meal

tolerance test to detect 2-hour postprandial plasma glucose, insulin and C-peptide levels. Pancreatic islet function (HOMA2-β), insulin sensitivity (HOMA2-S), and insulin resistance indexes (HOMA2-IR) will be estimated by updated homeostasis model assessment (HOMA2) from fasting plasma glucose and C peptide using the HOMA2 Calculator (v2 .2.3, http://www.dtu.ox.ac.uk/homacalculator/).

9.2.8. ANTHROPOMETRIC MEASUREMENT

- **Body weight and BMI**

  The subjects will be required to fasten, after urination and take off their coat during each measurement. The same subject used the same weight scale each time and avoided strenuous exercise before measurement.

  Weight and height will be used to calculate BMI according to the standard formula: BMI= weight/height^2 (kg/m^2).

- **Waist circumference**
  - standing position, relaxed shoulders and abdomen, smooth breathing, feet 25-30cm apart;
  - The horizontal position of measurement: the midpoint of the line between the anterior superior iliac spine and the inferior margin of the 12th costal line on the midaxillary line;
  - Use a tape ruler around the abdomen in the above-mentioned horizontal position, with the tape ruler closely adhering to the skin, but not strangling the skin;
  - The measurement should not be made consciously with the abdomen closed or lifted, and should be taken at the calm end of expiration, with the waist circumference in cm to the nearest mm (e.g., 69.3 cm).
- **Hip circumference**
  - The subject stands naturally, with shoulders relaxed, arms naturally drooping and moderately open, legs together, legs evenly loaded, hips relaxed, and eyes ahead;
  - Horizontal positions measured: symphysis pubis anteriorly and greater trochanter of femur posteriorly;
  - Generally equivalent to the most protruding part of the buttock;
  - Circle the buttocks horizontally with a tape ruler and record the values in cm to the nearest mm (e.g. 89.3 cm).
- **Blood pressure**

  An electronic sphygmomanometer will be required for blood pressure measurement. At the screening visit, blood pressure will be measured in both arms. If the difference in systolic or diastolic blood pressure is greater than 10 mmHg, the arm with the higher blood pressure measured at the screening visit must be used

for blood pressure measurements at subsequent visits.

Blood pressure measurements must be performed continuously throughout the study, only on the same arm for each visit, and the arm used for the measurement will be recorded. These measurements should be performed at least 10 hours apart after ingestion of caffeine, alcohol, or nicotine. Subjects should rest for at least 5 minutes prior to measurement. For sitting blood pressure measurements, subjects should have their arms on a table with back support and feet on the floor.

It is required to repeat the measurement twice, and the blood pressure shall be measured again after 2 minutes after the end of the first blood pressure measurement. The mean blood pressure is calculated according to the two measurements. If the difference between the two measurements of diastolic or systolic blood pressure is greater than 5 mmHg, the third blood pressure measurement should be performed, and the mean value of the three readings should be recorded and recorded in the original medical record.

10. STUDY PROCEDURE

10.1. TABLE SUMMARISING PATIENT FOLLOW-UP

Procedures/ Assessments	**Screening -2 to -1 week**	**Baseline -1 week to day 0**	**Treatment (Day 0 to 48 Weeks)**						
Visit	**1**	**2**	**3 week 4 ±2 days**	**4 week 8 ±3 days**	**5 week 16 ±3 days**	**6 week 24 ±3 days**	**7 week 32 ±3 days**	**8 week 40 ±3 days**	**9 week 48 ±7 days**
Screening/ Administrative									
Informed Consent	×								
Eligibility Criteria	×	×							
Randomization [a]		×							
Demographics	×								
Medical History	×								

Physical examination [b]	×	×	×	×	×	×	×	×	×
Laboratory Assessments									
Glycated hemoglobin	×					×			×
Liver function tests		×	×			×			×
Renal function tests		×	×			×			×
Fasting plasma glucose		×				×			×
2hr-postprandial plasma glucose		×							×
Fasting lipid profiles		×				×			×
Fasting and 2hr-postprandial insulin		×							×
Fasting and 2hr-postprandial C-peptide		×							×
Plasma neurodegenerative biomarkers [c]		×							×
Cognitive Assessments									

MMSE	×								×
MoCA	×					×			×
RBANS		×							×
Trial making test		×							×
Stroop color-word test		×							×
Functional Outcome Measures									
Barthel index	×								×
FAQ		×							×
Instrumental evaluations									
Structural MRI		×							×
Functional MRI		×							×
Olfactory function measurement [d]		×							×

Body composition analysis [e]		×				×			×
Liver ultrasound transient elastography [f]		×				×			×
Ongoing Subject Review									
Concomitant therapy	×	×	×	×	×	×	×	×	×
Adverse events			×	×	×	×	×	×	×

AD, Alzheimer disease; FAQ, Functional Activities Questionnaire; HbA1c, Glycated hemoglobin A1c; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, functional magnetic resonance imaging; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

10.2. SCREENING VISIT V1 (-2 to -1 WEEK)

Patient screening and selection will be conducted by endocrinologists qualified in neuropsychological assessment during routine follow-up consultations at the participating centers. The investigating endocrinologist will perform the following evaluations to verify the study's inclusion and exclusion criteria:

- Collect demographic data (age, gender, education, etc.).
- Record medical history, comorbidities, and all concomitant treatments, with specific attention to the current glucose-lowering regime.
- Document the presence or absence of subjective cognitive complaints as reported by the patient or an informant.
- Perform a comprehensive neurological and physical examination.
- Conduct a brief cognitive screening for cognitive impairment using the MoCA and MMSE, alongside an assessment of functional status using the Barthel Index. Suspected dementia is defined as MMSE score ≤20 if education 0–6 years, or MMSE score ≤24 if education >6 years, and will be excluded. Patients will be included if Barthel Index score is 60 or greater.
- Evaluate anxiety and depression symptoms using the HADS. Participants of whose score ≥8 on either subscale will be excluded.
- Assess glycemic control based on HbA_{1c} level.

Following the eligibility assessment, the endocrinologist will provide detailed information regarding the study's objectives, procedures, foreseeable risks, and potential benefits, addressing any patient questions. The physician will also explain patient rights in biomedical research and provide a copy of the informed consent form. Patients will then be granted a reflection period to consider their participation decision.

If, after this period, the patient decides to participate, the investigator will be responsible for obtaining written informed consent from the patient. The consent form must be signed before any clinical or paraclinical examination necessary for the study is performed. For patients agreeing to participate, the patient and the investigator will sign the consent form, on which they will clearly mark their full names. The various copies of the patient information and informed consent form will then be distributed as follows:

- A copy of the patient information and a signed informed consent form will be given to the patient.

- The original will be kept by the investigator, in a safe place inaccessible to third parties.

10.3. BASELINE EVALUATION AND RANDOMIZATION VISIT V2 (-1 WEEK to DAY 0)

The V2 visit will be conducted at the clinical investigation centers or endocrinology department of one of the participating centers within the window of 1 week prior to the intervention period. Patients will be evaluated at baseline, before the administration of study treatments.

The V2 visit will include the following evaluations:

- The patient will be further reassessed against inclusion and exclusion criteria for eligibility to participate in the study.
- A blood sample will be collected in the fasting state for laboratory testing:
- Haematology: red and white blood count, platelets.
- Serum chemistry: total bilirubin, gamma-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine phosphatase (ALT), creatinine, uric acid, estimated glomerular filtration rate, fasting blood glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol.
- Calcitonin testing.
- Thyroid function testing: thyroid-stimulating hormone.
- Vitamin B12 testing.
- Fasting insulin and C-peptide levels.
- APOE genotype and blood-based biomarkers for neurodegeneration.
- Additionally, a blood sample will be collected following a standard 100g steamed-bread meal tolerance test to detect 2-hour postprandial plasma glucose, insulin and C-peptide levels.
- Urinalysis
- Medical, surgical and neurological history and concomitant disease including patient's allergy medical history and patient's cardiovascular and cerebrovascular history (e.g., habits of smoking and alcohol consumption, etc.) will be recorded.
- All concomitant medications (glucose-lowering therapy and others) will be recorded.
- A neurological and physical examination will be performed with measurements of height, weight, blood pressure, heart rate, waist and hip circumference.
- RBANS, TMT and Victoria Stroop Color-Word will be carried out to assess various cognitive subdomain function.
- FAQ will be performed for evaluating instrumental activities of daily living.
- Pittsburgh Sleep Quality Index (PSQI) will be used to evaluate sleep quality.
- Body composition analysis and liver transient elastography measurement will be performed.
- Olfactory function measurement.
- Structural and functional MRI.

Note: To prevent interference between the olfactory function tests and the odorant stimuli used during the olfactory task-based fMRI, the assessments are scheduled on separate days within the designated assessment window. This separation mitigates the risk of cross-interference biasing the results of either the olfactory performance

measures or the functional brain activation patterns. All clinical assessments, laboratory tests, and cognitive and olfactory function testing will be completed on one day, and the fMRI scan will be conducted on a different day within this window.

Once the assessments are completed, patients will then be randomized in one of the three groups of the study.
In the event that abnormal or non-evaluable values are identified for laboratory parameters used in the eligibility criteria at the baseline visit (V2), the following procedure will apply:
The investigator will determine if the abnormality requires clinical intervention. If necessary, appropriate measures will be taken to address the condition. Following a sufficient period to allow for the stabilization or correction of the value, a single repeat test may be performed. This repeat test may be conducted at a local laboratory for the convenience of the patient, and no additional hospital visit will be required.

- If the results of the repeat test confirm that the values now meet all eligibility criteria, the patient may proceed with the randomization process.
- If the repeat test continues to show abnormal or non-evaluable values that do not meet the eligibility criteria, the patient will be considered a screen failure and will not be enrolled in the study.

Based on randomization, patients will be assigned to one of the following three treatment groups: liraglutide, empagliflozin, or linagliptin. Patients randomized to the liraglutide group will receive comprehensive training on the correct use of the self-injection pen. Under the supervision of the investigator or a medically qualified designee, each patient will be asked to demonstrate the injection technique on-site. The first dose may be administered during the baseline/randomization visit with assistance from the study nurse. Patients assigned to the oral medication groups (empagliflozin or linagliptin) will receive standardized verbal and written instructions on the proper administration of their assigned study drug.
All patients, regardless of treatment group, will be provided with a treatment diary and instructed on how to accurately record daily medication intake. This diary will be used to monitor and support adherence to the study treatment throughout the trial period.

10.4. FOLLOW-UP VISIT V3 (WEEK 4 ± 2 DAYs)

The V3 visit will be conducted after 4 weeks of treatment with the assigned study drug (liraglutide, empagliflozin, or linagliptin). The objectives of this visit are as follows:

- Safety evaluation: Blood routine examination, liver and renal function tests, along with urinalysis, will be performed. The investigator will review the results and determine if any abnormal values require clinical intervention.
- Glycemic monitoring: Capillary blood glucose will be measured. If a significantly abnormal value is detected, an additional venous blood sample will be drawn for confirmatory plasma glucose testing.
- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.

- Concomitant medications: All concomitant medications taken since the last visit will be documented.
- Adverse events: All AEs occurring since the last visit will be recorded.
- Treatment compliance and dispensing: Treatment compliance will be assessed using the patient diary, and a study drug accountability check will be performed. The subsequent 4-week supply of the study drug will be dispensed to the patient.

10.5. FOLLOW-UP VISIT V4 (WEEK 8 ± 3 DAYs)

The V4 visit will be conducted after 8 weeks of treatment with the assigned study drug (liraglutide, empagliflozin, or linagliptin). The objectives of this visit are as follows:

- Glycemic monitoring: Capillary blood glucose will be measured. If a significantly abnormal value is detected, an additional venous blood sample will be drawn for confirmatory plasma glucose testing.
- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.
- Concomitant medications: All concomitant medications taken since the last visit will be documented.
- Adverse events: All AEs occurring since the last visit will be recorded.
- Treatment compliance and dispensing: Treatment compliance will be assessed using the patient diary, and a study drug accountability check will be performed. The subsequent 8-week supply of the study drug will be dispensed to the patient.

At the end of V4 visit, patients assigned to the liraglutide group will receive the study treatment for the next 8 weeks at the dosage of 1.8 mg/day if the treatment is well tolerated. In case of intolerance to treatment (AE such as nausea, vomiting, etc.), the dose may be maintained at 1.2 mg / day until the end of the study (at the choice of the investigator).

10.6. FOLLOW-UP VISIT V5 (WEEK 16 ± 3 DAYs)

The V5 visit will be conducted after 16 weeks of treatment with the assigned study drug (liraglutide, empagliflozin, or linagliptin). The objectives of this visit are as follows:

- Glycemic monitoring: Capillary blood glucose will be measured. If a significantly abnormal value is detected, an additional venous blood sample will be drawn for confirmatory plasma glucose testing.
- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.
- Concomitant medications: All concomitant medications taken since the last visit

will be documented.

- Adverse events: All AEs occurring since the last visit will be recorded.
- Treatment compliance and dispensing: Treatment compliance will be assessed using the patient diary, and a study drug accountability check will be performed. The subsequent 8-week supply of the study drug will be dispensed to the patient.

10.7. FOLLOW-UP VISIT V6 (WEEK 24 ± 3 DAYs)

The V6 visit will occur on Week 24. This visit will include the following evaluations:

- At the beginning of this visit, a blood sample will be collected in the fasting state for blood routine examination, HbA_{1c} and serum chemistry analyses.
- Patients will then be assessed for vital signs and physical examination (body weight, blood pressure, heart rate, waist and hip circumference), concomitant medications, and AEs.
- Body composition analysis and liver transient elastography measurement will be performed.
- A cognitive assessment will be carried out with MoCA (additional version 7.2).
- Treatment compliance will be assessed (diary), study drug accountability will be performed and unused treatments will be collected. At the end of V6, patients will receive the study treatment for the next 8 weeks (until V7 on Week 32).

10.8. FOLLOW-UP VISIT V7 (WEEK 32 ± 3 DAYs)

The V7 visit will occur on Week 32. This visit will include the following evaluations:

- Glycemic monitoring: Capillary blood glucose will be measured. If a significantly abnormal value is detected, an additional venous blood sample will be drawn for confirmatory plasma glucose testing.
- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.
- Concomitant medications: All concomitant medications taken since the last visit will be documented.
- Adverse events: All AEs occurring since the last visit will be recorded.
- Treatment compliance and dispensing: Treatment compliance will be assessed using the patient diary, and a study drug accountability check will be performed. The subsequent 8-week supply of the study drug will be dispensed to the patient.

10.9. FOLLOW-UP VISIT V8 (WEEK 40 ± 3 DAYs)

The V7 visit will occur on Week 40. This visit will include the following evaluations:

- Glycemic monitoring: Capillary blood glucose will be measured. If a significantly

abnormal value is detected, an additional venous blood sample will be drawn for confirmatory plasma glucose testing.

- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.
- Concomitant medications: All concomitant medications taken since the last visit will be documented.
- Adverse events: All AEs occurring since the last visit will be recorded.
- Treatment compliance and dispensing: Treatment compliance will be assessed using the patient diary, and a study drug accountability check will be performed. The subsequent 8-week supply of the study drug will be dispensed to the patient.

10.10. FOLLOW-UP VISIT V9 (WEEK 48 ± 7 DAYs)

The V9 visit will occur on Week 48. Patients will undergo a similar assessment as the visit 2:

- A blood sample will be collected in the fasting state for laboratory testing:

- Haematology: red and white blood count, platelets.

- HbA_{1c} level.

- Serum chemistry: total bilirubin, gamma-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine phosphatase (ALT), creatinine, uric acid, estimated glomerular filtration rate, fasting blood glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol.

- Fasting insulin and C-peptide levels.

- Blood-based biomarkers for neurodegeneration.

- Additionally, a blood sample will be collected following a standard 100g steamed-bread meal tolerance test to detect 2-hour postprandial plasma glucose, insulin and C-peptide levels.
- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.
- Concomitant medications: All concomitant medications taken since the last visit will be documented.
- MMSE, MoCA (additional version 7.3), RBANS, TMT and Victoria Stroop Color-Word will be carried out to assess general cognition and various cognitive subdomain function.
- Barthel Index and FAQ will be performed for evaluating basic and instrumental

activities of daily living, respectively.

- PSQI will be used to evaluate sleep quality.
- Body composition analysis and liver transient elastography measurement will be performed.
- Olfactory function measurement.
- Structural and functional MRI.

Note: To prevent interference between the olfactory function tests and the odorant stimuli used during the olfactory task-based fMRI, the assessments are scheduled on separate days within the designated assessment window. This separation mitigates the risk of cross-interference biasing the results of either the olfactory performance measures or the functional brain activation patterns. All clinical assessments, laboratory tests, and cognitive and olfactory function testing will be completed on one day, and the fMRI scan will be conducted on a different day within this window.

This visit (V9) marks the conclusion of the core study period. Upon completion of all V9 procedures, eligible patients will be offered the option to enroll in an additional 28-week extension phase.

Patients who provide informed consent for the extension phase will continue to receive the same study treatment (liraglutide, empagliflozin, or linagliptin) to which they were originally randomized during the core period. No re-randomization will occur.

10.11. EXTENSION PHASE FOLLOW-UP VISITS

For patients who enter the extension phase, follow-up visits will continue after V9, scheduled as follows: V10 (Week 56 ± 3 Days), V11 (Week 64 ± 3 Days), and a final follow-up visit V12 at Week 76 ± 7 Days.

The V10 and V11 visits will include the same evaluations as performed during routine follow-up visits, comprising glycemic monitoring, physical examination, documentation of concomitant medications, recording of AEs, assessment of treatment compliance, and dispensing of the study drugs.

As the final study visit (V12), a complete re-assessment will be conducted, encompassing the following evaluations:

- A blood sample will be collected in the fasting state for laboratory testing
- Haematology: red and white blood count, platelets.
- HbA_{1c} level.

- Serum chemistry: total bilirubin, gamma-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine phosphatase (ALT), creatinine, uric acid, estimated glomerular filtration rate, fasting blood glucose, triglycerides, total cholesterol, high-

density lipoprotein cholesterol and low-density lipoprotein cholesterol.

- Fasting insulin and C-peptide levels.

- Additionally, a blood sample will be collected following a standard 100g steamed-bread meal tolerance test to detect 2-hour postprandial plasma glucose, insulin and C-peptide levels.
- Physical examination: A physical examination will be conducted, including measurements of body weight, blood pressure, heart rate, and waist and hip circumference.
- Concomitant medications: All concomitant medications taken since the last visit will be documented.
- MMSE, MoCA (version 7.1), RBANS, TMT and Victoria Stroop Color-Word will be carried out to assess general cognition and various cognitive subdomain function.
- Barthel Index and FAQ will be performed for evaluating basic and instrumental activities of daily living, respectively.
- PSQI will be used to evaluate sleep quality.
- Body composition analysis and liver transient elastography measurement will be performed.
- Olfactory function measurement.
- Structural and Resting-state functional MRI.

The evaluation schedule is provided in the flow chart (see table in section 10.1)
At the end of this visit, the patients will have completed the study.

10.12. DISCONTINUATIONS AND WITHDRAWALS

- **Discontinuation of Study Intervention**
  The study medication may be permanently discontinued for a participant for any of the following reasons:

- By request of the participant or participant's designee (eg. legal guardian)
- Occurrence of severe or recurrent hypoglycemia (defined as symptomatic episodes requiring assistance, occurring more than twice per week).
- Uncontrolled hyperglycemia (fasting capillary or venous blood glucose >13.3 mmol/L) despite additional therapeutic measures.
- Occurrence of any medical condition meeting the protocol-defined criteria for treatment discontinuation.
- Occurrence of a Serious Adverse Event (SAE), significant laboratory abnormality, or other intercurrent illness (e.g., acute cardiovascular event) that, in the investigator's judgment, warrants discontinuation.

- Pregnancy, planned pregnancy, or lactation.
- Requirement for a concomitant medication prohibited by the protocol.
- Participation in another interventional clinical trial or any medical research deemed incompatible with this study.
- Repeated poor adherence to the treatment plan.
- Decision by the investigator or sponsor for medical, safety, or regulatory reasons consistent with Good Clinical Practice (GCP).

Premature discontinuation of the trial treatment has to be notified to the coordinating investigator. The reason for and the date of end of trial treatment have to be documented. Any patient who stops the trial treatment has to be cared for as best as possible according his/her health status and medical knowledge. If a participant discontinues the study treatment but agrees to continue study visits and assessments, they should continue to be followed as outlined in the study plan.

- **Withdrawal from The Study**

A participant will be considered withdrawn from the study if they no longer wish to participate in any study-related procedures (including follow-up visits). It is the participant's right to withdraw at any time without providing a reason. Every effort should be made to schedule a final study visit (Early Termination Visit) for participants who withdraw, to collect data on the primary outcome variable and perform safety assessments, provided they consent. The coordinating investigator must be notified promptly of any withdrawal. The reason for withdrawal (if given) and the date of withdrawal must be documented in the source documents and the case report form (CRF). All withdrawn participants will continue to receive appropriate medical care as required by their health status.

11. MANAGEMENT OF ADVERSE EVENTS

11.1. DEFINITIONS

- **Adverse events (AEs)**

Any harmful event occurring in a person taking part in a research study, whether or not that event is linked to the study or to the product being investigated in the study.

- **Treatment-emergent adverse events (TEAEs)**

A TEAE is defined as any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

- **Serious adverse events (SAEs)**

A SAE is any TEAEs from this study that results in one of the following outcomes: death, initial or prolonged inpatient hospitalization, a life-threatening experience (that is, immediate risk of dying), persistent or significant disability/incapacity, congenital anomaly/birth defect, considered significant by the investigator for any other reason.

- **AEs leading to study drug discontinuation**
- **AEs of interest**

- Allergic reaction
- Injection site reaction
- Gastrointestinal adverse events (abdominal pain, bloating, constipation, diarrhoea, nausea, vomiting, etc.)
- Hypoglycemic events
- Acute coronary syndrome
- Stroke events
- Urinary tract infection
- Fractures

- **Hypoglycemic events**

According to the classification criteria for hypoglycemia of the American Diabetes Association (ADA)/European Association of Diabetes (EASD) 2017 version, hypoglycemia is defined as follows:

- Warning level (Grade 1) of hypoglycemia with a plasma glucose concentration no higher than 70 mg/dL (3.9 mmol/L)
  - Symptomatic hypoglycemia: plasma glucose concentration not greater than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) with symptoms associated with hypoglycemia.
  - Asymptomatic hypoglycemia: a plasma glucose concentration no greater than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) without symptoms associated with hypoglycemia.
  - Unclassified hypoglycemia: plasma glucose concentration no higher than 70 mg/dL (3.9 mmol/L) but greater than or equal to 54 mg/dL (3.0 mmol/L) with no documented information on hypoglycemic symptoms.
- Clinically significant hypoglycemia (Grade 2) with a plasma glucose concentration no greater than 54 mg/dL (3.0 mmol/L)
  - Symptomatic hypoglycemia: a plasma glucose concentration of less than 54 mg/dL (3.0 mmol/L) accompanied by symptoms associated with hypoglycemia.
  - Asymptomatic hypoglycemia: plasma glucose concentration not greater than 54 mg/dL (3.0 mmol/L) without symptoms associated with hypoglycemia.
  - Unclassified hypoglycemia: plasma glucose concentration no higher than 54 mg/dL (3.0 mmol/L) with no documented information on hypoglycemic symptoms.
- Severe hypoglycemia (Grade 3).

11.2. ACTIONS TO BE TAKEN IN THE CASE OF ADVERSE EVENTS

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study. All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. Each adverse event will be detailed concerning its duration, intensity, actions taken, and outcomes. The investigator must evaluate the causal relationship between the study drugs and the adverse event. If the adverse event is not related to the study, the investigator must determine the alternative causality (diabetes, concomitant treatment, other disease, et.). To ensure participants' safety, all serious adverse events will be promptly reported to the chief investigator, data monitoring and ethics committee within 24 hours and processed in a timely manner. Any serious adverse event that is ongoing when the subject completes or discontinues the study will be followed by the investigator until the event has resolved, stabilized, or returned to baseline status.

12. TRIAL OVERSIGHT

The chief investigator holds overall responsibility for the conduct of the trial, while the trial management group is responsible for the day-to-day oversight of the trial.

The trial scientific committee, comprised of independent clinicians and an independent statistician, acts as the oversight body for the trial on behalf of the sponsor. This committee will take responsibility for monitoring and guiding overall progress, scientific standards and operational delivery, ensuring the protection of participants' rights and safety throughout the trial. The scientific committee will meet at least four times a year to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The scientific committee will be blinded to subject treatment assignments during the trial.

An independent data and safety monitoring board (DSMB) will be established and composed of at least three members: an endocrinologist, a statistician and a vigilance specialist, independent from the study scientific team. The objective of the DSMB is to review safety and progress toward completion of study. The DSMB charter, outlining membership, terms of reference, roles, responsibilities, authority, decision-making processes and interactions (including the timing of meetings, methods of providing information to and from the board, frequency and format of meetings, statistical issues and relationships with other committees) for this trial is established, reviewed and approved prior to the inaugural committee meeting. Adverse events and serious adverse events will be reviewed by DSMB to determine the cause of these events and take any

necessary measures to ensure participant safety. Following each meeting, the DSMB will provide the study team with information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing or terminating the trial. The DSMB will provide a summary of the committee findings to the sponsor and coordinating investigator.

13. STATISTICAL ANALYSIS

13.1. SAMPLE SIZE CALCULATION

This superiority trial is powered for two independent primary comparisons (liraglutide vs. linagliptin and empagliflozin vs. linagliptin), each tested at two-sided α=0.05 without multiplicity adjustment. Based on our pilot data, we assumed 48-week MCI Reversion rates of 50% (liraglutide), and 30% (empagliflozin). Previous studies of DPP-4 inhibitors have shown neutral effect on cognitive function but the reversion rates from MCI to normal cognition is estimated to be approximately 10% to 15% in clinic-based studies, and therefore its MCI Reversion rates is assumed to be 15% in our study [40,41]. These assumptions yielded absolute differences of 35% (liraglutide vs linagliptin) and 15% (empagliflozin vs linagliptin). Using PASS 15.0 (NCSS, Kaysville, UT; www.ncss.com/software/pass) with 80% power and 1:1:1 allocation, the required sample sizes were 25 per group for liraglutide and 118 per group for empagliflozin comparisons. To ensure adequate power for both pre-specified tests, we selected the larger sample size (118 per group), ultimately enrolling 132 per arm (total N=396) after accounting for 10% attrition.

13.2. ANALYSIS POPULATIONS

Three study populations will be considered in the analysis as follows:

- Intent-to-Treat (ITT) population
  ITT population will consist of all randomized patients and analyzed according to their allocated treatment group, regardless of adherence, treatment discontinuation, protocol deviations or use of rescue medication.
- Per protocol (PP) population
  PP population will include only those patients who completed the study according to the protocol and reached all primary endpoints without major deviations. Patients with a treatment compliance rate of <50% will be defined as intervention deviation and excluded from the PP population.
- Safety population
  Safety population will include all patients who received at least one dose of study

medication and will be used for safety analysis.

13.3. DESCRIPTIVE STATISTICAL METHODS

Descriptive statistics of demographic data and baseline characteristics will be summarized by treatment group in the ITT population. Continuous outcomes will be summarized by treatment arm using number of subjects, mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum, as appropriate. Categorical variables will be summarized as counts and percent.

13.4. HANDLING OF MISSING DATA

Missing baseline covariates will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions. Missing data for the primary outcome and secondary outcomes will be handled using Multiple Imputation by Chained Equations (MICE), under a missing at random (MAR) assumption. The imputation will be performed in the ITT population before the primary and secondary outcome analyses.

13.5. PRIMARY OUTCOME ANALYSIS

The primary outcome is a binary outcome: MCI Reversion at 48 weeks of treatment and will be summarized using number (%) of patients achieving Reversion by treatment group. Two independent primary comparisons (liraglutide vs linagliptin; empagliflozin vs linagliptin) are prespecified and each will be tested at two-sided $\alpha = 0.05$. The primary analysis will be performed in the ITT population. The primary analysis will use a generalized estimating equation (GEE) model with Poisson distribution and log link function, treating group as a categorical variable (linagliptin as reference) and center as a cluster effects. If the GEE model dose not converge, the alternative models will be fitted until convergence is achieved. Additional supportive analysis on a PP basis will be carried out to examine the conclusions' robustness to different assumptions about departures from the randomization procedure.

13.6. SECONDARY OUTCOME ANALYSIS

All secondary outcomes will be analyzed for superiority test, differences in outcomes (liraglutide vs linagliptin, empagliflozin vs linagliptin) will be reported. Secondary outcome analyses will be based on the ITT population. Multiplicity adjustment will not be performed. Binary secondary outcomes will be summarized as number (%) of patients and analyzed using the GEE with Poisson distribution and log link function, treating group as a categorical variable (linagliptin as reference) and center as a cluster effect, with exchangeable covariance structure. Continuous outcomes will be summarized by treatment arm using number of subjects, mean (SD), median (IQR), minimum and maximum, as appropriate. Single measurement outcomes will be

analyzed using GEE model with Gaussian distribution and identity link function, treating group as a categorical variable (linagliptin as reference), center as a cluster effect, and baseline value of the outcome as covariates. For repeatedly measured continuous outcomes, linear mixed model will be used with treatment, visit, interaction between treatment and visit, center and subject as random effects, and baseline value of the given outcome as a covariate.

13.7. ANALYSIS OF FUNCTIONAL NEUROIMAGING OUTCOMES

A multi-stage generalized linear model strategy will be employed for neuroimaging outcomes, where first level individual analysis quantifies individual-level brain activation and second-level analysis measures group-wise differences. A flexible factorial design will be employed to compare brain activation between each active treatment group (liraglutide and empagliflozin) and the active comparator group (linagliptin). This neuroimaging-specific analytical strategy is selected to appropriately address the high dimensionality, spatial-temporal auto-correlation, and multiple comparison burden inherent to functional imaging data, which are not adequately handled by GEE-based approaches used for clinical endpoints.

13.8. SAFETY ANALYSIS

Safety analyses will be performed in the safety population according to the actual treatment group. AEs will be summarized as counts and percentage by treatment group. Treatment group comparison will be assessed using a Chi-square or Fisher's exact tests.

13.9. STATISTICAL ANALYSIS PLAN

A full, detailed statistical analysis plan (SAP) will be produced by the statistician before the database freeze.

13.10. ANALYSIS SOFTWARE

The analyses will be performed using SAS V.9.4 or higher (SAS Institute, Cary, North Carolina).

13.11. INTERIM ANALYSIS

No interim statistical analysis is planned for this trial.

14. DATA MANAGEMENT AND QUALITY CONTROL

14.1. DATA COLLECTION AND RECORDING

All data specified in the protocol must be promptly recorded in the Case Report Forms (CRFs). An explanation is required for any missing data collections. Data should be transcribed clearly and legibly into the CRFs as soon as they are obtained. If an error is

identified in a CRF, the incorrect entry must be struck through with a single line (remaining legible), and the correct data entered adjacent to it. The individual making the correction (the investigator or an authorized delegate) must initial, date, and, where appropriate, provide a reason for the change.

14.2. DATA ENTRY

Electronic Data Capture (EDC) systems (Jiandaoyun, Fanruan company) will be employed for data entry and management. All the information required by the protocol must be entered in the electronic case report forms (eCRFs) and an explanation must be provided for each piece of information which is missing. The data must be collected as and when they are obtained, and transcribed into eCRFs in a clear and legible manner by trained data entry personnel. The EDC system is designed to maintain a complete audit trail for all data modifications. Any change to entered data must be performed using the system's correction function, which requires the investigator or an authorized delegate to provide initials, date, and reason for the change, thereby ensuring a permanent and traceable record of all data entries and revisions.

14.3. DATA MANAGEMENT

Personally identifiable information will be anonymized upon entry into the eCRF. Access to the EDC system is restricted via unique user credentials, with role-based permissions (e.g., data entry, review-only). Data quality will be safeguarded through programmed edit checks, source data verification, and monitoring. Final database lock will be performed using the EDC system's functionality to prevent further alterations before analysis.

14.4. QUALITY CONTROL

A Clinical Research Associate (CRA), designated by the Chief Investigator, will perform monitoring visits to each study site to ensure adherence to the protocol and the integrity of the collected data. The monitoring schedule will include an initiation visit, periodic monitoring visits (frequency of which will be determined by the site's enrollment rate), and a close-out visit. During these visits, the CRA will verify the following key areas:

- Informed Consent Process: Documentation of proper and timely informed consent from all participants.
- Protocol Compliance: Site adherence to the approved study protocol and all defined procedures.
- Data Quality and Verification: Accuracy, completeness, and consistency of the data entered in the Case Report Forms (eCRFs) against source documents (e.g., medical records, laboratory reports).

- Investigational Product Management: Accountability, storage, and dispensing records of the study drugs.

A comprehensive monitoring report will be issued following each visit to document the findings.

15. ETHICAL CONSIDERATIONS

This study will be conducted only after ethical approval has been obtained from the Institutional Review Boards of all participating centers. The study protocol will be performed in full compliance with the principles of the Declaration of Helsinki and Good Clinical Practice (ICH GCP E6).

Prior to any study-related procedures, all participants will provide written informed consent for both participation and biological sample collection. Clinical trial insurance will be purchased to provide compensation for any trial-related physical injury.

Any substantial amendments to the protocol initiated by the sponsor-investigator must receive approval from the respective ethics committees prior to implementation. Approved amendments will be promptly communicated to all involved parties, and the informed consent form will be updated accordingly.

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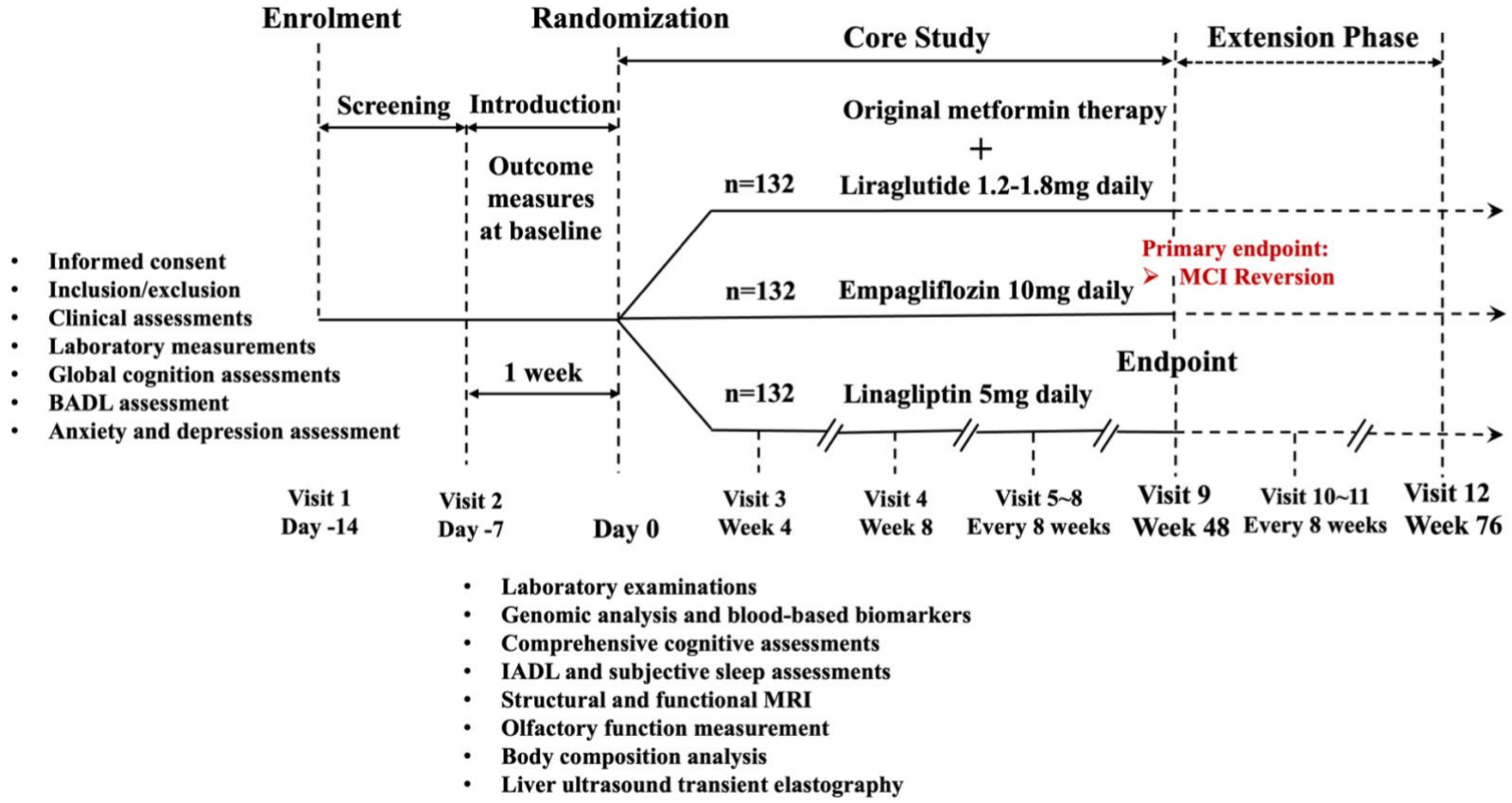
17. APPENDICES

APPENDIX 1. THE LIGHT-MCI TRIAL DESIGN



APPENDIX 2. THE CUTOFF SCORES FOR VARIOUS COGNITIVE SUBDOMAINS

Scores/Education	Average (SD)						Cognitive impairment					
	Primary education		Secondary education		Higher education		Primary education		Secondary education		Higher education	
RBANS												
Immediate memory	70 (15)		76 (15)		85 (15)		55		61		70	
Visuospatial construction	99 (13)		105 (13)		109 (13)		87		91		96	
Language	96 (9)		98 (9)		100 (9)		85		89		91	
Attention	96 (12)		104 (12)		110 (12)		84		92		98	
Delayed memory	88 (14)		92 (14)		96 (14)		74		78		82	
Age (years)	40-60	60-80	40-60	60-80	40-60	60-80	40-60	60-80	40-60	60-80	40-60	60-80
Processing speed	148(66)	202(80)	128(60)	160 (66)	99(40)	148(64)	214	282	188	226	140	212
Executive function	86(27)	93(31)	72(21)	80(22)	66(19)	73(20)	113	93	85	124	102	93

Immediate memory, visuospatial construction ability, language, attention, delayed memory, processing speed and executive function are assessed by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Processing speed and executive function are evaluated with the following time tests: the Trail Making Test (parts A and B) and the Stroop Colour-Word Test (parts I, II and III). A longer time for completion (in seconds) represents worse processing speed and executive function. RBANS scores are standardized for age. SD, standard deviation.

APPENDIX 3. LIST OF INVESTIGATORS

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HISTORY OF REVISIONS TO LIGHT-MCI TRIAL PROTOCOL

VERSION	DATE	SUMMARY OF CHANGES
1.0	**01/04/2022**	The initial version submitted to the ethics committee.
2.0	**01/12/2023**	- **Increase in Study Centers:** Added two new centers: Changzhou Second People's Hospital and Nanjing Jiangning Hospital. - **Updated list of investigators.**
3.0	**01/05/2024**	- **Extended Study Duration:** An optional 28-week extension phase has been added. Subjects completing the core study may continue, resulting in a total possible intervention duration of 76 weeks. - **Addition of Secondary Endpoint:** A new secondary endpoint has been added: the MCI (Mild Cognitive Impairment) Reversion rate at 76 weeks. - **Addition of Secondary Endpoint Time Point:** The assessment time point for all secondary efficacy endpoints has been extended to Week 76. - **Formal Specification of Primary Endpoint Criteria:** The definition of the primary endpoint, MCI reversion, which underpinned the original study design and sample size calculation, has now been formally specified in the protocol with a detailed, operationalized set of three objective criteria. This ensures standardized and unambiguous assessment across all study sites. - **Addition of Exploratory Endpoint:** The assessment of neurodegenerative blood-based biomarkers has been added to the protocol as an exploratory study endpoint.
4.0	**01/08/2024**	- **Specification of Primary Hypotheses and Sample Size:** The primary hypotheses and corresponding sample size calculation were revised in this protocol amendment. The original sample size calculation was based on preliminary randomized data, which suggested the strongest cognitive and brain-

		functional signal with liraglutide; accordingly, the initial design focused on comparisons of liraglutide with empagliflozin and linagliptin. After trial initiation, external evidence regarding the potential cognitive effects of SGLT2 inhibitors continued to accumulate. On the basis of this emerging external evidence, and before database lock, before treatment unblinding, and without any interim efficacy analysis, the primary objective was revised to specify two independent superiority hypotheses using linagliptin as a shared active comparator: liraglutide versus linagliptin and empagliflozin versus linagliptin. Consequently, the sample size was recalculated according to the revised hypotheses and updated reversion-rate assumptions. The required sample size was determined to be 132 participants per group, corresponding to a total sample size of 396 participants after accounting for attrition, providing 80% power for both pre-specified comparisons. - **Clarification of Medication Exclusion Criterion:** The exclusion criterion for prior use of GLP-1 receptor agonists has been refined to explicitly and separately list GLP-1/GIP receptor dual agonists and GLP-1/GCG receptor dual agonists. This change is intended to eliminate any potential ambiguity.
5.0	**17/11/2025**	- **Reclassification of Exploratory Endpoint:** The endpoint of neurodegenerative blood-based biomarkers has been upgraded from an exploratory endpoint to a secondary study endpoint. - **Specification of Secondary Efficacy Indicators:** The description of secondary efficacy indicators has been revised from a general statement to a detailed and specific list of these indicators.