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Protocol for Study M23-515

Alzheimer's Disease: Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ABBV-552

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ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-552	EU CTR #:	2022-501918-55-00

FULL TITLE: A Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ABBV-552 in Participants with Mild Alzheimer's Disease

Incorporating Versions 1.0, 2.0, 3.0, 4.0, and 5.0

PRINCIPAL INVESTIGATOR(S): Investigator information is on file at AbbVie.

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1 SYNOPSIS

Title: A Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ABBV-552 in Participants with Mild Alzheimer's Disease	
Background and Rationale:	Alzheimer's disease (AD) is a progressive, irreversible, fatal neurodegenerative disorder and the most common cause of dementia in the elderly population. No new symptomatic treatments have been introduced in the AD population for more than 15 years despite the increasing number of patients suffering from the disorder. ABBV-552 is a novel, high affinity (IC_{50}, 13nM) small molecule positive modulator of synaptic vesicle glycoprotein 2A (SV2A). To date, the development program of ABBV-552 includes 3 completed Phase 1 studies conducted in a total of 72 healthy young male participants and 16 healthy elderly male and female participants. Positron emission tomography (PET) imaging study showed a correlation between plasma concentration of ABBV-552 and SV2A receptor occupancy in human brain at dose levels between 1 mg and 20 mg.
Objective and Endpoint:	This is a proof-of-concept, dose-finding study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of ABBV-552 once daily for the treatment of dementia due to mild AD. The primary endpoint is the change from Baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 14) score at Week 12. Safety endpoints include AE, weight, vital sign measurements, electrocardiogram (ECG) variables, Columbia-Suicide Severity Rating Scale (C-SSRS), and clinical laboratory testing.
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Study Sites:	Approximately 60 sites will enroll participants in this study.
Study Population and Number of Participants to be Enrolled:	Approximately 240 participants with mild AD who are between 50 and 90 years of age at the start of Screening will be enrolled into this study.
Investigational Plan:	This is a Phase 2b, proof-of-concept, dose-finding, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety, efficacy, PK, and PD of ABBV-552 in participants with mild AD. The study will consist of a Screening Period of approximately 30 days, a Double-Blind Treatment Period of 12 weeks, and a Safety Follow-up Period of 30 days. Two clinic visits will be completed during the Screening Period: Screening Visit 1 and Screening Visit 2. Procedures required to evaluate participant eligibility at Screening Visit 1 will include cognitive/clinical assessments, a clinical laboratory panel, ECG, MRI, and neurological and physical examinations. Following the confirmation of eligibility after Screening Visit 1, participants will return for Screening Visit 2 where the cognitive assessments, ADAS-Cog 14, Cogstate Computerized Battery, and Altoida Digital Neuro-signature (DNS), will be repeated for familiarization purposes.

	Screening Visit 2 must take place at least 7 days after Screening Visit 1 and at least 7 days before Baseline/Day 1. The Baseline/Day 1 visit will take place at least 7 days after Screening Visit 2. During this visit, baseline assessments (e.g., laboratory procedures and cognitive/clinical assessments) will be completed before the participants receive the first dose of study drug. Upon the completion of all baseline assessments, eligible participants will be randomized in a 1:1:1:1 ratio to receive 1 of 3 doses of ABBV-552, 1 mg, 5 mg, or 15 mg, or placebo to be taken once daily. The first dose of study drug should be taken at the study clinic; this will initiate the 12-week Double-Blind Treatment Period. Upon completion of the Double-Blind Treatment Period, participants will enter a 30-day Safety Follow-up Period. The total study duration is anticipated to be approximately 20 weeks.
Key Eligibility Criteria:	Male and female participants, between 50 and 90 years of age, inclusive, with a diagnosis of probable Alzheimer's disease according to the National Institute of Aging-Alzheimer's Association (NIA-AA) (2011) criteria. Participants must have a Mini-Mental State Examination (MMSE) score of 20 to 26, a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0, with a CDR memory score of 0.5 or higher, and at least 1 CDR functional domain (community affairs, home and hobbies, or personal care) score of 0.5 or higher at Screening Visit 1.
Study Drug and Duration of Treatment:	ABBV-552 1 mg, 5 mg, or 15 mg or placebo to be taken once daily.
Date of Protocol Synopsis:	13 December 2023

2 INTRODUCTION

2.1 Background and Rationale

Alzheimer's disease (AD) is a progressive, irreversible, fatal neurodegenerative disorder and the most common cause of dementia in the elderly population. The available symptomatic treatments for AD are sparse with only 2 mechanisms of action available and with limited beneficial effect. The most common treatment option is acetylcholinesterase inhibition (AChEI) used for mild to moderate AD, comprising donepezil, rivastigmine and galantamine. The other mechanism of action approved for use in AD is the voltage-dependent, moderate-affinity, uncompetitive NMDA-receptor antagonist memantine used for moderate to severe AD. These treatments have shown limited but statistically significant benefit in clinical trials.[1,2] No new symptomatic treatments have been introduced in the AD population for more than 15 years despite the increasing number of patients suffering from the disorder. Thus, there is a significant unmet medical need for symptomatic treatments.

Synaptic loss is the major neurobiological correlate of cognitive deficits of AD.[3] Synaptic vesicle glycoprotein 2A (SV2A) is a protein expressed in virtually all synapses in the brain and is located in synaptic vesicles at presynaptic terminals.[4] Through its interaction with synaptotagmin, SV2A plays a role in regulating calcium-evoked vesicle fusion and, thus, neurotransmitter release. With SV2A positron emission tomography (PET) imaging, studies have shown that the decrease in synaptic density in AD affected brain regions is correlated with AD severity and cognitive performance.[5]

ABBV-552 is a novel, high affinity (IC_{50}, 13nM) small molecule (molecular weight [MW] 331 g/mol) positive modulator of SV2A. ABBV-552 has been demonstrated to have pro-cognitive activity in a range of cognitive deficit models in rodents. Thus, ABBV-552, through direct modulation of synaptic function, holds the potential for pro-cognitive effects in a number of human disorders characterized by cognitive deficits, such as AD. To date, the development program of ABBV-552 includes 3 completed Phase 1 studies conducted in a total of 72 healthy young male participants and 16 healthy elderly male and female participants. These studies showed a correlation between plasma concentration of ABBV-552 and SV2A PET occupancy at dose levels between 1 mg and 20 mg.

2.2 Benefits and Risks to Participants

Three Phase 1 studies have been completed for ABBV-552 as well as 2 Phase 1 studies terminated for business reasons. ABBV-552 was found to be safe and well tolerated in single ascending dose (SAD) doses up to 80 mg, and multiple ascending dose (MAD) doses up to 20 mg once daily for 14 days in healthy male participants. It was also safe and well tolerated in healthy male and female elderly volunteers in a 20 mg single dose regimen and a multiple dose regimen of 20 mg once daily for 14 days. No deaths, no serious adverse events (SAEs), and no discontinuations due to safety were seen in any Phase 1 study. Adverse events (AEs) were mostly mild and transient. The most common treatment-emergent AEs (TEAEs) were central nervous system (CNS)-related, including somnolence, dizziness, headache, and dizziness postural. Most of these CNS-related TEAEs occurred during the first days of treatment, and they lasted only a few hours. No changes in vital signs were associated with any of the AEs.

No clinically significant trends in laboratory values, electrocardiogram (ECG) variables or Columbia-Suicide Severity Rating Scale (C-SSRS) were seen.

The safety and clinical findings from these trials, in addition to available preclinical data, suggest that the benefit/risk profile supports further development of ABBV-552 in Phase 2 studies in participants with mild AD. For further details, please see findings from completed studies, including safety data in the current ABBV-552 Investigator's Brochure.

Considering the coronavirus disease – 2019 (COVID-19) pandemic, the benefit and risk to participants in this study have been evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of ABBV-552. Based on the mechanism of action, it is not expected that there is an increased risk to participants in the study.

3 OBJECTIVES AND ENDPOINT

3.1 Objectives, Hypotheses, and Estimands

This is a proof-of-concept, dose-finding study to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of ABBV-552 once daily for the treatment of dementia due to mild AD.

Clinical Hypothesis

The primary clinical hypothesis is that at least 1 dose of ABBV-552 (i.e., 1 mg, 5 mg, or 15 mg) is superior to placebo on the primary endpoint in participants with mild AD.

The administration of ABBV-552 once daily will be well tolerated and provide clinical benefit for participants with mild AD.

It is hypothesized that by positively modulating SV2A, ABBV-552 will increase neurotransmitter release, restore neural connectivity, and improve cognitive function in individuals with dementia due to mild AD.

3.2 Primary Endpoint

The primary endpoint is the change from Baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 14) score at Week 12.

The main attributes of the primary estimand are summarized below:

- Treatment: Placebo, ABBV-552 1 mg, 5 mg, and 15 mg taken once daily.
- Endpoint: Change from Baseline in ADAS-Cog 14 score at Week 12.
- Population: modified Intent-to-Treat (mITT) population which includes participants who received at least 1 dose of study drug and have at least 1 post baseline assessment of ADAS-Cog 14.
- Handling of Intercurrent Events: Efficacy data which is missing due to a participant's discontinuation from the study will be assumed missing at random and will not be included in the statistical analyses. Efficacy data collected after a start, stop or dose change of AD

medication during the study will not be included in the primary analysis and will be assumed missing at random.

- Population Summary: mean difference between each ABBV-552 dose and placebo in ADAS-Cog 14 change from baseline at Week 12.

3.3 Additional Efficacy Endpoints

Additional Efficacy Endpoints are:

1. Change from Baseline in the Cogstate Computerized Battery at specified timepoints, including Weeks 1, 2, 6, and 12.
2. Change from Baseline in the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog 14) score at Week 6.
3. Change from Baseline in the Mini-Mental State Examination (MMSE) score at Week 12.
4. Change from Baseline in the Clinical Dementia Rating sum of boxes (CDR-SB) score at Week 12.
5. Change from Baseline in the Alzheimer's Disease composite score (ADCOMS) at Week 12.
6. Change from Baseline in Neuropsychiatric Inventory (NPI) at Week 12

3.4 Safety Endpoints

Safety evaluations include AE monitoring, weight, vital sign measurements, ECG variables, C-SSRS, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic Endpoints

Blood samples to determine plasma ABBV-552, and metabolite(s) concentrations will be collected at the visits indicated in Appendix D, to assess population PK and explore the exposure-response. Predose samples are specified as such. Participants will not take their daily dose until the predose PK sample is collected. All other PK samples may be drawn at any time during the study visits indicated. For all PK samples, the date and clock time at which the sample is collected and the date and clock time at which the participant's last dose of study medication taken prior to the PK sample collection must be documented in the eCRF. The PK will be evaluated using the existing population PK model, updated with data from this study. Individual predictions of ABBV-552 exposure (including but not limited to steady-state $AUC_{0\text{-}Tau}$, C_{max} and C_{min}) will be evaluated graphically for potential relationships with efficacy, biomarkers, and/or safety endpoints. If graphical evaluation identifies possible trends, exploratory PK/PD analyses will be performed for the evaluation and quantification of potential relationships via nonlinear mixed effects modeling. The results of population PK and exposure-response analyses will be included in a stand-alone report and may not be included in the clinical study report.

3.6 Pharmacodynamic Endpoints

Change from Baseline using different brain magnetic resonance imaging (MRI) measures at Week 12:

a. Change in cerebral brain perfusion as measured by arterial spin labeling (ASL).
b. Change in functional connectivity as measured using resting state functional MRI (rs-fMRI).
c. Change in the concentration of specific biochemical compounds in brain as measured using magnetic resonance spectroscopy (MRS).

3.7 Biomarker Research Endpoints

Biospecimens (e.g., whole blood for plasma and whole blood for DNA and RNA) will be collected at specified time points (Appendix D) throughout the study, to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Types of biomarkers may include, but are not limited to nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include, but are not limited to, amyloid beta (Abeta), apolipoprotein E (apoE), plasma phospho-tau epitopes (pTau), untargeted metabolomics to identify any patterns of metabolic signals in participants and highly exploratory biomarkers of interest such as, but not limited to blood based synaptic markers (e.g., GAP-43) and the development of plasma neuronal-derived exosomes such as synaptophysin and synaptopodin. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to the disease, and/or to develop new therapies and diagnostic tests. The biomarker research results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual (Appendix F), Section 3.7.

Provision of biospecimens for biomarker research is mandatory, except for the whole blood collected for RNA, which will be optional. Samples from this study may be stored for future use. The samples may also be used to develop new therapies, research methods, or technologies as well as assay development. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests. The samples may be retained for no longer than 20 years after study completion or per local requirements.

3.8 Exploratory Research and Validation Endpoints

Digital Biomarker

- Change from Baseline in Altoida Digital Neuro-signature (DNS) during the study.

Results from the Altoida DNS analyses are exploratory in nature only and may not be included in the study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2b, proof-of-concept, dose-finding, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety, efficacy, PK, and PD of ABBV-552 in participants with mild AD.

This study will enroll approximately 240 participants with mild AD between 50 and 90 years of age. Participants may be naïve to AD therapy or be on a stable dose of AD therapy which should remain unchanged throughout the study. Participants who discontinued prior AD therapies at least 90 days before Screening Visit 1 may also participate; reason(s) for discontinuing prior AD therapies must be recorded.

The study will consist of a Screening Period of approximately 30 days, a Double-Blind Treatment Period of 12 weeks, and a Safety Follow-up Period of 30 days.

Two clinic visits will be completed during the Screening Period: Screening Visit 1 and Screening Visit 2. Procedures required to evaluate participant eligibility at Screening Visit 1 will include neuropsychological/clinical assessments, a clinical laboratory panel, ECG, MRI, and neurological and physical examinations. MRI may be performed anytime during the screening period, but with sufficient time to allow for central read and confirmation of eligibility prior to Baseline Day 1.

If a participant fails initial screening, the site must contact the sponsor if a participant would like to consider rescreening. All assessments must be repeated during rescreening with the following exceptions: MRI assessment does not need to be repeated if it was performed within 6 months of the rescreening visit and if there has been no significant change in the participant's medical condition per investigator's discretion.

Following the confirmation of eligibility at Screening Visit 1, with the exception to MRI, participants will return for Screening Visit 2 where the cognitive assessments (which include ADAS-Cog 14, Cogstate Computerized Battery, and Altoida DNS) will be repeated for familiarization purposes. Screening Visit 2 must take place at least 7 days after Screening Visit 1 and at least 7 days before Baseline/Day 1.

Where relevant, participants undergoing methylmalonic acid (MMA) reflex testing but who are otherwise eligible may proceed to Screening Visit 2 while MMA testing takes place in parallel; however, Baseline/Day 1 must occur only after their MMA results confirm that there is no vitamin B_{12} deficiency.

The Baseline/Day 1 visit will take place at least 7 days after Screening Visit 2. Participant eligibility, including all clinical laboratory, ECG, and MRI results must be confirmed before the Baseline/Day 1 visit takes place. During this visit, baseline assessments (e.g., laboratory procedures, blood biomarkers, and neuropsychological/clinical assessments) will be completed before the participants receive the first dose of study drug. Upon the completion of all baseline assessments, participants will be randomized in a 1:1:1:1 ratio to receive 1 of 3 doses of ABBV-552, 1 mg, 5 mg, or 15 mg, or placebo to be taken once daily. The first dose of study drug should be taken at the study clinic after all other assessments have been completed. Since the participant's ability to drive or to operate heavy machinery subsequent to dosing, especially during the first days of treatment, is not yet fully known, participants should be

advised to avoid these activities in the first days of treatment until they have gained sufficient experience on study drug to gauge whether it might impair their ability to drive.

Participants will return to the study site for assessments at the conclusion of Week 1, Week 2, Week 6, and Week 12. Optimally, participants will return to the clinic at approximately the same time of day for each in-clinic visit, if possible. Additionally, 4 telephone visits will be completed as part of the study requirements: the first will be completed on Day 3 (2 days after the baseline visit); the subsequent visits will be completed at the conclusion of Week 4, Week 8, and Week 10. Upon completion of the Double-Blind Treatment Period, participants will enter a 30-day Safety Follow-up Period.

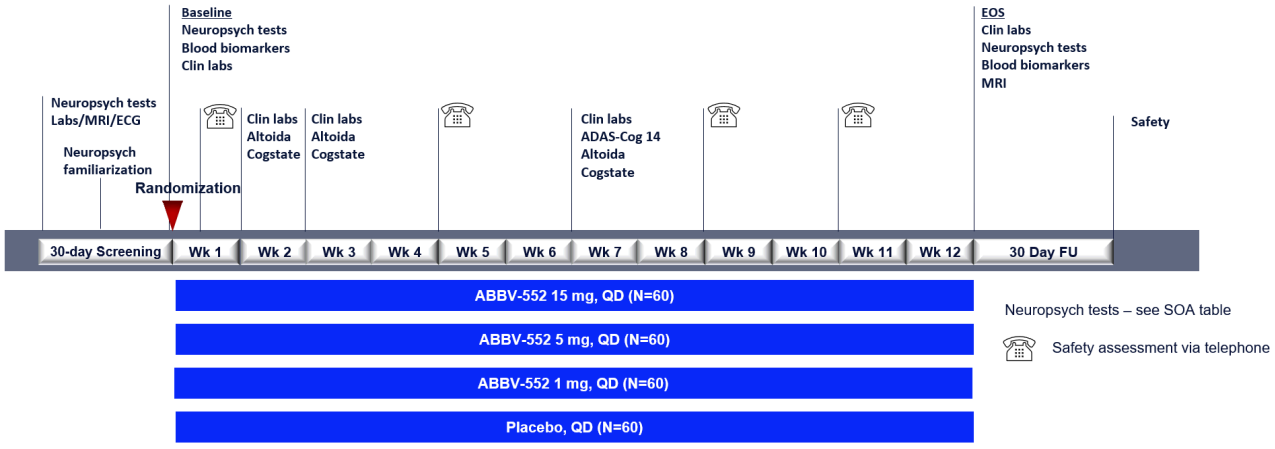
There will be a total of 12 scheduled study visits as shown in Figure 1. The total study duration is approximately 20 weeks.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F).

See Section 5.1 of the protocol for information regarding eligibility criteria.

An interim analysis may be conducted. Study sites and participants will remain blinded for the duration of the study.

Figure 1. Period 1 Schematic



ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; Clin = clinical; EOS = end-of-study; ECG = electrocardiogram; FU = follow-up; MRI = magnetic resonance imaging; QD = once a day; SOA = schedule of activities; Wk = week

4.2 Discussion of Study Design

Choice of Control Group

Study M23-515 is a Phase 2b, proof-of-concept, dose-finding, multicenter study designed to evaluate the safety and efficacy of ABBV-552 in participants with mild AD. This study will employ a double-blind, randomized, placebo-controlled design, which is considered the most robust approach in eliminating bias and/or incorrect estimate of the effect of treatment by keeping the investigator and participants blinded.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in participants with AD. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Participant Population

The selection of participants with mild AD as defined in the eligibility criteria and without other significant medical issues that could compromise participation in the study is standard for studies with similar objectives.

Selection of Doses in the Study

The dose selection in this study is based on extrapolation of nonclinical toxicology studies, nonclinical efficacy models and analysis of PK, PD, and safety data from Phase 1 studies in both healthy young and healthy elderly participants.

Participants will be randomized in a 1:1:1:1 ratio to placebo, ABBV-552 1 mg once a day (QD), ABBV-552 5 mg QD, or ABBV-552 15 mg QD. These doses are appropriate based on nonclinical safety data that establish a safety margin of 3-fold at the 15 mg dose. The NOAELs in the 13-week GLP rat and dog studies were 100 mg/kg/day and 40 mg/kg/day, respectively. The 15 mg daily dose in humans is predicted to result in steady state exposures [redacted] These correspond to [redacted] AUC exposure margins as compared to the exposure in the 13-week GLP rat and dog studies, respectively.

The dose selection was also informed by the in vivo data obtained in various rodent cognition models that showed ABBV-552 activity in improving cognitive measures at doses providing approximately between 10% and 80 % occupancy of SV2A in the brain. Receptor occupancy measurements in the Phase 1 SAD study (SYND001) using PET imaging showed a good correlation between plasma concentrations of ABBV-552 and the SV2A receptor occupancy. There was a dose-dependent inhibition of [^{11}C]-UCB-J binding to SV2A by ABBV-552, confirming brain penetration and target engagement of ABBV-552. Based on the SV2A receptor occupancy obtained by PET imaging in the brain of healthy participants in Study SYND001, together with simulation of PK profile after multiple doses, the selected doses of 1, 5, and 15 mg will explore 35%, 67%, and 80% receptor occupancy, respectively.

The appropriateness of the doses is further supported by PK and tolerability of ABBV-552 from the first-in-human (FIH)-SAD study in young healthy participants, and MAD studies in both young and elderly healthy participants (Studies SYND001, SYND002, SYND003) that included ABBV-552 SAD doses of

0.3 mg to 80 mg in young healthy participants, MAD doses of 5 mg, 10 mg, and 20 mg in young healthy participants, and single and multiple doses of 20 mg in elderly healthy participants. No deaths, no SAEs, and no discontinuations due to safety were seen in any Phase 1 study, and all drug-related AEs were mostly mild and transient. Overall, all 3 Phase 1 studies have demonstrated that ABBV-552 is safe and well tolerated at doses above those being evaluated in this study.

In summary, the current safety, tolerability, PK, and SV2A receptor occupancy data from both nonclinical and clinical studies (FIH SAD and MAD studies SYND001, SYND002, SYND003) support the proposed Phase 2 ABBV-552 dosing regimens of 1 mg, 5 mg, and 15 mg PO QD for up to 12 weeks. These doses are expected to be safe and are predicted to provide exposures to engage a broad range of the target receptor.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Participants must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Participant or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), before the initiation of any screening or study-specific procedures.
- 2. Participant has a study partner who:
  - Spends a minimum average of 10 hours per week with the participant.
  - Is able and willing to accompany the participant to study visits and be available by telephone at designated visits throughout the duration of the study.
  - According to the investigator's opinion, is able and willing to complete the protocol-specified questionnaires.
  - Must provide a separate Independent Ethics Committee/Institutional Review Board (IEC/IRB) approved written informed consent to participate in the study.

Demographic and Laboratory Assessments

- 3. Adult **male or female**, between 50 and 90 years of age, inclusive, at the time of consent.
- 4. Participant must not have any contraindications or inability to tolerate MRI.
- 5. Participant must have a body mass index of 18 to 33 kg/m^2, inclusive.
- 6. Participants are willing and able to comply with procedures required in this protocol.
- 7. Participants must have adequate renal function as defined by eGFR ≥ 60 mL/min.
- 8. Participants must have adequate hepatic function as defined by:
  - Alanine aminotransferase increased ≤1.5 x ULN of normal

- Aspartate aminotransferase increased ≤ 1.5 x ULN of normal
- Total bilirubin ≤ 1.8 mg/dL, with the exception of participants with Gilbert's syndrome

Disease/Condition Activity

Participant meets the following disease activity criteria:

- 9. Diagnosis of probable Alzheimer's disease according to the National Institute of Aging-Alzheimer's Association (NIA-AA) (2011) criteria.
- 10. MMSE score of 20 to 26 at Screening Visit 1.
- 11. Clinical Dementia Rating Scale (CDR) global score of 0.5 or 1, CDR memory score of 0.5 or higher, and at least 1 CDR functional domain (community affairs, home and hobbies, or personal care) score of 0.5 or higher at Screening Visit 1.
- 12. MRI that does not show evidence of alternative etiology for dementia, including but not limited to, multiple lacunes or severe white matter disease. Participant must have no evidence or history of benign or malignant intracalvarial tumor, or any acute or chronic macrohemorrhage, or 4 or more microhemorrhages.
- 13. Must not have another contributing cause of cognitive impairment that, if addressed, would likely abate the cognitive impairment and/or would necessitate an initiation or adjustment of a concomitant medication in the investigator's opinion (e.g., abnormally low vitamin B_{12}, abnormally low thyroxine [T4] or abnormally high thyroid-stimulating hormone [TSH]).
- 14. Participant must have no history of any significant neurologic disease other than AD, including Parkinson's disease, multi-infarct or vascular dementia, Huntington's disease, normal pressure hydrocephalus, progressive supranuclear palsy, multiple sclerosis, mental retardation, or a history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.

Participant History

- 15. No history of epilepsy, recurrent seizures (except febrile seizures or self-limited epilepsy with centrotemporal spikes [formerly known as benign rolandic epilepsy]) or a history of a seizure within the last 6 months before Screening.
- 16. No history of advanced chronic heart failure, unstable angina, clinically significant conduction abnormalities, nor a myocardial infarction within the 6 months before Screening.
- 17. Participant has not presented with a clinically significant, unstable, psychiatric illness within the 1 year before Screening.
- 18. Participant must not have current suicidal ideation within 1 year before Screening, as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the C-SSRS completed at Screening Visit 1, or any history of suicide attempts within 24 months prior to Screening.

- 19. No history of or evidence of a malignancy within the 2 years before Screening. Participants with indolent malignancies (e.g., basal cell carcinoma or squamous cell carcinoma), a history of in situ cervical cancer, or remission from any malignancy for more than 5 years are eligible to participate in this study.
- 20. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the 2 years before Screening. A positive drug screen from prescribed medications, as well as a positive cannabinoid test is allowed if, in the investigator's opinion, its use would not interfere with the participant's adherence to the protocol.
- 21. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 22. No known history of or positive test result(s) for hepatitis C virus (unless effectively cured) or hepatitis B virus, human immunodeficiency virus (HIV), or other immunodeficiencies.
- 23. No other clinically significant and/or unstable medical conditions or any other reason that the investigator determines would interfere with participation in this study (e.g., unlikely to adhere to the study or procedures, keep appointments, or is planning to relocate during the study) or would make the participant an unsuitable candidate to receive ABBV-552.
- 24. Participant must not have any elective procedure from 2 weeks before randomization or elective procedure anticipated to be performed throughout the study.
- 25. Participant is not employed by or is an immediate family member (parents, spouses, siblings, or children) of one of the investigators, study staff or AbbVie.
- 26. Participant and their study partner must have, in the investigator's judgment, adequate premorbid literacy and visual or auditory acuity to complete the required neuropsychological assessment.

Contraception

- 27. For all females of childbearing potential, a **negative serum pregnancy test** at Screening Visit 1 and a negative urine pregnancy test at baseline before the first dose of study drug.
- 28. Female participants of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 30 days after the last dose of study drug. Female participants of non-childbearing potential do not need to use birth control.
- 29. Female who is not **pregnant or breastfeeding and is not considering becoming pregnant** or donating eggs during the study or for approximately 30 days after the last dose of study drug.
- 30. **If male**, and **sexually active with female partner(s) of childbearing potential**, the participant must agree, from Study Day 1 through 90 days after the last dose of study drug, to practice the protocol-specified contraception.
- 31. Male who is not considering **fathering a child or donating sperm** during the study or for 90 days after the last dose of study drug.

Concomitant Medications

- 32. Participant taking acetylcholinesterase inhibitors (AChEIs) must be on a stable dose for at least 90 days before Screening, with no expected change in dosing during the course of the study. Participants who have been on AChEIs in the past, but discontinued treatment, are eligible to participate as long as they have stopped the drug for at least 90 days before Screening.
- 33. Participant taking permitted anti-depressants and/or anti-epileptics must be on a stable dose for at least 30 days before screening, with no expected changes in dosing during the study. (Antiepileptics may not be used for the treatment of seizures.)
- 34. Participant may not be taking levetiracetam and/or brivaracetam within 30 days before Screening through the Safety Follow-up Period.
- 35. Participant must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) before the first dose of study drug or is currently enrolled in another clinical study or was previously enrolled in this study.
- 36. Participant must not have systemically used known strong or moderate cytochrome P450 (CYP)3A inhibitors or strong or moderate CYP3A inducers from for least 30 days or 5 half-lives (whichever is longer) before Screening through the end of the study. See Section 5.3.

5.2 Contraception Recommendations

Contraception Requirements for Females

Participants must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 International Units (IU)/L.

3. Females, of Childbearing Potential

   - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug.
   - Females must commit to one of the following methods of birth control:
     - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal,* transdermal,* injectable) associated with inhibition of ovulation-initiated at least 30 days before Baseline/Day 1.
     - Progestogen-only hormonal birth control (oral, injectable,* implantable*) associated with inhibition of ovulation initiated at least 30 days before Baseline/Day 1.
     - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
     - Intrauterine device (IUD).
     - Intrauterine hormone-releasing system (IUS).
     - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial participant).
     - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the participant (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Note: methods marked with an asterisk (*) are not approved in Japan for the indication of contraception.

The next section includes recommendations for adjunctive contraceptive methods which may be used based on the local label. These should not be used in place of one of the highly effective methods listed in the previous section.

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days before Baseline/Day 1.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Contraception Requirements for Males

Male participants who are sexually active with a female partner of childbearing potential, must agree **to use male condoms, even if the male participant has undergone a successful vasectomy**, from Baseline/Day 1 through at least 90 days after the last dose of study drug:

Female partner(s) must also use at least 1 of the following methods of birth control:

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal*, transdermal*, injectable) associated with inhibition of ovulation initiated at least 30 days before Baseline/Day 1
- Progestogen-only hormonal birth control (oral, injectable*, implantable*) associated with inhibition of ovulation initiated at least 30 days before Baseline/Day 1
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy, and is the sole sexual partner of the trial participant)

Note: methods marked with an asterisk (*) are not approved in Japan for the indication of contraception.

5.3 Prohibited Medications and Therapy

Any exposure to anti-amyloid beta monoclonal antibodies prior to screening is NOT permitted nor at any time during the study.

Prior exposure to the following medications/medication classes are NOT permitted within the 30 days or 5 half-lives, whichever is longer, before Screening Visit 1 or at any time during the study:

- Tricyclic antidepressants
- Non-selective MAO-inhibitors
- Fluoxetine
- Paroxetine
- Nefazodone
- Antipsychotics with significant sedation/anticholinergic risks (e.g., chlorpromazine, chlorprothixene, clozapine, loxapine, mesoridazine, molindone, perphenazine, pimozide, thioridazine, thiothixene, trifluoperazine, or quetiapine)
- Levetiracetam and brivaracetam
- Antiepileptic drugs that are administered for purposes of controlling seizures
- Strong or moderate cytochrome P450 (CYP)3A inhibitors or strong or moderate CYP3A inducers

The following medications/products are NOT permitted within 14 days or 5 half-lives, whichever is longer, before Screening Visit 1 or at any time during the study:

- Long-acting benzodiazepines and sedatives (e.g., chlordiazepoxide, clonazepam, diazepam, flurazepam) and barbiturates (including Corvalol)

- Nootropic agents (e.g., phenibut, piracetam, vinpocetine)
- St John's wort (*Hypericum perforatum*), a P450 CYP3A4 inducer
- Grapefruit/grapefruit juice, a P450 CYP3A4 inhibitor

If it becomes necessary for a participant to receive any of the prohibited medications listed above during the course of the study, the AbbVie Medical Monitor should be contacted to discuss the situation.

5.4 Prior and Concomitant Therapy

Participants may be taking stable doses of AChEI for at least 90 days before Screening Visit 1 and should remain on the same stable dose regimen throughout the duration of the study. Unless medically necessary, participants entering the study who are not on any AD medications should not initiate any AD medications during the study, and participants who enter the study on stable doses of AD medications should not change their doses during the study. When possible, participants should return for an unscheduled visit before AD medication adjustment for neuropsychological assessments.

Participants' previous AD medications must not have been discontinued solely for the purpose of qualifying for this study. For participants who discontinued prior AD therapies 90 days or more before Screening Visit 1, the reason(s) for discontinuing prior AD therapies must be recorded.

Participants are permitted to take the following medications with psychotropic effects during the study, provided they began taking them at least 30 days before Screening Visit 1 and no dosing changes are anticipated during the study:

- Anti-depressants: duloxetine, escitalopram, mirtazapine, reboxetine, sertraline, trazodone, venlafaxine, citalopram, vilazodone, vortioxetine, and levomilnacipran. (Tricyclic antidepressants and non-selective MAO inhibitors are not allowed.)
- Antiepileptic medications are allowed for treatment of mood. (Participants for whom anti-epileptic drugs are used to treat seizures are not allowed to participate in this study.)
- Anxiolytics/hypnotics (administered at low, stable doses): short-acting benzodiazepines (alprazolam, lorazepam, oxazepam, temazepam) or buspirone, ramelteon, zaleplon, zolpidem, eszopiclone. PRN use is allowed; however, cognitive testing, ASL, and rsFMR should be avoided for 24 hours after the last dose of these medications.
- Antipsychotics (administered at low, stable doses): aripiprazole, asenapine, haloperidol (oral), melperone, olanzapine, pipamperone, risperidone, sulpiride, cariprazine, brexpiprazole, lumateperone. PRN use is allowed; however, cognitive testing, ASL, and rsFMR should be avoided for 24 hours after the last dose of these medications.
- Opiate medications (administered at low, stable doses): codeine, hydrocodone, meperidine, oxycodone, propoxyphene, and tramadol. PRN use is allowed; however, cognitive testing, ASL, and rsFMR should be avoided for 24 hours after the last dose of these medications.
- The use of melatonin is permitted.
- Centrally acting antihistaminergic or anticholinergic medications prescribed for symptomatic (PRN) relief will be allowed if deemed medically necessary in the investigator's opinion. Usage

should not exceed 1 week during the study period. Examples include oxybutynin, cyproheptadine, dicyclomine, diphenoxylate or difenoxin with atropine, promethazine, benztropine, trihexyphenidyl, hyoscyamine, meclizine, biperidine, scopolamine, dimenhydrinate, diphenhydramine, hydroxyzine and dimebolin. Cognitive testing, ASL, and rsFMR should be avoided within 8 hours of the last dose of these medications.

- If, in the investigator's opinion, the use of cannabinoids would not interfere with participant adherence to the protocol, the participant may continue its use but should refrain from using cannabinoids for 24 hours before scheduled cognitive assessments, ASL, and rsFMR.
- Use of any other medications with psychotropic effects (over-the-counter and/or prescription) either during the study or during the screening period is prohibited unless previously discussed with the AbbVie Medical Monitor.

In general, dose changes or administration of additional medications with psychotropic effects (including opiates) on an as-needed (PRN) basis should be avoided. Low doses of anxiolytic/hypnotic agents, antipsychotic or opiate-containing medications are permitted in the interest of participant safety or emergent symptom control. In the event a benzodiazepine is prescribed, it is preferable to prescribe a short-acting agent.

Vitamins, herbal supplements (with the exception of huperzine), and medications to treat urinary incontinence (antispasmodics), besides ongoing oxybutynin use, are permitted during the study if the dose has been stable for at least 30 days before Screening Visit 1 and no dose changes are anticipated during the study.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, minerals, and/or herbal supplements) that the participant receives 30 days before Screening Visit 1 or receives during the study must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose and frequency.

Participants may receive COVID-19 vaccinations during the course of the study. The site will need to record the day and time on which the vaccination was received by the participant. For participants who have received the COVID-19 vaccination before study participation, participants must not be screened until 4 weeks after the final dose of the vaccination has been received if a multiple-dose vaccine or 4 weeks after administration of the vaccine if a single-dose vaccine. The date(s) of COVID-19 vaccinations received prior to the study should be recorded.

The AbbVie Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy(ies).

There are no rescue medications to be administered as part of this study.

5.5 Withdrawal of Participants and Discontinuation of Study

A participant may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the Sponsor.
- The investigator believes it is in the best interest of the participant.
- The participant requests withdrawal from the study.
- Eligibility criteria violation was noted after the participant started study drug and continuation of the study drug would place the participant at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the participant at risk.
- The participant becomes pregnant while on study drug.
- The investigator determines the participant is significantly noncompliant with study procedures.

For participants to be considered lost to follow-up, reasonable attempts must be made to obtain information on the participant's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the participant's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up After Participant Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, participants who prematurely discontinue study drug treatment should complete the follow-up visit approximately 30 days after study drug discontinuation, unless participants have decided to discontinue the study participation entirely (withdrawal of informed consent).

If a participant prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if participant is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all TEAEs/SAEs have been resolved.

In the event a participant withdraws informed consent from the clinical study, biomarker research will continue using the participant's samples, unless the participant explicitly requests analysis of their samples be stopped. When AbbVie is informed the participant has withdrawn and no longer wishes for their biomarker samples to be tested, further sample analysis will not be conducted, and no new biomarker data will be collected for the withdrawn participant. Data generated for biomarker research before participant withdrawal of consent will remain part of the study results.

5.7 Study Drug

ABBV-552 or placebo manufactured by AbbVie will be taken orally once daily beginning on Day 1 (Baseline) and should be taken at approximately the same time each day. On Day 1 and Day 8 (days in

which predose PK and biomarker samples are collected), participants will not take their daily dose until after the PK sample is collected. The study drug can be taken with or without food. If participants forget to take their ABBV-552 or placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember, as long as it is at least 12 hours before their next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

Investigational product is a small molecule active pharmaceutical ingredient in a size-3 hydroxypropyl methylcellulose capsule. Capsules will come in forms of ABBV-552 1 mg, 5 mg, and 10 mg and placebo will be provided for oral route of administration. Each participant will receive 2 bottles of capsules with 10 capsules in each bottle. Participants will take 2 capsules for each dose.

The participant will be instructed to return all drug packaging (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will provide study drug for ABBV-552 or placebo. AbbVie-issued study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

ABBV-552 and placebo will be packaged with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a participant via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the participant's corresponding study visit. Study drug will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all remaining study drug capsules (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

Digital Health Tools Accountability

The investigator or his/her representative will verify that the digital health tools are received intact and in the correct amounts. A proof of receipt or similar document will be kept in the site files as a record of what was received.

The Altoida DNS tool is registered and listed with Food and Drug Administration (FDA), and the use in this trial is per the intended use and on label. Where available on the market, the Altoida DNS may also be used in countries outside the US.

In addition, sites will maintain records of traceability, accountability, and return including but not limited to date received/dispensed/returned, participant number, and the identification of the person returning the digital health tools.

5.8 Randomization/Drug Assignment

All participants will be assigned a unique identification number by the IRT system at Screening Visit 1. For participants who rescreen, the screening number assigned by the IRT system should be used throughout the study. The IRT will assign the participant to a treatment group at Baseline/Day 1 according to the randomization schedule.

Randomization will be in a 1:1:1:1 ratio to placebo, ABBV-552 1 mg QD, ABBV-552 5 mg QD, or ABBV-552 15 mg QD.

Participants will be stratified, based on whether they are currently not taking symptomatic treatment for AD vs. those who are receiving a stable dose of symptomatic treatment for AD, at Baseline/Day 1.

Each stratum should contain approximately 40% to 60% of all randomized participants.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the participant will remain blinded to each participant's treatment throughout the study. To maintain the blind, the ABBV-552 tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded participant treatment information in the case of a medical emergency.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study participants. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each participant for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure that occurs during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Participant	An event that results in the death of a participant.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the participant's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study participant. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the participant and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of participant, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the participant. In addition, study procedure-related serious and nonserious adverse events will be collected from the time the participant signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an investigational medicinal product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to participants.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0 or higher).

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study participant must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Participants who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study participant or in the partner of a study participant, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a participant's partner during the study, written informed consent from the partner must be obtained before collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a participant's partners will be collected from the date of the first dose through 90 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on the safety and primary efficacy analysis. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The primary efficacy analysis will be conducted following a database lock after all participants have completed Visit 11 (Week 12) or prematurely discontinued study drug.

An unblinded interim analysis may be conducted for the purpose of project planning after a proportion of participants have completed the Week 12/PD visit and is further discussed in Section 7.6.

7.2 Definition for Analysis Populations

The modified Intent-to-Treat (mITT) analysis set includes all randomized participants who received at least 1 dose of study drug and have at least 1 post-baseline assessment in ADAS-Cog14. The participants will be grouped according to treatment as randomized. The mITT analysis set will be used for all efficacy and demographic analyses.

The safety analysis set consists of all participants who received at least 1 dose of study drug. The participant will be grouped according to treatment actually received the majority of the time. The safety analysis set will be used for all safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Efficacy data that are missing due to a participant's discontinuation from the study will be assumed missing at random and will be handled using a mixed-effects model for repeated measures (MMRM) for the primary analysis.

Efficacy data collected after a participant initiates, changes, or stops treatment with an AD medication during the study will be treated as missing and not included in the primary analysis. Additional sensitivity analyses including these data will be specified in the SAP.

7.4 Statistical Analyses for Efficacy

Analysis of the primary and all other efficacy endpoints will be conducted on the mITT analysis set based on 2-sided $\alpha = 0.1$ level, unless otherwise specified in the SAP.

Summary and Analysis of the Primary Endpoint

The primary analysis of ADAS-Cog 14 will be conducted using an MMRM including treatment group, visit, treatment-by-visit interaction, and the randomization stratum as fixed effects and the baseline ADAS-

Cog 14 score as a covariate. The unstructured covariance structure will be used to estimate the within participant variance-covariance. Denominator degrees of freedom will be computed using the Kenward-Roger method. The group mean treatment difference between each dose and placebo at Week 12 will be based on contrasts from this model.

Summary and Analysis of Additional Efficacy Endpoint

The following analyses will generally apply unless otherwise noted in the SAP. For continuous efficacy endpoints, the mean, standard deviation, median, minimum, and maximum will be reported for each treatment group. For endpoints measured at a single post-baseline time point, the between-group treatment summary will be based on an analysis of covariance (ANCOVA) including treatment group, randomization stratum, and baseline for that respective parameter. For endpoints measured at multiple post-baseline time points, the between-group treatment summary at each visit will be conducted using an MMRM including treatment group, visit, treatment-by-visit interaction, and the randomization stratum as fixed effects and the baseline values associated with the endpoint as a covariate. Missing data will not be imputed before performing the MMRM.

Subgroup Analysis for Efficacy

Subgroup analyses of the primary endpoint will be conducted for the following subgroups.

- On symptomatic treatment for AD at baseline: Yes, No
- Sex
- Age: < 65 years or ≥ 65 years and < 75 years or ≥ 75 years

7.5 Statistical Analyses for Safety

General Considerations

Safety analyses will be carried out using the safety analysis set. Safety will be assessed by AEs, lab values, vital sign measurements, ECG, and C-SSRS. For continuous safety outcomes, the change from Baseline will be analyzed in a descriptive manner by treatment group and by visit. For categorical safety outcomes, the number and percentage of participants in each category will be summarized by treatment group and by visit. Shift of laboratory values from Baseline to defined time points will be tabulated. Hypothesis testing will not be performed for safety parameters.

Analysis of Adverse Events

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with TEAEs, treatment-emergent SAEs, AEs with a reasonable possibility of being related to study drug, and AEs leading to study drug discontinuation will be summarized by treatment group and will be tabulated using primary MedDRA system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be defined as all events that begin or worsen (increased in intensity or became serious) on or after first dose of study drug. An AE occurs more than 30 days after the last dose will not be counted as a TEAE.

Analysis of Laboratory Data

Changes from Baseline in continuous laboratory parameters will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group and all participants overall for each continuous hematology, chemistry, and urinalysis variable.

Laboratory observations will be categorized according to CTCAE Version 4.0 and higher. For each hematology, chemistry, and urinalysis with a reference range, shift tables will be prepared for shifts from baseline to highest post-baseline grade and shifts from Baseline to the final value during the entire study for each treatment group.

Analysis of Vital Signs

Change from Baseline to each planned visit and to the minimum, maximum, and final value during the Treatment Period will be summarized in a descriptive manner for each treatment group and all participants overall for each vital sign and weight variable. For each variable, a summary of the number and percentage of participants who have at least 1 post-baseline observation that meets the potentially clinically significant criteria and is more extreme than their baseline value will be provided for each treatment group and all participants overall.

Other Safety Analysis

Further details and additional safety analyses will be specified in the SAP.

7.6 Interim Analysis

An interim analysis may be conducted to trigger future study planning. Details regarding an unblinded interim efficacy analysis will be specified in the SAP and a separate interim unblinding plan. Study sites and participants will remain blinded for the duration of the study.

7.7 Overall Type I Error Control

This is a Phase 2b dose-ranging and hypothesis-generating study; therefore, there will be no control of Type I error for testing multiple doses or multiple efficacy endpoints in the study.

7.8 Sample Size Determination

It is assumed that the treatment difference of ADAS-Cog 14 score change from Baseline at Week 12 between ABBV-552 and placebo is 2.85 with a pooled standard deviation of 5.7. Assuming a 20% discontinuation rate, 60 participants randomized per group will provide about 80% power to detect the above treatment difference in ADAS-Cog 14 score at the 2-sided 10% significance level.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Participant Confidentiality

To protect participants' confidentiality, all participants and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

For the personal data that AbbVie Deutschland GmbH & Co acting as sponsor of the submitted study ("AbbVie") controls and maintains, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's Information Security policies taking into account the sensitivity of the data.

Before participant data are shared with AbbVie, the study doctor and staff will replace any information that could directly identify a participant (such as name, address, and contact information) with a generic code which AbbVie cannot link to that participant's identity to protect the confidentiality of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains and these processing activities respect privacy of clinical trial participants. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH good clinical practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human participant protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end of study participation by the last participant in the last country where the study was conducted (Visit 11).

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Abeta	amyloid beta
AChEI	acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCOMS	Alzheimer's Disease composite score
AE	adverse event
ANCOVA	analysis of covariance
apoE	apolipoprotein E
ASL	arterial spin labeling
BP	blood pressure
CBB	Cogstate Brief Battery
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating sum of boxes
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CNS	central nervous system
COA	clinical outcomes assessments
Cr	creatine
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CYP3A	cytochrome P450 3A isoform subfamily
DNA	deoxyribonucleic acid
DNS	Digital Neuro-signature
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration

FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GLP	Good Laboratory Practice
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	Investigational Medicinal Product
IRB	institutional review board
IRT	interactive response technology
ISLT	International Shopping List Test
IU	International Unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
MAD	multiple ascending dose
Max	maximum
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
mITT	modified Intent-to-Treat
MMA	methylmalonic acid
MMRM	mixed-effects model for repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MW	molecular weight
NIA-AA	National Institute of Aging-Alzheimer's Association
NCI	National Cancer Institute
NCS	not clinically significant
NOAEL	no-observed-adverse-effect level
NPI	Neuropsychiatric Inventory
PCS	potentially clinically significant

PD	pharmacodynamic(s)
PD visit	Premature Discontinuation visit
PET	positron emission tomography
PK	pharmacokinetic(s)
PO	orally (*per os)*
PT	preferred term
pTau	phospho-tau epitopes
QD	once a day
RNA	ribonucleic acid
rs-fMRI	resting state functional MRI
RSI	reference safety information
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
SV2A	Synaptic vesicle glycoprotein 2A
T4	thyroxine
TEAEs	treatment-emergent AEs
TSH	thyroid stimulating hormone
US	United States
vs.	versus

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M23-515: A Randomized, Double-blind, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of ABBV-552 in Participants with Mild Alzheimer's Disease

Protocol Date: 13 December 2023

Clinical research studies sponsored by AbbVie are subject to the ICH GCP and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate IRB/IEC, except when necessary to protect the participant from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all participants, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly (within one [1] calendar day to AbbVie, the ethics committees/IRBs [as required] and other appropriate individuals [e.g., coordinating investigator, institution director]):
    - All changes in the research activity and all unanticipated problems involving risks to human participants or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the participants in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development, Neuroscience Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities during the study. The individual activities are described in detail in the **Operations Manual (Appendix F)**.

Study Activities Table

Activity	Screening/Visit 1	Screening/Visit 2	Baseline/Day 1 Visit 3	Day 3 /Visit 4 (Telephone Visit)	Week 1 /Visit 5	Week 2 Visit 6	Week 4/Visit 7 (Telephone Visit)	Week 6 /Visit 8	Week 8/Visit 9 (Telephone Visit)	Week 10 /Visit 10 (Telephone Visit)	Week 12/Visit 11 (Premature Discontinuation)	30-Day Follow Up Visit	Unscheduled Visit
Week Relative to Study Drug Start			0	0	1	2	4	6	8	10	12	16	
Day Relative to Study Drug Start			1	3	8	15	29	43	57	71	85	115	
Study Visit Window (days)				±1	±2	±2	±3	±3	±3	±3	±3	±3	
INTERVIEWS & QUESTIONNAIRES													
Informed consent	✓												
Eligibility criteria	✓												
Medical/surgical history	✓												
Alcohol and nicotine use	✓												
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assess study drug compliance				✓	✓	✓	✓	✓	✓	✓	✓		
Assess Altoida DNS performance compliance				✓	✓	✓	✓	✓	✓	✓	✓		
IMAGING													
MRI	✓										✓		✓
CLINICAL OUTCOMES ASSESSMENTS													
ADAS-Cog 14	✓	✓	✓					✓			✓		✓
C-SSRS	✓		✓		✓	✓		✓			✓	✓	✓
CDR	✓										✓		✓
MMSE	✓										✓		✓
Cogstate Computerized Battery (CBB and ISLT)	✓	✓	✓		✓	✓		✓			✓		✓
Altoida DNS (clinic only)	✓	✓											✓
Altoida DNS (once daily, clinic or home)			✓	✓	✓	✓	✓	✓	✓	✓	✓		
Neuropsychiatric Inventory (NPI)			✓								✓		✓

Activity	Screening/Visit 1	Screening/Visit 2	Baseline/Day 1 Visit 3	Day 3 /Visit 4 (Telephone Visit)	Week 1 /Visit 5	Week 2 Visit 6	Week 4/Visit 7 (Telephone Visit)	Week 6 /Visit 8	Week 8/Visit 9 (Telephone Visit)	Week 10 /Visit 10 (Telephone Visit)	Week 12/Visit 11 (Premature Discontinuation)	30-Day Follow Up Visit	Unscheduled Visit
Week Relative to Study Drug Start			0	0	1	2	4	6	8	10	12	16	
Day Relative to Study Drug Start			1	3	8	15	29	43	57	71	85	115	
Study Visit Window (days)				±1	±2	±2	±3	±3	±3	±3	±3	±3	
EXAM													
12-lead ECG	✓										✓		✓
Height (screening only) and weight	✓							✓			✓		✓
Vital signs	✓	✓	✓		✓	✓		✓			✓	✓	
Physical examination	✓		✓		✓	✓		✓			✓	✓	
Neurological examination	✓		✓		✓	✓		✓			✓	✓	
LAB													
HAV-IgM, HBsAg, HCV Ab, HIV Ab	✓												
Drug and alcohol screen	✓												
Urine pregnancy test (for WOCBP only)			✓			✓		✓			✓		✓
Serum pregnancy test (for WOCBP only)	✓												
FSH test (for postmenopausal females ≤ age 55 only)	✓												
Blood chemistry, hematology (CBC), urinalysis	✓		✓		✓	✓		✓			✓	✓	✓
Blood samples (plasma) for PK			✓		✓	✓		✓			✓		✓
Blood biomarker sample (plasma)			✓								✓		
Blood biomarker sample (DNA) – collected at any visit			✓										
Blood biomarker sample (PAXgene RNA) – optional collection			✓								✓		
TREATMENT													
Randomization/drug assignment			✓										
Dispense study drug			✓		✓	✓		✓					✓
Perform drug reconciliation					✓	✓		✓			✓		✓

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	10 June 2022
Version 2.0	22 September 2022
Version 3.0	13 January 2023
Version 4.0	13 October 2023

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

- Protocol Section 5.2 – Updated contraception requirements for male.
- Operations Manual (Appendix F), Section 2.1 – Deleted footnote in Screening Visit 1
- Operations Manual (Appendix F), Section 1, Updated back-up fax number.
- Operations Manual (Appendix F) Section 4.2 – Updated fax number.

APPENDIX F. OPERATIONS MANUAL