NIHR RDN commercial eligibility & feasibility submission form

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Section B: The information in this section has been provided by the commercial company in the non-confidential section of the submission. While catergorised as non-confidential for the purposes of the RDN feasibility and eligibility process, the information is COMMERCIALLY SENSITIVE and should be managed as defined in the RDN business processes. It may be distributed to third parties involved in supporting the delivery of RDN feasibility and eligibility process WITHOUT the need for a formal RDN Confidential Disclosure Agreement, however the confidentiality terms of the Performance and Operating Framework for RDN Host or Partner Organisations remain applicable.

Full study title	CN012-0023: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of KarXT for the Treatment of Agitation Associated with Alzheimer's Disease
Study protocol reference number	CN012-0023

SPONSORSHIP & FUNDING

B4: Name of research sponsor:	Bristol Myers Squibb
B5: Is Research Funder different to above?	No
B5a: If yes, please specify:	
The name and organisation of the Chief Investigator is required to submit a request for the Study Resource Review service.	
B6: Name of Chief Investigator	tbc
B6a: Chief Investigator Organisation	tbc No identified LCRN or health board

STUDY TYPE

B8: Category of research	Clinical trial of an investigational medicinal product
B8a: Are any of the investigational medicinal products (IMPs) advanced therapy investigational medicinal products (ATIMPs)?	No
B11: Phase of development	
N/A	No

I	No
II	No
III	Yes
IV	No
B12a: If this is a Phase IV study, is this at the request of regulators?	
B12b: Category of medical device study	
B12d: Phase of clinical investigation	
B12e: Is this post-marketing study a regulatory follow up requirement?	

APPROVAL

B6b: Select the type of approval you will be applying for	HRA Approval
B6c: Provide details of the ethical approval you will be applying for	
B6d: Explain why you will not be applying for ethical approval	
B6e: Date of approval submission	01/05/2025

STUDY DESIGN

B13: What is the disease indication / target patient population for the study?	Agitation associated with Alzheimer's Disease
B13a: Is your trial recruiting UK subjects under 16 years of age?	No
B13b: If Yes, has a Paediatric Investigation Plan (PIP) been developed?	
B13c: If a PIP has not been developed, please give details why not:	
B15: Please briefly describe the treatment and (if applicable) the randomisation schedule. Please include details of all study related treatments including comparator drugs, other protocol	CN0120023 and CN0120024 are two Phase 3 randomized, double-blind, placebo controlled, multicenter, global studies of KarXT in participants with

specified treatment regimens and the ratio of treatment groups.	agitation related to AD. The primary objective of the studies will be to evaluate the efficacy of KarXT compared with placebo in the treatment of participants with agitation associated with AD, as measured by the Cohen Mansfield Agitation Inventory (CMAI). Approximately 710 participants (anticipating a ~55% screen-fail rate) will enroll in each study, such that approximately 320 participants per study will be randomized (1:1) into the Double-blind Randomized Treatment Period to receive either KarXT or placebo. The studies include up to a 30-day Screening Period, a 14-week Double-blind Treatment Period, and a Safety Follow-up (SFU) visit two weeks following the end of treatment (EOT). The maximum duration after screening for each participant will be 16 weeks. Screening Period (7-30 Days) Consented participants will enter the Screening Period (7-30 Days) for assessment of study eligibility. During Screening, each participant or informant/caregiver will provide medical and psychiatric history. The International Prostate Symptom Score (IPSS, males only), MMSE, NPI-NH, CMAI, CGI-S, CSSRS, BARS, AIMS, and ADAS-Cog-13 tests will be performed, as well as ECG, clinical laboratory assessments, and physical examination. Any prohibited concomitant medications will be tapered and discontinued during the Screening Period. The Screening Period may be extended up to 2 weeks with approval of the Sponsor/Medical Monitor. To qualify for study enrollment, participants must meet the eligibility criteria including the following clinical criteria at Screening: • NPI-NH Agitation/Aggression Score ≥ 4 • CMAI Factor 1 Positivity • CGI-S score ≥ 4 (moderate) Randomized Treatment Period (14 Weeks) Eligible participants will be randomized (1:1) to KarXT or matching placebo. Eligibility for randomization requires: • CGI-S score ≥ 4 (moderate) at Baseline (Visit 2/Day 1) • NPI-NH Agitation/Aggression ≥ 4 • CMAI Factor 1 Positivity. Safety Follow-up Period (2 Weeks) A Safety Follow-up visit will occur 2 weeks after the EOT/ET visit.
B15a: Are the study drugs / comparators being provided or will they be reimbursed?	Provided
B16: Primary objective(s)	

To evaluate the efficacy of KarXT compared with placebo in the treatment of participants with agitation associated with AD as measured by the CMAI.

B17: Secondary objective(s)

- To evaluate the efficacy of KarXT compared with placebo in the treatment of participants with agitation associated with AD as measured by the CGI-S score as related to agitation.
- To evaluate the efficacy of KarXT compared with placebo in the treatment of participants with agitation associated with AD as measured by the: NPI-NH Total Score, CMAI Factors, and CMAI responder rates.
- To evaluate the safety and tolerability of KarXT compared with placebo in this participant population.

B18: Full inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:
• Is a male or female aged 55 to 90 years, inclusive, at Screening (Visit 1)
• Participants or their legally acceptable representative must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This ICF must be obtained before performing any protocol-related procedures that are not part of normal patient care. If the participant is deemed not competent to provide IC, the following requirements for consent must be met:
o The participant's legally acceptable representative (LAR) must provide ICo The participant must provide informed assent
• Diagnosis of probable Alzheimer disease, defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria
• Mini-Mental State Examination (MMSE) score of 5 to 22, inclusive, at Screening (Visit1)
• Has a magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain (completed within the past 5 years) taken during or subsequent to the onset of dementia to rule out other central nervous system (CNS) disease that could account for the dementia syndrome (e.g., major stroke, neoplasm, subdural hematoma). If not available, a non-contrast brain MRI or

non-contrast head CT must be done during screening. (Note: if waiting for MRI or CT results, an extension [up to 2 weeks] of the Screening Period may be allowed with approval of the Sponsor/Medical Monitor)
• Stable living environment for at least 6 weeks prior to Screening (Visit 1). Participants are eligible if they are in nursing homes, assisted living facilities, memory care facilities, or living at home.
• Capable of self-locomotion (alone or with the aid of an assistive device; wheelchairs and other mobility aids are acceptable)
• Have one identified caregiver who should have sufficient contact (approximately 10 hours a week or more) and is willing to:
o Attend all visits and report on participant's status
o Oversee participant compliance with medication and study procedures
o Participate in the study assessments and provide IC to participate in the study
o The caregiver role in non-institutionalized settings may or may not be the same individual who fulfills the role of caretaker. In institutionalized settings (e.g., nursing homes or memory care facilities), a caregiver may be a staff member of the institutionalized setting or another individual (e.g., family member, family friend, hired professional caregiver) who fulfills the above criteria.
• History of agitation with onset at least two weeks prior to Screening (Visit 1).
• AD participants are required to have NPI Agitation/Aggression score ≥ 4 at Screening (Visit 1) and Baseline (Visit 2).
• CGI-S ≥ 4, as related to agitation, at Screening (Visit 1) and Baseline (Visit 2)
• At least 1 of the following 3 criteria must be established from the CMAI at Screening (Visit 1) and Baseline (Visit 2; CMAI Factor 1 Positivity):
o 1 or more aggressive behaviors occurring several times per week
o 2 or more aggressive behaviors occurring once or twice per week
o 3 or more aggressive behaviors occurring less than once per week
• If the participant is taking a cholinesterase inhibitor and/or memantine, they must have been on a stable dose for 6 weeks prior to Screening (Visit 1) and be willing to maintain a stable dose for the duration of the study
• Participant is willing and able to visit the clinic in an outpatient setting for the study duration, follow instructions, and comply with the protocol requirements

• BMI must be within 18 to 40 kg/m2 inclusive
• Individuals of childbearing potential (IOCBP), or male participants whose sexual partners are IOCBP, must be able and willing to use at least 1 highly effective method of contraception during the study and for at least 1 menstrual cycle (e.g., 30 days) after the last dose of IMP. A female participant is considered to be an IOCBP after menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). For the definition and list of highly effective methods of contraception, refer to the appendix for contraception guidelines. Sperm donation is not allowed for 30 days after the final dose of the IMP.

B19: Full exclusion criteria

Participants are excluded from the study if any of the following criteria apply:
• Agitation symptoms that are primarily attributable to a condition other than the AD causing the dementia
• History of major depressive episode with psychotic features during the 12 months prior to Screening (Visit 1)
• History of bipolar disorder, schizophrenia, or schizoaffective disorder
• Significant or severe medical conditions including pulmonary, hepatic*, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, cardiovascular, or oncologic disease or any other condition or ongoing treatment that, in the opinion of the Investigator, could jeopardize the safety of the participant, ability to complete or comply with the study procedures or validity of the study results
*Note: participants with any grade of hepatic impairment will be excluded from the study
• History of ischemic stroke within 12 months prior to Screening (Visit 1) or any evidence of hemorrhagic stroke
• History of cerebral amyloid angiopathy, epilepsy, CNS neoplasm, unstable thyroid function, or unexplained syncope
• History of any of the following:
o New York Heart Association Class II or greater congestive heart failure
o Grade 2 or greater angina pectoris
o Sustained ventricular tachycardia

o Ventricular fibrillation
o Torsade de pointes
o Implantable cardiac defibrillator
• Myocardial infarction within the 6 months prior to Screening (Visit 1)
• Personal or family history of symptoms of long QT syndrome as evaluated by the Investigator
• Human immunodeficiency virus (HIV), cirrhosis, biliary duct abnormalities, hepatobiliary
carcinoma, and/or active hepatic viral infections as indicated by medical history or LFT results
• History of (or at high risk for) urinary retention, gastric retention, or narrow-angle glaucoma
as evaluated by the Investigator
• Male participants are excluded from the study if any of the following criteria apply:
o History of bladder stones
o History of recurrent urinary tract infections
o Serum prostate-specific antigen > 10 ng/mL at Screening (Visit 1)
• An IPSS score of 5 (almost always) on items 1, 3, 5, or 6
o A sum of scores on IPSS items 1, 3, 5, and 6 of ≥ 9
• History of irritable bowel syndrome (with or without constipation) or serious constipation
requiring treatment within the last 6 months
• Risk of suicidal behavior during the study as determined by the Investigator's clinical
assessment and/or C-SSRS as confirmed by the following:
o Answers "Yes" on items 3, 4, or 5 (C-SSRS – ideation) with the most recent episode
occurring within the 2 months before screening or,
o Answers "Yes" to any of the 5 items (C-SSRS behavior) with an episode occurring
within the 12 months before Screening
• Clinically significant abnormal finding on the physical examination, ECG, or clinical
laboratory results at Screening (Visit 1)
• Urine toxicology screen is positive for substances other than cannabis or benzodiazepines (both
cannabis and short- or medium-acting benzodiazepines are allowed in limited quantities during
the first 6 weeks of the study) unless approval has been given by the Medical Monitor
• Recent history of receiving monoamine oxidase inhibitors, anticonvulsants (e.g., lamotrigine,
divalproex), mood stabilizers (e.g., lithium), tricyclic antidepressants (e.g., imipramine, desipramine), or any other psychoactive medications except for as- needed anxiolytics (e.g.,
lorazepam)

	• Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors taken at a stable dose for at least 8 weeks prior to Screening (Visit 1) may be permitted • Mirtazapine or trazodone may be used as a hypnotic if started at least 8 weeks prior to Screening (Visit 1) • If, in the opinion of the Investigator and/or Sponsor/Medical Monitor, participant is unsuitable for enrollment in the study or participant has any finding that, in the view of the Investigator and/or Sponsor/Medical Monitor, may compromise the safety of the participant or affect his/her ability to adhere to the protocol visit schedule or fulfill visit requirements • Known acute infection or symptomatic illness within 2 weeks before Screening (Visit 1); local testing can be done at the discretion of the Investigator. Rescreening can be permitted after the infection/illness is resolved and consultation with the medical monitor. • Unable to taper and discontinue a concomitant medication that would preclude participation in this study • Prior exposure to KarXT • History of hypersensitivity to KarXT excipients or trospium chloride

PRODUCT INFORMATION

B7: Name(s) and class(es) of investigational product	BMS-986510
B7a: Route of study drug(s)	
Inhalational	No
Intramuscular (IM)	No
Intranasal	No
Intravenous (IV)	No
Oral	Yes
Rectal	No
Subcutaneous (SC)	No
Sublingual / buccal	No
Transdermal	No

Vaginal	No
Other (please specify)	No
B7b: Other route of study drug(s)	
B7c: Type of investigational product / GMDN classification	
Active implantable devices	No
Anaesthetic and respiratory devices	No
Dental devices	No
Electro mechanical medical devices	No
Hospital hardware	No
In vitro diagnostic devices	No
Non-active implantable devices	No
Ophthalmic and optical devices	No
Reusable devices	No
Single use devices	No
Assistive products for persons with disability	No
Diagnostic and therapeutic radiation devices	No
Complementary therapy devices	No
Biological-derived devices	No
Healthcare facility products and adaptations	No
Laboratory equipment	No
Other	No
B7d: Other	
B9: Who is responsible for the development of the product(s)?	Bristol Myers Squibb

DELIVERY CONSIDERATIONS

B27: What is the care setting you anticipate for	

each of the following activities (select Not known if you are unsure which setting applies):

B27a: Participant identification

Primary care	Yes
Hospital	Yes
Community based	No
Residential care	Yes
Not known	No
Not applicable	No

B27b: Participant recruitment

Primary care	Yes
Hospital	Yes
Community based	No
Residential care	No
Not known	No
Not applicable	No

B27c: Participant treatment

Primary care	Yes
Hospital	Yes
Community based	No
Residential care	No
Not known	No
Not applicable	No

B27d: Participant follow up

Primary care	Yes
Hospital	Yes
Community based	No

Residential care	No
Not known	No
Not applicable	No
B22: Does the study involve any investigations using ionising radiation (this includes examinations which would be considered standard care in this patient group)?	No
B22a: Does the study involve any additional investigations using ionising radiation not viewed as part of standard care, (please note there may be variation in practice between trial sites)?	
B23: Are there any other study requirements / practicalities which may have an impact on feasibility?	There are several specialist rating scales that sites will need to be either familiar with or trained on before they can open the study (e.g. CMAI, IPSS (males only), MMSE, NPI-NH, CGI-S, CSSRS, BARS, AIMS, and ADAS-Cog-13 tests. Also capacity to perform an ECG.

TRIAL MANAGEMENT

B33a: Planned Final Protocol date	31/01/2025
B33e: Duration of study treatment	0 Years 3 Months 7 Days
B33f: Duration of follow up	0 Years Months 14 Days
B33j: Is or will the study be running globally i.e. outside of the UK?	Yes
UK Study Timelines	
B33b: Planned date to have site selection finalised	20/01/2025
B33c: Planned FPFV (First Participant First Visit)	01/07/2025
B33d: Planned LPFV (Last Participant First Visit)	01/11/2027
B33g: Planned LPLV (Last Participant Last Visit)	30/04/2028

Global Study Timelines

B33h: Planned FPFV (First Participant First Visit) globally	01/07/2025
B33i: Planned LPLV (Last Participant Last Visit) globally	30/04/2028

RECRUITMENT TARGETS

B34: Is the study already open to recruitment in other countries?	No
B35a: If yes, have any issues with recruitment been identified?	
B35b: Please provide the global recruitment to date versus target	
B36: What is the target recruitment:	
B36a: In the UK?	tbc
B36b: In the EU (if applicable)?	tbc
B36c: Worldwide (if applicable)?	710
B36d: What is the minimum recruitment target for individual sites?	tbc
B38: If worldwide recruitment applies, is this competitive?	Yes
B39: What is the planned total number of study sites within the UK?	10

SITE INTELLIGENCE

B24: In order for the NIHR RDN to best support your study, we need to understand how far you have progressed in the site selection process. Therefore please provide details of sites which you have already contacted about the study and their current feasibility status. This is important, so that we do not duplicate work or cause misunderstanding when we discuss your study with investigators.	

Name of site/practice	Status	Investigator Name	Investigator Email Address	Investigator Specialty	Additional Information

SITE IDENTIFICATION

B28: How many sites would you like us to identify as part of this Site Identification service?	10
B31a: In which geographical locations would you like us to identify sites? (for UK wide, tick all four nations)	
England	Yes
Northern Ireland	Yes
Scotland	Yes
Wales	Yes
B32: Are there any specific questions in relation to deliverability for this particular study that you would like interested sites to respond to?	Yes
As standard, sites will provide information around their research expertise and a suggested target recruitment for your study.	
B32a: Additional question 1	This study will recruit moderate to severe patients who have Alzheimer's disease with agitation. In your experience, where do are these patients usually seen? Keen to know % of patients being seen in GP care, versus hospital or memory clinics etc.
B32b: Additional question 2	Are there any privacy concerns around audio/video recordings of assessment/rater scales being taken via an official tablet during visits?
B32c: Additional question 3	What percentage of patients with AD Agitation have a caregiver that sees the patients a minimum of 10 hours per week and would be able to accompany patients to study visits? (Note: this can be a legally authorized representative e.g. head nurse, etc.)
B32d: Additional question 4	Would your facilities allow for a private room to be available for the length of the visit including a carer being present to accompany the participant on their

visits?

CONFIRMATION

B42: Please provide any additional information or questions you have below :

BMS has contacted the following sites already and therefore do not need additional feedback from them: Prof Clive Ballard, and Ross Dunne in Manchester. Thank you!

The information provided in the submission will be treated as CONFIDENTIAL however it may be distributed to third parties without the need for a formal confidentiality agreement, to support site feasibility. NIHR RDN site level feasibility is based on the information supplied, the schedule of events and any additional information supplied that can be circulated without the need for a CDA.