Title Page

Protocol Title:
A Randomized, Placebo-Controlled, Double-Blind Study of XPro1595 in Patients with Early Alzheimer's Disease with Biomarkers of Inflammation

Protocol Number: XPro1595-AD-02;

EU CT: 2023-505396-71-00

Compound: XPro1595

Indication: Early Alzheimer's Disease

Study Phase: Phase 2

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Protocol Version/Date	Document Version	Approval Date
	Original (v1.0)	08 September 2021
	Amendment 7.0	13 May 2024

CONFIDENTIALITY NOTICE

Sponsor Signatory:

Protocol Number: XPro1595-AD-02

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A Randomized, Placebo-Controlled, Double-Blind Study of XPro1595 in Patients with Early Alzheimer's Disease with Biomarkers of Inflammation

I, the undersigned, have approved of the XPro1595-AD-02 clinical trial protocol.

PPD , PhD PPD	**Date**
PPD , MD INmune Bio PPD	**Date**

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR AGREEMENT

Protocol Number: XPro1595-AD-02

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I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by INmune Bio or specified designees. I will discuss the material with them to ensure that they are fully informed about XPro1595, understand this study, and are able to comply.

_____ _____

Principal Investigator Name (printed) Signature

_____

Date

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1. Introduction

1.1. Study Rationale

The Phase 2 is a randomized clinical study using XPro1595 to treat patients with Early Alzheimer's Disease with biomarkers of inflammation (ADi). Early ADi patients are defined as patients with Mild Alzheimer's Disease or Mild Cognitive Impairment with a biomarker of inflammation. The goal of this Phase 2 Alzheimer's study is to determine whether 1.0 mg/kg XPro1595 confers a benefit on cognition, function, and biomarkers of white matter and to further evaluate safety and tolerability. The objectives of this study are to determine the safety, tolerability, and efficacy of XPro1595 in patients with early ADi.

1.2. Background

1.2.1. Disease Background

Alzheimer's disease and related dementia afflicts 44 million people worldwide, a number projected to triple by 2050 at a cost of more than $1 Trillion USD (Alzheimer's Association). Mild cognitive impairment (MCI) is an early stage of memory loss or other cognitive ability loss (eg., difficulty in word finding or losing items) in individuals who maintain the ability to independently perform most activities of daily living. People with MCI due to Alzheimer's disease (AD) have biomarker evidence of Alzheimer's (amyloid) and may progress to AD. Approximately 12-18% of people over 60 years of age have a diagnosis of MCI (Alzheimer's Association, 2020). Despite the widespread acknowledgement of this public health crisis and committed resources, anti-amyloid therapies that modestly slow the rate of decline are the only approved disease modifying treatments for early AD in the United States.

To effectively treat AD, therapies that target non-amyloid mechanisms are required. The brain changes associated with early AD start decades before symptoms appear in the brain, indicating a progressive disorder as one ages (Parker, Sloane et al., 2019). Immune dysregulation is associated with both aging and dementia (Lutshumba, 2021). In a similar manner, TNF increases with age, suggesting that TNF may have a role in earlier stages of the disease (Parker, Sloane et al., 2019). Further, TNF has been mechanistically linked to all aspects of early AD, including, Aβ and tau pathology, impaired synaptic plasticity, and cell death.

1.2.2. Tumor Necrosis Factor

Tumor necrosis factor biology is complex; it is a multifunctional cytokine that plays important roles in cellular events such as cell survival, proliferation, differentiation, and death. TNF exerts its biological functions through activating distinct signaling pathways such as NF-κB and JNK and is produced as functionally distinct tmTNF and solTNF molecules. Typically, solTNF interacts with TNFR1, which is responsible for inflammation and apoptosis; in the tumor microenvironment (TME), it is responsible for upregulation of the many mechanisms that help the tumor evade the patient's immune system and immunotherapy. In AD, solTNF increases pathological processing and accumulation of both amyloid and tau, induces changes in synaptic function, and drives cell death. In general, tmTNF/TNFR2 interactions promote cell survival and function, protein synthesis, immunocompetence, and remyelination. The most clinically relevant consequences of blocking tmTNF within the CNS is progressive multifocal leukoencephalopathy and demyelination. As a result, commercially available nonselective TNF inhibitors are contraindicated for neurologic

disease. In patients with AD, solTNF can perpetuate AD pathology as TNF-induced amyloid and tau become TNF-inducing damage-associated molecular patterns (DAMPs).

The first hint that TNF might be involved in AD came nearly 3 decades ago when plasma levels of TNF were found to be elevated in AD patients (Fillit, 1991). Subsequent analyses have found increased TNF in the CSF of AD patients (Tarkowski, 2003) and histological analysis of postmortem AD brains have shown that TNF is co-localized with plaques (Dickson, 1997). TNF levels have been shown to correlate with disease progression (Paganelli, Di et al., 2002). Longitudinal studies report that age, the greatest risk factor for AD, accounts for more than 80% of the explained variance for increased TNF (Parker, Sloane et al., 2019). Finally, a review of more than 60 million insurance claims shows the risk of developing AD is 50% to 70% less than the general population in patients treated with anti-TNF therapies despite the fact that the diseases for which these drugs are indicated increasing risk 800% over the general population (Chou, Kane et al., 2016). Notably, this risk was reduced only in patients treated with TNF inhibitors and not by any of the other immunosuppressive therapies (Chou, Kane et al., 2016).

1.2.3. INmune Bio Investigational Product Background

XPro1595 is a recombinant protein variant of the soluble form of TNF monomer; the native solTNF is a homotrimer of cleaved monomers. XPro1595 has [redacted] mutations engineered in the TNFR binding interfaces, which eliminate its ability to bind to or activate TNFRs (TNFR1 and TNFR2).

XPro1595 is a first-in-class agent that acts by a novel "dominant-negative" mechanism to eliminate pro-inflammatory solTNF homotrimers through exchange of monomeric subunits between the compound and the native cytokine, whereby the native homotrimer becomes an inactive heterotrimer. Because XPro1595 cannot bind TNFR, it does not activate TNF-associated signaling pathways. XPro1595 selectively alter solTNF, acting only by exchanging subunits with solTNF, thereby destroying the biological activity of solTNF, but not altering the function of membrane bound tmTNF because each monomeric subunit of the homotrimer is anchored to the membrane. This selectivity differentiates XPro1595 from currently available nonselective TNF inhibitors that block the function of both solTNF and tmTNF.

XPro1595 has been shown to inhibit solTNF in various cell-based assays of TNF bioactivity including activation of apoptosis, NFκB translocation, and NFκB-mediated gene activation (see Steed and Tansey et al., 2003).

Nonclinical Safety Data

Non-clinical safety pharmacology was assessed in a 13-week non-human PK/toxicology primate study. No dose limiting SAE were reported. All animals completed the 13-week study. There were no deaths. Necropsy has been performed on all animals and there were no unusual findings. The presence of vacuolated macrophages in lymph nodes and a small number of other organs were observed and is consistent with the uptake and metabolism of the pegylated protein test article and are believed to be benign. Further details can be found in the Investigator Brochure (IB).

There were no clinically observable consequences of either toxicity. The NOAELs were considered to be 10 mg/kg/day administered SC QD to rats, and 30 mg/kg administered SC QOD to monkeys. The HED was considered to be 11.3 mg/kg/week in rats, and 34 mg/kg/week in monkeys.

Pharmacology in Nonhuman Primates

Because the drug is given as a SC injection, the trough level must be high enough to neutralize the expected level of sTNF in blood. The target level in non-human primate at trough is based on the estimated maximum sTNF level in pathologic tissue for the indication. sTNF levels in synovial fluid of patients with advanced disease can be as high as 20 ng/mL (avg: 6 ng/mL). The goal was for the trough level of the drug to be high enough to prevent the formation of any function sTNF – a target level of 1 µg/mL of blood. This was modeled in nonhuman primates. Allometric scaling of cyno PK data suggests weekly dosing of 1.0 mg/kg SC in humans will sustain >1 µg/mL trough serum levels of XPro1595.

Overview of Clinical Studies

Two Phase 1 clinical trials were run using an open label dose escalation strategy. In each trial, patients received either 0.3, 0.6, 1.0, or 3.0 mg/kg by SC injection until tumor progression (oncology Phase 1; completed) or for 12 months (AD Phase 1-completed). The trials were run in Australia under the authority of the TGA.

The Phase 1 open label dose escalation trial in patients with advanced solid tumors enrolled 11 patients with a variety of solid tumors who had failed multiple lines of previous therapy, some including immune checkpoint inhibitors (ACTRN12618000675224). Inclusion criteria included the need for a hsCRP > 4.0 mg/L. Following guidance provided by the FDA as part of the previous IND filing, drug levels were determined by using an assay for human sTNF. Patients received XPro1595 by SC injection once a week until progression. All patients discontinued due to progressive disease. No patients discontinued drug due to an AE or SAE.

The target trough level in the oncology Phase 1 was 2 logs greater than the expected maximum TNF level in patients' blood. Depending on the disease, pathologic blood levels were rarely > 100 ng/mL. The target trough level was set at > 10,000 ng/mL to ensure at least 2 logs excess of XPro1595 in the blood – the amount needed to neutralize > 99.9% of circulating TNF.

Trough levels for the 1 mg/kg and 3 mg/kg exceed 10,000 ng/mL at all time points up to the 29 days of the proposed study. The drug level exceeds 10,000 ng/mL within 8 hours of the first dose. Three days after the first dose, the drug level was more than 6 times the desired minimal trough level.

A second Phase 1, open-label dose-escalation trial in patients with inflammation with AD (ClinicalTrials.gov Identifier: NCT03943264) was conducted. The trial enrolled 20 patients with the diagnosis of AD who had biomarkers of inflammation including 1 of: i) hsCRP > 1.5 mg/L; ii) HbA1c > 6%; iii) ESR > 10 sec and/or iv) APOE4. The primary goal of the trial was to evaluate whether XPro1595 reversed neuroinflammation in patients with AD. Other than safety, i) inflammation in blood and CSF; ii) white matter free water (neuroinflammation) by MRI; iii) neurodegenerative/neuroplasticity biomarkers, iv) white matter/gray matter brain quality by MRI, v) cognition and or cognitive performance, and vi) neuropsychiatric changes were assessed.

Twenty patients with AD (5M/15F) with a mean age of 68 years (range 56-86 years) were treated in Study XPRO1595-AD with 1 of 3 doses, 0.3 mg/kg (N = 5), 0.6 mg/kg (N = 6), and 1.0 mg/kg (N = 9). Patients received as many as 48 doses. The drug has been well-tolerated with no serious AEs, although 3 patients discontinued treatment due to injection site reaction after their second dose. A further analysis of AEs and early results of the biomarker data is available in the IB.

A Phase 2, double-blind, randomized, placebo-controlled clinical trial of XPro1595 in participants with pulmonary complications due to COVID-19 infection (ClinicalTrials.gov Identifier: NCT04370236), has also been completed. The goal of that study was to determine whether XPro1595 can prevent the progression of respiratory complications in COVID-19 patients. Eligible patients received a single injection of 1.0 mg/kg XPro1595 or placebo at randomization and a second injection if they remained in the hospital 1 week later for a maximum of 2 doses.

79 patients were randomized, and 77 were dosed. Safety and efficacy have been reported in a planned futility analysis and the study was terminated based on futility.

A detailed description of the chemistry, pharmacology, efficacy, and safety of XPro1595 is provided in the IB.

1.3. Benefit/Risk Assessment

This will be the third clinical trial using XPro1595 and second study of XPro1595 in patients with ADi. XPro1595 has been well tolerated in all clinical trials and in pivotal toxicology studies conducted in rats and cynomolgus monkeys. Until there is more data from human trials, all risks are potential and are based on animal data and events that have been noted with other TNF-antagonists.

Injection site reactions are common with protein biologics delivered by subcutaneous injection and may occur. These reactions are typically observed within the first four injections and most often present as mild in duration. Rarely there is regional cutaneous inflammation. Management of injection site reactions should be discussed with the Medical Monitor (See Section 5.0 and associated ISR supplemental guide regarding pre-meds and on-going management of ISRs).

Allergic reactions may occur. These manifest with symptoms typical of serum sickness or a type 2 hypersensitivity reaction which could include symptoms of fever/chills and/or joint pain.

Anaphylaxis has not been seen, but theoretically, as with any protein therapeutic, could occur. The risk for anaphylaxis is most probable with the first two doses. Supportive measures should be available for the first three doses and may include, but are not limited to epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen. It is recommended to observe patients a minimum of 2 hours after the first three doses.

While disease-modifying treatment has not been approved for AD in regions in which this study will be conducted, the approval of one or more anti-amyloid therapies (i.e., aducanumab, lecanemab, or donanemab) is expected in some regions during the trial. The use of XPro1595 would not prevent any participant in this study from receiving a potential therapeutic benefit from an anti-amyloid therapy should they begin anti-amyloid treatment after they have participated in this clinical trial.

Currently, XPro1595 is being evaluated as a potential therapeutic protein with a planned once a week SC injection in humans. As with any injected therapeutic protein, there is the potential for an anti-drug immune response. Consequently, antibodies which develop in response to drug treatment (immunogenicity) to native TNF or XPro1595 is a potential safety concern and will be closely monitored throughout the clinical studies.

Anti-TNF antibody therapy has been previously reported to increase the risk of serious infections and malignancy (Bongartz, Sutton et al., 2006). A possible explanation for the increased risk of infection and other side effects arising from the use of current anti-TNF agents comes from studies using TNF knockout and tmTNF knock-in mice, which demonstrate that tmTNF signaling plays a role in immunity to listeria and mycobacterial infection (Olleros, Guler et al., 2005). Consistent with this hypothesis, XPro1595 (which selectively targets sol TNF) did not compromise the innate immune response and has demonstrated improved survival when compared to etanercept in murine models of infectious challenge with *Listeria monocytogenes* and *M. tuberculosis* (Olleros, Vesin et al., 2009; Zaleysky, Secher et al., 2007).

Increased risk of malignancy is considered likely to be attributable to anti-TNF antibody therapy inhibiting NK/DC crosstalk mediated by tmTNF. NK/DC crosstalk leads to a high Th1 response (which efficiently controls Tumor growth). By selective targeting of solTNF, XPro1595 does not interfere with NK/DC crosstalk.

Thus, infection and malignancy risks associated with registered anti-TNF therapies are not expected in patients treated with XPro1595.

XPro1595 should not be administered to subjects with reported hypersensitivity to any of the excipients listed in the IB.

There are no human reproductive or fetal developmental toxicology data available for XPro1595. The teratogenicity of XPro1595 is not known. Women who are pregnant or who are trying to become pregnant should not participate in clinical studies of XPro1595. Women of childbearing potential must use 2 effective forms of contraception including at least 1 barrier method during the study and for 30 days after last dose. Men with partners of childbearing potential must use a highly effective method of contraception during the study and for 90 days after last dose of study drug. Please refer to Appendix 4 for specific information on contraception requirements.

The maximum tolerated dose of XPro1595 has not been established. Doses in this study should not exceed 1.0 mg/kg.

In a case of severe toxicity or overdose with XPro1595, the subject should be managed with standard supportive care directed at the underlying problems. No specific antidote for XPro1595 is available.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of XPro1595 may be found in the IB.

1.3.1. Benefit Assessment

A key element of the study is to focus on early AD patients who are most likely to benefit from targeted anti-TNF therapy by identifying and enrolling patients with inflammation. Inflammatory biomarkers have been identified that are associated with or predict risk for disease. Patients with at least 1 of the designated inflammatory biomarkers described will be eligible for the current study. The success of anti-TNF drugs in other disease states has yielded considerable data that supports stratifying AD patients based on inflammatory biomarkers. Inflammation can be easily measured in blood. hsCRP, HbA1C, ESR, and APOE4 have been shown to be representative of underlying inflammation and potential predictors of patients that might respond to anti-inflammatory- treatment (Raison, Rutherford et al., 2013; Siegel and Melmed, 2009).

1.3.2. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with XPro1595 are justified by the anticipated benefits that may be afforded to patients with early ADi.

2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of XPro1595 compared with placebo on cognitive performance in patients with early ADi	Change in the Early and Mild Alzheimer's Cognitive Composite (EMACC) from Baseline to Week 24 in the following assessments: • International Shopping List Test-Immediate Recall • Digit Span Forward and Backward • Category Fluency Test (DKEFS) • Letter Fluency Test (DKEFS) • Trail Making Test Parts A and B • Digit Symbol Coding Test
Key Secondary	
To assess the effect of XPro1595 compared with placebo on cognition and global function in patients with early ADi	Change from Baseline to Week 24 in Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)
To evaluate the effect of XPro1595 compared with placebo on E-Cog in patients with early ADi	Change from Baseline to Week 24 in Everyday Cognition (E-Cog)
To assess the effect of XPro1595 compared with placebo on noncognitive behavioral symptoms in patients with early ADi	Change from Baseline to Week 24 in (Neuropsychiatric Inventory [NPI-12] study partner items)
Secondary	
To assess the effect of XPro1595 compared with placebo on ADL in patients with early ADi	Change from Baseline to Week 24 in Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS--MCI-ADL)
To assess the efficacy of XPro1595 compared with placebo on blood inflammatory and neurodegeneration biomarkers in patients with early ADi	Change from Baseline to Week 24 in blood inflammatory and neurodegeneration biomarkers.

Objectives	Endpoints
To assess the efficacy of XPro1595 compared with placebo on brain structure neurodegeneration in patients with early ADi	Changes from Baseline to Week 24 in volumetric magnetic resonance imaging (MRI)
To assess the safety and tolerability of XPro1595 compared with placebo in patients with early ADi	Changes from Baseline to Week 24 in the following assessments: • Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Vital signs • Clinical laboratory values • Physical exam findings • Electrocardiogram (ECG) • Columbia-Suicide Severity Rating Scale (C-SSRS) Change from Baseline to Week 12 and Week 24 in T2-weighted and hemorrhagic brain lesions on MRI.
Exploratory	
To evaluate the effect of XPro1595 compared with placebo on goal attainment scores in patients with early ADi	Change in individual goals based on the Goal Attainment Scale (GAS)
To evaluate the effect of XPro1595 compared with placebo on delayed word list recall in patients with early ADi	Change in delayed recall of the International Shopping List (ISRL)
To assess the effect of XPro1595 compared with placebo on *DSST* in patients with early ADi	Change from Baseline to Week 24 in DSST test.
To assess the efficacy of XPro1595 compared with placebo on myelin in patients with early ADi	Change from Baseline to Week 24 in myelin content of the normal appearing (outside of white matter hyperintensities) white matter
To evaluate the predictability of the patient response observed after placebo administration and potential influence of study partners on outcome evaluation	Association of baseline patient features with the placebo response using Placebell©TM MCI models

3. Study Design

3.1. Overall Design

This study is designed as a double-blind randomized, placebo-controlled, study investigating the safety, tolerability, and efficacy of XPro1595 in patients with early ADi. The planned dose is 1.0 mg/kg of XPro1595 and matching placebo.

AD patients that meet the diagnostic criteria of MCI of probable AD (Jack et al. 2018; NIA-AA) or Mild AD (McKhann, 2011) that are confirmed to have MCI or Mild AD through screening assessments will be randomized 2:1 (XPro1595: placebo) and treated with 1.0 mg/kg of XPro1595 or placebo as a SC injection once a week for 23 weeks. Randomization will be stratified by indication (MCI, mAD) and sex (Male, Female). Biological measures including blood and imaging will be taken at Baseline/Screening, 3, and 6 months. The EMACC will be administered every 6 weeks for 6 months. All other clinical rating measures will be completed every 3 months (Baseline/Screening, 3, and 6 months).

Patients will be seen in the clinic when assessments need to be performed. Visits that are only drug administration may be performed in the clinic or administration may occur in the patient's home through self-administration, study partner administration or support from a planned third party.

3.1.1. Study Duration for Participation

Patients will be on the study for approximately 33 weeks. Data will be collected as detailed in the Schedule of Activities.

3.1.2. Number of Patients

Approximately 201 patients will be enrolled into the study.

3.1.3. Number of Sites

Approximately 60 sites will take part in the study.

3.2. Scientific Rationale for Study Design

The goal of this Phase 2 AD study is to determine whether 1.0 mg/kg XPro1595 is superior to placebo at either improving or slowing disease progression on measures of cognition, functioning and behavior in individuals with early ADi. At the time of this writing, disease-modifying treatment has not been approved for AD in all regions in which this study will be conducted, thus use of placebo is justified.

In addition to efficacy, this study will also evaluate safety and tolerability. Preclinical and IND enabling studies show a 10-fold gradient in blood to brain concentrations of XPro1595 in which brain levels of XPro1595 are in the low ng/mL range. Pathological levels of TNF in the brain have been reported to be ~80 pg/mL suggesting that 1.0 mg/kg dose levels should be sufficient to block neuroinflammation.

A key element of the study is to focus on AD patients who are most likely to benefit from targeted anti-TNF therapy by identifying and enrolling patients with inflammation. A number of inflammatory biomarkers have been identified that are associated or predict risk for disease. The success of anti-TNF drugs in other disease states has yielded considerable data that supports stratifying AD patients based on inflammatory biomarkers. Inflammation can be easily measured

in blood. Patients with at least 1 of the following inflammatory biomarkers described below will be eligible for the current study.

A recent report indicates that anti-inflammatory therapy may be predicted by elevated HbA1C (Valcarce et al., 2019). A subgroup analysis from a recent clinical trial showed a significant cognitive benefit with corresponding reduction in the loss of brain volume and ventricular space compared to patients with a low blood level of HbA1C in AD patients treated with an anti--inflammatory. These results are consistent with a large dataset suggesting that inflammation may underlie the metabolic changes observed in patients with AD (see [Clark et al., 2012] for review). Much like hsCRP, HbA1C may be a reliable marker of underlying inflammation and anti-inflammatory treatment response in patients with AD.

Erythrocyte sedimentation rate is a commonly used measure of inflammation. A recently published study by Kantor and colleagues (Kantor et al., 2019) reported that an elevated ESR in young men increased risk of dying early (46%) via a variety of diseases.

Apolipoprotein E4 (APOE4) is the major genetic risk factor for late-onset AD (Liu et al., 2013). A number of studies have demonstrated that APOE is expressed by immune cells and plays a role in immune responses. Specifically, APOE4 impairs the function of human immune cells in the brain (Konttinen et al., 2019).

Disease heterogeneity would predict that inflammatory-driven disease might manifest in different ways. hsCRP, HbA1C, ESR, and APOE4 have been shown to be representative of underlying inflammation and potential predictors of patients that might respond to anti-inflammatory treatment.

3.3. Justification for Dose

The Sponsor intends to administer XPro1595 at 1.0 mg/kg SC injection once a week for 23 weeks in this AD study. The dose has been selected based on clinical and nonclinical studies of XPro1595. The target dose for therapeutic efficacy in primates is considered to be 1 mg/kg/week. The dosing decision is based on the mechanism of action, the pharmacology in a non-human primate model and human data from 2 completed Phase 1 studies in oncology and ADi (refer to the XPro1595 IB). To effectively neutralize 99.99% of sTNF trough levels of drug must be at least 2 logs greater than the TNF level. A dose biodistribution study of 1 mg/kg of XPro1595 delivered by SC injection to rats predicted brain levels of 130 ng/g. Pathological levels of TNF in the brain are usually < 20 pg/mL, although 100 pg/mL have been reported. Regardless, 1 mg/kg/week exceeds the expected level of soluble TNF by 3 logs. Moreover, proteomic analysis of CSF in the Phase 1b study of ADi patients demonstrated a greater reduction in proteins related to AD pathology (e.g., neuroinflammatory, synaptic plasticity, neurodegeneration) in patients treated with 1 mg/kg but not 0.3 mg/kg.

The NOAEL of XPro1595 administered daily to rats is 10 mg/kg/day (70 mg/kg/week; HED: 11.3 mg/kg/week). In cynomolgus monkeys, the NOAEL is 30 mg/kg QOD (approximately 105.3 mg/kg/week; HED: 34 mg/kg/week). The proposed dose of 1 mg/kg once a week is 70 times lower than the NOAEL dose.

The 1.0 mg/kg dose provides a 3-fold safety margin while providing a 10-fold excess of drug predicted to achieve near complete neutralization of solTNF.

The dose selected therefore will provide an adequate safety margin for a clinical study, and a reasonable assumption of potential for a pharmacological effect of XPro1595 in the target patient population.

3.4. Definition of End of Study and Study Completion

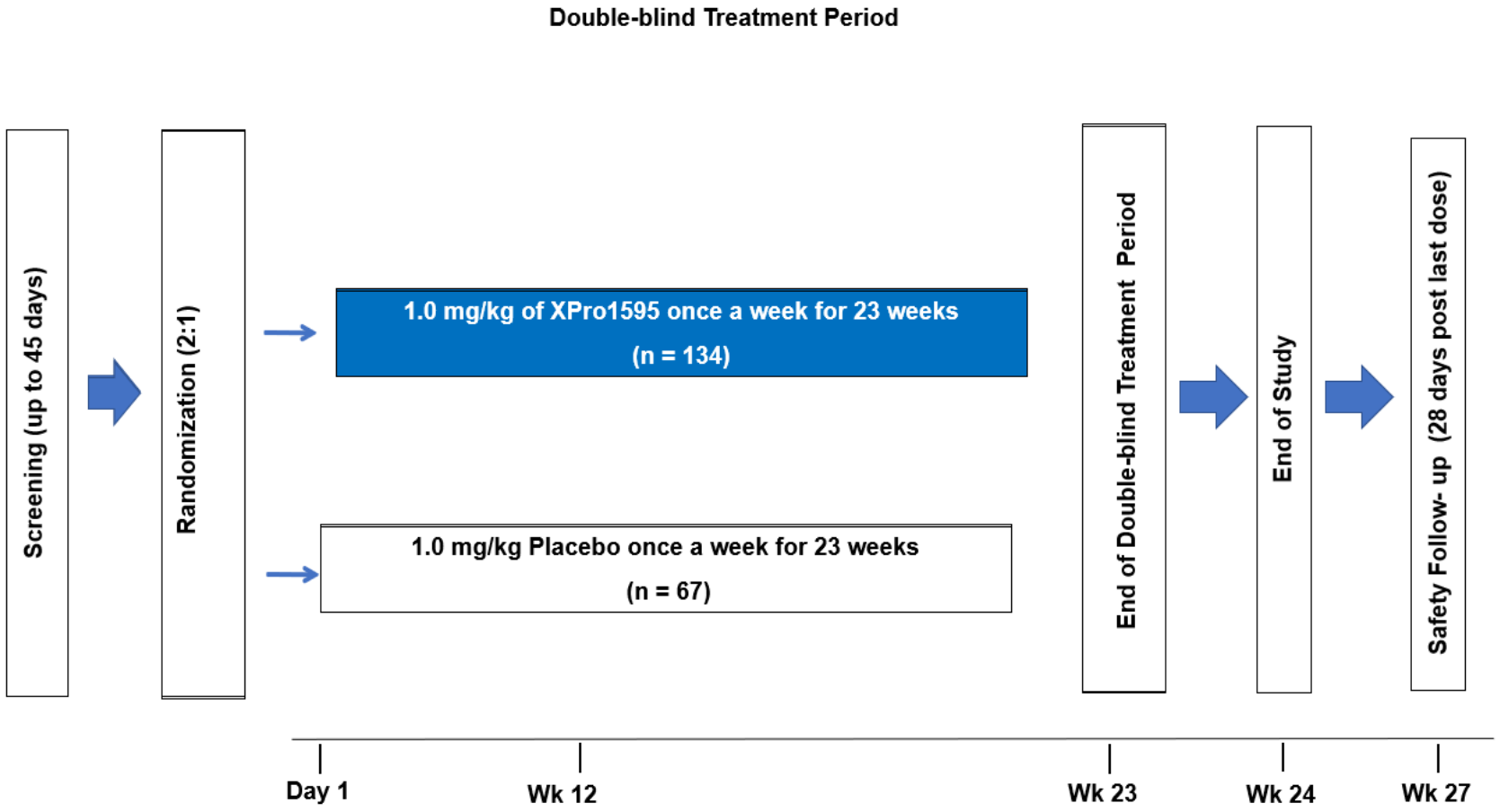
The end of the study is defined as the last visit of the last patient in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last patient in the study globally.

Following database lock and unblinding, investigators will be made aware of the treatment arm assignments for the patients at their respective site through a communication from the Sponsor.

A patient is considered to have completed the study if all study visits have been completed including the last visit or the last scheduled procedure shown in the SoA. Patients that enroll in the OLE will not need a Safety Follow-Up Phone Call.

Patients that terminate the study early should still have a Week 24/EOS visit and the Safety Follow-Up phone call at least 28 days following the last dose.

3.5. Schema


Double-blind Treatment Period
Screening (up to 45 days)
Randomization (2:1)
1.0 mg/kg of XPro1595 once a week for 23 weeks
(n = 134)
1.0 mg/kg Placebo once a week for 23 weeks
(n = 67)
End of Double-blind Treatment Period
End of Study
Safety Follow- up (28 days post last dose)
Day 1
Wk 12
Wk 23
Wk 24
Wk 27

3.6. Schedule of Activities

Table 1: Schedule of Activities

			Treatment Period												
	Weeks	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7-11**	**12**	**13-17**	**18**	**19-23**	**24 /EOS[9]**	**Safety Follow-up Phone Call[12] (28 days after last dose)**
	Days	**Screening (up to 45 days before Day - 1)**	**1/ Baseline**	**8**	**15**	**22**	**29**	**36**	**43-71**	**78**	**85-113**	**120**	**127-155**	**162**	
Procedure		**Visit Windows**		**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 2**	**+ 7**
In-person visit to site required		X	X	X	X	X		X		X		X		X	
Informed consent		X													
Inclusion and exclusion criteria		X													
Demography		X													
Full physical examination		X								X				X	
Height and weight		X								X[1]				X[1]	
Medical history (includes substance use)		X													
Prior medication history		X													
12-lead ECG		X								X				X	
Vital signs[16]		X	X							X				X	
Mandatory Prophylactic Injection Site Reaction (ISR) treatment[21]			X	X	X	X									
Study intervention[2]			X	X	X	X	X[4]	X	X[4]	X	X[4]	X	X[4]		

			Treatment Period												
	Weeks	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7-11**	**12**	**13-17**	**18**	**19-23**	**24 /EOS[9]**	**Safety Follow-up Phone Call[12] (28 days after last dose)**
	Days	**Screening (up to 45 days before Day - 1)**	**1/ Baseline**	**8**	**15**	**22**	**29**	**36**	**43-71**	**78**	**85-113**	**120**	**127-155**	**162**	
Procedure		**Visit Windows**		**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 2**	**+ 7**
MRI[3]		X								X				X	
AE review			X	X	X	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X
Prior/Concomitant medication review		X	X	X	X	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X
Blood Sample Collection[5]															
Serology		X												X[5]	
Hematology		X		X[5]		X[5]				X[5]				X[5]	
Clinical chemistry		X		X[5]		X[5]				X[5]				X[5]	
hsCRP, HbA1C, ESR[22]		X													
APOE[7]		X													
Amyloid Test[7]		X													
Blood TNF (XPro1595)[6]		X		X		X				X				X	
Blood Plasma for Inflammatory and Neurodegeneration Markers[6]		X								X				X	
Anti-drug antibody		X		X		X				X				X	

			Treatment Period												
	Weeks	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7-11**	**12**	**13-17**	**18**	**19-23**	**24 /EOS[9]**	**Safety Follow-up Phone Call[12] (28 days after last dose)**
	Days	**Screening (up to 45 days before Day - 1)**	**1/ Baseline**	**8**	**15**	**22**	**29**	**36**	**43-71**	**78**	**85-113**	**120**	**127-155**	**162**	
Procedure		**Visit Windows**		**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 2**	**+ 7**
Anti-PEG		X		X		X				X				X	
Urine Sample Collection															
Urinalysis		X												X	
Dipstick pregnancy test		X	X				X		X[19]		X[19]		X[19]	X[19]	
Questionnaires[15]															
MMSE		X													
EMACC[14]		X[18]	X					X		X		X		X	
GAS		X[8]	X[8]							X				X	
ECog		X	X[14]							X				X	
ADCS-ADL or ADCS-MCI-ADL [14,17]			X							X				X	
NPI-12[14]			X							X				X	
C-SSRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDR[14]		X	X[13]							X				X	
DSST[20]		X	X	X	X	X	X	X	X	X	X	X	X	X	
MPsQs		X[10]	X[11]												

1 - Weight only.

2 - Patients/study partners may be taught to self-administer drug during as early as their first or second injection. Injections 3 and 4 may be administered by the patient/study partner under supervision of clinic staff to confirm ability to administer at home. For visits that do not require an in-person site visit, home administration is allowed. The last dose of study drug will be administered at Week 23.
3 - MRIs at Week 12 and Week 24 may be completed within a +/- 4-day visit window.
4 - Compliance with study drug administration, AEs and concomitant medications will be assessed via phone calls on weeks patients do not visit the clinic.
5 - All blood samples should be collected between 8 AM and 12 PM **prior to investigational product administration** (if collection is on a dosing day).
6 - Blood plasma for inflammatory and neurodegeneration markers are specified in Section 7.5. It is preferable to collect blood for biomarkers on the same day as dosing, between 8 AM and 12 PM. Whenever possible, aim to collect all samples for a specific patient at the same time of the day.
7 - Amyloid and APOE4 status will be analyzed via the central lab for all patients. Historical documentation of Amyloid positivity satisfies Inclusion criteria 3. Historical documentation of at least one APOE4 allele satisfies Inclusion criteria 7. For patients who do not have documented historical evidence of Amyloid positivity, eligibility may be determined during screening according to guidance in the lab manual. For patients that do not have at least one APOE4 allele, inclusion criteria 3 can be satisfied if they meet the requirement for CRP, ESR, or HbA1c.
8 - Initial GAS interview at screening. All goals and scales finalized at Day 1 **prior to investigational product administration.**
9 - In the event a patient discontinues the study early, the Week 24/EOS visit should be performed.
10 - BAS-MPsQ and HBB-MPsQ by patient; BAS-MPsQ-CGV and HBB-MPsQ-CGV by study partner.
11 - STT-MPsQ and PDS-MPsQ by patient **prior to investigational product administration**, STC-MPsQ-CGV and PSC-MPsQ-CGV by study partner **prior to investigational product administration.**
12 - The Safety Follow-up Phone Call may be performed over the phone.
13 - If screening CDR was conducted > 30 days from Day 1, CDR must be repeated on Day 1. If the screening ECog was conducted > 30 days from Day 1, ECog must be repeated on Day 1.
14 - The CDR rater cannot administer the EMACC, NPI, and ADCS-ADL scales to any patient for which they are a CDR rater.
15 - All questionnaires must be completed prior to investigational product administration.
16 - 3 consecutive blood pressure measurements will be recorded at intervals of at least 1 minute.
17 - Patients enrolled before Amendment 5 will complete the ADCS-ADL. Patients enrolled after Amendment 5 will complete the ADCS-MCI-ADL.
18 - The EMACC should be administered within 45 days of D1, so the patient is familiar with the test on D1. If the EMACC needs to be repeated during screening to be within 45 days of D1, it should be repeated at least one week before D1.
19 - Dipstick tests for pregnancy must be performed monthly for women of childbearing potential.
20 - To be done by the patient at home on the provided study tablet, at least once per week on a day where they are not in the clinic. This task will only apply to patients in regions where the tablet is approved for use by Ethics and available for patient use.
21 - Prophylactic ISR treatment to be given at least one hour before injection according to section 5 and the current ISR management guideline document. On weeks 1, 6, 12, 18 and 24, ISR premedication should be given after cognitive and functional study assessments.
22 - ESR must be done during screening even if the patient meets eligibility with APOE4 status, hsCRP and/or HbA1C.

4. Study Population

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 9.1.2). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

To be eligible for study entry, patients must satisfy all of the following criteria:

1. Adult patients 50 years to ≤ 85 years of age at the time of consent;
2. Meets the diagnostic criteria of MCI of probable Alzheimer's disease (Jack et al., 2018; NIA-AA) or mild dementia as clinically described in McKhann, (2011) and corresponding to stages 3 or 4 of the revised AD staging system (Jack et al., 2018). (NIA - AA);
3. Amyloid positive (documented in medical history or assessed during screening through blood test);
4. CDR global rating at screening of 0.5 or 1;
5. MMSE ≥ 22;
6. ECog memory subscale items mean > 1.5;
7. Presence of at least 1 inflammatory biomarker. All inflammatory biomarkers must be assessed during screening, but only one of the following is required for eligibility:
   - hsCRP > 1.5 mg/L
   - ESR > 10 mm/h
   - HbA1C > 6 DCCT %
   - At least 1 APOE4 allele (documented in medical history or assessed during screening through blood test)
8. Consents to APOE genotyping;
9. Modified Hachinski Ischemic Score ≤ 4 (see Section 9.8 for additional details);
10. Either currently or previously (in pre-AD condition) literate and capable of reading, writing, and communicating effectively with others in the language of the study assessments;
11. Must have a sixth-grade education or work experience to exclude developmental causes of cognitive dysfunction;
12. Residence in an assisted living is allowed as is personal assistances provided in the home, however at time of enrollment participant must be able to perform most ADL with minimal assistance, and participant must be permitted sufficient independence to allow assessment of change in ADL;
13. May be using the following concomitant medications for management of AD at Screening and during the study, including cholinesterase inhibitors (donepezil, rivastigmine, and galantamine), glutamate inhibitors (memantine), and multi-modal treatments (Namzaric®). Other, non-immunosuppressive therapies such as medications to treat behavior symptoms

including: suvorexant (insomnia), SSRIs for depression and anxiety, and drugs for narcolepsy (Xyrem® or modafinil) may also be used and should be discussed with the sponsor. These medications must be started at least 90 days before the first dose of XPro1595 and the regimens must remain constant throughout the study.

14. The patient must be willing and able to provide informed consent prior to any study procedures being performed.
15. Has a study partner for the duration of the trial who either lives in the same household or interacts with the patient at least 4 hours per day and on at least 4 days per week, who is knowledgeable about the patient's daytime and night-time behaviors and who can be available to attend all clinic visits in person at which study partner assessments are performed. This study partner should agree to monitor and report on concomitant medications, understand the study requirements, and assist the participant in meeting study requirements. Patients with study partners that interact with the patient on at least 4 days per week but for less than 4 hours per day who the investigator determines as able to provide an adequate assessment of the patient may also participate with prior approval from the Sponsor.
16. All male subjects who are sexually active with a female of childbearing potential (FCBP) must agree to use a highly effective method of contraception during the treatment period and until 90 days after the last dose of treatment. All females of childbearing potential (FCBP) must have a negative urine pregnancy test and agree to use two highly effective method of contraception (including at least one barrier method) during the treatment period and 30 days after the last dose of treatment.

4.2. Exclusion Criteria

Patients will be excluded from the study if 1 or more of the following criteria are applicable:

1. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (e.g., in-skull and cardiac devices other than those approved as safe for use in MRI scanners).
2. Have any evidence of other clinically significant lesion(s) that could confound or indicate a dementia diagnosis other than AD on brain CT and/or MRI at Screening.
    - Exhibit other significant pathological findings at the Screening MRI including but not limited to: an area of cortical superficial siderosis; evidence of cerebral vasogenic edema (ARIA-E); macro-hemorrhage(s) (>10mm); multiple (>15) cerebral microbleeds (ARIA-H); one large (>15 mm on axial plane) infarct or multiple (≥2) lacunes (as defined by STRIVE consensus criteria); an area of encephalomalacia suspect of prior head trauma; aneurysm(s); subdural hematoma; severe small vessel or diffuse white matter disease (defined as Fazekas scale score of 3); any space occupying lesion(s), or brain tumor(s), also including infective lesions. Lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary. Radiological evidence for another dementia etiology (such as stroke, traumatic brain injury, Lewy Body disease, substance/medication use, CNS infection, Prion disease, Parkinson's disease, Huntington's disease, etc.) major brain diseases, or other CNS trauma, that interfere with the participant's ability to comply, and dementia-related disease as determined by clinical diagnosis.

3. Receives considerable help to carry out basic ADL living either in the home or as a resident in a nursing home or similar facility.
4. Lifetime history of a major psychiatric disorder including schizophrenia and bipolar disorder. (Major) depressive disorder or recurrent depressive disorder (ICD F33.x) that has resulted in 2 or more hospitalizations in a lifetime. Major depressive episode (DSM) or depressive episode (ICD10 F32.x) within the past 5 years that is judged by the clinical team unlikely to have been part of the Alzheimer's prodrome, OR a recurrent depressive disorder with most recent episode during past 5 years (ICD F.33x) that is judged by the clinical team unlikely to have been part of the Alzheimer's prodrome. History of suicidal behavior, or answer of 'yes" to C-SSRS suicidal ideation items 4 or 5 within 12 months of screening.
5. History of substance abuse within 12 months; use of cannabis or cannabis products within 6 months of consent.
6. Have taken within the last 90 days from Day 1: corticosteroids (except topical corticosteroids) or other immunosuppressive drugs, thalidomide or other TNF active drugs, minocycline, first- or second-generation antipsychotics (e.g., aripiprazole) or aducanumab or other anti-amyloid therapies. Topical corticosteroids for cutaneous, nasal, or ocular applications can be used with approval from Medical Monitor. Patients taking cholinesterase inhibitors, memantine and those that have a B12 deficiency or are taking B12 therapy or antidepressant medication for less than 90 days from Day 1 (i.e., must be on stable dose for at least 90 days prior to Day 1).
7. Narcotic medications within 4 weeks of baseline or the PRN use of opioids.
8. Approval by the Medical Monitor is required if a patient takes any drug known to alter cognitive functioning. Examples include benzodiazepines, sedating antihistamines, anticonvulsants, sedating antidepressants (e.g., tricyclic antidepressants), anticholinergics (benztropine), antiparkinsonian medications (amantadine, selegiline, benztropine), psychostimulants within 4 weeks of baseline.
9. Any untreated infection or any infection that the PI deems is not currently controlled with current therapies.
10. Enrolled in another clinical trial where patients receive treatment with an investigational drug or treatment device or have had previous treatment with any investigational medicinal product within 60 days or 5 half-lives (whichever is longer) prior to study drug treatment.
11. A prior organ or stem cell transplant.
12. A major adverse cardiac event within 6 months before consent.
13. Lymphoma, leukemia, or any malignancy within the past 5 years with the exception of malignancies with negligible risk of metastasis or death, such as basal cell or squamous cell carcinomas of the skin or cervical carcinoma in situ that have been resected with no evidence of metastatic disease for 3 years.
14. Jaundice, active hepatitis, or known hepatobiliary disease (except asymptomatic cholelithiasis).
15. Positive screening assessment for viral HBsAg or HCV antibody and positive HCV RNA or HIV, or a history of illicit drug injecting.
16. Seated blood pressure of ≥ 165/105 mmHg at Screening.

17. Unable to comply with the study procedures and assessments.
18. Known hypersensitivity to investigational product or its excipients.
19. Any investigator site personnel directly affiliated with this study and their immediate families. "Immediate family" is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
20. Those who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

4.3. Lifestyle Considerations

Not applicable.

4.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE that leads to screen failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened upon consultation with the medical monitor. Sites should work in conjunction with their medical monitor and the sponsor to determine if certain assessments do not need to be repeated.

4.5. Replacement of Patients

Subjects who withdraw from the study or who discontinue study drug administration within the first month may be replaced at the discretion of INmune Bio in consultation with the investigator.

5. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

XPro1595 is manufactured for INmune Bio by CCI [redacted], using recombinant DNA technology. The manufacture was performed in compliance with GMP. XPro1595 is a PEGylated protein variant of solTNF. Refer to the IB for additional formulation and manufacturing specifics and Table 2. Study Intervention(s) Administered for specifications. The final drug product is formulated in CCI [redacted] at a dose strength of 60 mg/mL.

XPro1595 drug product is a liquid product supplied in single-use glass vials. A 1.5 mL volume of drug product contains CCI [redacted] mg of XPro1595 and the following inactive ingredients: CCI [redacted].

XPro1595 placebo product is a liquid product supplied in single-use glass vials. A 1.5 mL of placebo product contains the following inactive ingredients: CCI [redacted].

XPro1595 will be stored, labelled, and distributed to the pharmacy of each study site.

Prophylactic treatment for injection site reactions (ISRs) are described in the ISR management guidelines document and include:

- Oral Antihistamines
- Oral Acetaminophen and/or NSAIDs or Naproxen
- Topical corticosteroid

Sedating antihistamines (e.g., diphenhydramine HCl) and oral corticosteroids (e.g,, prednisone) are not be used as prophylactic treatment. Please refer to the ISR management guidelines document for approved medications. All prophylactic treatment should be recorded as concomitant medications with the indication of prophylaxis for ISR.

5.1. Study Intervention(s) Administered

Table 2: Study Intervention(s) Administered

Intervention Label	Treatment	Placebo
Intervention Name	XPro1595	Placebo
Intervention Description	One SC injection administered once a week for 23 weeks	One SC injection administered once a week for 23 weeks
Type	Drug	Drug
Dose Formulation	Vial	Vial
Unit Dose Strength(s)	60 mg/ml	Not applicable
Dosage Level(s)	1.0 mg/kg of XPro1595	1.0 mg/kg of placebo
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP/AxMP	IMP	IMP

Intervention Label	Treatment	Placebo
Sourcing	Provided centrally by INmune Bio.	Provided centrally by INmune Bio.
Packaging and Labeling	XPro1595 drug product is a liquid product supplied in single 2-mL Type I glass vial.	Placebo will be provided in a single 2-mL Type I glass vial.
Current/Former Name(s) or Alias(es)	INB03/XPro1595, XENP1595 and DN-TNF	Not applicable

Source: IB

Table 3: Study Arm(s)

Arm Title	Treatment	Placebo
Arm Type	Study Drug	Placebo
Arm Description	Patients will receive 1.0 mg/kg of XPro1595 as a SC injection once a week for 23 weeks	Patients will receive 1.0 mg/kg of placebo as a SC injection once a week for 23 weeks

Source: IB

5.1.1. Preparation, Handling, Storage, and Accountability

XPro1595 should be stored under refrigeration (2°C–8°C). Prior to use, the drug product should be allowed to come to room temperature. The drug should be administered via SC injection within 8 hours of preparation in syringes.

Prior to administration, the vial should be removed from the refrigerator and inspected visually to confirm absence of particulate matter. The required amount of XPro1595 solution should be withdrawn from the vial for dosing. The required dose will be determined by patient weight during screening visit, with the maximum dose calculated based on a maximum weight of 135 kg.

XPro1595 should not be mixed or diluted with other drugs or solutions. Vials are unit-dose containers. The contents of 1 vial of XPro1595 solution should not be mixed with, or transferred into, the contents of another vial of XPro1595. Any partially used vials should be discarded using appropriate drug disposal procedures.

The investigator or designer must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only patients enrolled in the study may receive study intervention, and only staff authorized on the delegation of authority log may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the (study reference manual or other specified location).

5.2. Measures to Minimize Bias: Randomization and Blinding

Type of Study	Phase 2: Randomized, Placebo-controlled, weekly XPro1595 or placebo dosing
Randomization (IVRS/IWRS)	A central randomization tool will be utilized for enrollment to ensure proper randomization. Randomization will be 2:1 (active: placebo) and will be stratified by indication (MCI, mAD) and sex (Male, Female). Randomization will be capped within disease indication strata so no more than 60% of either treatment arm is either MCI or mAD. An independent statistician will perform the randomization of the live list to support the central randomization tool. Details of how to use the tool will be provided to sites by the CRO.
Blind break (IVRS/IWRS)	This is a double-blind study in which (patients/care providers/investigators/outcomes assessors, etc.) are blinded to study intervention. The IVRS/IWRS will be programmed with blind-breaking instructions. The study blind should not be broken except in a medical emergency, where knowledge of the study drug received would affect the treatment of the emergency or obtaining this information is a regulatory requirement. If time permits, the Investigator should notify the Sponsor prior to making their request to the IVRS/IWRS. All calls resulting in an unblinding event will be reported by the IVRS/IWRS to the Sponsor.

Sponsor safety staff may unblind the intervention assignment for any patient with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the patient's intervention assignment, may be sent to investigators in accordance with local regulations and/or Sponsor policy.

5.3. Study Intervention Compliance

Treatment cohorts will be placebo and XPro1595 at 1.0 mg/kg/week administered as SC injections. Screening weight will be used to calculate dose. Visits that are only for drug administration may be performed in the clinic or in the patient's home through self-administration, study partner administration, or support from a planned third-party.

The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of the study drug and patient identification will be confirmed at the time of dosing by a member of the site staff other than the person administering the study drug.

When patients self-administer the study drug at home, compliance with the study drug will be assessed weekly through a site phone call with the patient/study partner. Compliance will be assessed by direct questioning and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of XPro1595 dispensed to and administered by each patient must be maintained and reconciled with the study drug and compliance records. Study drug start and stop dates, including dates for study drug delays will also be recorded.

5.4. Dose Modification

Dose modifications may be allowed for safety reasons but require Medical Monitor approval. All instances of study drug dose modification (interruption, reduction and titration or discontinuation) require Medical Monitor approval.

The following Dose Modification schedule for ISRs should be used with Medical Monitor approval:

- 1 Week post-ISR administer 25% (0.25 mg/kg) of original dose.
- 2 Weeks post-ISR administer 50% (0.50 mg/kg) of original dose.
- 3 Weeks post-ISR administer 75% (0.75 mg/kg) of original dose.
- 4 Weeks post-ISR administer 100% (1 mg/kg) of original dose.

5.5. Continued Access to Study Intervention after the End of the Study

INmune Bio reserves the unilateral right, at its sole discretion, to determine whether to supply XPro1595 and by what mechanism, after termination of the study and before the product is available commercially.

5.6. Treatment of Overdose

The maximum tolerated dose of XPro1595 has not been established. Dosing should be given only per the clinical study protocols.

INmune Bio does not recommend specific treatment for an overdose. In the event of a suspected overdose the Investigator should contact the Medical Monitor.

5.7. Concomitant Therapy

Concomitant therapy is any drug or substance administered between subject consent (at Screening) and the last study visit. At Screening, subjects will be asked what medications they are currently taking. Medication use in the 90 days prior to Day 1 must be recorded on the subject's CRF.

At each subsequent study visit, subjects will be asked what medications they have taken since the last study visit. Any medications taken prior to the start of dosing will be documented as prior medications. Medications taken after the first dose of study medication will be documented as concomitant medications. Medications that start before the first dose of study medication and continue into the study are considered both prior and concomitant medications.

Prior and concomitant medications will be assessed according to the SoA.

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements; e.g., Souvenaid) or other specific categories of interest that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

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

5.7.1. Prohibited Concomitant Therapy

The following medications may not be taken within the last 90 days from Day 1:

- Corticosteroids (except topical corticosteroids) or other immunosuppressive drugs, thalidomide or other TNF active drugs, minocycline.
- First- or second-generation antipsychotics (e.g., aripiprazole).
- Aducanumab, lecanemab or other anti-amyloid therapies.

The following medications known to affect cognition must not be taken within 12 hours before a scheduled study task:

- Short/medium acting benzodiazepines (e.g., alprazolam, lorazepam, oxazepam, temazepam diazepam, loprazolam, clonazepam).
- Insomnia medications (e.g., Ambien, zolpidem, Lunesta, sedating antipsychotics such as quetiapine).
- Anti-cholinergics (benztropine) or any other medication or substance known to affect cognition must not be consumed within 12 hours prior to the scheduled tasks.
- Long-acting benzodiazepines must not be consumed within 24 hours of cognitive testing.

5.7.2. Permitted Concomitant Therapy

With the exception of those medications allowed for ISRs (refer to ISR management guidance), permitted medications must have been started at least 90 days before the first dose of study drug and the regimens must remain constant throughout the study.

The following concomitant medications may be used for the management of AD at Screening and during the study:

- cholinesterase inhibitors (donepezil, rivastigmine, galantamine),
- glutamate inhibitors (memantine), and
- multi-modal treatments (Namzaric®).

The following concomitant medications known to alter cognitive functioning and/or behavior may be permitted with prior approval by the Medical Monitor:

- benzodiazepines, anticonvulsants, sedating antidepressants (e.g., tricyclic antidepressants), anticholinergics (benztropine), antiparkinsonian medications (amantadine, selegiline, benztropine), psychostimulants, narcotic medications. Sedating antihistamines may only be used to treat an ISR as described in the ISR management guidelines and are not to be used on weeks 6, 12, 18, and 24 or on any other day the patient will be administered the EMACC.
- suvorexant (insomnia), SSRIs for depression and anxiety, and drugs for narcolepsy (Xyrem® or modafinil)

Other, non-immunosuppressive therapies may also be used but should be discussed with the Medical Monitor.

6. Participant Discontinuation/Withdrawal

Patients have the right to withdraw from investigational product and/or other protocol required therapies, protocol procedures, or the entire study any time and for any reason without prejudice to their future medical care by the physician or at the institution.

If, in the Investigator's opinion, a patient becomes permanently incapable of providing informed consent while on the study, they should immediately be withdrawn from the study. Transient incapacity (e.g., related to concomitant disorders or procedures) should not result in a withdrawal from the study unless the transient incapacity is then determined to become permanent.

The Investigator and/or Sponsor can decide to withdraw a patient(s) from the investigational product, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion. Some examples that may lead to discontinuation include (but are not limited to):

- Occurrence of AEs for which study treatment and/or study participation discontinuation is desired by the subject or considered necessary by the Investigator, in consultation with the Medical Monitor;
- Unacceptable tolerability of the study drug in the opinion of the Investigator;
- Investigator's decision (i.e., if in the Investigator's opinion it is not in the best medical interest for the subject to continue participation in the study);
- Need for administration of a prohibited concomitant medication;
- Any other protocol deviation that may result in a significant risk to the subject's safety or protocol deviations that will interfere with assessment of the efficacy endpoints of this study, including subject's non-compliance with the study procedures/study protocol;
- Pregnancy
- Lost to follow-up (the subject stopped coming for visits, and study personnel are unable to contact the subject);
- Inability to fulfil study requirements and procedures;
- Death

6.1. Participant Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

- At the time of discontinuation from the study, if possible, a Week 24/EOS visit should be conducted 7 days following the last dose of study drug, as shown in the SoA.
- The patient should, if possible, receive a follow-up phone call 28 days following the last dose of study drug. If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

6.2. Lost to Follow up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls, and if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

7.1. General Assessments

All cognitive and functional assessments are to be performed prior to receiving prophylactic Injection Site Reaction (ISR) pre-medications and study drug.

7.1.1. Medical History

The Investigator or designee will collect a complete medical and surgical history that starts within 12 weeks prior to Screening through the time of signing the informed consent. The medical history will include information on the patient's concurrent medical conditions. All findings will be recorded on the medical history CRF. The current severity grade will be collected for each condition that has not been resolved.

7.1.2. Prior Therapy

Prior therapies that were being taken/used in the 90 days prior to screening Day 1 will be collected. For all prior therapies, collect therapy name, indication, dose, unit, frequency, start date, and stop date.

7.1.3. Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with patient safety and treatment effectiveness.

7.2. Efficacy Assessments

The primary efficacy assessment scale(s) selected for this study are the list scales for the primary efficacy endpoints. Planned timepoints for all efficacy assessments are provided in the SoA. Every effort should be made to ensure that the protocol required tests and procedures are completed as

described. However, it is anticipated that, from time to time, there may be circumstances, outside of the control of the Investigator, that make it not feasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and wellbeing of the participant. When a protocol required assessment cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions which he/she has taken/will take to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.2.1. Early and Mild Alzheimer's Cognitive Composite (EMACC)

The EMACC will be administered every 6 weeks for 6 months. The EMACC consists of a battery of validated and established neuropsychological tests. This composite was derived quantitatively to optimize sensitivity to change over time in 4 independent longitudinal early AD samples ([ADNI], [AIBL], 2 Knight Alzheimer Disease Research Center studies at Washington University, [MCSA]). To derive the EMACC, clinical neuropsychological test data collected longitudinally in these cohorts were filtered for adaptability to global, multi-language, multiculture trials and then strictly quantitative methods were used to derive and test candidate "batteries" of measures for sensitivity to change. The final EMACC battery takes about 25 minutes to administer and is composed of tests of verbal learning, language fluency, information processing speed, and working memory. The EMACC will serve as the primary cognitive measure of clinical effect. The EMACC will be administered at screening, D1, Week 6, Week 12, Week 18 and Week 24, before study intervention administration on IP administration days. The EMACC should be administered within 45 days of D1, so the patient is familiar with the test on D1. If the EMACC needs to be repeated during screening to be within 45 days of D1, it should be repeated at least one week before D1.

7.2.2. Brain Magnetic Resonance Imaging (MRI)

Brain screening MRI will be conducted to assess the MRI-related inclusion criterion and for the measurement of global and regional brain atrophy changes during the study. To ensure the accuracy of MRI imaging diagnosis and analysis, a central MRI acquisition vendor will be established in this study and each machine will be qualified by the imaging vendor before the collection of images. Brain MRIs will be done during screening and at Weeks 12 and 24.

Safety-relevant endpoints include on all brain MRIs: volume of white matter hyperintensities on FLAIR, cerebral microbleeds count, presence of intracerebral hemorrhage, presence of focal subarachnoid hemorrhage, presence of cortical superficial siderosis. Lesions on imaging will be defined following STRIVE consensus criteria version 2 (Duering et al., Lancet Neurology 2023).

As an exploratory endpoint, myelin-sensitive contrasts will be used to probe the change in myelin content of the normal appearing (outside of white matter hyperintensities) white matter.

Detailed information about MRI analysis is provided in the Imaging Review Charter.

7.2.3. Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)

The CDR scale is a clinician-rated dementia staging system that tracks the progression of cognitive impairment in 6 categories (memory, orientation, judgement, and problem solving, community affairs, home and hobbies, and personal care). Each category is scored on a 5-point scale in which None = 0, Questionable = 0.5, Mild = 1, Moderate = 2, and Severe = 3. The global CDR score is established by clinical scoring rules and has values of 0 (no dementia), 0.5, (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR-SB (Sum

of Boxes) is obtained by adding the ratings in each of the 6 categories and ranges from 0 to 18 with higher scores indicative of greater impairment.

The CDR will be administered at the Screening visit for inclusion. The CDR will need to be repeated at D1 if not done within 30 days of D1. The CDR will then be administered at Week 12 and Week 24 (before study intervention administration) and will be used as a secondary endpoint of clinical effect. The CDR will be administered by a trained member of the investigational team. At each site, the same individual, whenever possible, will perform the CDR evaluation on a specific patient throughout the study. The CDR rater must be blinded to the EMACC, NPI, and ADCS-ADL scales for the subjects for which they are a CDR rater.

7.2.4. Goal Attainment Scale (GAS)

Goal Attainment Scaling is an individualized outcome measure that quantifies the effects of an intervention based on personalized goals. With the help of a trained interviewer, participants, and their family/study partners set treatment goals that are meaningful to them, relevant to their condition, and their potential response to the treatment.

Initially developed in the 1960s to evaluate mental health services (See Kiresuk et al., 1968), GAS offers a semi-structured approach to individualized, patient-centric outcome measurement. It has been used in a variety of indications (e.g., Alzheimer disease, cerebral palsy, autism) and typically is a highly responsive method of capturing patients' lived experience with their condition and treatment.

The achievement of each goal is rated on a 5-point attainment scale (-2, -1, 0, +1, +2) to allow standardized scoring of personalized outcomes. A participant's overall goal attainment is quantified using a formula that takes into account the number of goals that have been set, and the extent to which they are correlated with each other. GAS also offers a valuable second level of inference in demonstrating which goals were attained, as well as those that do not respond to treatment. Especially when used early in the course of drug development, this can help set expectations, both for treatment and for understanding where health utility inquiries might be focused. The open-ended nature of goal-setting can reveal treatment effects unanticipated by investigators. In this way, we can understand not just if an intervention is working, but how it is working.

During the Screening visit, a trained GAS interviewer will guide the study partner in the identification and development of the goals and goal scales of treatment. During the Baseline visit, a trained GAS interviewer will guide the study partner on the finalization of goals and goal scales of treatment. It is required that at least 3 goals are set per participant, and that these goals be related to the participant's condition, be measurable over the course of the trial, and could potentially be influenced by treatment with XPro1595. For each identified goal area, the study partner will be asked to give a detailed description of the patient's current (baseline) status and goal status, which will be recorded at the -1 and 0 levels on the 5-point scale, respectively. The remaining levels of the scale will then be set: somewhat better than the goal (+1), much better than the goal (+2), and much worse than the goal (-2).

At the scheduled follow-up visits (Weeks 12 and 24, before study intervention administration), the interviewer will ask the study partner to describe the patient's current status related to each goal area. Once this description is documented, the study partner will review the 5-point scale and be

asked to rate the current level of attainment. The GAS interviewer will also record their own attainment rating for each goal, which need not be the same as the study partner's rating.

At each site, the same individual, whenever possible, will perform the GAS assessment for a specific patient throughout the study.

7.2.5. Everyday Cognition (E-Cog)

The ECog is a 39-item questionnaire that asks the respondent (informant) to gauge the patient's performance on specific everyday activities as they are at present relative to 10 years ago, on a 4-point scale ranging from "Better or no change" (score of 1) to "consistently much worse" (score of 4). Only the Informant version of the ECog will be used. The activities being rated reflect the everyday operations of specific cognitive functions affected in AD including Memory, Language, Visual Spatial and Perceptional, and Executive Functions.

The ECog will be administered at the Screening visit for eligibility. The ECog will need to be repeated at D1 if not done within 30 days of D1. The ECog will then be administered at Week 12 and Week 24, before study intervention administration.

7.2.6. Neuropsychiatric Inventory (NPI-12)

The NPI is a rater-administered, fully structured interview in which all questions are provided and read verbatim. The sole source of information is the interview with a study partner who knows the patient well. This study uses the NPI version with 12 behavioral domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, and aberrant motor behavior.

The NPI-12 total score is calculated by adding the scores of the domains (each domain scores ranges from 0 to 12). The NPI-12 total score is based upon the first 10 items and ranges from (0 to 10) with higher scores indicating greater behavioral impairment. The last 2 items (sleep and appetite) are included for exploratory purposes.

The study partner distress scores in each of the domains are not included in the NPI-12 total score and will be explored separately. The study partner NPID total score is calculated by adding the scores of study partner distress in each of the domains (score ranges from 0 to 5 in each domain). The NPID total score ranges from 0 to 50 with higher scores indicating greater distress.

The NPI-12 will be administered at D1,Week 12 and 24 before study intervention administration. These assessments will be used as a secondary cognitive behavioral measure of clinical effect. The NPI-12 will be administered by an independent, trained, and certified member of the investigational team. At each site, the same individual, whenever possible, will perform the NPI-12 evaluation on a specific patient throughout the study.

7.2.7. Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) and ADCS-MCI-ADL

The ADCS-ADL and ADCS-MCI ADL assess the competence of patients with AD and MCI, respectively, in basic and instrumental ADLs. It will be administered by a clinician/researcher as a structured interview with a study partner. All responses should relate to the 4 weeks prior to the time of rating. Each ADL item takes an ADL (e.g., eating) and provide descriptions of level of competence with the rater selecting the most appropriate option (e.g., ate without physical help

and used a knife; used a fork or spoon but not a knife; used fingers to eat; was usually fed by someone else).

Patients enrolled before Amendment 5 will complete the ADCS-ADL. Patients enrolled after Amendment 5 implementation will complete the ADCS-MCI-ADL.

The ADCS-ADL or ADCS-MCI-ADL will be administered at D1, Week 12 and Week 24, before study intervention administration.

7.2.8. Multidimensional Psychological Questionnaire (MPsQ)

The Multidimensional Psychological Questionnaire (MPsQ) questionnaires have been designed to specifically measure patient personality characteristics associated with the placebo response. A composite covariate integrating these psychological features with other pertinent baseline patient features has been developed in several indications. With this method, the Placebell©™ covariate is calculated at baseline to characterize/quantify the placebo responsiveness for each patient, the prognosis of patients, and to improve the statistical analysis when computing drug effect (Branders et al., 2018[1]). The concept of using baseline covariates has been addressed in a recent FDA draft guidance (FDA draft Guidance issued in April 2019 and revised in May 2021[2]), and the Placebell©™ method was presented to the FDA at a Critical Path Innovation Meeting (CPIM). The CPIM recommended to pursue the development of Placebell©™ in the context of individual drug development programs.

The MPsQ questionnaires are self-reported, and each item is rated on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). At screening, BAS-MPsQ and HBB-MPsQ will be completed by the patient, BAS-MPsQ-CGV and HBB-MPsQ-CGV by the study partner. At Visit 1/D1 before the first study intervention administration, patient will complete STT- and PDS-MPsQ, study partner will complete STC-MPsQ-CGV and PSC-MPsQ-CGV.

7.2.9 Digit-Symbol Substitution Test "*Symbol Swap*"

This task is based on a well-established paradigm, commonly administered in studies involving patients. The patients refer to a key presented on screen throughout each trial. A row of symbols is presented, paired with empty boxes. Digits are presented in a separate row. Patients match each symbol to its missing digit in turn. This task takes approximately 2-3 minutes to complete and is a measure of executive function. The outcome measure is the number of boxes correctly completed within 90 seconds.

7.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

7.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems typical of a general medical examination. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs and symptoms related to known safety concerns of the currently available TNF inhibitors or biologics used in the treatment

of Alzheimer's disease. If a subject presents with new onset of neurological symptoms, dosing will be held for up to two weeks while full neurologic evaluation is completed.

Although non-clinical and clinical studies suggest these risks are not associated with XPro1595, investigators should pay special attention to symptoms indicative of the following:

- Demyelination and Multiple Sclerosis (MS). Currently available TNF inhibitors increase the risk for demyelination and multiple Sclerosis. (Thompson, Banwell et al. 2018) Previous studies have found that the most common symptoms following treatment with TNF inhibitors include sensory loss, limb weakness, and visual dysfunction that resolve following cessation of treatment (Thompson, Banwell et al. 2018; Hutto, Rice et al. 2021). If symptoms are reported, treatment should be postponed while patients receive a clinical evaluation, including, at a minimum an MRI (Thompson, Banwell et al. 2018).
- Amyloid Related Imaging Abnormalities (ARIA) are radiological abnormalities and symptoms observed in AD patients treated with anti-amyloid therapies. Patients reporting symptoms of ARIA should receive the appropriate clinical evaluation, including an MRI. These events require immediate consultation with the Medical Monitor. There will be specific instructions provided to all sites on how to report these events for DMC to review them as contemporaneously as possible.

7.3.2. Vital Signs

- Temperature by any standard measurement, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

7.3.3. Electrocardiograms (ECG)

- Single 12-lead ECG(s) will be obtained per standard of care as outlined in the SoA (see Section 3.6) using an ECG machine that automatically calculates the heart rate (HR) and interprets the ECG.

7.3.4. Clinical Safety Laboratory Tests

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 3.6)for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an Adverse Event (AE). The laboratory reports must be filed with the source documents.

- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant/any values do not return to normal/baseline within a time-period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Appendix 2 (Section 9.2), must be conducted in accordance with the laboratory manual and the SoA (Section 3.6).
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

The following clinical safety laboratory samples will be evaluated during the study:

- Serology: tests HBsAg, HCV, HCV RNA, and HIV.
- Hematology: Hemoglobin, hematocrit, RBC count, platelet count, WBC count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), MCV, MCH, and mean cell hemoglobin concentration.
- Clinical chemistry: albumin, total protein, blood glucose, sodium, potassium, urea creatinine, AST, ALT, ALP, GGT, total bilirubin, triglyceride, total cholesterol, LDH, calcium, and uric acid, SGOT, Total and direct bilirubin, BUN, SGPT.
- Urinalysis: urine specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, leukocyte esterase and blood by dipstick.
- Urine dipstick pregnancy test - Urine dipstick pregnancy test will be performed at Screening and monthly for female patients who are of child-bearing potential.
- Clinical chemistry, hematology and urinalysis do not need to be repeated during screening unless clinically indicated.

7.3.5. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated in this study should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment. Consideration should be given to discontinuing the study medication in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and study partners of participants being treated in this study should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the

emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior/treatment emergent suicidal ideation and behavior will be monitored at each visit using C-SSRS. If study drug administration occurs at home, the C-SSRS will be administered over the phone.

7.3.6. Pregnancy Testing

Refer to Section 4.1 for pregnancy testing entry criteria.

Women of childbearing potential will have urine pregnancy testing done monthly. Additional urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the patient's participation in the study.

7.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 9.3.

The definitions of unsolicited and solicited AEs can be found in Section 9.3.1.

AEs will be reported by the patient (or, when appropriate, by a study partner, study partner or surrogate).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs or AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study drug (see Section 9.3.1).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 9.3.3.

7.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 9.3.3). SAEs during screening that either lead to a screen failure or are a result of a screening procedure will also be collected.

All AEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA- (Section 9.3.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 9.3, Section 9.3.3, and 9.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be

reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

7.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

7.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs (as defined in Section 9.3 will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 6.2). Further information on follow-up procedures is provided in Appendix 3, Section 9.3.3.

7.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators.
- An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR)s according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

7.4.5. Pregnancy

- Details of all pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for post-intervention contraception determined in Section 4.1.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female patient or female partner of male patient (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The patient/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 7.4.4. While the investigator is not obligated to actively seek this information in former study patients/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study or may request continuation of study intervention.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The patient gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the patient and her offspring.

7.4.6. Stopping Criteria

- Enrollment will stop if 20% of patients develop the same severe drug related toxicity. The 20% threshold assumes more than 10 patients have been treated. If 2 of the first 5 patients or 3 of the first 10 patients have the same severe drug related toxicity, the stopping rule will apply. The Independent Data Monitoring Committee (DMC) will evaluate the clinical data on the patients and determine if the study should continue or if changes to the protocol or patient management is justified. The DMC can request unblinded data if it is needed to assess the clinical situation. Patient enrollment will not restart until approved by the DMC.
- Enrolment in the study will be paused, all sites will be notified, and there will be an ad hoc DMC meeting if there is a death probably or definitely related to XPro1595 therapy, as deemed by the Investigator.
- Subject enrolment will be temporarily suspended in the event additional safety data is required following a DMC meeting. Ongoing dosing of study participants will not be suspended unless directed to do so by the DMC.

All study activity may be discontinued following any DMC meeting due to an unfavourable safety signal, a significant and unfavourable change in risk/benefit ratio or the scientific value of the trial is deemed insufficient.

7.5. Biomarkers

- Blood samples will be collected for neurodegenerative and neuroinflammatory biomarkers, including, but not limited to, proinflammatory cytokines, amyloid, phosphoTau 217 and 181, Neurofilament Light, YKL-40 and others for analysis in the central laboratory. Samples will be collected according to the schedule described in the SoA and as detailed in laboratory manual provided separately to sites.

- INmune Bio may store samples for up to 15 years after the end of the study to achieve study objectives. Additionally, with patients' consent, samples may be used for further research by INmune Bio or others such as universities or other companies to contribute to the understanding of AD or other diseases, the development of related or new treatments, or research methods.

7.6. Immunogenicity Assessments

Antibodies to XPro1595 will be evaluated in serum samples collected from all patients according to the SoA. Additionally, serum samples should also be collected at the final visit from patients who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to XPro1595 and the titer of confirmed positive samples will be reported.

The detection and characterization of antibodies to XPro1595 will be performed using a validated assay method by or under the supervision of the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Samples may be stored for a maximum of 15 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to XPro1595.

7.7. Health Economics

For all patients throughout the study, the Investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will:

- Include the reasons and duration of hospitalizations and emergency room visits and
- Exclude procedures, tests, and encounters mandated by the protocol.

The Sponsor may use the collected data to conduct economic analyses.

8. Statistical Considerations

Details of statistical parameters and methods to be used will be described in a SAP. The SAP will be finalized prior to unblinding, and database lock and it will include a more technical and detailed description of the statistical analyses described in this section. The SAP will describe details regarding the statistical methodology to assess differences between treatment groups, all data handling procedures, and definitions, including further details on the methods used for managing missing data. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

8.1. Sample Size Determination

The sample size estimation is established based on expected changes in EMACC scores over 24 weeks as well as the key secondary endpoints. A total sample size of 201 subjects will be randomized 2:1 in a blinded fashion to XPro1595 (N = 134) or placebo (N = 67) respectively. Randomization will be stratified by indication (MCI, mAD) and sex (Male, Female). A sample size of 201 will provide ~87% power to observe a difference between XPro1595 and placebo of 0.15 units in the change from Baseline in EMACC composite at week 24 with SD = 0.36. Sample sizes were computed using a 1-sided t-test with a 5% level of significance. A 1-sided 0.05 alpha level was chosen instead of 1-sided 0.025 alpha level for practical purposes as this is a phase 2 signal detection proof of concept study.

Changes from Baseline in CDR-SB at Week 24 is the first key secondary endpoint that will be statistically tested if the primary endpoint is successful. Using a gatekeeping hierarchical approach, CDR-SB will be tested following significance of the primary endpoint analysis to control multiplicity. The change from Baseline in CDR-SB at Week 24 endpoint will have at least 75% power to observe a clinically meaningful difference between XPro1595 and placebo.

Assumptions used for power calculations for CDR-SB include a placebo mean increase of 0.45 units over 24 weeks with SD = 1 and that treatment with XPro1595 will result in a 0.1 increase in CDR-SB score ($\Delta = 0.35$). A 1-sided t-test with a 5% level of significance was used.

8.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Patient Analysis Set	Description
ITT	All enrolled patients who are randomized to a study treatment arm will be included in the ITT analysis set. The ITT will be the analysis set for disposition and demographic reporting purposes. The ITT analysis set will be used for sensitivity and supporting analyses of efficacy endpoints. Analyses will be based on the randomized treatment.
mITT	The modified ITT analysis set is defined as patients who are included in the ITT analysis set who also receive any amount of study drug and have at least 1 post-baseline efficacy assessment. The mITT will be the primary analysis set for all efficacy reporting purposes. Analyses will be based on the randomized treatment
PPS	The PPS includes all patients in the mITT analysis set who did not have any major protocol violations. This set will be used for sensitivity analyses.

SAF	All patients who have received any amount of XPro1595 or Placebo are included in the SAF. The SAF will be the analysis set for safety reporting and will be based on treatment received.

Abbreviations: ITT = Intent-to-treat; MITT = Modified Intent-to-treat; PPS = Per Protocol Set; SAF = Safety Analysis Set

The mITT set is used to analyze endpoints related to the efficacy objectives and the SAF is used to analyze the endpoints and assessments related to safety.

8.3. Statistical Hypotheses

The primary objective is to demonstrate that XPro1595 is superior to placebo in the change from baseline in the EMACC score at Week 24. Thus, the null hypothesis to be tested is as follows:

Null hypothesis: XPro1595 is not different from placebo with respect to the change from baseline in the EMACC score at Week 24.

The first key secondary objective is to demonstrate that XPro1595 is superior to placebo in the change from baseline in CDR-SB scores at Week 24. The null hypotheses corresponding to the key secondary endpoint is:

Null hypothesis: XPro1595 is not different from placebo with respect to the change in CDR-SB at Week 24.

The remaining key secondary objectives test similar null hypotheses such that XPro1595 is not different from placebo.

8.3.1. Multiplicity Adjustment

Statistical analysis and reporting of the key secondary endpoints will only be performed if the primary endpoint analysis rejects the null hypothesis with 1-sided alpha level of 0.05. Each key secondary endpoint will be tested in order, with each test performed only once the preceding test rejects the null hypothesis. This gatekeeping approach controls Type 1 error rate. The key secondary efficacy endpoints will be tested using the same statistical methods described for the primary efficacy endpoint. If the null hypothesis is not rejected for the primary endpoint, all key secondary endpoint testing will be nominal in nature.

8.4. Statistical Analyses

8.4.1. General Considerations

Statistical analyses will be performed using SAS 9.4 or higher. In general, continuous variables will be summarized using number of patients (n), mean, SD, median, minimum, and maximum. Categorical variables will be tabulated with frequency counts and percentages. All summary tables will be presented by treatment arm. Where appropriate, 95% CIs will be provided. All data will be listed.

Any changes in the protocol planned analyses will be described and documented in the SAP and/or clinical study report.

8.4.2. Efficacy Endpoints

Statistical analysis for the primary and the key secondary efficacy endpoints will be performed with a 1-sided $\alpha = 0.05$ level of significance. All other secondary endpoints will be analyzed,

however no adjustment for multiplicity is planned for the non-key secondary endpoints. Therefore, nominal p-values will be provided for the non-key secondary efficacy endpoints. Analyses and summary statistics will be based on the mITT analysis set. All endpoints will be summarized by the treatment group over time as appropriate. Sensitivity and other supplemental analyses may be performed, details will be included in the SAP.

8.4.2.1. Primary Endpoint(s) Analysis

The primary endpoint is the change from baseline in the EMACC score at Week 24. The EMACC score is calculated as the average of the standardized score of each of the 6 components of the EMACC.

- International Shopping List Test-Immediate Recall (Word List Learning Test)
- Digit Span Forward and Backward
- Category Fluency Test (DKEFS)
- Letter Fluency Test (DKEFS)
- Trail Making Test Parts A and B
- Digit Symbol Coding Test

The standardized scores of each of the above components are calculated based on the SDs at baseline. Prior to computing the standardized mean value, direction of the trail making test scores will first be reversed by subtracting the test result from the maximum allowable score so that for all components, higher values reflect better performance.

The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) analysis method to assess differences in changes from baseline between treatment groups. The model will include fixed effect of randomized treatment group, visit (categorical), treatment-by-visit interaction, indication, sex, Placebell©™ covariates, and baseline EMACC score as covariates. An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. LS means at each visit and the difference in LS means between treatment groups will be presented together with the corresponding 95% CIs. The difference in LS means at Week 24 will be evaluated using a 1-sided alpha = 0.05.

8.4.2.1.1 Primary Estimand

The estimand for the primary efficacy analysis is described below and includes strategies to deal with specific intercurrent events.

Treatment Arms	Xpro1595 (1 mg/kg) and Placebo, given via SC injection.
Target Population	Patients with early AD who have been randomized to Xpro1595 or Placebo (2:1 randomization ratio) and received any amount of study drug
Endpoint	Change from Baseline to Week 24 in the EMACC score where EMACC includes the following 6 components: • International Shopping List Test-Immediate Recall (Word List Learning Test) • Digit Span Forward and Backward

	• Category Fluency Test (DKEFS) • Letter Fluency Test (DKEFS) • Trail Making Test Parts A and B • Digit Symbol Coding Test	
Population Summary	Difference between treatment arms in the change from Baseline to Week 24 in the EMACC score	
Analysis Method	Mixed Model Repeated Measures Analysis	
Intercurrent events	**Event**	**Strategy**
	Discontinue randomized study drug prior to Week 24	Treatment policy – assume event did not occur and use post-ICE data. If missing post-ICE data, treat as MAR
	AE with lasting cognitive impairment - Stroke - Fall with concussion - Traumatic Brain injury	Hypothetical strategy – data post ICE will not be used. Missing data is assumed to be MAR
	AE due to infection (i.e..: UTI)	Treatment policy – assume event did not occur, use all available data
	Tested positive for COVID-19	Hypothetical strategy – data post ICE will not be used. Missing data is assumed to be MAR
	Interruption of randomized study treatment - Due to AE	Treatment policy – assume event did not occur and use all data
	Interruption of randomized study treatment - Due to being out of town/drug left at home	Hypothetical strategy – missing post-ICE data will be assumed to be MAR
	Lost to follow-up, withdrawal of consent	Hypothetical strategy – data post ICE will not be used. Missing data is assumed to be MAR
	Received prohibited medication	Hypothetical strategy – data post ICE will not be used. Missing data is assumed to be MAR

Abbreviations: AD = Alzheimer's disease; AE = adverse event; COVID-19 = Coronavirus disease; EMACC = Early and Mild Alzheimer's cognitive composite; ICE = intercurrent event; MAR = missing at random; UTI = urinary tract infection.

8.4.2.2. Key Secondary Endpoint Analysis

Descriptive statistics will be provided for each key secondary endpoint and reported by treatment group. Original values and changes from baseline will be summarized. Graphical presentation of endpoint data may be presented and will be described in the SAP. Order of key secondary endpoints is as follows:

- Change in CDR-SB
- Change in E-Cog
- Change in NPI-12

The statistical analysis model for key secondary endpoints will use a MMRM model as described above for the primary efficacy endpoint, with baseline values included with respect to the specific endpoint. Endpoints that are not normally distributed will have their data transformed (i.e., log transformation) prior to analysis to ensure parametric assumptions are met. P-values will be included similarly to the Primary endpoint analysis. Multiplicity will be addressed in a sequential manner as per Section 8.3.1.

8.4.2.3. Secondary Endpoint Analysis

Descriptive statistics will be provided for each secondary endpoint and reported by treatment group. Original values and changes from baseline will be summarized. Graphical presentation of endpoint data may be presented and will be described in the SAP.

- Change in ADCS-ADL-MCI
- Change in blood inflammatory and neurodegeneration biomarkers
- Change in volumetric MRI – neurodegeneration
- Change in volume of T2-weighed MRI lesions. Number of new hemorrhagic brain lesions on SWI/T2*-weighted MRI.

The statistical analysis model for secondary endpoints will use a MMRM model as described above for the primary efficacy endpoint, with baseline values included with respect to the specific endpoint. Endpoints that are not normally distributed will have their data transformed (i.e., log transformation) prior to analysis to ensure parametric assumptions are met. P-values may be provided for descriptive purposes.

8.4.2.4. Exploratory Endpoint Analysis

Descriptive statistics will be provided for each exploratory endpoint and reported by the treatment group. Original values and changes from baseline will be summarized. Graphical presentation of endpoint data may be presented and will be described in the SAP.

8.4.2.4.1 Placebell©™ Covariate

The Placebell©™ technology will be applied and Placebell© covariates will be estimated based on previous models from other indications.

The Placebell©™ covariate will be summarized descriptively by treatment group.

8.4.2.5. Missing Data

Missing efficacy data will not be imputed. For the primary analysis, missing data will be assumed to be MAR and the MMRM analysis method used to analyze the primary and key secondary efficacy endpoints is able to accommodate data that is MAR and provide unbiased results. Sensitivity analyses may be performed which impute missing data assuming MNAR. Details will be included in the SAP.

8.4.2.6. Sensitivity and Supplementary Analysis

The following sensitivity and supplemental analyses will be performed for both the primary and key secondary endpoints.

- Statistical analysis will be repeated on the PP set.
- Statistical analysis will be performed using an ANCOVA. Missing Week 24 data will not be imputed.

Additional sensitivity analysis will be specified in the SAP.

8.4.3. Safety Analyses

Adverse events, clinical laboratory data for safety, vital sign and ECG assessments will support in the evaluation of the safety of study drug. Data will be summarized by treatment group and study visit, where applicable.

All safety summaries will be provided for the SAF.

8.4.3.1. Adverse Events

All AEs will be coded using the MedDRA classification system. Treatment-emergent AEs are defined as events occurring after the first dose of study drug or any pre-existing condition that worsens in severity after receiving the first dose of study drug. Relationship to study drug will be assessed by the investigator and reported on the CRF. The incidence of TEAEs, SAEs, and related TEAEs will be summarized by treatment arm and overall and by SOC and by preferred term.

8.4.3.2. Vital Signs, Electrocardiogram, and Laboratory Assessments

Vital signs and laboratory tests will be summarized as observed values and change from Baseline by treatment arm at each timepoint. Baseline is defined as the latest value in the database prior to randomization. Listings of abnormal laboratory parameter results will be provided.

Electrocardiogram data will be provided in data listings. Abnormal findings will be flagged.

8.4.4. Subgroup Analyses

Subgroups may be explored including age, sex, and strata; details will be included in the SAP.

8.4.5. Other Analyses

8.4.5.1. Demographics and Baseline Characteristics

Patient demographics and disease history will be summarized on the ITT analysis set.

8.4.5.2. Prior and Concomitant Medications

Prior and concomitant medications will be collected throughout the study and recorded in the CRF. All medications will be coded according to the WHO Drug Dictionary and provided in patient listings.

8.5. Interim Analysis

A blinded interim analysis will be performed once approximately 20% of subjects complete the Week 24 visit. The blinded interim analysis will be focused on assessing the variability of the EMACC score and change from baseline to ascertain if the current variability in the AD-02

population is following the assumptions used in the original sample size calculation or if a sample size adjustment is required. The sample size will be increased if the pooled standard deviation is SD>0.40 to ensure 80% power up to a sample size of 1.5 times the original sample size of N=201, resulting in a maximum sample size of N=303. The table below provides an example of how the sample size would increase. The sample size will be re-estimated based on the observed standard deviation at this interim analysis. No unblinding will occur during this interim analysis.

Power	Xpro1595 N	Placebo N	Total N	Standard Deviation	Increase Sample Size
80%	134	67	201	0.40	No
80%	134+34=168	67+17=84	252	0.45	Yes
80%	134+68=202	67+34=101	303	0.497	Yes – to the max sample size

A DMC will assess ongoing safety at pre-specified time points as detailed in the DMC charter.

8.6. Final Analysis

The final analysis will occur once all patients complete their EOS visit or their last scheduled assessment per the SoA, or the Sponsor terminates the study for any reason.

9. Supporting Documentation and Operational Considerations

9.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, IDFU, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.
- Study conduct will be terminated in the event of revocation of regulatory approval by the responsible health authority.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

9.1.1. Financial Disclosure

Investigators and sub investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests throughout the course of the study and for 1 year after completion of the study.

9.1.2. Informed Consent Process

- At the screening visit and before any study-specific activities/procedures, the appropriate written informed consent must be obtained.
- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient.

If, in the investigator's opinion, a patient lacks capacity to consent at any point during the conduct of the study (other than instances of transient incapacity, as described in Section 6), the patient should be immediately withdrawn (refer to Section 6.1).

9.1.3. Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

9.1.4. Committees Structure

9.1.4.1. Early Safety Data Review AND Committee

- Patient safety will be continuously monitored by an external safety review committee, which includes safety signal detection at any time during the study.

9.1.5. Dissemination of Clinical Study Data

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by local laws and regulations.

9.1.6. Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided during site training and linked to the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

9.1.7. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in source data acknowledgment or monitoring guidelines.
- The investigator must maintain accurate documentation (source data) that supports the information entered into the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are attributable, legible, contemporaneous, original, and accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

9.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

The study will be suspended or terminated at any time in case of:

- New information or other evaluation regarding the safety of XPro1595 that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Occurrence of local or global events (e.g., COVID-19 Pandemic) that would impact the safety of subjects in the study.
- Revocation of regulatory or ethics approval for the study.
- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the investigator
- Total number of patients enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The sponsor and CRO will communicate with the investigators how to manage ongoing and in screening patients. The investigator shall promptly inform the patient and should ensure appropriate patient therapy and/or follow-up.

9.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor for review before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

9.1.10. Sample Storage and Destruction

- Any blood and biomarker sample collected according to the SoA (Section 3.6) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study patients. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.
- All samples and associated results will be coded prior to being shipped from the site for analysis or storage. The laboratory manual (to be supplied to study sites) will include a description of the collection, handling, storage and shipping procedures of all samples retained for pharmacokinetic/pharmacodynamic/pharmacogenomic or other biomarker assessments during the trial. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.
- Sample processing, for example DNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy. Further information on genetic testing is included in Appendix 5: Genetics.
- Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.
- If informed consent is provided by the patient, INmune Bio can do additional testing on remaining samples (i.e., residual and back-up) to investigate and better understand the AD, the dose response and/or prediction of response to XPro1595, (characterize antibody response), and characterize aspects of the molecule (e.g., mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 15 years (or according to local regulations). At the end of the storage period, samples will be destroyed.

Since the evaluations are not expected to benefit the patient directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the patient's medical record and are not to be made available to the patient, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

- The patient retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the patient, the investigator is to provide the sponsor with the required study and patient number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by INmune Bio.
- The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the patient through the investigator, at the end of the storage period, or as appropriate (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The patient has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. (See Section 9.1.3 for patient confidentiality).

9.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 4. Protocol-required Safety Laboratory Tests will be performed by the clinical laboratory.

- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 4.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit ESR	RBC indices: MCV MCH %Reticulocytes Mean cell Hemoglobin concentration		WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry[1]	BUN	Potassium	AST Albumin Total protein sodium Potassium GGT Total bilirubin Triglyceride Total cholesterol LDH Calcium Uric acid	Total and direct bilirubin
	Creatinine	Sodium	ALT	Total protein
	Glucose	Calcium	ALP[2]	
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Urine dipstick pregnancy test will be performed at Screening and monthly for patients who are of childbearing potential			
Other screening tests	• Serology (HIV antibody, HBsAg, and HCV antibody), HCV RNA. • Anti-drug antibody • Anti-PEG			

NOTES:
1 Details of liver chemistry stopping criteria and required actions and follow-up are given in Section (7.1.1 Liver Chemistry Stopping Criteria) and Appendix (6: Liver Safety: Suggested Actions and Follow-up Assessments [and Study Intervention Rechallenge Guidelines]). All events of ALT (or AST) ≥ 3 × ULN and total bilirubin ≥

2 × ULN (> 35% direct bilirubin) or ALT (or AST) ≥ 3 × ULN and INR > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to (sponsor) in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

2 If alkaline phosphatase is elevated, consider fractionating.

Investigators must document their review of each laboratory safety report.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase, APOE = apolipoprotein E; AST = aspartate transaminase; BUN = blood urea nitrogen; CRP = C-reactive protein; GGT = gamma glutamyl transferase; HbA1C = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; RBC = Red blood cell; RNA = ribonucleic acid; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TNF = tumor necrosis factor; WBC = white blood cell.

9.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

9.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

9.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

9.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the patient's medical records to Syneos Health Safety in lieu of completion of the SAE form/required form.
- There may be instances when copies of medical records for certain cases are requested by Syneos Health Safety. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Syneos Health Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Syneos Health Safety. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Syneos Health Safety.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by INmune Bio to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide Syneos Health Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.

- The investigator will submit any updated SAE data to Syneos Health Safety within 24 hours of receipt of the information.

9.3.4. Reporting of SAEs

SAE Reporting to Syneos Health Safety via an Electronic Data Collection Tool
The primary mechanism for reporting an SAE to Syneos Health Safety will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Syneos Health Safety by telephone.

SAE Reporting to Syneos Health Safety via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Syneos Health Safety. • SAE information should be faxed to 877-464-7787 or emailed to safetyreporting@syneoshealth.com.

9.3.5. Definition of AESI

AESI Definition
• An AESI, an adverse event of special interest (serious or non-serious), is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. • NOTE: An AESI might warrant further investigation in order to characterize and understand it.

9.4. Appendix 4: Contraceptive and Barrier Guidance

Woman of Nonchildbearing Potential

Women in the following categories are considered WONCBP:

Premenopausal female with permanent infertility due to 1 of the following:

1. Documented hysterectomy
2. Documented bilateral salpingectomy
3. Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement (> 40 IU/L or mIU/mL) is required.

Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

9.4.1. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- IUD
- IUS[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
    - oral
    - intravaginal
    - transdermal
    - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
    - oral
    - injectable
- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

9.5. Appendix 5: Genetics

- Use/analysis of DNA
- Genetic variation may impact a patient's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.
- DNA samples will be used for research related to XPro1595. They may also be used to develop tests/assays, including diagnostic tests related to XPro1595. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for APOE4 status. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be labelled with a unique identifier (in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] E15 guidelines, or locally applicable guidelines) in order to maintain subject privacy.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to XPro1595 or study interventions of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on XPro1595 continues but no longer than 15 years or other period as per local requirements.

9.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase 2 Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5 × ULN
ALT Increase	ALT ≥ 3 × ULN persists for ≥ 4 weeks
Total bilirubin[1, 2]	ALT ≥ 3 × ULN **and** total bilirubin ≥ 2 x ULN (> 35% direct bilirubin)
INR[2]	ALT ≥ 3 × ULN **and** INR > 1.5, if INR measured
Cannot Monitor	ALT ≥ 3 × ULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring, and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention. • Report the event to the sponsor **within 24 hours.** • Complete a SAE data collection tool if the event also met the criteria for an SAE.[2] • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). **MONITORING:** **<u>If ALT ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline.	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain serum CPK, LDH, GGT, GLDH, and serum albumin • Fractionate bilirubin, if total bilirubin ≥ 2 × ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event/expedited reporting form, • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs, and other over-the-counter medications)

- A specialist or hepatology consultation is recommended.

If ALT ≥3 × ULN AND total bilirubin < 2 × ULN and INR ≤ 1.5:

- Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.**
- Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.
- Record alcohol use on the liver event alcohol intake form.

If ALT ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5 obtain the following in addition to the assessments listed above:

- Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins.
- Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging form
- Liver biopsy may be considered and discussed with local specialist if available:
  - In participants when serology raises the possibility of AIH
  - In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention
  - In participants with acute or chronic atypical presentation
- If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record the absence/presence of detectable urinary bilirubin on dipstick which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT ≥ 3 x ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
4. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

9.7. Appendix 7: Country-specific Requirements

Not applicable.

9.8. Appendix 8: Modified Hachinski Ischemic Score

The HIS is a simple clinical tool for differentiating major types of dementia such as primary degenerative, vascular or multi-infarct, and mixed type. A high HIS is closely related with cerebrovascular disease and its vascular factors.

The table below is used to derive the Modified HIS. Answers to the following questions are determined from the participant, study partner, and/or medical record. For each "Yes" response, add the corresponding value to the score column. Then add the scores for all the questions. If the total score is 4 or less, the dementia is not likely to be due to vascular causes and the participant meets the AD inclusion criteria for the Modified HIS.

Question	Yes Response	Score
Abrupt onset of dementia	2	
Stepwise deterioration of dementia	1	
Somatic complaints	1	
Emotional incontinence	1	
History of hypertension	1	
History of stroke	2	
Focal neurologic symptoms	2	
Focal neurologic signs	2	
	Total Score	

9.9. Appendix 9: National Institute on Aging-Alzheimer's Association Diagnostic Guidelines for Alzheimer's Disease

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of 2 of the following domains:
    a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
    b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, and inability to plan complex or sequential activities.
    c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
    d. Impaired language functions (speaking, reading, and writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
    e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, and socially unacceptable behaviors.

The differentiation of dementia from MCI rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities. This is inherently a clinical judgment made by a skilled clinician on the basis of the individual circumstances of the patient and the description of daily affairs of the patient obtained from the patient and from a knowledgeable informant.

Probable Alzheimer's disease dementia is diagnosed when the patient meets criteria for dementia described above, and in addition, has the following characteristics:

6. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;
7. Clear-cut history of worsening of cognition by report or observation;

8. The initial and most prominent cognitive deficits are evident in history and examination in 1 of the following categories.
    a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least 1 other cognitive domain, as defined earlier in the text.
    b. Nonamnestic presentations:
        i. Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
        ii. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
        iii. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
9. The diagnosis of probable AD dementia *should not* be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant FTD; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Note: All patients who met criteria for "probable AD" by the 1984 NINCDS–ADRDA criteria would meet the current criteria for probable AD dementia mentioned in the present article.

Source: McKhann, 2011

9.10. Appendix 10: National Institute on Aging-Alzheimer's Association Diagnostic Guidelines for Mild Cognitive Impairment due to Alzheimer's Disease

Summary of clinical and cognitive evaluation for MCI due to AD:

Establish clinical and cognitive criteria

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
- Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities
- Not demented
- **Examine etiology of MCI consistent with AD pathophysiological process**
- Rule out vascular, traumatic, medical causes of cognitive decline, where possible
- Provide evidence of longitudinal decline in cognition, when feasible
- Report history consistent with AD genetic factors, where relevant Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment

9.11. Appendix 11: Jack 2018 Staging Guidance

Stage 1

Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (the choice of the investigators) for age, sex, education, etc.*

Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern.

No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available.

Stage 2

Normal performance within expected range on objective cognitive tests.

Transitional cognitive decline: Decline in previous level of cognitive function, which may involve any cognitive domain(s) (i.e., not exclusively memory).

May be documented through subjective report of cognitive decline that is of concern to the participant. Represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months. May be corroborated by informant but not required.

Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required.

Or may be documented by both subjective report of decline and objective evidence on longitudinal testing. Although cognition is the core feature, mild neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist. In some individuals, the primary compliant may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persists and cannot be explained by life events. y

No functional impact on daily life activities

Stage 3

Performance in the impaired/abnormal range on objective cognitive tests.

Evidence of decline from baseline, documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments.

May be characterized by cognitive presentations that are not primarily amnestic. z

Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner.

Stage 4

Mild dementia

Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing.

Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.

Stage 5

Moderate dementia

Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.

Stage 6

Severe dementia

Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

**For stages 1–6: Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.*

yFor stages 2–6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.

zFor stages 3–6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

Source: Jack et al. 2018; NIA-AA

9.12. Appendix 12: Abbreviations

AD	Alzheimer's disease
ADi	Alzheimer's disease with biomarkers of inflammation
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADCS-MCI-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment
ADL	activities of daily living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
AESI	adverse event of special interest
AFD	apparent fiber density
AIBL	The Australian Imaging, Biomarkers and Lifestyle study
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
APOE	apolipoprotein E
APOE4	apolipoprotein E4
ARIA	amyloid related imaging abnormalities
AST	aspartate transaminase
AUS	Australia
Aβ	amyloid beta
BUN	blood urea nitrogen
CDM®	Cortical Disarray Measurement
CDR	Clinical Dementia Rating scale
CDR-SB	Clinical Dementia Rating scale Sum of Boxes
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CT	computed tomography
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization

CRP	C-reactive protein
CSF	cerebral spinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTFG	Clinical Trial Facilitation Group
DAMP	damage-associated molecular patterns
DCCT	Diabetes Control and Complications Trial
DILI	drug induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSST	Digit symbol substitution test
E-Cog	Everyday Cognition
ECG	electrocardiogram
eCRF	electronic case report form
EMACC	Early and Mild Alzheimer's cognitive composite
EOS	end of study
ESR	erythrocyte sedimentation rate
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FTD	Frontotemporal dementia
GAS	Goal Attainment Scale
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
GMP	Good Manufacturing Practice
HbA1C	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
hsCRP	highly specific CRP
HED	human equivalent dose
HIS	Hachinski Ischemic Scale
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormonal replacement therapy
IB	investigators brochure

ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IDFU	investigational directions for use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ISR	injection site reaction
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JNK	c-Jun N-terminal kinase
K_2EDTA	di-potassium ethylenediaminetetraacetic acid
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LS	least-square
MAR	missing at random
MedDRA	Medical Dictional for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCI	mild cognitive impairment
MCSA	Mayo Clinic Study of Aging
MCV	mean corpuscular volume
mITT	modified intent-to-treat
MMRM	Mixed Model for Repeated Measures
MMSE	Mini Mental State Examination
MNAR	missing not at random
MPsQ	Multidimensional Psychological Questionnaire

MRI	magnetic resonance imaging
MS	multiple sclerosis
MTR	magnetization transfer ratio
MT	magnetization transfer
MWF	myelin water fraction
NIA-AA	National Institute on Aging – Alzheimer's Association
NIMP	non investigational medicinal product
NINCDS–ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NK/DC	natural killer/dendritic cell
NOAEL	no observed adverse effect level
NPI	neuropsychiatric inventory
NPI-12	neuropsychiatric inventory version with 12 behavior domains
NPID	neuropsychiatric inventory distress
PK	pharmacokinetics
PP	per protocol
PPS	per protocol set
QD	once daily
QOD	every other day
RBC	red blood cell
RDt	radial diffusivity
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoA	schedule of activities
SOC	system organ class
solTNF	soluble tumor necrosis factor alpha
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
T	telephone contact

T1	spin-spin relaxation time 1
T2	spin-spin relaxation time 2
TBI	traumatic brain injury
TEAE	treatment-emergent adverse event
TGA	Therapeutic Goods Administration
Th1	T helper cells 1
TME	tumor microenvironment
tmTNF	transmembrane tumor necrosis factor
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
TNFR	tumor necrosis factor receptor
TNFR1	tumor necrosis factor receptor 1
TNFR2	tumor necrosis factor receptor 2
ULN	upper limit of normal
USA	United States of America
USD	United States Dollar
UTI	urinary tract infection
WHO	World Health Organization
WBC	white blood cell
WOCBP	women of childbearing potential
WONCBP	woman of nonchildbearing potential

9.13. Appendix 13: Protocol Amendment History

Protocol Version/Date	Document Version	Approval Date
	Original (v1.0)	08 September 2021
	Amendment 1.0	05 November 2021
	Amendment 2.0	13 October 2022
	Amendment 3.0	08 November 2022
	Amendment 4.0	09 January 2023
	Amendment 5.0	25 April 2023
	Amendment 6.0	02 November 2023
	Amendment 7.0	13 May 2024

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