CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761248Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 17, 2023

From: Lois M. Freed, Ph.D.
Director, Division of Pharmacology/Toxicology-Neuroscience
Office of Neuroscience

Subject: BLA 761248 (KISUNLA, donanemab-azbt, LY3002813)

BLA 761248 was submitted by the sponsor (Eli Lilly and Co) to support marketing of donanemab-azbt (donanemab) for the treatment of Alzheimer's disease under accelerated approval regulations. The proposed labeling states that "Treatment with KISUNLA should be initiated in patients with mild cognitive impairment or mild dementia stage of disease…" The initial rolling BLA submission (September 3, 2021) contained the nonclinical studies and summaries. The final portions of the BLA were submitted on May 18, 2022.

The nonclinical studies conducted to support the BLA included primary pharmacology (in vitro, ex vivo, and in vivo) and toxicology studies and a tissue cross-reactivity study (monkey and human tissues). Donanemab is not pharmacologically active in normal rodent or nonrodent; therefore, toxicity studies were conducted in cynomolgus monkey (6-week IV donanemab) to assess for any off-target toxicity, and in the PDAPP transgenic mouse model (6-week and 6-month SC mE8c, a murine surrogate) to assess for relevant on-target effects (toxicity and pharmacology). As agreed to by the division during clinical development, reproductive and developmental toxicology studies were not conducted because of the age of the intended patient population, and carcinogenicity studies were not considered feasible because of the lack of pharmacologically relevant species.

The nonclinical data were reviewed by Dr. Thompson under the IND (Pharmacology/Toxicology IND Review and Evaluation, IND 109157, D. Charles Thompson, Ph.D., March 27, 2013) and by Dr. Hawver under the BLA (Pharmacology/Toxicology BLA Review and Evaluation, BLA 761248, David B. Hawver, Ph.D., January 17, 2023). Dr. Hawver has concluded that the nonclinical

data "…adequately support the approval of donanemab-azbt for the treatment of [redacted](b) (4)."

Pharmacology

Donanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta.

PK/ADME

Following administration of an acute IV dose (1 mg/kg) in monkey, the $t_{1/2}$ was 168-192 hours. Toxicokinetic analyses were included in the toxicity studies in monkey (donanemab) and PDAPP mouse (mE8c).

Toxicology

Cynomolgus monkey: in the 6-week (GLP-compliant) IV toxicity study (with 3-month recovery), donanemab was administered by IV injection at doses of 0, 1, 10, and 100 mg/kg QW. No drug-related findings were observed on a standard battery of safety parameters. On Day 36, plasma C_0 and AUC$_{(0\text{-}166\ hr)}$ at the high dose were 2800 ± 936 μg/mL and 139000 ± 21400 μg*hr/mL, respectively, in males and 2680 ± 414 μg/mL and 146000 ± 20300 μg*hr/mL, respectively, in females.

PDAPP mouse: in GLP-compliant studies, a murine surrogate (mE8c) was administered by SC injection for 6 weeks at doses of 0, 10, 30, and 100 mg/kg QW or for 6 months at doses of 0, 30 and 100 mg/kg QW. No drug-related findings were observed on a standard battery of safety parameters. Toxicokinetic analysis was included in both studies but are not considered appropriate for calculation of safety margins, as these studies are only for hazard identification.

Tissue Cross Reactivity: no relevant (non-cytoplasmic), specific staining was detected with donanemab in normal human or cynomolgus monkey tissues.

Conclusions and Recommendation

The nonclinical data are sufficient and adequate to support approval for the proposed indication, with appropriate labeling. Labeling recommendations are provided separately.

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/s/

LOIS M FREED
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	761248
Supporting document:	1
Applicant's letter date:	September 3, 2021
CDER stamp date:	September 3, 2021
Product:	KISUNLA (donanemab-azbt)
Indication:	(b) (4) of Alzheimer's disease
Applicant:	Eli Lilly and Company
Division:	Pharmacology/Toxicology-Neuroscience
Reviewer:	David B. Hawver, Ph.D.
Supervisor:	Lois M. Freed, Ph.D.
Project Manager:	Emilios A. Papanastasiou

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Donanemab-azbt is a humanized immunoglobulin 1 (IgG1) monoclonal antibody that binds a variant of the human amyloid beta (Aβ) peptide in which the first two N-terminal amino acids are absent and the third is modified to form pyroglutamate ($A\beta_{N3pE\text{-}x}$; x indicates that Aβ can vary between 37 and 43 amino acids in length). Binding of donanemab to $A\beta_{N3pE\text{-}x}$, which is present in amyloid deposits in the brain, facilitates the removal of amyloid plaques through microglial-mediated phagocytosis. The proposed indication is (b) (4) .

1.2 Brief Discussion of Nonclinical Findings

Pharmacology studies demonstrated that donanemab binds specifically to a truncated pyroglutamate-modified form of the human Aβ peptide, $A\beta_{N3pE\text{-}x}$, which is found in amyloid deposits in the brain present in AD patients and ~30% of cognitively normal subjects ≥67.5 years old (Jansen et al., 2015, *JAMA* 313(19):1924-1938). In vivo and ex vivo studies provided evidence that binding of mE8c, the murine analog of donanemab, to $A\beta_{N3pE\text{-}x}$ in brain from AD patients or in aged PDAPP mice resulted in reduction of deposited amyloid through a pathway involving microglial phagocytosis.

The toxicology of donanemab and its murine analog, mE6c, was adequately assessed in general toxicity studies in cynomolgus monkey and PDAPP mouse, respectively. In the pivotal (GLP) repeated-dose study in monkey, administration of donanemab (0, 1, 10, or 100 mg/kg/week IV) for 6 weeks resulted in no adverse effects. Donanemab serum exposure (AUC) in high dose (HD) animals after the final dose was ~10-fold greater than that expected in humans at steady-state at the maximum proposed clinical dose (1400 mg IV every 4 weeks) after adjusting for differences in the dosing interval.

Potential “on-target” toxicity was assessed in aged PDAPP mice, a mouse model in which amyloid deposits in the brain accumulate with age. In the pivotal (GLP) studies, no adverse effects were related to subcutaneous (SC) administration of mE8c for 6 weeks or 5 months up to the highest dose evaluated (100 mg/kg/week). In a separate study, intraperitoneal (IP) administration of mE8c (12.5 mg/kg/week) to 23- to 24-month-old PDAPP mice for 13 weeks did not increase the number of brain microhemorrhages per animal, in contrast to the same dose of a comparator antibody targeting amino acids 1-6 of the Aβ peptide in deposited plaques. However, the ability of anti-amyloid antibodies to induce microhemorrhages in such animal models has not been demonstrated to reliably predict the risk of microhemorrhages or vasogenic edema in humans.

1.3 Recommendations

1.3.1 Approvability

The nonclinical data submitted adequately support the approval of donanemab-azbt for the treatment of (b) (4) .

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The sponsor's proposed labeling for the nonclinical sections should be revised as specified below (suggested deletions are crossed out; additions are underlined and bolded):

(b) (4)

2 Drug Information

2.1 Drug

Nonproprietary Name
donanemab-azbt

Proprietary Name
KISUNLA

Code Name
LY3002813

CAS Number
1931944-80-7

Molecular Weight
145 kDa (peptide sequences only); 148 kDa (including oligosaccharides at the Asn295 residues and pyroglutamic acid formation at Gln 1 at the heavy chain N-terminus)

Biochemical Description
Donanemab-azbt is a recombinant humanized IgG1 monoclonal antibody composed of two identical gamma heavy chains and two identical kappa light chains. Carbohydrate moieties (predominantly a fucosylated, complex biantennary glycan with 0 galactose residues on either arm) are linked to asparagine residue 295 on the heavy chains.

Pharmacologic Class
Donanemab-azbt targets the N-terminus of a variant of the human Aβ peptide in which the first two amino acids are absent and the third is modified as a pyroglutamate.

2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 109157 donanemab for the treatment of Alzheimer's disease

2.3 Drug Formulation

Donanemab Injection is formulated as a sterile, non-pyrogenic, preservative-free solution for IV infusion in a 20 mL glass vial. The concentrations of donanemab and other components of the solution are listed in Table 2.3.P.1-1 below:

Table 2.3.P.1-1 Composition of Donanemab Injection

Ingredient	Quantity (mg/mL)	Quantity (mg/vial)[a]	Function	Reference to Standards
Active Ingredient				
Donanemab	17.5	350	Drug Substance	Internal Standard: See Section 3.2.S.4.1, Specification
Other Ingredients				
Sodium Citrate (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP-NF, Ph.Eur., JP
Citric Acid Anhydrous	0.32	6.4		USP-NF, Ph.Eur., JP
Sucrose	80	1600		USP-NF, Ph.Eur., JP
Polysorbate 80	0.20	4.0		USP-NF, Ph.Eur., JP
Water for Injection	(b) (4)			USP-NF, Ph.Eur., JP

Abbreviations: USP-NF = United States Pharmacopoeia-National Formulary; Ph.Eur. = European Pharmacopoeia; JP = Japanese Pharmacopoeia; (b) (4)

[a] An overfill volume of (b) (4) mL is included to enable delivery of 20 mL. Quantities in the table do not include overfill.

(page 1, section 2.3.P, Drug Product)

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product.

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern were identified.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication is (b) (4) . The proposed dosing regimen is administration by IV infusion over approximately 30 minutes every four weeks, titrating upward from 700 mg (infusions 1, 2, and 3) to 1400 mg (infusions 4 and beyond), until amyloid plaque is cleared.

2.7 Regulatory Background

During a Pre-IND meeting on October 14, 2010, the sponsor was informed that testing of only females in the 6-month study in PDAPP mouse and the adequacy of the high dose (12.5 mg/kg/week) used in that study would need to be addressed (Pre-IND 109157 Meeting Minutes, November 12, 2010). These issues were resolved by submission of a 5-month study in male and female PDAPP mice at doses up to 100 mg/kg/week.

In the May Proceed Letter (April 1, 2013), the sponsor was informed that the 3-month study of mE8c (a murine surrogate antibody) in aged PDAPP mouse conducted to assess the potential for LY3002813-induced microhemorrhage was inadequate due to the lack of sufficient justification for the high dose selection. The sponsor was told to either conduct a histopathological assessment for the presence of microhemorrhage in brain samples from the subsequent 5-month study in PDAPP mouse or to conduct a new study assessing a range of doses up to a high dose associated with dose-limiting toxicity or demonstrated to be a maximum feasible dose. This issue was resolved when the Division eliminated the requirement for a microhemorrhage study in a transgenic mouse model to support development of compounds expected to reduce Aβ in the brain (see Letter to Sponsor, June 26, 2014).

In a Type C Meeting (see July 20, 2020, Written Responses), the sponsor was informed that reproductive and developmental toxicology studies are generally not required to support clinical development or marketing approval for products intended for the treatment of Alzheimer's disease, based on the age of the population with that condition, and that carcinogenicity studies would not be needed to support clinical development or a BLA for donanemab.

In a Pre-BLA meeting on August 26, 2021, the Division agreed that the nonclinical data described in the meeting package were sufficient to support review of the proposed BLA (see Pre-BLA Meeting Minutes, October 7, 2021).

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology
In Vitro Binding Affinity and Epitope Determination of N3pG Antibodies by Surface Plasmon Resonance

Ex Vivo Phagocytosis Studies with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)

Ex Vivo Target Engagement Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanized Antibodies (LY3002813)

In Vivo Target Engagement Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanized Antibodies (LY3002813)

In Vivo Plasma Aβ Accumulation Studies with Anti-Aβ Antibodies Including Anti-N3pG Murine Surrogate and Humanized Antibodies (LY3002813)

In Vivo Therapeutic Plaque Lowering Studies in Aged PDAPP Mice with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogates for LY3002813)

In Vivo Plaque Lowering Studies in Aged PDAPP Mice with Anti-N3pG Antibody mE8c (Murine Surrogate for LY3002813) to Determine Minimum Efficacious Dose

In Vivo Plaque Prevention Study in PDAPP Mice with Anti-Aβ Antibodies Including mE8c (Murine Surrogate for LY3002813)

Pharmacokinetics
Analytical Methods and Validation Studies
Method Validation of LSN3026818 (mE8C murine analog of LY3002813, anti-N3Pg Abeta Antibody) in Mouse Serum and Plasma using ELISA Methodology

Method Validation of LY3002813 (N3Pg-Abeta Antibody) in Cynomolgus Monkey Serum using ELISA Methodology

Validation of a Qualitative Method for the Detection of LY3002813-reactive Antibodies in Cynomolgus Monkey Serum Using ELISA Methodology

Absorption
Serum and Plasma Exposure with Three Lots of mE8c (LSN3026818) in CD1 Mice Following a Single Subcutaneous Dose of 10 mg/kg

Serum Pharmacokinetics of LY3002813 in Cynomolgus Monkeys After Intravenous or Subcutaneous Administration: Comparison of 3 Material Lots

Pharmacokinetics of LY3002813 in Cynomolgus Monkeys Following a Single Intravenous or Subcutaneous Dose of 1 mg/kg LY3002813

Repeat-Dose Toxicity
A Repeat-Dose Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY3002813 by Intravenous Injection Once Weekly for 6 Weeks with a 3-Month Recovery Phase

A Chronic Pharmacology/Toxicity Study in Aged Female PDAPP Mice Given Weekly Subcutaneous Doses of mE8 Derivative C (Murine Analog of LY3002813) for Six Months

A Repeat-dose Toxicity and Exposure Study in PDAPP Mice Given LSN3026818, mE8 Derivative c (mE8c, Murine Analog of LY3002813) by Subcutaneous Injection Once Weekly for 6 Months

A Repeat-Dose Toxicity and Exposure Study in PDAPP Mice Given LSN3026818, mE8 Derivative c (mE8c, Murine Analog of LY3002813) by Subcutaneous Injection Once Weekly for 6 Weeks

Cerebral Microhemorrhage and Neuropathology Study in Aged PDAPP Mice Given LSN3026818, mE8 Derivative C (mE8c, Murine Analog of LY3002813), by Intraperitoneal Injections Weekly for 3 Months

In Vivo Microhemorrhage Study in Aged PDAPP Mice with Anti-Aβ Antibodies Including mE8 and mE8c (Murine Surrogate for LY3002813)

Other
Tissue Cross-Reactivity of LY3002813 with Human and Cynomolgus Monkey Tissues Ex Vivo

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND 109157 Donanemab for Alzheimer's Disease

- Pharmacology/Toxicology Review, D. Charles Thompson, R.Ph., Ph.D., D.A.B.T., March 27, 2013
- Pharmacology/Toxicology IND Assessment and Evaluation, David B. Hawver, Ph.D., February 4, 2021

4 Pharmacology

4.1 Primary Pharmacology

All primary pharmacology studies submitted were reviewed under IND 109157 (see Pharmacology/Toxicology Review by Dr. Thompson, March 27, 2013) except an in vitro binding affinity and epitope determination study. In that study, donanemab was shown to bind with the highest affinity to the human $A\beta_{N3pE-42}$ peptide (K_D = 0.82 ± 0.05 nM); affinity for a C-terminal truncated form, $A\beta_{N3pE-16}$, was still relatively high (K_D = 3 ± 2 nM) compared to non-pyroglutamate human $A\beta_{E3-16}$ (K_D = 420 nM). There was no detectable binding to human $A\beta_{1-40}$ or mouse $A\beta_{N3pE-16}$. The epitope for donanemab binding to human $A\beta_{N3pE-16}$ was mapped to the five amino acids at the N-terminus ($A\beta_{N3pE-7}$).

In ex vivo studies, murine analogs of donanemab (mE8 [IgG1] and mE8c [IgG2a]) facilitated microglial cell phagocytosis of deposited $A\beta_{1-42}$ in brain sections from AD patients (resulting in $A\beta_{1-42}$ reductions of ~51% and ~82%, respectively), and both mE8 and donanemab showed binding to deposited Aβ in brain sections from PDAPP mouse and human AD patients using immunohistochemistry.

In in vivo studies of aged PDAPP mice, donanemab and mE8 demonstrated binding to amyloid deposits in cortex and hippocampus, and mE8 and mE8c reduced amyloid levels in hippocampus and cortex. Hippocampal $A\beta_{1-42}$ was reduced ~38% and ~53% after dosing with mE8 and mE8c, respectively, at 12.5 mg/kg/week for 3 months; and ~31% and ~39% after dosing with mE8c at 4 and 12.5 mg/kg/week, respectively, for 6 months. $A\beta_{1-42}$ in cortex was reduced ~19% and ~33% after dosing with mE8 and mE8c, respectively, at 12.5 mg/kg/week for 3 months; and ~25% and ~38% after dosing with mE8c at 4 and 12.5 mg/kg/week, respectively, for 6 months. Acute SC administration of mE8c or donanemab in young PDAPP mice did not increase plasma levels of $A\beta_{1-40}$, suggesting low affinity for soluble full-length Aβ monomers. In a prevention study, young PDAPP mice (5.5 months old) administered mE8c at 12.5 mg/kg/week SC for 7 months showed a non-significant ~30% reduction in hippocampal $A\beta_{1-42}$ compared to IgG2a controls.

4.2 Secondary Pharmacology

No secondary pharmacology studies of donanemab were submitted.

4.3 Safety Pharmacology

No stand-alone safety pharmacology studies were submitted. Safety pharmacology was assessed in the 6-week toxicity study of donanemab in cynomolgus monkey. There were no donanemab-related effects on body temperature, cardiovascular function, neurological examinations, or respiratory function. It should be noted that the young monkeys used in these studies would not be expected to express the pharmacological target, $A\beta_{N3pE-x}$.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Two of the 3 pharmacokinetic studies submitted (acute SC dosing of mE8c in CD1 mice, and acute IV and SC dosing in cynomolgus monkey) were reviewed under IND 109157 (see Pharmacology/Toxicology Review by Dr. Thompson, March 27, 2013). In the mouse study, administration of 3 different lots of mE8c at 10 mg/kg SC to male CD1 mice resulted revealed that mE8c plasma concentrations at 48 hours postdose were ~30-fold greater than serum concentrations, suggesting the method used to process whole blood to serum resulted in a substantial loss in recovery. In the monkey study, administration of a single dose of 1 mg/kg SC vs. IV resulted in similar AUC_{0-672} (1690 vs. 1860 µg*hr/mL), $t_{½}$ (161 vs. 173 hr), and CL/F (0.59 vs. 0.53 mL/hr/kg), but lower C_{max} (7.6 vs. 25.2 µg/mL). Bioavailability of the SC dose was 91%. In the third study, 3 lots of donanemab (formulations T, C1, and C2) were compared by IV administration at 1 mg/kg, and C2 was also administered SC in groups of 3 male cynomolgus monkeys. There were no notable differences in PK parameters among the 3 formulations evaluated. Compared to IV, SC administration of formulation C2 resulted in similar AUC_{0-672} (1910 vs. 1710 µg*hr/mL IV) and CL/F (0.49 vs. 0.55 mL/hr/kg), longer T_{max} (48.0 hr vs. 0.5 hr) and $t_{1/2}$ (233 vs. 179 hr), greater volume of distribution (156 vs. 114 mL/kg), and lower C_{max} (6.7 vs. 19.3 µg/mL).

5.2 Toxicokinetics

Toxicokinetic analyses were reviewed with the pivotal toxicity studies.

5.3 Methods of Analysis

The validation studies (listed in Section 3.1) for the determination of donanemab and anti-drug antibody (ADA) concentrations in cynomolgus monkey serum and mE8c and ADA concentrations in mouse serum and plasma were reviewed and found to adequately support the conclusions of the pivotal toxicology studies conducted in cynomolgus monkey and PDAPP mouse.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicity studies were submitted.

6.2 Repeat-Dose Toxicity

A Repeat-Dose Toxicity and Toxicokinetic Study in Cynomolgus Monkeys Given LY3002813 by Intravenous Injection Once Weekly for 6 Weeks with a 3-Month Recovery Phase

(Study 8242713; initiated February 24, 2011; GLP; QA; signed pathology report, with peer review; reviewed by Dr. Thompson, March 27, 2013)

Cynomolgus monkeys (3/sex/group + 3/sex control and HD 13-week recovery; 2-4 years old) were administered vehicle ((b) (4) sodium citrate, (b) (4), 0.02% [w/v] polysorbate 80, pH 6.0) or donanemab (1, 10, or 100 mg/kg) by slow bolus IV injection at 5 mL/kg weekly for 6 weeks. Based on their relatively young age, these monkeys would not be expected to have amyloid deposits in the brain; therefore, this study assessed potential “off-target” toxicity of donanemab.

There were no donanemab-related effects on mortality, clinical signs, body weight, food consumption, neurological examination, respiratory function, body temperature, ophthalmic or ECG parameters, hematology, coagulation, clinical chemistry, or organ weights, and no macroscopic or microscopic findings. Anti-drug antibodies (ADA) were present in samples from 1/12 control, 1/6 LD, 1/6 MD, and 4/12 HD animals; donanemab concentrations in serum were only affected by ADA in the 2 HD recovery animals with the highest titers—these animals had reduced exposure during the recovery period. The NOAEL was the HD, which was associated with mean serum donanemab Day 36 C_{max} and $AUC_{0\text{-}166\ hr}$ values of 2593 µg/mL and 142219 µg*hr/mL, respectively (mean of M and F). The study was adequately conducted.

A Repeat-Dose Toxicity and Exposure Study in PDAPP Mice Given LSN3026818, mE8 Derivative c (mE8c, Murine Analog of LY3002813) by Subcutaneous Injection Once Weekly for 6 Weeks

(Study 504299; initiated February 23, 2011; GLP; QA; signed pathology report, with peer review; reviewed by Dr. Thompson, March 27, 2013)

PDAPP mice (9-10/sex/group; 12-15 months old at initiation of dosing) were administered vehicle (PBS, pH 7.4) or mE8c (10, 30, or 100 mg/kg) by SC injection at 5 mL/kg weekly for 6 weeks.

There were no m2E6c-related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, or macroscopic or microscopic findings. The NOAEL was the HD. Determination of m2Ec plasma concentrations at group termination confirmed systemic exposure in all 3 m2Ec

dose groups, but toxicokinetic analyses were not conducted. The study was adequately conducted.

A Repeat-dose Toxicity and Exposure Study in PDAPP Mice Given LSN3026818, mE8 Derivative c (mE8c, Murine Analog of LY3002813) by Subcutaneous Injection Once Weekly for 6 Months

(Study 504531; initiated August 2, 2011; GLP; QA; signed pathology report, with peer review; reviewed by Dr. Thompson, March 27, 2013)

PDAPP mice (19-20/sex/group; 12-15 months old at initiation of dosing) were administered vehicle (PBS, pH 7.4) or m2Ec (30 or 100 mg/kg) by SC injection at 5 mL/kg weekly; groups were terminated early due to age-related mortality (primarily associated with lymphoma and murine progressive cardiomyopathy) on Day 140/141 (F) or Day 151/152 (M). The dosing period was approximately 5 months.

There were no m2E6c-related effects on mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or macroscopic or microscopic findings. The NOAEL was the HD. Determination of m2Ec plasma concentrations at the end of the dosing period confirmed systemic exposure at both doses. The study was adequately conducted.

A Chronic Pharmacology/Toxicity Study in Aged Female PDAPP Mice Given Weekly Subcutaneous Doses of mE8 Derivative C (Murine Analog of LY3002813) for Six Months

(Study 8222743; initiated July 20, 2009; non-GLP; non-QA; signed pathology report, with peer review; reviewed by Dr. Thompson, March 27, 2013)

Female PDAPP mice (15/group for toxicity endpoints; 15/sex for efficacy endpoints reported in Pharmacology Study NDG78; 16 months old at initiation of dosing) were administered vehicle (PBS), m2Ec (1.5, 4.0, or 12.5 mg/kg), or isotype control IgG2a (12.5 mg/kg) by SC injection in 100 µL PBS weekly for 6 months.

There were no m2E6c-related effects on mortality, hematology, clinical chemistry, organ weights, or macroscopic or microscopic findings. Mean plasma concentrations of mE8c 27.8 ± 2.6, 62.5 ± 5.7, and 234.6 ± 20.9 µg/mL at 1.5, 4.5, and 12.5 mg/kg/week, respectively, 72 hours after the final dose.

Cerebral Microhemorrhage and Neuropathology Study in Aged PDAPP Mice Given LSN3026818, mE8 Derivative C (mE8c, Murine Analog of LY3002813), by Intraperitoneal Injections Weekly for 3 Months

(Study MB135; initiated February 22, 2008; non-GLP; non-QA; reviewed by Dr. Thompson, March 27, 2013; the microhemorrhage data were also reported in Study NDG80)

PDAPP mice (15-16 M and 23-27 F/group; 23-24 months old at initiation of dosing) were administered vehicle (PBS, pH 7.4) or antibody (IgG2a isotype control, 3D6 anti-Aβ comparator, mE8, or mE8c; 12.5 mg/kg) by IP injection at 3.47 mL/kg weekly for 13 weeks.

There were no drug-related effects on mortality. Microhemorrhages were assessed by counting Perls' Prussian blue stained hemosiderin-containing macrophages in meningeal regions of brain sections. The mean number of meningeal hemosiderin-positive cells was increased substantially (from near 0 to ~3000 cells per animal) in the group administered 3D6; no increases were seen with mE8 or mE8c. Mean plasma concentrations of mE8c, mE8, and 3D6 were 82.16, 107.86, and 82.87 µg/mL, respectively, 72 hours after the final dose.

7 Genetic Toxicology

No genotoxicity studies of donanemab were conducted because antibodies are generally unable to interact with genetic material.

8 Carcinogenicity

Carcinogenicity studies of donanemab were not conducted because its target, human $A\beta_{N3pE\text{-}x}$ peptide, is not present in wild-type rodents, and carcinogenicity studies in transgenic rodents are not feasible. Following review of an initial carcinogenicity assessment, the sponsor was informed that carcinogenicity studies of donanemab would not be required to support a BLA (see July 20, 2020, Type C Meeting Written Responses, and review by Dr. Hawver, February 4, 2021).

There is currently no evidence that long-term treatment with donanemab would increase cancer risk. However, the effect of donanemab administration on the risk of malignancy in humans is unknown.

9 Reproductive and Developmental Toxicology

The sponsor was informed that reproductive and developmental toxicology studies are generally not required to support clinical development or marketing approval for products intended for the treatment of Alzheimer's disease, based on the age of the population with that condition (see July 20, 2020, Type C Meeting Written Responses, and review by Dr. Hawver, February 4, 2021). No reproductive and developmental toxicology studies were submitted. A comprehensive assessment of the reproductive safety of donanemab was submitted to the BLA but was not reviewed.

10 Special Toxicology Studies

Tissue Cross-Reactivity of LY3002813 with Human and Cynomolgus Monkey Tissues Ex Vivo

(Study 20008867; initiated February 7, 2011; reviewed by Dr. Thompson, March 27, 2013; GLP; QA)

The potential tissue cross-reactivity of donanemab was evaluated in cryosections from a full panel of tissues from human (N=3 donors + 3 additional donors for cerebral cortex) and cynomolgus monkey (N=3) at concentrations of 5 and 25 µg/mL using standard immunohistochemical methods. One sample of healthy human cerebral cortex showed specific staining of amyloid plaques with donanemab as well as with mouse anti-amyloid mAb 3D6; samples from 3 additional donors were subsequently examined and found to be negative for donanemab staining. Cytoplasmic staining was observed in lymphocytes in multiple tissues in both species (primarily B-cells in human; B- and T-cells in monkey) and in peripheral nerve myelin in monkey. Cytoplasmic and/or nuclear staining was observed in adrenal medulla, cerebellum, testes, thyroid, fallopian tubes, and pituitary in monkey. Cytoplasmic and nuclear staining was not toxicologically relevant because donanemab would not be expected to enter cells. Results from assessments of positive and negative control tissues and an IgG1 isotype control antibody confirmed the validity of the study.

11 Integrated Summary and Safety Evaluation

Donanemab-azbt is a humanized immunoglobulin 1 (IgG1) monoclonal antibody designed to bind to a variant of the human amyloid beta (Aβ) peptide in which the first two amino acids are absent, and the third amino acid is modified to form pyroglutamate ($Aβ_{N3pE-x}$). Binding of donanemab to $Aβ_{N3pE-x}$, which is present in insoluble amyloid deposits in the brain, facilitates the removal of amyloid plaques through microglial-mediated phagocytosis. The proposed indication is for (b) (4) .

Pharmacological studies of donanemab (and murine analogs, mE8 and mE8c) adequately evaluated species specificity, target selectivity, and pharmacodynamic activity. Donanemab specifically bound to human peptides $Aβ_{N3pE-42}$ and $Aβ_{N3pE-16}$, with much lower affinity to non-pyroglutamated human $Aβ_{E3-16}$, and did not bind to human $Aβ_{1-40}$ or mouse $Aβ_{N3pE-16}$.

Donanemab and mE8 bound to deposited Aβ in brain sections from aged PDAPP mice and human AD patients, and mE8 and mE8c reduced amyloid deposits ex vivo in AD brain sections via stimulation of microglial phagocytosis and in vivo in cortex and hippocampus of PDAPP mice.

The greater efficacy of mE8c (a murine IgG2a analog, which has greater Fc activity than IgG1 in mouse) compared to mE8 (a murine IgG1 analog) in reducing amyloid levels in

the ex vivo and in vivo studies, provided evidence to support the conclusion that the removal of brain amyloid involved microglial phagocytosis of opsonized amyloid.

A pivotal (GLP) toxicity study was conducted in young cynomolgus monkeys to assess potential “off-target” toxicity, because the intended target, $A\beta_{N3pE-x}$, is generally only present in the brain of aged animals and humans. Donanemab (0, 1, 10, or 100 mg/kg) was administered by slow bolus IV injection weekly for 6 weeks, followed by a 3-month recovery period for HD and controls. There were no adverse effects related to the test article.

Potential “on-target” toxicity was assessed in aged PDAPP mice, which overexpress the human mutated form of the amyloid precursor protein (APP^{V717F}) and develop amyloid deposits that contain the intended target $A\beta_{N3pE-x}$, starting at 6 to 9 months of age. These studies used mE8c, the murine analog of donanemab, to avoid immunogenicity that would be expected with donanemab, a humanized antibody, in mouse. In the pivotal (GLP) studies, mE8c was administered to 12- to 15-month-old PDAPP mice weekly for 6 weeks (0, 10, 30, or 100 mg/kg SC) or 5 months (0, 30, or 100 mg/kg SC). There were no adverse effects related to the test article.

In a non-GLP study, the potential of mE8 and mE8c to exacerbate age-related brain microhemorrhages in 23- to 24-month-old PDAPP mice was compared to that of an IgG2a isotype control and a comparator anti-amyloid antibody, 3D6, which had been previously shown to increase microhemorrhages in this animal model. Following 13 weeks of administration at 12.5 mg/kg/week IP, the number of microhemorrhages per animals was substantially increased with 3D6; no increases were observed with mE8 or mE8c.

Genotoxicity studies of donanemab were not conducted because antibodies are generally unable to interact with genetic material.

Carcinogenicity studies of donanemab were not conducted because wild-type rat and mouse are not pharmacologically relevant species.

Developmental and reproductive toxicity studies were not conducted based on the age of the indicated population.

Tissue cross-reactivity studies conducted in a panel of normal human and cynomolgus monkey tissues demonstrated specific binding of donanemab that was exclusively cytoplasmic and/or nuclear, and, therefore, toxicologically irrelevant based on the inability of donanemab to enter cells.

In summary, there were no drug-related adverse effects in aged PDAPP mice administered mE8c at 100 mg/kg/week SC for 5 months, or in cynomolgus monkeys administered donanemab for 6 weeks at 100 mg/kg/week IV. The HD in monkey was associated with a mean serum donanemab Day 36 $AUC_{0\text{-}166\ hr}$ value of ~142000 µg*hr/mL (mean of M and F), ~2.5-fold greater than the expected $AUC_{0\text{-}30\ days,\ SS}$ (58000 µg*hr/mL; based on the Population PK Report, Study AACG) in humans at the

maximum proposed clinical dose of 1400 mg/month IV donanemab. Adjusting for the differences in dosing frequency (weekly in monkey vs. every 4 weeks in human), the estimated AUC exposure margin was ~10-fold.

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