CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761269Orig1s000

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 3, 2023

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

Subject: BLA 761269 (LEQEMBI, lecanemab)

BLA 761269 was submitted on September 27, 2021, by the sponsor (Eisai Inc.) for the treatment of Alzheimer's disease. Clinical development of lecanemab (BAN2401) was conducted under IND 105081.

The nonclinical studies submitted in support of the BLA include in vitro studies to characterize the pharmacological activity of lecanemab and intravenous toxicity studies of lecanemab in cynomolgus monkey.

Reproductive and developmental toxicology studies were not conducted for lecanemab because of the age of the intended patient population. Genetic toxicology studies were not conducted because monoclonal antibodies are not expected to interact directly with DNA. Carcinogenicity studies were not conducted because of the lack of pharmacological activity in rodent species (mouse, rat), making standard carcinogenicity studies infeasible.

The nonclinical studies were reviewed Dr. Toscano (Pharmacology/Toxicology BLA Review and Evaluation, BLA 761269, Christopher D. Toscano, Ph.D., December 19, 2022). Based on his review, Dr. Toscano has concluded that "…the nonclinical data adequately support the approval of lecanemab for the treatment of Alzheimer's disease."

Selected nonclinical data are briefly summarized below.

Pharmacology

Lecanemab is an amyloid beta-directed humanized IgG1 monoclonal antibody intended for the treatment of patients with mild cognitive impairment or mild dementia stage of Alzheimer's disease. In vitro studies demonstrated binding to soluble and insoluble forms of amyloid beta. Lecanemab also demonstrated high binding affinity for human FcγRs (FcγRI and FcγRIII), which is thought be involved in amyloid beta clearance but may also contribute to cerebral microhemorrhage.

In vivo studies in transgenic animal models to characterize the pharmacodynamic effects of lecanemab were not conducted because of immunogenicity.

Toxicology

The pivotal (4- and 39-week) toxicity studies of lecanemab were conducted in cynomolgus monkey, the only pharmacologically relevant species. In both studies, lecanemab was administered weekly by intravenous bolus injection.

In the 4-week study (0, 5, 15, and 50 mg/kg/week), the only lecanemab-related findings were increases in absolute spleen weight and microscopic changes in spleen (increased size and number of germinal centers) in mid- (MD) and high-dose (HD) males and HD females, reflecting administration of a foreign protein.

In the 39-week study (0, 15, 50, and 100 mg/kg/week) (with 2-week recovery), increases in absolute spleen weight and microscopic changes in spleen (increased number of germinal centers) were observed only in HD females. No adverse effects on male or female reproductive organs were observed.

Both the 4- and 39-week studies included a focused neurohistopathology evaluation; however, normal monkeys do not have the Aβ accumulation in the brain that occurs in patients with Alzheimer's disease.

Plasma exposures ($AUC_{(0\text{-}168h)}$) at the HD (100 mg/kg/week) in the 39-week study were 463,000 and 574,000 μg*hr/mL in males and females, respectively. For comparison, steady-state plasma exposure ($AUC_{(0\text{-}t)}$) in humans at the recommended human dose of 10 mg/kg IV Q2W is 37,700 μg*hr/mL.

Recommendation

The nonclinical data submitted to the BLA are adequate to support approval of lecanemab for the proposed indication, with appropriate labeling. Labeling recommendations were conveyed in a separate document.

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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:	761269
Supporting document:	1
Applicant's letter date:	9/27/2021
CDER stamp date:	9/27/2021
Product:	LEQEMBI (lecanemab; BAN2401)
Indication:	Alzheimer's disease
Applicant:	Eisai Inc.; Nutley, NJ
Clinical Division:	DN1
Clinical Division Director:	Teresa Burrachio, MD
Review Division	DPT-N
Reviewer:	Christopher D. Toscano, Ph.D., DABT
Supervisor:	Lois M. Freed, Ph.D.
Division Director:	Lois M. Freed, Ph.D.
Project Manager:	Emilios A. Papanastasiou

All figures and tables are from the applicant unless otherwise indicated.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Lecanemab is a recombinant immunoglobulin gamma 1 (IgG1) anti-human amyloid beta peptide monoclonal antibody that binds to amyloid protofibrils and fibrillar amyloid beta. The proposed indication for lecanemab is, " the treatment of Early Alzheimer's disease (mild cognitive impairment due to AD and mild AD dementia, with confirmed amyloid pathology)."

1.2 Brief Discussion of Nonclinical Findings

Lecanemab binds with higher affinity to amyloid beta protofibrils than to amyloid beta monomers, in vitro. The rodent surrogate of lecanemab, mAb158, decreased the burden of amyloid protofibrils in the brain of transgenic rodents that overexpress amyloid beta (Tg2576 and APP_{ArcSwe}). There were no adverse lecanemab-related findings observed in rats given a single IV injection up to the maximum feasible dose of 100 mg/kg, monkeys given a daily dose of up to 50 mg/kg for 4 weeks, or monkeys dosed up to the maximum feasible dose of 100 mg/kg once weekly for 39 weeks. Repeat-dose toxicology studies in rodent were not feasible based on the formation of anti-lecanemab antibodies. Therefore, rodent carcinogenicity studies were not conducted with lecanemab; the Division concurred with this approach. Reproductive and development studies were deemed unnecessary based on the age range of the intended clinical population. Since genotoxicity studies are generally not required for antibodies, none were conducted for lecanemab. Except for extracellular binding to amyloid plaques, all binding observed in the tissue cross reactivity study was cytosolic, and, therefore, not clinically relevant. There was no mAb158-related microhemorrhage observed in studies specifically conducted to detect such findings in Tg2576 and APP_{ArcSwe} mice.

1.3 Recommendations

1.3.1 Approvability

The provided nonclinical data are adequate to support the approval of lecanemab for the treatment of patients with Alzheimer's disease.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Sponsor's Proposed Labeling	Recommended Labeling
--------INDICATIONS AND USAGE--------- LEQEMBI, (b) (4) indicated for the treatment of (b) (4) Alzheimer's Disease (b) (4)	**--------INDICATIONS AND USAGE---------** *No changes recommended*

8.2. Lactation Risk Summary There are no data on the presence of lecanemab-irmb in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQEMBI and any potential adverse effects on the breastfed infant from LEQEMBI or from the underlying maternal condition.	**8.2. Lactation** Risk Summary *No changes recommended*
8.4. Pediatric Use (b) (4) safety and effectiveness of LEQEMBI have not been established in pediatric patients.	**8.4. Pediatric Use** *No changes recommended*
11 Description Lecanemab-irmb is a recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody (b) (4)	**11 Description** *No changes recommended.*
12.1. Mechanism of Action Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody (b) (4)	**12.1. Mechanism of Action** *No changes recommended*
13 Nonclinical Toxicology **13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility**	**13 Nonclinical Toxicology** **13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis

Carcinogenesis Carcinogenicity studies have not been conducted. (b) (4) [redacted]	Carcinogenicity studies have not been conducted.
Mutagenesis Genotoxicity studies have not been conducted.	Mutagenesis *No changes recommended.*
Impairment of Fertility (b) (4) [redacted]	Impairment of Fertility (b) (4) [redacted]

2 Drug Information

2.1 Drug

CAS Registry Number: 1260393-98-3
Generic Name: Lecanemab
Code Name: BAN2401
Molecular Weight: 150 kDa
Structure: Applicant's Figure, below

Heavy Chain (HC):

Leader Sequence: MEWSWVFLFFLSVTTGVHS

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EVQLVESGGG LVQPGGSLRL SCSASGFTFS SFGMHWVRQA PGKGLEWVAY  50
ISSGSSTIYY GDTVKGRFTI SRDNAKNSLF LQMSSLRAED TAVYYCAREG  100
GYYYGRSYYT MDYWGQGTTV TVSSASTKGP SVFPLAPSSK STSGGTAALG  150
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL  200
GTQTYICNVN HKPSNTKVDK RVEPKSCDKT HTCPPCPAPE LLGGPSVFLF  250
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE  300
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP  350
REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT  400
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL  450
SPGK                                                    454
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Light chain (LC):

Leader Sequence: MSVPTQVLGL LLLWLTDARC

DVVMTQSPLS LPVTPGAPAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK 50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLRI SRVEAEDVGI YYCFQGSHVP 100
PTFGPGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC 219

Pharmacologic Class: Recombinant IgG1 anti-human amyloid beta peptide monoclonal antibody

2.2 Relevant INDs

IND 105081

2.3 Drug Formulation:

The formulation is detailed in the table, below.

Table 2.3.P.1-1 Quantitative Composition of Drug Product

Component	Function	Quality Standard	Amount per mL	Nominal Concentration	Nominal Amount (mg) per Vial [a]	
					200 mg	500 mg
Lecanemab	Active Ingredient	Eisai Standard (3.2.S.4.1 Specification)	100 mg	100 mg/mL	200	500
Histidine (free base) [b]	(b) (4)	USP/NF, Ph. Eur., JP	0.18 mg	1.2 mmol/L	0.36	0.90
Histidine hydrochloride monohydrate [b]		Ph. Eur., JP	4.99 mg	23.8 mmol/L	9.98	24.95
Arginine hydrochloride		USP/NF, Ph. Eur., JP	42.13 mg	200 mmol/L	84.26	210.65
Polysorbate 80		USP/NF, Ph. Eur., JP	0.50 mg	0.05% (w/v)	1.00	2.50
Water for Injection		USP/NF, Ph. Eur., JP	(b) (4)			

JP = Japanese Pharmacopoeia, NF = National Formulary (US), Ph. Eur. = European Pharmacopoeia, USP = United States Pharmacopeia, q.s. = *quantum sufficit*.
a: Nominal quantity excludes overfill, see further discussion in 3.2.P.2.2 Drug Product.
b: (b) (4)

2.4 Comments on Novel Excipients

No novel excipients are present in the drug product.

2.5 Comments on Impurities/Degradants of Concern

There are no nonclinical concerns regarding impurities or degradants.

2.6 Proposed Clinical Population and Dosing Regimen

Lecanemab is indicated for the treatment of Early Alzheimer's Disease (mild cognitive impairment due to AD and mild AD dementia, with confirmed amyloid pathology). The recommended dose of Lecanemab is 10 mg/kg by IV infusion once every two weeks.

2.7 Regulatory Background

During the Pre-IND meeting (IND 105081, June 12, 2009), the applicant was informed that their proposed nonclinical program appeared, on face, to be adequate to support the proposed first-in-human study. Additionally, the Division requested that the applicant include an enhanced neurohistopathology assessment in the planned chronic study to be conducted in monkey. A Study May Proceed Letter was issued to the applicant on October 27, 2010.

At the End of Phase 2 meeting (IND 105081, November 6, 2012), the applicant was informed that reproductive and development toxicology studies would not be required to support an application because of the age of the patient population but that a weight of evidence justification for not conducting carcinogenicity studies of lecanemab would need to be submitted. The applicant was also informed of the need to conduct specialized studies to assess for microhemorrhages in an appropriate animal model of Alzheimer's Disease.

On March 19, 2014, the applicant was informed that a carcinogenicity assessment of lecanemab would not be necessary based on the development of neutralizing anti-drug antibodies in rodents treated with lecanemab or the mouse surrogate, mAb158.

In a letter from the Division dated July 2, 2014, the applicant was informed that a nonclinical assessment of the potential for lecanemab to cause microhemorrhage would no longer be required.

3 Studies Submitted

3.1 Studies Reviewed

All submitted nonclinical studies were reviewed.

3.2 Studies Not Reviewed

All submitted studies were reviewed.

3.3 Previous Reviews Referenced

The following reviews are available under IND 105081:

- Toscano CD, Nonclinical Review, July 31, 2010
- Toscano CD, Nonclinical Review, March 5, 2012
- Toscano CD, Nonclinical Review, April 4, 2013

4 Pharmacology

4.1 Primary Pharmacology

In vitro:
Lecanemab (BAN2401) is a humanized IgG1 monoclonal antibody that binds amyloid β protofibrils and fibrils; the murine analog of lecanemab is mAb158. Lecanemab and mAb158 have similar affinity for Aβ monomers (IC_{50}= 600 nM and 700 nM, respectively) and Aβ protofibrils (IC_{50}= 3 nM and 5 nM, respectively) (Study AD-TR-006). When incubated with brain extracts from human AD patients, lecanemab exhibited a higher affinity for $Aβ_{(x-42)}$ than $Aβ_{(x-40)}$ (Study AD-TR-61). Studies with sequential deletion of N-terminal amino acids demonstrated that N-terminal amino acids 2 and 3 of Aβ peptides were crucial for binding of lecanemab to Aβ peptides (Study BR-035). Lecanemab (100 µg/ml) and mAb158 (100 µg/ml) were shown to inhibit the *in vitro* formation of Aβ oligomer beta sheets to a similar degree (Study W-20090273). These antibodies were also shown to inhibit the neurotoxicity of protofibrils (lecanemab, mAb158) and Aβ oligomers (lecanemab). Specifically, rat medial septal neurons incubated with Aβ protofibrils in the presence of lecanemab or mAb158 released less LDH (a marker of cell damage) to the cell incubation media when compared to cells incubated with IgG1 and IgG2a (Study W-20090274). Both mAb158 and lecanemab completely inhibited the *in vitro* binding of Aβ protofibril to the dendritic spines of primary hippocampal neurons (Studies W-20090258 and M09007).

In vivo:
The applicant confirmed the immunogenicity of lecanemab by injecting 24 mg/kg/day lecanemab intraperitoneally (IP) into Tg2576 mice daily for 14 days. At the end of the 14-day dosing period, all mice (6/6) dosed with lecanemab had detectable levels of anti-human IgG and IgM Abs (Study #W-20090269). Therefore, a series of in vivo studies were performed to assess the ability of the murine analog, mAb158, to alter the levels of Aβ protofibrils in the brains of two mouse models of Alzheimer's disease (Tg2576 and APP_{ArcSwe}). Tg2576 mice express human APP containing the Lys^{670} to Asn and Met^{671} to Leu mutations. APP_{ArcSwe} express the human APP containing the Swedish KM670/671NL and Arctic E693G mutations.

Short-Term Studies (≤ 1 month):
a) Study W-20090278: Female Tg2576 mice (n=6/group; 14 months old) were dosed IP (one dose per week) with either PBS or 24 mg/kg/week mAb158 for 1, 2 or 4 weeks. Mice were euthanized one week after the final dose and the concentration of Aβ protofibrils/oligomers and mAb158 in the brains of these animals was determined. In animals dosed with mAb158, the level of Aβ protofibrils/oligomers was not changed after one week but was reduced by 27-28% after 2-4 weeks.

b) Study W-20100295: Female Tg2576 mice (10/group; 20 months old) were dosed IP once a week for 4 weeks with 24 mg/kg mAb158 or PBS. At the end of the dosing period, levels of circulating anti-mAb158 did not differ between mice dosed with PBS or mAb158. Aβ protofibrils and soluble $Aβ_{(x-42)}$ levels were decreased by 30% in the brains of Tg2576 mice dosed with mAb158.

c) Study AD-TR-008: Fourteen- to fifteen-month-old wild-type or APP_{ArcSwe} mice were dosed with 10 mg/kg mAb158 by IP or IV injection (n=7/group, 5 M, 2 F/group). Mice dosed intravenously were dosed once a day for 4 days and those dosed IP were dosed once a week for 4 weeks. There was no reduction in Aβ protofibril levels in the brains of mice dosed intravenously. However, a 30% reduction in protofibrils was observed in the brains of mice dosed IP with mAb158, relative to untreated mice.

d) Study AD-TR-010: Nine- to sixteen-month-old APP_{ArcSwe} mice (n=6/group; 1-2 F, 4-5 M/group) were dosed with 0, 1(LD), 3 (MD) or 10 (HD) mg/kg mAb158 by IP injection, once a week for 4 weeks and were euthanized 7 days after the final dose. Brain concentrations of mAb158 increased in a dose-dependent manner in mice (3.6, 9.8, 20.3 ng/mL; LD, MD, HD, respectively). Additionally, the concentration of brain Aβ protofibrils was decreased in a dose-dependent manner, relative to controls (26%, 59%, 69%; LD, MD, HD, respectively).

e) Study AD-TR-014: Eleven-month-old APP_{ArcSwe} mice (three groups of mice, n= 7/group; sex not specified) were dosed with either 0 or 10 mg/kg mAb158 by IP injection, once a week for 4 weeks. Mice dosed with mAb158 were euthanized either 24 hours (n=7) or 7 days (n=7) after the final dose was administered. Although the differences were not considered statistically significant, the concentration of mAb158 in the brain (24 hr= 13.1 ng/mL vs. 7 d= 5.2 ng/mL), CSF (24 hr= 427 ng/mL vs. 7 d= 289 ng/mL) and plasma (24 hr= 126 µg/mL vs. 7 d= 84 µg/mL) were reduced in mice euthanized at 7 days after the final dose when compared to mice euthanized 24 hours after the final dose. Brain protofibril and CSF protofibril levels were decreased in mice dosed with mAb158 (Brain= 34-35% reduction in both groups; CSF=61-74% reduction in both groups).

Long-Term Studies (>1 month):

a) Study W-20090277: Female Tg2576 mice (n=15/group; 4 months old) were dosed IP once a week for 4 months with 0, 3 (LD), 6 (MD), 12 (HD) mg/kg mAb158 and euthanized 5 days after the last dose. Brain and CSF Aβ protofibril concentrations were decreased in a dose-dependent manner in MD and HD mice by 15-17% and 20-48%, respectively.

b) Study AD-TR-007: Nine- to ten-month-old APP_{ArcSwe} mice were dosed IP once a week for 18 weeks with 12 mg/kg mAb158 or PBS (n=4 F and 6 M/group) and euthanized 1-3 days after the final dose. Brain levels of Aβ protofibrils were decreased by 80% in mice dosed with mAb158, relative to controls. However, there was no difference between mice dosed with mAb158 and controls in the brain levels of soluble Aβ, insoluble Aβ, plaques, or phosphorylated Tau.

c) Study AD-TR-011: Twelve- to fourteen-month-old APP_{ArcSwe} mice (n=4-5 M and 4-5 F/group) were dosed with 0, 0.3, 1, 3, 10 mg/kg mAb158 by IP injection (once a week for four months) and euthanized 7 days after the final dose. Brain and CSF concentrations of mAb158 increased in a dose-dependent, but not dose-proportional, manner (Brain=1.8, 2.8, 4.3, 5.7 ng/ml; CSF= 27, 102, 493, 1300 ng/ml; 0.3, 1, 3, 10 mg/kg respectively). Brain, but not CSF, Aβ protofibril levels were decreased, relative to control, in all mAb158 dose groups (28%, 33%, 54%, 50%; 0.3, 1, 3, 10 mg/kg respectively). However, there

was no test article-related alteration in the levels of total Aβ40, total Aβ42, soluble Aβ40, or soluble Aβ42 in either brain or CSF. There were no treatment-related histopathology findings in the liver, kidneys, heart, lung, spleen, stomach, small intestine, large intestine, or lymph nodes.

d) Study W-20100159: Four-month-old APP_{ArcSwe} female mice (n=15/group) were dosed with 0, 3, 6, 12 mg/kg mAb158 by IP injection, once a week for 18 weeks. Beginning the day after the 16th injection, the mice were assessed in the contextual and auditory-cued fear conditioning memory test. There was no statistically significant difference in performance in the contextual fear conditioning memory test in any experimental group in this study when compared to the control. Although it was not statistically significant, a slight increase in performance in the auditory-cued test was observed in mice dosed with 6 and 12 mg/kg mAb158. Overall, this study demonstrates that mAb158 did not improve the performance of transgenic mice in the contextual or auditory-cued fear conditioning memory test.

4.2 Secondary Pharmacology

Lecanemab did not directly interact with fibrinogen (BIOMT-2012 001), but did interact with thrombospondin 1 (THBS1), a protein that shares a sequence similarity with amino acids 3 to 8 in Aβ protofibrils (AD-TR-060). Immunogenic reactions were observed in peripheral blood monocytes from 2 out of 25 donors when incubated in vitro with 300 nmol/L lecanemab (AD-TR-145).

4.3 Safety Pharmacology

Safety pharmacology assessment of the cardiovascular, CNS, and respiratory function were conducted in the 4-week study conducted in monkey (B090486, reviewed below).

5 Pharmacokinetics/ADME

5.1 PK/ADME

PK parameters were determined after a single IP injection of 1, 5, or 15 mg/kg mAb158 in Tg2576 mice (table, below; B09013).

Table 2.6.4-1 Pharmacokinetic Parameters for mAb158 in Female Tg2576 Mice After a Single Intraperitoneal Dose

Dose (mg/kg)	1	5	15
Pharmacokinetic Parameters for Plasma			
$t_{½}$ (h)	69.70	104.74	56.04
C_{max} (µg/mL)	11.101	52.113	170.080
t_{max} (h)	4	24	8
$AUC_{(0\text{-}168h)}$ (µg·h/mL)	1068.135	6711.346	17,637.855
$AUC_{(0\text{-}inf)}$ (µg·h/mL)	1297.104	9876.685	19,977.531
$MRT_{(0\text{-}inf)}$ (h)	97.29	148.38	78.91
Pharmacokinetic Parameters for CSF			
C_{max} (µg/mL)	0.051	0.245	0.562
t_{max} (h)	72	24	24
$AUC_{(0\text{-}168h)}$ (µg·h/mL)	5.638	29.859	53.217

Plasma and CSF concentration profiles of mAb158 in female Tg2576 mice were evaluated after a single intraperitoneal dose. Each parameter was calculated with the mean concentration of 3 or 4 animals. $AUC_{(0\text{-}168h)}$ = AUC from zero time to 168 hours, $AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, CSF = cerebrospinal fluid, $MRT_{(0\text{-}inf)}$ = mean residence time from time zero extrapolated to infinite time, $t_{½}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs.

The half-life of lecanemab in plasma, CSF, and brain of Tg-APP$_{ArcSwe}$ and non-transgenic mice after a single 10 mg/kg IP dose of lecanemab is provided in the table, below (AD-TR-059).

Table 2.6.4-2 Elimination Half-lives of Lecanemab in Plasma, Cerebrospinal Fluid, and Brain of Tg-APP$_{ArcSwe}$ and Non-Tg Mice After a Single 10 mg/kg Intraperitoneal Administration

Matrix	Elimination Half-Life (days)	
	Tg-APP$_{ArcSwe}$	Non-Tg
Plasma	1.4	1.6
Cerebrospinal Fluid	1.4	2.5
Brain	3.5	1.8

Each group/time point consisted of 6 animals, and the half-life was estimated by using results of 3 to 6 animals after excluding results considered to be inappropriate such as blood contamination.
Tg = transgenic, Tg-APP$_{ArcSwe}$ = transgenic mice expressing human amyloid β precursor protein with Arctic and Swedish mutations.

PK parameters for lecanemab were determined in cynomolgus monkeys given a single IV injection of 5 or 50 mg/kg lecanemab or an SC injection of 50 mg/kg lecanemab (table, below; B121284). A tissue distribution study conducted in Tg2576 and non-transgenic mice demonstrated there was no preferential uptake or retention of radiolabeled mAb158 in peripheral organs (BIOMA-2012-057).

Table 2.6.4-5 Pharmacokinetic Parameters for Lecanemab in Male Cynomolgus Monkeys After a Single Intravenous or Subcutaneous Dose

Pharmacokinetic Parameters	Dose (mg/kg)/Route		
	5/IV	50/IV	50/SC
$t_{½}$ (h)	289.3±52.4	312.3±22.8	255.6±51.9
C_{5min} for IV (µg/mL)	139.0±35.1	1336.2±341.7	NA
C_{max} for SC (µg/mL)	NA	NA	472.1±18.2
t_{max} (h)	NA	NA	72.0±27.7
$AUC_{(0\text{-}672h)}$ for IV (µg•h/mL)	21,415.4±2193.2	226,441.7±16,735.6	NA
$AUC_{(0\text{-}840h)}$ for SC (µg•h/mL)	NA	NA	194,842.8±22,096.0
$AUC_{(0\text{-}inf)}$ (µg•h/mL)	NC	NC	218,759.0±32,805.5

Values represent the mean ±SD of 3 animals for IV and 4 animals for SC.
$AUC_{(0\text{-}672/840h)}$ = AUC from zero time to 672/840 hours, $AUC_{(0\text{-}inf)}$ = AUC from zero time extrapolated to infinite time, C_{5min} = concentration at 5 minutes after the dose, IV = intravenous, NA = not applicable, NC = not calculated, SC = subcutaneous, $t_{½}$ = terminal elimination phase half-life, t_{max} = time at which the highest drug concentration occurs.

6 General Toxicology

6.1 Single-Dose Toxicity

6.1.1 Rat

Study title: BAN2401: Single Intravenous Dose Toxicity Study in Rats

Study no.:	S09060
Study report location:	EDR
Conducting laboratory and location:	Eisai Co, Ltd., Gifu, Japan
Date of study initiation:	8/26/09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lecanemab, Lot# P358614, 99.3%

Key Study Findings

- **The NOAEL was ≥ 100 mg/kg lecanemab, administered intravenously.**
- **100 mg/kg lecanemab is the MFD for the intravenous route in rats.**
- **C_{max} and AUC increased linearly with dose and $t_{1/2}$ ranged from 9 to 11.5 days.**

Methods

Doses:	0, 10 (LD), 30 (MD), 100 (HD) mg/kg; HD is the MFD in rats due to a maximum bolus iv injection volume of 10 mL/kg in rats and the available formulation of 10 mg/mL
Frequency of dosing:	Single dose; Main study animals were euthanized 17 days after administration of the single dose.
Route of administration:	Intravenous, bolus via tail vein
Dose volume:	10 mL/kg
Formulation/Vehicle:	(b) (4) polysorbate 80
Species/Strain:	Sprague Dawley rat (Crl:CD(SD))
Number/Sex/Group:	5/sex/group in main study; 3/sex/group for TK
Age:	8 weeks
Weight:	239-269 g M; 155-173 g F

Findings: All animals survived until terminal sacrifice, and there were no clinical signs related to lecanemab. There were no lecanemab-related adverse effects observed on body weight, food consumption, ophthalmic examination, hematology and clinical chemistry parameters, organ weight, gross pathology assessment, or histopathology assessment.

Toxicokinetics: Blood samples (200 µL) were collected via the jugular vein at 1,2,4,8,24,48,72, 96,120, 144,168, 336 and 384 hours after dosing. TK parameters for lecanemab are provided in the table, below.

Table Toxicokinetic Summary

Dose (mg/kg)	Male			Female		
	C_{5min} (µg/mL)	$AUC_{0-384hr}$ (µg·hr/mL)	half-life (hr)	C_{5min} (µg/mL)	$AUC_{0-384hr}$ (µg·hr/mL)	half-life (hr)
10	279.7	23727.3	278.1	255.7	23135.8	251.3
	11.6	711.2	23.8	17.6	1561.1	59.2
30	897.9	61222.5	229.3	727.6	53621.8	207.2
	42.2	4030.7	27.8	43.6	4270.3	27.3
100	2458.9	216832.0	226.6	2257.1	188217.9	222.9
	234.9	7945.0	23.5	275.2	2825.8	17.5

Upper values: Mean, Lower values: SD are presented. N=3

6.1.2 Monkey

Study title: BAN2401: Single Intravenous Dose Range Toxicity Study in Monkeys
Study no.: S09019
Study report location: EDR
Conducting laboratory and location: Eisai Co, Ltd., Ibaraki, Japan
Date of study initiation: April 6, 2009
GLP compliance: No
QA statement: Yes
Drug, lot #, and % purity: lecanemab, Lot# P358614, 99.3%

Key Study Findings

- **The NOAEL was ≥ 50 mg/kg lecanemab, administered intravenously.**
- **C_{max} and AUC increased linearly with dose, and $t_{1/2}$ ranged from 12 to 13 days.**

Methods

Doses: 5 or 50 mg/kg.
Frequency and Route of dosing: Single intravenous dose via saphenous vein at 2 mL/min. Monkeys were observed for 29 days after the administration of the test article.
Dose volume: 0.5 or 5 mL/kg
Formulation/Vehicle: [redacted] (b) (4) polysorbate 80
Species/Strain: Cynomolgus monkey
Number/Sex/Group: 3 males/group
Age and weight: 4 years; 2.9-3.9 kg

Findings: All monkeys survived until terminal sacrifice, and there were no clinical signs related to lecanemab. There were no lecanemab-related adverse effects observed on body weight or food consumption. No other assessments were performed.

Toxicokinetics: Blood samples (500 µL) were collected via the femoral vein at 5 min, 1, 2, 8, 24, 48, 96 hours and 1, 2, 3 and 4 weeks after administration of the single dose. TK parameters for lecanemab are provided in the table, below.

Table Toxicokinetic Summary

Dose (mg/kg)	C_{5min} (µg/mL)	$AUC_{0\text{-}4week}$ (µg·hr/mL)	half-life (hr)
5	139.0 ± 35.1	21415.4 ± 2193.2	289.3 ± 52.4
50	1336.2 ± 341.7	226441.7 ± 16735.6	312.3 ± 22.8

Mean ± S.D. of 3 animals are presented.

6.2 Repeat-Dose Toxicity

Study B200192: "*A 4-week subcutaneous local irritation study in monkeys*." Male and female cynomolgus monkeys (n=4/sex/group) were given a subcutaneous injection of lecanemab once daily for 4 weeks at a dose of 0 or 10 mg/kg (200 mg/mL) in (b) (4) histidine, (b) (4) polysorbate 80. Monkeys were necropsied 3 days after the final administration of lecanemab. There were no early deaths, clinical signs, or antidrug antibodies detected. No local irritation was observed in the histopathology assessment. The TK parameters for lecanemab are provided in the table, below.

Toxicokinetic Summary

Dose (mg/kg)	Day	Male			
		C_{max} (µg/mL)	t_{max} (hour)	$AUC_{(0\text{-}24h)}$ (µg·h/mL)	$AUC_{(0\text{-}72h)}$ (µg·h/mL)
10	1	52.4 ± 11.6	24.0 ± 0.0	657 ± 145	NA
	28	1470 ± 110	1.50 ± 1.73	32,000 ± 1300	92,900 ± 3500

Dose (mg/kg)	Day	Female			
		C_{max} (µg/mL)	t_{max} (hour)	$AUC_{(0\text{-}24h)}$ (µg·h/mL)	$AUC_{(0\text{-}72h)}$ (µg·h/mL)
10	1	54.6 ± 15.1	20.0 ± 8.0	797 ± 366	NA
	28	1610 ± 170	5.00 ± 3.83	32,600 ± 4000	90,100 ± 9300

Data represent the mean ± SD of 4 animals.
$AUC_{(0\text{-}24h)}$ = area under the concentration-time curve from zero time to 24 hours,
$AUC_{(0\text{-}72h)}$ = area under the concentration-time curve from zero time to 72 hours,
C_{max} = maximum observed concentration, t_{max} = time at which the highest drug concentration occurs.
NA: not applicable.

Study title: BAN2401: A 4-Week Intermittent Intravenous Dose Toxicity Study with 5-Week Recovery Period in Monkeys

Study no.:	B090486
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Jun 25, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	lecanemab, Lot # P358614, 99.3%

Key Study Findings

- **The NOAEL was ≥ 50 mg/kg lecanemab, administered intravenously.**

- **An adaptive increase in splenic germinal centers (white pulp) was observed at the end of the dosing period in females at all doses and in males dosed with >5 mg/kg/week; these effects were not observed at the end of recovery.**
- **C_{5min} and AUC increased linearly with dose, and $t_{1/2}$ ranged from 13 days in males to 17 days in females.**

Methods

Doses:	0 (C), 5 (LD), 15 (MD), 50 (HD) mg/kg/week.
Frequency of dosing:	Once/week for 4 weeks (Days 1, 8,15, 22, 29)
Route of administration:	Intravenous bolus into saphenous vein at rate of 2 mL/min
Dose volume:	0.5, 1.5 and 5 mL/kg
Formulation/Vehicle:	(b) (4) polysorbate 80, pH (b) (4) at concentration of 10 mg/mL lecanemab
Species/Strain:	Cynomolgus monkey; (b) (4)
Number/Sex/Group:	3/sex/group in main group; recovery group 2/sex/group (control and HD only)
Age:	Male 5 years old; Female 3 years old
Weight:	M= 4.1-5.9 kg; F=2.4-3.1 kg
Deviation from study protocol:	Minor and not expected to affect the validity of the study.

Findings: All animals survived until terminal sacrifice, and there were no clinical signs related to lecanemab. There were no lecanemab-related adverse effects observed on body weight, food consumption, ophthalmic examination, hematology and clinical chemistry parameters, gross pathology assessment, or histopathology assessment.

Organ Weights: An increase in spleen weight in MDM (1.7-fold), HDM (1.3-fold), LDF (1.3-fold), MDF (1.7-fold) and HDF (2.2-fold), relative to controls, occurred in the animals that exhibited an increase in size and number of germinal centers in the spleen. At the end of the recovery period, spleen weights remained elevated in 1 of 2 HDM (8.1 g, 6.7 g) and 1 of 2 HDF (4.4 g, 2.4 g) relative to control animals (Control M= 4.1 g, 6.3 g; Control F=2.6 g, 2.6 g).

Histopathology: Adequate Battery: Yes. As requested by the division (DNP) during the pre-IND meeting, the applicant performed an expanded histopathology assessment of the brain sections. Peer Review: Conducted by Dr. (b) (4)

An increase in the incidence of splenic germinal centers (white pulp; B-cell areas) occurred in MDM, HDM and at all doses in females, when examined at the end of the 4-week dosing period. There was no histologic change in splenic macrophage number

in any dose group, relative to controls. At the end of the five-week recovery period, the incidence of splenic germinal centers was no different between controls and HDM or HDF, suggesting that the effect observed in the dosing phase of the study is reversible.

Males

TABLE - 1
STUDY NO. B090486
BAN2401: A 4-Week Intermittent Intravenous Toxicity Study with 5-Week Recovery Period in Monkeys
SUMMARY OF HISTOPATHOLOGY DATA
-ALL LESIONS MALE
- TERMINAL SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 3	5 / 3	15 / 3	50 / 3
Spleen		(3)	(3)	(3)	(3)
Normal		2	2	0	1
Increased germinal center	1+	0	0	2	2
	2+	1	1	1	0

-ALL LESIONS MALE
- RECOVERY SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 2	5 / 0	15 / 0	50 / 2
Spleen		(2)	(0)	(0)	(2)
Normal		0	0	0	1
Increased germinal center	1+	1	0	0	0
	2+	1	0	0	1

GRADE; 1+: slight, 2+: moderate,

Females

-ALL LESIONS FEMALE
- TERMINAL SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 3	5 / 3	15 / 3	50 / 3
Spleen		(3)	(3)	(3)	(3)
Normal		3	2	2	0
Increased germinal center	1+	0	1	1	2
	2+	0	0	0	1

-ALL LESIONS FEMALE
- RECOVERY SACRIFICE

ORGAN AND FINDINGS	DOSE (mg/kg) -- / NO. OF ANIMALS EXAMINED --	0 / 2	5 / 0	15 / 0	50 / 2
Spleen		(2)	(0)	(0)	(2)
Normal		2	0	0	2

GRADE; 1+: slight, 2+: moderate,

Safety Pharmacology:

Respiratory: Whole body plethysmography (WBP) was conducted on Days -14, -9 and day 4. During the WBP session, respiratory rate, tidal volume, and minute volume were assessed in conscious animals. There were no dose-dependent findings.

Cardiovascular: On Days -7 and -8 and 35 days after the initial dose, monkeys were subjected to electrocardiography. Animals in the recovery group were assessed on Day 61. RR interval, PR interval, QRS duration, QT interval, and QTc (Bazett's correction) were determined during each ECG session. Blood pressure (diastolic, systolic, MBP) and pulse rate were measured on Days -7, -8, and 7. There were no test article-related findings.

Functional Observational Battery: On Days 3 and 4 before dosing and the day of the first dose, monkeys were assessed for posture, consciousness, lacrimation, salivation, eyelid position, visual/head response, coordinated movement, and pupillary reflexes. There were no test article-related findings. There was also no effect on body temperature when assessed on Day 7.

Toxicokinetics: Blood (1.5 mL) was sampled from the cephalic vein before dosing, 5 min, 1, 2, 8, 24, 48, 96, and 168 hrs after the initial and final doses. Blood samples were also collected during the recovery phase, on Days 43, 50, 57 and 64. In addition, blood samples were collected before each IV injection of lecanemab and on Days 7, 14, 21, 28 and 35 of the recovery period for anti-drug antibodies; anti-lecanemab antibodies were not detected. TK parameters for lecanemab are provided in the tables, below.

Text Table Toxicokinetic Summary

Dose (mg/kg)	Day	Male		Female	
		C_{5min} (µg/mL)	$AUC_{0\text{-}168hr}$ (µg•hr/mL)	C_{5min} (µg/mL)	$AUC_{0\text{-}168hr}$ (µg•hr/mL)
5	Day 1	145 ± 21	10400 ± 600	127 ± 7	8800 ± 1030
	Day 29	292 ± 11	29700 ± 1300	203 ± 52	20800 ± 1700
15	Day 1	416 ± 55	31300 ± 5200	383 ± 45	26000 ± 2100
	Day 29	905 ± 100	82100 ± 9700	710 ± 106	65600 ± 5300
50	Day 1	1370 ± 150	103000 ±14000	1210 ± 280	83000 ± 7100
	Day 29	2640 ± 370	268000 ±20000	1970 ± 210	189000 ±19000

C_{5min} and $AUC_{0\text{-}168hr}$ values represent the mean ± SD of 3 or 5 animals

Dose (mg/kg)	Day	Recovery Group			
		Male		Female	
		$AUC_{0\text{-}840hr}$ (µg•hr/mL)	$t_{1/2}$ (hr)	$AUC_{0\text{-}840hr}$ (µg•hr/mL)	$t_{1/2}$ (hr)
50	Day 29	617000	320	461000	417

$AUC_{0\text{-}840hr}$ and $t_{1/2}$ values represent the mean of 2 animals

Study title: BAN2401: A 39-week intermittent intravenous dose toxicity study with 13-week recovery period in monkeys

Study no.: B100068
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: April 13, 2010
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: lecanemab, PD09148 and PD09229, 99.4% and 99.6%, respectively.

Key Study Findings

- **There were no adverse lecanemab-related effects observed in monkeys dosed with up of 100 mg/kg once per week for 40 weeks. The HD of 100 mg/kg was considered a maximum feasible dose based on IV injection volume.**

Methods

Doses: 0, 15, 50, 100 mg/kg
Frequency of dosing: Once per week for a total of 40 injections
Route of administration: Intravenous, bolus
Dose volume: LD: 1.5 mL/kg; 5 mL/kg all other groups
Formulation/Vehicle: (b) (4) polysorbate 80 (b) (4)
Species/Strain: Cynomolgus monkey; (b) (4)
Number/Sex/Group: 4/sex/group
Age: 2- to 4- years old

Dosing Formulation: Formulations were within +/- 10% of the nominal protein concentration.

Findings: There were no drug-related clinical signs, and all animals survived to the terminal sacrifice. There was no drug-related effect on absolute BW, BW change, or food consumption. When assessed on Days 279 and 359 by direct and indirect ophthalmoscopy, there were no drug-related ophthalmology findings. ECG parameters were assessed on Days 91 and 275; there were no drug-related findings. When assessed on Days 91, 182, 281, and 365, there were no drug-related findings in the hematology and clinical chemistry assessment.

Organ Weights: Absolute weight of the spleen was increased by 31% in HDM and 55% in HDF at the end of the dosing period. At the end of the recovery period, spleen weight in one HDM was increased by 78%. Organ weights were similar between all females at the end of the recovery period.

Histopathology: Adequate Battery: Yes; Peer Review: Yes; Signed and Dated by Pathologist: Yes. At the end of the dosing period, an expanded neurohistopathology assessment was conducted to assess for hemorrhage. There were no drug-related findings or hemorrhage in the brain. An increase in germinal centers in the spleen was observed at all dose levels, including the controls, at the end of the dosing period (table, below). The severity of this finding was greater in HDF when compared to control. There were no drug-related findings at the end of the recovery period.

Text Table Incidence of test article related microscopic findings on Day 281

Sex			Male				Female			
Organ	Finding	Dose (mg/kg)	0	15	50	100	0	15	50	100
		No. of animals examined	4	4	4	4	4	4	4	4
Spleen										
Increased germinal center		1+	1	1	1	2	0	1	1	0
		2+	1	1	0	0	1	1	0	2

GRADE; 1+: minimal, 2+: mild

Toxicokinetics: No anti-lecanemab antibodies were detected throughout the study. TK parameters for lecanemab are provided in the tables, below. Mean half-life at the HD ranged from 410 to 419 hours (~17.5 days). Serum concentration of lecanemab on Day 365 at the HD was 2% of the concentration at the end of the dosing period (Day 274).

Study No. B100068

Dose (mg/kg)	Day	Recovery Group			
		Male		Female	
		$AUC_{0\text{-}2187hr}$ (µg•hr/mL)	$t_{1/2}$ (hr)	$AUC_{0\text{-}2187hr}$ (µg•hr/mL)	$t_{1/2}$ (hr)
100	Day 274	1960000	419	2290000	410

$AUC_{0\text{-}2187hr}$ and $t_{1/2}$ values represent the mean of 2 animals

Text Table Toxicokinetic Summary

Dose (mg/kg)	Day	Male		Female	
		C_{5min} (µg/mL)	$C_{3hr\ 5min}$ (µg/mL)	C_{5min} (µg/mL)	$C_{3hr\ 5min}$ (µg/mL)
15	Day 01	421 ± 85	-	340 ± 32 [a]	-
	Day 92	988 ± 157	-	812 ± 135	-
	Day 274	1170 ± 300	-	937 ± 272	-
50	Day 01	1520 ± 140	-	1280 ± 260	-
	Day 92	3680 ± 440	-	2950 ± 290	-
	Day 274	3310 ± 850	-	2610 ± 390	-
100	Day 01	1170 ± 110	2270 ± 250	1140 ± 110	2340 ± 270
	Day 92	4050 ± 400	5390 ± 240	3470 ± 370	4190 ± 330
	Day 274	3590 ± 400	4150 ± 280	4100 ± 500	4760 ± 950

The values are the mean ± SD from 4 or 6 animals.
a: The values are the mean ± SD from 3 animals, since the concentrations from 1 female (Animal No. 50203) were excluded from calculation.

Dose (mg/kg)	Day	Male	Female
		$AUC_{(0\text{-}168hr)}$ (µg•hr/mL)	$AUC_{(0\text{-}168hr)}$ (µg•hr/mL)
15	Day 01	28100 ± 5700	26900 ± 800 [a]
	Day 92	106000 ± 36000	92100 ± 16400
	Day 274	120000 ± 41000	103000 ± 29000
50	Day 01	114000 ± 6000	96400 ± 18800
	Day 92	405000 ± 37000	361000 ± 42000
	Day 274	353000 ± 75000	293000 ± 60000
100	Day 01	173000 ± 5000 [b]	171000 ± 18000
	Day 92	584000 ± 57000	485000 ± 37000
	Day 274	463000 ± 40000	574000 ± 72000

$AUC_{(0\text{-}168h)}$ values are the mean ± SD from 4 or 6 animals.
a: The values are the mean ± SD from 3 animals, since the concentrations from 1 female (Animal No. 50203) were excluded from calculation.
b: The values are the mean ± SD from 5 animals, since AUC from 1 male (Animal No. 10401) was excluded from calculation.

8 Carcinogenicity

Carcinogenicity studies were not conducted for lecanemab. The Division informed the applicant on March 19, 2014, that carcinogenicity studies of lecanemab would not be required to support a BLA primarily because of the development of neutralizing anti-drug antibodies in rodents treated with lecanemab or the mouse surrogate, mAb158.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted with lecanemab. The sponsor was informed on November 6, 2012, that reproductive and development toxicology studies are not required to support development of drugs to treat Alzheimer's

disease unless the indication is modified to include a younger population. The applicant states that lecanemab is being developed for treatment of adult Alzheimer's disease patients 50 years of age and older. Therefore, reproductive and developmental toxicology studies of lecanemab are not needed to support the BLA.

10 Special Toxicology Studies

10.1 Cross Reactivity Studies:

Study title: BAN2401: Cross-Reactivity Study with Normal Rat and Monkey Tissues

Study no.:	S09058
Study report location:	EDR
Conducting laboratory:	Eisai Co., Ltd, Gifu, Japan
Date of study initiation:	10/6/2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	lecanemab, P358614, 99.3%
Negative Control:	Human IgG1
Test System:	5-year-old, male and female Cynomolgus monkey tissue and 17-week-old, male and female Crl:CD(SD) rat tissue

Findings: The applicant examined the binding of lecanemab in a panel of normal rat and monkey tissues. The negative control antibody, human IgG1, did not exhibit any binding in the panel of animal tissues. Lecanemab did not exhibit any binding in the negative control tissue (rat and monkey skeletal muscle). There was binding of lecanemab to extracellular plaques in the brain tissue of positive controls (cerebrum of Tg2576 mice). Lecanemab did not exhibit specific binding in the panel of rat tissue tested. In the panel of monkey tissues, specific binding was observed in the cytosol of endocrine cells in the intermediate lobe of the pituitary, proximal tubular cells of the kidney and pia mater of the cerebrum, cerebellum and spinal cord.

Study title: Preliminary Studies to Establish the Conditions for Cross-Reactivity of BAN2401 with Selected, Normal Human Tissues

Study no.:	IM1553
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	10/7/2008
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	lecanemab, lot #L16720/C7, unknown
Negative Control:	Human IgG1
Test System:	Human brain sections from patient with Alzheimer's disease (age 70 and 88 years) and brain, kidney, lung and

pituitary sections from healthy normal subjects (age 84 and 78 years)

Summary and Conclusions: Brain tissue from two Alzheimer's disease patients and two normal controls were used to detect binding of lecanemab or a human IgG1 negative control. There was no binding of the negative control detected in brain sections from normal controls or Alzheimer's disease patients. Binding of lecanemab to extracellular plaques and occasional binding to cortical neuron and glial cytosol was observed in brain sections from Alzheimer's patients. Rare to occasional binding of lecanemab to extracellular plaques was observed in the brain sections of normal controls. There was no binding of lecanemab to sections of human kidney or lung from healthy normal subjects.

Study title: Cross-Reactivity Study of BAN2401 with Normal Human Tissues

Study no.:	IM1559
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9/8/09
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	lecanemab, P358614, 99.3%
Negative Control:	Human IgG1
Test System:	Fresh-frozen human tissues.

Summary and Conclusions: Staining was observed with lecanemab in the positive control (extracellular plaques in cerebrum from an Alzheimer's disease patient) but not the negative control, tissue. There was no staining observed in any of the sections when incubated with the negative control antibody, human IgG1. Lecanemab did exhibit extracellular binding to amyloid plaques in the cerebrum. There was cytosolic, but not membrane, binding observed in CNS and PNS neurons, glial cells, adrenals, GI tract, kidney, liver, lung, pancreas, placenta, salivary gland, testis, thyroid, and uterus.

10.2. Cerebral Microhemorrhage Studies:

The methods chosen to detect microhemorrhage (i.e., Perl's Berlin blue staining for hemosiderin detection and hematoxylin and eosin (H&E) staining for microhemorrhage) were adequate. The Tg2576 mice and APP_{ArcSwe} mice in the microhemorrhage studies were of sufficient age (> 1 year old and 18-23 months old, respectively) to ensure adequate levels of Aβ plaque formation in the central nervous system.

Study W-20090276: Female Tg2576 mice (12.5 months old) were dosed IP once a week for 18 weeks with 12 or 24 mg/kg mAb158 (21 mice/group), PBS (n=22), or IgG (n=22) and euthanized five days after the final dose was administered. Mice dosed with mAb158 exhibited a 2.5 to 3-fold decrease in soluble $Aβ_{x-42}$, a 1.3-fold decrease in insoluble $Aβ_{x-42}$, a 1.4 to 1.6-fold decrease in protofibrils, and a 30-50% decrease in Aβ plaques in the

cerebral cortex and hippocampus. The levels of soluble and insoluble $A\beta_{x-40}$ were not altered in mice dosed with mAb158, relative to the saline and IgG control. In 4 µm formalin-fixed, paraffin-embedded brain sections stained with H&E or Berlin blue, there was no difference in the incidence of microhemorrhage or hemosiderin in the brains of mice dosed with mAb158 when compared to saline and IgG controls (Table 3, below). The Berlin blue staining in the meninges and hippocampus of animals dosed with PBS, presented in the table below, was detected in two animals. Therefore, there were a total of 2 animals in the PBS group with microhemorrhage. Microhemorrhage in the 12 mg/kg mAb158 and the control IgG groups was observed in two animals in each group.

Table 3. Microhemorrhage in Tg2576 mice after treatment with mAb158.

	PBS	Control IgG 24 mg/kg	mAb158 12 mg/kg	mAb158 24 mg/kg
Number of animals	20	20	20	20
Hematoxylin-Eosin stain				
Cortex	2	1	1	0
Hippocampus/Cortex	0	0	1	0
Berlin Blue stain				
Cortex	0	1	0	0
Meninges	1	0	0	0
Hippocampus	1	0	0	0

Study AD-TR-009: Eighteen- to twenty-three-month-old APP_{ArcSwe} mice were dosed with PBS or 12 mg/kg mAb158 by IP injection (n=12/group, 4 F and 8 M), once a week for 3 months and were euthanized 7 days after the final dose. Although there was a 3-fold decrease in protofibril levels in the brains of mice dosed with mAb158, there was no difference in the number of plaques or microhemorrhages (determined by hemosiderin staining and H&E staining of 4 paraffin-embedded sections/mouse) in the brains of mice dosed with PBS or mAb158 (figure, below).

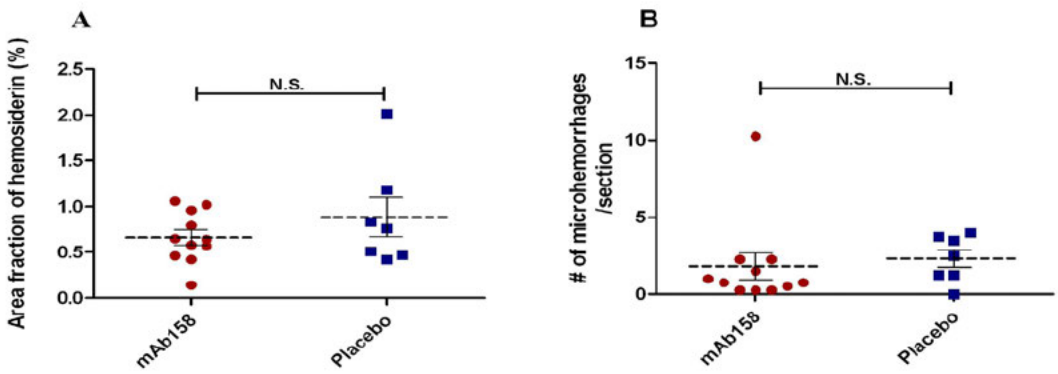

Figure 1. No difference in microbleeding in old Tg-APP$_{ArcSwe}$ mice treated with mAb158 and placebo. **(A)** Hemosiderin staining of paraffin sections (AD-SO-021) from Tg-APP$_{ArcSwe}$ mice that received weekly i.p. injections of 12 mg/kg mAb158 (n=11) or PBS (n=7) for 3 months. Presented in the graph are the mean of the area fraction ± SD of hemosiderin staining per section. There was no significant difference in microbleeding between mice treated with mAb158 compared to placebo (PBS). **(B)** Hematoxylin and eosin staining of paraffin sections (AD-SO-049) from Tg-APP$_{ArcSwe}$ mice that received weekly i.p. injections of 12 mg/kg mAb158 (n=11) or PBS (n=7). Presented in the graph is the mean of the number of microhemorrhages/sections ± SD. There was no significant difference in microbleeding between mice treated with mAb158 compared to placebo (PBS).

Study title: A pharmacological study with supplemental histopathological examination: The effect of mAb158 on amyloid protofibril in Tg2576 mouse brains.

Study no.:	W-20100318
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8/6/2009
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	mAb158, lot#090608, purity unknown

Key Study Findings

- **Cerebral microhemorrhage and hemosiderin staining was not observed in the brains of Tg2576 mice dosed with mAb158 intraperitoneally for 18 weeks.**
- **A marked anti-drug antibody response was observed, which decreased the systemic exposure of mice to mAb158 in all dose groups.**

Methods

Doses:	0, 1, 5, 15, 50 mg/kg mAb158
Frequency of dosing:	Once/week for 18 weeks, euthanized 5 days after final dose.
Route of administration:	Intraperitoneal
Formulation/Vehicle:	PBS
Species/Strain:	Tg2576 (APP heterozygous); (b) (4)
Number/Sex/Group:	17-18/group; female only
Age:	53 weeks

Mortality: Six mice died during the 4-month dosing period (3 in control, 1 in 5 mg/kg, 1 in 15 mg/kg, 1 in 50 mg/kg). These deaths were not considered to be drug related.

Protofibril and Plaque Clearance: Brain protofibril levels were decreased by 24% and 75%, relative to control, in mice dosed with 15 mg/kg and 50 mg/kg, respectively. The decrease was greater in the 50 mg/kg dose group that did not exhibit an anti-drug antibody response (6/17 mice; 90% reduction in Aβ protofibrils, relative to control; 11/17 mice positive for ADA, 65% reduction in Aβ protofibrils). Mice dosed with 50 mg/kg also exhibited a 59% decrease in soluble $A\beta_{(x-42)}$ and a 67% decrease in soluble $A\beta_{(1-42)}$. The brain level of insoluble Aβ, thioflavin S-positive plaques, 6E10-positive plaques, Aβ42 plaques and Aβ40 plaques was not changed in any of the mAb158 dose groups.

Histopathology: Microhemorrhage and hemosiderin staining (assessed by H&E and Berlin blue staining in paraffin-embedded sections, respectively) were not observed in the brains of Tg2576 mice dosed with mAb158 for 4 months, including the mice (6/17) that did not exhibit an anti-drug antibody response in the 50 mg/kg/week dose group. In the histopathological analysis, there were no dose-related findings in any of the dose groups, including animals that did not exhibit an anti-drug antibody response.

Anti-Drug Antibody and Toxicokinetics: A marked anti-drug antibody response was observed in all mAb158 dose groups (15/17, 16/16, 13/16, 10/16; 1, 5, 15, 50 mg/kg/week mAb158, respectively). The AUC_{0-168h} ratios of the final dose to the initial dose were 0.41, 0.03, 0.47 and 0.59 in the 1, 5, 15 and 50 mg/kg/week dose groups, respectively (table, below).

Table 4.1–12: Comparison of Pharmacokinetic Parameters between 1st and 17th mAb158 Administration

Parameter	First Injection	17th Injection
1 mg/kg/week		
C_{max} (µg/mL)	10.602 ± 2.819	5.461 ± 3.025
t_{max} (hours)	8 – 24	2 – 168
$AUC_{(0\text{-}168h)}$ (µg·h/mL)	1283.288 ± 328.833	532.550 ± 347.765
AUC Ratio (17th/first)	NA	0.41 ± 0.18
5 mg/kg/week		
C_{max} (µg/mL)	68.416 ± 15.362	3.808 ± 2.406
t_{max} (hours)	8 – 24	2 – 168
$AUC_{(0\text{-}168h)}$ (µg·h/mL)	8167.874 ± 1972.163	243.726 ± 61.791
AUC Ratio (17th/first)	NA	0.03 ± 0.01
15 mg/kg/week		
C_{max} (µg/mL)	149.096 ± 29.927	94.504 ± 23.765
t_{max} (hours)	8 – 24	2 –24
$AUC_{(0\text{-}168h)}$ (µg·h/mL)	17438.682 ± 2274.296	8221.313 ± 3847.217
AUC Ratio (17th/first)	NA	0.54 ± 0.28
50 mg/kg/week		
C_{max} (µg/mL)	585.740 ± 90.830	355.724 ± 85.513
t_{max} (hours)	8 – 24	8 – 24
$AUC_{(0\text{-}168h)}$ (µg·h/mL)	67450.520 ± 10370.202	40439.007 ± 12794.197
AUC Ratio (17th/first)	NA	0.53 ± 0.13

Tg2576 mice were administered mAb158 intraperitoneally weekly for 17 weeks. Plasma mAb158 concentrations were determined by enzyme-linked immunosorbent assay.
$AUC_{(0\text{-}168h)}$ = area under the concentration × time curve from time zero to 168 hours, C_{max} = maximum concentration, NA = not applicable, t_{max} = time of maximum concentration.
Source data: W-20100318.

11 Integrated Summary and Safety Evaluation

Lecanemab is a recombinant IgG1 anti-human amyloid beta peptide monoclonal antibody for the treatment of early Alzheimer's disease. The drug product, LEQEMBI, is formulated as a sterile solution of 10 mg/kg lecanemab for IV infusion of approximately one hour, once every two weeks.

Primary pharmacology studies of lecanemab and a murine analog (mAb158) were conducted in in vitro systems and in vivo in transgenic mice. Lecanemab has a high affinity (nanomolar range) for amyloid beta protofibrils, approximately 200- to 1000-fold greater than the affinity for amyloid beta monomers. Lecanemab inhibited the neurotoxicity of protofibrils in rat medial septal neurons cultured in vitro and the binding of amyloid beta protofibrils to the dendritic spines of primary hippocampal neurons. In vivo studies conducted in Tg-APP_{ArcSwe} and Tg2576 mice demonstrated the ability of lecanemab to reduce brain amyloid beta protofibril levels in these two animal models of Alzheimer's disease. The results of the primary pharmacology in vitro and in vivo studies support the description of the mechanism of action in the Indications and Usage, Description (Section 11), and Mechanism of Action (Section 12.1) sections of the applicant's proposed labeling. Specifically, the data demonstrate that lecanemab expresses the highest affinity to amyloid beta protein protofibrils.

The core battery of safety pharmacology assessments was conducted in the 4-week pivotal study conducted in monkey. There were no adverse effects on cardiovascular, respiratory, or CNS function.

The general toxicology program consisted of single-dose intravenous toxicity studies in rat and monkey and the pivotal 4-week and 39-week studies conducted in cynomolgus monkey. Pivotal general toxicology studies were conducted in a single species based on the demonstration that repeat administration of lecanemab or the rodent surrogate, mAb158, resulted in the development of neutralizing anti-drug antibodies; the same justification was used to conclude that a carcinogenicity assessment of lecanemab was not needed to support a marketing application. There were no adverse lecanemab-related findings in the pivotal studies conducted in monkeys dosed up to the maximum feasible dose of 100 mg/kg for 39 weeks. In the tissue cross-reactivity studies conducted with rat, monkey, and human tissue, binding to amyloid plaques was the only extracellular binding exhibited. All other binding was cytoplasmic, and, therefore, not clinically relevant due to the inability of antibodies to access the intracellular space. Microhemorrhage studies were conducted in mice dosed with mAb158 based on the concern for lecanemab-induced cerebral hemorrhage. Given the production of anti-drug antibodies against lecanemab in rodents, microhemorrhage studies were conducted with the rodent surrogate, mAb158. Drug-induced microhemorrhages were not observed in Tg2576 (weekly dosing for 18 weeks) or APP_{ArcSwe} (weekly dosing for 3 months) mice.

Genotoxicity studies are not generally required for antibodies because of the inability to attain access to the nuclear compartment of cells to interact with DNA and were, therefore, not conducted with lecanemab.

Reproductive and developmental toxicity studies of lecanemab were not conducted to support the BLA for LEQEMBI because of the age of the proposed clinical population.

Overall, the applicant has provided an adequate battery of nonclinical studies in support of the marketing application for LEQEMBI. From a nonclinical perspective, the nonclinical data adequately support the approval of lecanemab for the treatment of Alzheimer's disease.

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/s/

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