

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761248Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum**

Date: June 28, 2024

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Subject: ARIA Sufficiency Memorandum

Drug Name(s): KISUNLA (donanemab-azbt)

Application Type/Number: BLA-761248

Applicant/sponsor: Eli Lilly and Company

TTT #: 2024-7677



EXECUTIVE SUMMARY (place "X" in appropriate boxes)

Memo type		
-Initial		
-Interim		
-Final	X	
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?	Regulatory gap: clinical safety outcomes among Alzheimer's disease patients including subpopulations	Regulatory gap: characterizing risk in broad population of Alzheimer's disease patients
-Yes		
-No	X	X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population	X	
-Exposure		
-Outcome(s) of Interest	X	X
-Covariate(s) of Interest	X	
-Surveillance Design/Analytic Tools		



A. General ARIA Sufficiency Template

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1. BACKGROUND INFORMATION

1.1. Medical Product

KISUNLA (donanemab-azbt) is an amyloid beta-directed monoclonal antibody with a proposed indication for the treatment of Alzheimer's disease.¹ Donanemab targets N-truncated pyroglutamate amyloid beta at positron 3, which is present in brain amyloid plaques.² Extracellular deposits of amyloid beta (amyloid plaques) are a pathological feature of Alzheimer's disease.³ Another amyloid beta-directed monoclonal antibody, lecanemab, received accelerated approval on January 6, 2023⁴, and traditional approval on July 6, 2023.⁵ Aducanumab, also an amyloid beta-directed monoclonal antibody, received accelerated approval on June 7, 2021.⁶ Other FDA-approved treatments for Alzheimer's disease include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine along with the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine.⁷

Alzheimer's disease is a neurodegenerative disease that impacts 6.7 million individuals 65 years of age and older in the United States (1). Average survival after diagnosis is four to eight years (1). Alzheimer's disease is more common in females, non-Hispanic Blacks, and Hispanics (1).

Donanemab is administered as an intravenous infusion over 30 minutes every four weeks. The first three doses are 700 mg with subsequent doses of 1400 mg.⁸ The half-life of donanemab is 12.1 days.⁹

1.2. Describe the Safety Concern

Overall Safety

The Division of Neurology 1 (DN1) identified several safety concerns in the review of a supplemental application for lecanemab. The supplemental application included additional safety information beyond what is known from the clinical development program for donanemab. Safety concerns for donanemab are also informed by aducanumab. Key safety concerns for lecanemab and aducanumab include amyloid-related imaging abnormalities (ARIA) with edema (ARIA-E), ARIA with hemosiderin deposition (ARIA-H), and intracerebral hemorrhage (>1 cm).¹⁰ Hypersensitivity

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¹ BLA 761248 DRAFT labeling. June 26, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

² Mani M, Yasuda SJ, Freilich E, Buracchio T. DRAFT Summary Memorandum. BLA 761248. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

³ Ibid.

⁴ BLA 761269 ORIG-1 Approval Letter. January 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5105416.

⁵ BLA 761269 SUPPL-1 Approval Letter. July 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5230890.

⁶ BLA 761178 ORIG-1 Approval Letter. June 7, 2021. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4807032.

⁷ See footnote 2.

⁸ See footnote 1.

⁹ Ibid.

¹⁰ BLA 761178 SUPPL-11 Label. August 30, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5235778.; BLA 761269 SUPPL-1 Label. July 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5203190.

reactions¹¹ and infusion-related reactions¹² are also included in the warnings and precautions of labeling of aducanumab and lecanemab, respectively.

Safety data for donanemab stems from the placebo-controlled period of Study AACI (a phase 3, randomized, double-blind, placebo-controlled study) as well as two pooled data sets. Pooled placebo-controlled safety data for donanemab includes data from Study AACG (a phase 2 randomized, double-blind, placebo-controlled study) and the placebo-controlled period of Study AACI. Safety data from an all-donanemab-treated pool of subjects includes data from the donanemab treated subjects from Study AACG and the placebo-controlled portion of Study AACI as well as data from donanemab-treated subjects in the long-term extension period of Study AACI (double-blind long-term extension of Study AACI), AACI Safety Addendum (phase 3, open-label study addendum to AACI), Study AACH Part B (phase 2, open-label follow-on study for Study AACG), and AACN-Dona Cohort (phase 3, randomized, open-label, active comparator study).¹³

Participants who were females, of a minority race and ethnicity, and over 85 years of age were underrepresented, compared to the U.S. population with Alzheimer's disease, in the placebo-controlled pool.¹⁴ Subjects with more advanced stages of Alzheimer's disease were not enrolled in studies AACI and AACG.¹⁵

As displayed in Table 1, donanemab exposure was associated with both treatment emergent¹⁶ ARIA-E and ARIA-H in the placebo-controlled period of Study AACI and the placebo-controlled pool.¹⁷ Both lecanemab and aducanumab are also associated with an increased risk of both ARIA-E and ARIA-H.¹⁸

The incidence of intracerebral hemorrhage (>1 cm) was 0.2% in the placebo-group and 0.5% in the donanemab treated group in the placebo-controlled period of Study AACI; the incidence was 0.2% in the placebo group and 0.4% in the donanemab treated group in the placebo-controlled pool.¹⁹ In a confirmatory study for lecanemab, there was a noted increase in intracerebral hemorrhage (>1 cm) in those exposed to lecanemab, compared to placebo.²⁰ In aducanumab clinical trials, the incidence of intracerebral hemorrhage (>1 cm) was similar between aducanumab and placebo.²¹

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¹¹ BLA 761178 SUPPL-11 Label. August 30, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5235778.

¹² BLA 761269 SUPPL-1 Label. July 6, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5203190.

¹³ Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

¹⁴ Ibid.

¹⁵ Ibid.

¹⁶ On study drug or within 57 days of a dose of donanemab

¹⁷ See footnote 13.

¹⁸ Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.; Trummer B. BLA 761178 Aduhelm (aducanumab). Clinical Review (ARIA). June 7, 2021. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4807069.

¹⁹ See footnote 13.

²⁰ Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.

²¹ Trummer B. BLA 761178 Aduhelm (aducanumab). Clinical Review (ARIA). June 7, 2021. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4807069.



Table 1. Incidence of treatment emergent ARIA or intracerebral hemorrhage >1 cm in the placebo-controlled period of Study AACI and placebo-controlled pool

	Placebo-Controlled Period of Study AACI		Placebo-Controlled Pool	
	Placebo N=874 n (%)	Donanemab N=853 n (%)	Placebo N=999 n (%)	Donanemab N=984 n (%)
ARIA Overall ^a	122 (14.0)	307 (36.0)	131 (13.1)	357 (36.3)
ARIA-E ^a	17 (1.9)	201 (23.6)	18 (1.8)	236 (24.0)
ARIA-H ^a	111 (12.7)	263 (30.8)	119 (11.9)	303 (30.8)
Intracerebral hemorrhage >1 cm ^b	2 (0.2)	4 (0.5)	2 (0.2)	4 (0.4)

Source: Table 31, 96, & 98 Draft Clinical Safety Review by Natalie Branagan, MD, dated June 28, 2024.

^aBased on MRI dataset

^bBased on MRI datasets, adverse event dataset, and narratives

Abbreviations: ARIA, Amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition

At the end of the study period (76 weeks), there were more deaths in subjects randomized to donanemab (2.2% [17/853]) than those randomized to placebo (1.2% [10/874]) in the placebo-controlled period of Study AACI (risk difference=1.0% [95% confidence interval (CI): -0.3%, 2.3%]; hazard ratio=1.80 [95% CI: 0.83, 3.94]).²² In the placebo-controlled period of study AACI, there were three ARIA-related deaths (one was in a subject with intracerebral hemorrhage in the setting of ARIA-E and ARIA-H) in donanemab-treated subjects and none in placebo.²³ In the all-donanemab pool, there was an additional ARIA-related death and an additional intracerebral hemorrhage-related death in the setting of ARIA-E.²⁴

Other treatment emergent adverse events from the placebo-controlled period of Study AACI that occurred at a higher frequency among donanemab treated participants, compared to placebo, include, but are not limited to, headache (13.5% [115/853] versus 9.8% [86/874]), seizure (1.2% [10/853] versus 0.3% [3/874]) infusion-related reactions (8.7% [74/853] versus 0.5% [4/874]), hypersensitivity reactions other than infusion-related reactions (2.9% [25/853] versus 0.7% [6/894]), intestinal obstruction (0.4% [3/853] versus 0.0% [0/874]), and intestinal perforation (0.2% [2/853] versus 0.1% [1/874]).²⁵

Subpopulation - ApoE ε4 Status

Among those treated with donanemab in the placebo-controlled period of Study AACI and the placebo-controlled pool, ARIA-E and ARIA-H were more common among ApoE ε4 carriers, with the highest incidence in ApoE ε4 homozygotes (See Tables 2 and 3). Among participants treated with donanemab in the placebo-controlled period of Study AACI, serious and symptomatic ARIA were more common among ApoE ε4 homozygotes, compared to heterozygotes and non-carriers.²⁶

²² Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

²³ Ibid.

²⁴ Ibid.

²⁵ Ibid.

²⁶ Ibid.

There were few intracerebral hemorrhage events in the placebo-controlled period of Study AACI or the placebo-controlled pool.²⁷ In a published meta-analysis, there was evidence of an association between ApoE ϵ 4 alleles and lobar intracerebral hemorrhage (meta-analysis overall adjusted²⁸ odds ratio =1.51 (95% CI: 1.14, 1.99) (2).

Table 2. Incidence of ARIA stratified by ApoE ϵ 4 Status^a in placebo-controlled period of Study AACI

	Carrier – Homozygote		Carrier – Heterozygote		Non-Carrier	
	Placebo N=146 n (%)	Donanemab N=143 n (%)	Placebo N=474 n (%)	Donanemab N=452 n (%)	Placebo N=250 n (%)	Donanemab N=255 n (%)
ARIA-E or ARIA-H ^{b,c}	32 (21.9)	79 (55.2)	60 (12.7)	164 (36.3)	29 (11.6)	63 (24.7)
ARIA-E ^c	5 (3.4)	58 (40.6)	9 (1.9)	102 (22.6)	2 (0.8)	40 (15.7)
ARIA-H ^c	30 (20.5)	72 (50.3)	54 (11.4)	142 (31.4)	27 (10.8)	48 (18.8)
Intracerebral hemorrhage >1cm ^d	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.7)	0 (0.0)	1 (0.4)

Source: Table 40, Draft Clinical Safety Review by Natalie Branagan, MD, dated June 28, 2024.

^aExcludes those with unknown ApoE status

^bIncludes those with ARIA-E alone, ARIA-H alone, or both ARIA-E and ARIA-H

^cBased on MRI dataset

^dBased on MRI datasets, adverse event dataset, and narratives

Abbreviations: ApoE, Apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition

Table 3. Incidence of ARIA stratified by ApoE ϵ 4 Status^a in placebo-controlled pool

	Carrier – Homozygote		Carrier – Heterozygote		Non-Carrier	
	Placebo N=174 n (%)	Donanemab N=168 n (%)	Placebo N=538 n (%)	Donanemab N=522 n (%)	Placebo N=282 n (%)	Donanemab N=291 n (%)
ARIA-E or ARIA-H ^{b,c}	36 (20.7)	97 (57.7)	63 (11.7)	189 (36.2)	31 (11.0)	70 (24.1)
ARIA-E ^c	6 (3.4)	69 (41.1)	9 (1.7)	123 (23.6)	2 (0.7)	43 (14.8)
ARIA-H ^c	33 (19.0)	90 (53.6)	57 (10.6)	157 (30.1)	29 (10.3)	55 (18.9)
Intracerebral hemorrhage >1cm ^d	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.6)	0 (0.0)	1 (0.3)

Source: Table 115, Draft Clinical Safety Review by Natalie Branagan, MD, dated June 28, 2024.

^aExcludes those with unknown ApoE status

^bIncludes those with ARIA-E alone, ARIA-H alone, or both ARIA-E and ARIA-H

^cBased on MRI dataset

^dBased on MRI datasets, adverse event dataset, and narratives

Abbreviations: ApoE, Apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA with edema; ARIA-H, ARIA with hemosiderin deposition

Among the two intracerebral hemorrhage-related deaths in subjects treated with donanemab, one was an ApoE ϵ 4 heterozygote.²⁹

²⁷ Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

²⁸ Adjusted for demographic and intracerebral hemorrhage risk factors

²⁹ See footnote 27

In the confirmatory trial for lecanemab, there was an increase in ARIA-E, ARIA-H, and intracerebral hemorrhage (>1cm) among ApoE ε4 carriers, specifically homozygotes. Furthermore, symptomatic ARIA-E and serious adverse events of ARIA were also more common in ApoE ε4 homozygotes.³⁰

Subpopulation – Concomitant Antithrombotic Medications

Studies AACI, AACC, and AACH did not exclude participants for antithrombotic use (aspirin, other antiplatelets, anticoagulants).³¹ In AACN, participants were excluded for antithrombotic use, except for aspirin ≤325 mg/day.³²

Table 4 and 5 display the risk for ARIA-H and intracerebral hemorrhage (>1 cm) by antithrombotic exposure in the placebo-controlled period of Study AACI and the placebo-controlled pool, respectively. The frequency of ARIA-H was 30.4% (106/349) among participants in the placebo-controlled period of Study AACI exposed to donanemab and antithrombotics, compared to 29.4% (148/504) among those exposed to donanemab and not on antithrombotics. For intracerebral hemorrhage (>1 cm), the frequencies were 0.6% (2/349) and 0.4% (2/504), respectively.³³

Table 4. Frequency of ARIA-H and intracerebral hemorrhage (>1 cm) in placebo-controlled period of Study AACI, stratified by antithrombotic use^a

	ARIA-H		Intracerebral hemorrhage (>1 cm)	
	Placebo	Donanemab	Placebo	Donanemab
Not on antithrombotic	63/513 (12.3%)	148/504 (29.4%)	2/513 (0.4%)	2/504 (0.4%)
On antithrombotic	47/361 (13.3%)	106/349 (30.4%)	0/361 (0.0%)	2/349 (0.6%)
<i>Aspirin ≤81 mg daily</i>	35/260 (13.5%)	83/261 (31.8%)	0/260 (0.0%)	0/261 (0.0%)
<i>Aspirin >81 mg daily, or antiplatelet therapy, or aspirin and antiplatelet therapy</i>	10/62 (16.1%)	15/70 (21.4%)	0/62 (0.0%)	2/70 (2.9%)
<i>Anticoagulant</i>	11/86 (12.7%)	20/83 (24.1%)	0/86 (0.0%)	0/83 (0.0%)

Source: Table 44 & 45, Draft Clinical Safety Review by Natalie Branagan, MD, dated June 28, 2024.

^aAntithrombotic use within 30 days prior to event

Abbreviations: ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA with hemosiderin deposition

³⁰ Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.

³¹ Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

³² Ibid.

³³ Ibid

Table 5. Frequency of ARIA-H and intracerebral hemorrhage (>1 cm) in placebo-controlled pool, stratified by antithrombotic use^a

	ARIA-H		Intracerebral hemorrhage (>1 cm)	
	Placebo	Donanemab	Placebo	Donanemab
Not on antithrombotic	66/571 (11.6%)	168/573 (29.3%)	2/571 (0.4%)	2/573 (0.3%)
On antithrombotic	52/428 (12.1%)	124/411 (30.2%)	0/428 (0.0%)	2/411 (0.5%)
<i>Aspirin ≤81 mg daily</i>	40/313 (12.8%)	98/311 (31.5%)	0/313 (0.0%)	0/311 (0.0%)
<i>Aspirin >81 mg daily, or antiplatelet therapy, or aspirin and antiplatelet therapy</i>	11/74 (14.9%)	19/80 (23.8%)	0/74 (0.0%)	2/80 (2.5%)
<i>Anticoagulant</i>	12/100 (12.0%)	22/95 (23.2%)	0/100 (0.0%)	0/95 (0.0%)

Source: Table 127 & 128, Draft Clinical Safety Review by Natalie Branagan, MD, dated June 28, 2024.

^aEvent while on antithrombotic or used an antithrombotic within 30 days prior to the event

Abbreviations: ARIA, amyloid-related imaging abnormalities; ARIA-H, ARIA with hemosiderin deposition

In the completed confirmatory trial for lecanemab, participants with antithrombotic exposure had an increased risk of intracerebral hemorrhage, with the highest risk among those with anticoagulant exposure.³⁴

Notably, in the all-donanemab pool there was one intracerebral hemorrhage-related death in a subject who had thrombolytic administration (tenecteplase) in the setting of ARIA-E.³⁵ In the placebo-controlled period of Study AACI, there was one intracerebral hemorrhage-related death in a subject with concomitant aspirin exposure.³⁶

Subpopulation – Cerebral Amyloid Angiopathy (CAA)

The definitive diagnosis of CAA is made post-mortem; however there are biomarkers of CAA such as lobar cerebral microbleeds, lobar intracerebral hemorrhage, and cortical superficial siderosis (3). Subjects with certain baseline magnetic resonance imaging (MRI) findings of ARIA-E, >4 cerebral microhemorrhages, >1 area of superficial siderosis, any macrohemorrhage, or severe white matter disease, were excluded from studies AACI, AACG, and AACN-Dona Cohort.³⁷ However, there was a greater risk of ARIA-E and ARIA-H among subjects in the all-donanemab pool with two to four baseline microhemorrhages or one baseline area of superficial siderosis.³⁸

Among the two intracerebral hemorrhage-related deaths in subjects treated with donanemab, one had a screening MRI that showed white matter disease while the other had a screening MRI that

³⁴ Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.

³⁵ Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

³⁶ Ibid.

³⁷ Ibid.

³⁸ Ibid.

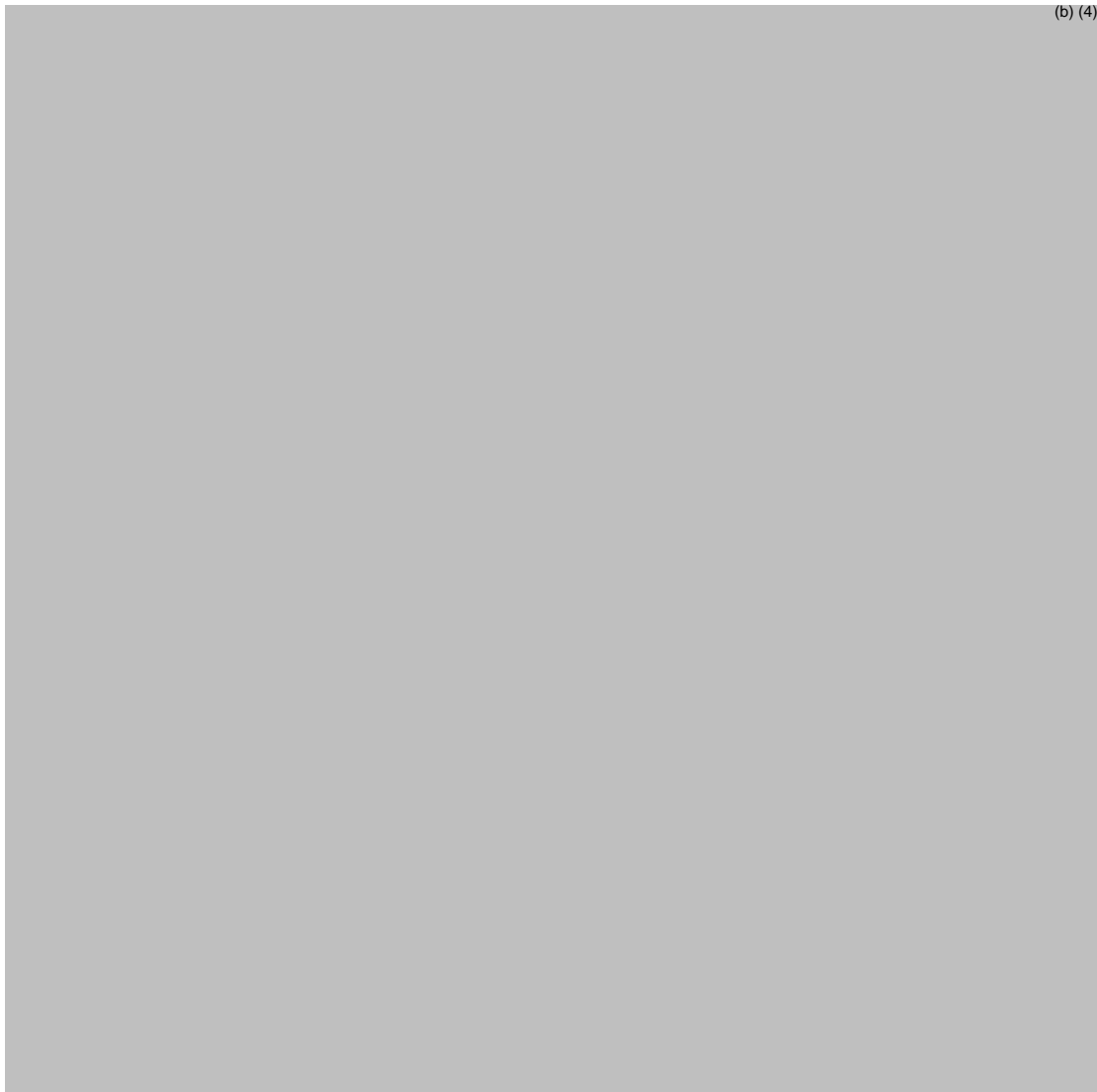


showed white matter disease and superficial siderosis.³⁹ In the confirmatory trial for lecanemab, there were two deaths in the open-label extension with evidence of underlying CAA.⁴⁰

Labeling

The proposed, draft labeling for donanemab includes language relevant to safety concerns and risks overall and in subpopulations.⁴¹

There is a boxed warning for amyloid related imaging abnormalities:⁴²



The relevant sections of the Warnings & Precautions are provided in Appendix A.

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³⁹ Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

⁴⁰ Erten-Lyons D. BLA 761269 S001 LEQEMBI (lecanemab). Clinical Safety Review. July 5, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5202624.

⁴¹ BLA 761248 DRAFT labeling. June 26, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

⁴² Ibid.

Requested pharmacovigilance will include expedited reporting of deaths and intracerebral hemorrhage (>1 cm). Postmarketing pharmacovigilance will also characterize the risk of ARIA, intracerebral hemorrhage >1cm, hypersensitivity and infusion reactions, and intestinal perforation and intestinal obstruction.⁴³

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Table 5. FDAAA Purpose

Assess a known serious risk	X ^a
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

^aIn alignment with the PMR/PMC development template, the FDAAA Purpose is to assess a known serious risk of ARIA and intracerebral hemorrhage (>1 cm), which will be included in the boxed warning of labeling. In addition, there are subpopulations that may have differential risks of ARIA and intracerebral hemorrhage (>1 cm). Please see section 1.4 for a complete list of additional subpopulation and outcomes of concern, along with the regulatory goal for each.

1.4. Statement of Purpose

DN1 requested that the Division of Epidemiology I (DEPI-I) conduct an assessment to determine whether the Sentinel Active Risk Identification and Analysis system would be sufficient to assess the safety of donanemab in a broad, overall population of Alzheimer’s disease patients and three subpopulations of interest—ApoE ε4 homozygotes, patients with concomitant exposure to antithrombotics, and patients with underlying CAA. Based on discussions with DN1, the main regulatory gaps are with respect to ARIA (including both ARIA-E and ARIA-H) and intracerebral hemorrhage (>1 cm) safety outcomes. These two safety concerns will be the primary outcomes of interest and the focus of the Active Risk Identification and Analysis system assessment.⁴⁴

Per DN1⁴⁵, ARIA and intracerebral hemorrhage (>1 cm) are known serious risks that will be included in the boxed warning of final labeling. In addition to these known serious risks, there are subpopulations that may have differential risks of ARIA and intracerebral hemorrhage (>1 cm). Subpopulations of interest and types of risk include:

- Among ApoE ε4 homozygotes
  - ARIA in this subpopulation is a known serious risk included in the boxed warning of the final labeling.
  - Intracerebral hemorrhage (>1 cm) has signals of a serious risk in this subpopulation.
- Among those concomitantly exposed to an antithrombotic,
  - ARIA and intracerebral hemorrhage (>1 cm) have signals of a serious risk in this subpopulation.
- Among those with underlying CAA,
  - There is an unexpected serious risk of ARIA and intracerebral hemorrhage (>1 cm)

⁴³ Branagan N. BLA 761248 Kisunla (donanemab). DRAFT Clinical Safety Review. June 28, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

⁴⁴ Agreed upon at the Safety Assessment Meeting (SAM) held June 23, 2023, for lecanemab and aducanumab. Donanemab Active Risk Identification and Analysis system assessment will follow the same focus as agreed upon for lecanemab and aducanumab.

⁴⁵ Type of risk agreed upon at the Safety Assessment Meeting (SAM) held June 23, 2023, for lecanemab and aducanumab. Donanemab Active Risk Identification and Analysis system assessment will follow the same risk classifications agreed upon for lecanemab and aducanumab.

in this subpopulation; the available data indicate potential for serious risk.

The regulatory goal differs by population and outcome.⁴⁶ The regulatory goals by population are:

- Overall population: signal evaluation for ARIA and intracerebral hemorrhage (>1 cm). This goal is consistent with the boxed warning for donanemab for both ARIA and serious intracerebral hemorrhage (>1 cm). Further characterization of risk is needed in the broad, overall Alzheimer's disease population, beyond what was evaluated in the clinical trials.
- ApoE ϵ 4 homozygotes subpopulation: signal refinement for intracerebral hemorrhage (>1 cm) and signal evaluation for ARIA.
- Concomitant exposure to antithrombotics subpopulation: signal refinement for ARIA and intracerebral hemorrhage (>1 cm).
- CAA subpopulation: signal detection for ARIA and intracerebral hemorrhage (>1 cm).

Obtaining more precise risk estimates for ARIA and intracerebral hemorrhage (>1 cm) in a broad, overall population of Alzheimer's disease patients and among subpopulations for which data is limited could further inform labeling for ARIA and intracerebral hemorrhage (> 1 cm) risk in the postmarketing setting.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The effect size of interest and the estimated sample size desired will be negotiated and determined once the draft protocol is submitted.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The population of interest is patients with Alzheimer's disease. Within that population, there are several subpopulations for which further characterization of risk is needed. Those subpopulations include ApoE ϵ 4 homozygotes, patients with concomitant exposure to antithrombotics, and patients with underlying CAA. Within those exposed to antithrombotics, there is additional interest in those on anticoagulants. Comparators for ApoE ϵ 4 homozygotes could possibly include ApoE ϵ 4 heterozygotes and non-carriers. Comparators for patients with concomitant exposure to antithrombotics could possibly include patients without concomitant exposure to antithrombotics. Similarly, for those on anticoagulants, a comparator could possibly be those not on anticoagulants. Comparators for patients with CAA would possibly be patients without CAA.

2.2 Is Active Risk Identification and Analysis sufficient to assess the intended population?

The Active Risk Identification and Analysis system is sufficient to identify the broad, overall population of patients with Alzheimer's disease; however, it is insufficient to identify the three subpopulations. Validated, algorithms of International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes can be used to identify patients with Alzheimer's disease (4). For comparative analyses, it may be important to identify patients with amyloid beta pathology. For ApoE ϵ 4 status, there may be Current Procedural Terminology (CPT) codes for ApoE testing. However, the Sentinel Distributed Database (SDD) data would not include the results of

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⁴⁶ Regulatory goals agreed upon at the Safety Assessment Meeting (SAM) held June 23, 2023, for lecanemab and aducanumab. Donanemab Active Risk Identification and Analysis system assessment will have the same regulatory goals agreed upon for lecanemab and aducanumab.

such testing. For antithrombotics, claims could be used to identify a subset of patients with prescription anticoagulant or antiplatelet exposure, but not any over-the-counter aspirin exposure. For CAA, per the Boston Criteria version 2.0, the definitive diagnosis is made postmortem and probable/possible diagnoses require brain MRIs (3). Neuroimaging results are not available in the SDD. Although there is an ICD-10 code for CAA, it is not clear how this code is used in clinical practice; it has not been validated, including against the Boston Criteria.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is donanemab, which will be administered at infusion centers.

3.2 Comparator Exposure(s)

It may be informative to consider the background risk of these outcomes in Alzheimer's disease patients who are untreated or exposed to other FDA approved medications indicated for the treatment of Alzheimer's disease.

3.3 Is Active Risk Identification and Analysis sufficient to identify the exposure of interest?

Yes, once a Healthcare Common Procedure Coding System (HCPCS) code is assigned for donanemab, the Active Risk Identification and Analysis system will be sufficient to identify donanemab exposure.

There is a HCPCS code in place for aducanumab (J0172) (5) and lecanemab (J0174) (6), so the Active Risk Identification and Analysis system will be sufficient to identify aducanumab and lecanemab exposure. Other Alzheimer's disease treatments should be captured in prescription claims via National Drug Codes.

4 OUTCOME(S)

4.1 Outcomes of Interest

The primary outcomes of interest include ARIA-E, ARIA-H, and intracerebral hemorrhage (>1 cm).

4.2 Is Active Risk Identification and Analysis sufficient to assess the outcome of interest?

There are no ICD codes or validated, computable phenotypes for ARIA-E or ARIA-H, which are radiographic findings. However, there are ICD codes that may plausibly be used by providers to capture ARIA. The validity of algorithms for intracerebral hemorrhage in claims is high (positive predictive value ~98%) (7, 8). Although there are validated algorithms for intracerebral hemorrhage, the validity may not be applicable to patients with Alzheimer's disease taking amyloid beta-directed monoclonal antibodies. Because there are no ICD codes for ARIA, providers could be coding ARIA-H as intracerebral hemorrhage, making intracerebral hemorrhage codes less specific in this treated, patient population. Additionally, claims cannot restrict to intracerebral hemorrhage by size (i.e., >1 cm). It is important that the outcome of intracerebral hemorrhage should distinguish between ARIA-H and intracerebral hemorrhage > 1 cm. Validation of claims codes for these outcomes in patients with Alzheimer's disease is needed. Medical chart review capabilities are not available in the Sentinel Active Risk Identification and Analysis system. Given medical chart

review is needed, the Active Risk Identification and Analysis system would be insufficient for assessing any of the primary outcomes of interest in a population of patients with Alzheimer's disease and the defined subpopulations of interest.

5 COVARIATES

5.1 Covariates of Interest

The covariates required for analyses would depend on whether the analysis is addressing the risk of ARIA and intracerebral hemorrhage in the broad, overall population of Alzheimer's disease patients or a specific subpopulation.

To examine the incidence of ARIA and intracerebral hemorrhage in the broad, overall Alzheimer's disease population, covariates of interest include sociodemographics (i.e., age, sex, race, insurance type), clinical characteristics (i.e., comorbidities, disease duration, disease severity, concomitant medications), and healthcare access/utilization (frequency of care, provider type, setting of care). These covariates will help characterize the population of Alzheimer's disease patients who receive donanemab outside of clinical trials.

For analyses of risk, especially in the three subpopulations, in addition to the aforementioned covariates, ApoE ϵ 4 status, antithrombotic use, and underlying CAA are also important covariates. There may be interaction and/or effect modification in risk in one subpopulation by the defining features of the other subpopulation(s), requiring capture of these additional covariates (i.e., ApoE ϵ 4 status, antithrombotic use, underlying CAA). For example, the risk of ARIA or intracerebral hemorrhage in patients taking antithrombotics may differ by underlying CAA or ApoE status, thus capture of CAA and ApoE status is important. Also, ApoE ϵ 4 alleles are associated with CAA (9), making ApoE ϵ 4 status a potential confounder for an assessment of associations between CAA and ARIA or intracerebral hemorrhage.

5.2 Is Active Risk Identification and Analysis sufficient to assess the covariates of interest?

Several of the covariates listed above can be captured in claims data (age, sex, race, insurance type, comorbidities, disease duration, concomitant medications, frequency of care, provider type, setting of care). For disease severity, although not directly available in claims, it could possibly be captured through a proxy, such as the Claims-Based Frailty Index (10).

The variables ApoE ϵ 4 status, antithrombotic use, and underlying CAA are critical to defining the subpopulations of interest. For the subpopulation analyses, given possible interaction and/or effect modification in risk in one subpopulation by the defining features of the other subpopulation(s), capture of these covariates is also important. These covariates that would need to be derived from brain MRIs (i.e., evidence of underlying CAA), or genetic testing (i.e., ApoE ϵ 4 status) would not be available in claims data. Consequently, the Active Risk Identification and Analysis system would be insufficient to capture the necessary covariates to define these subpopulations and to address risk in the subpopulation analyses.

The Active Risk Identification and Analysis system would be sufficient to capture covariates for the analysis of the incidence of ARIA and intracerebral hemorrhage in the broad, overall population of Alzheimer's disease patients. Although it would be helpful to know ApoE ϵ 4 status, concomitant antithrombotic use, and underlying CAA for risk analyses, these covariates are not essential in estimating incidence of ARIA and intracerebral hemorrhage in the broad, overall population of

patients on donanemab, irrespective of ApoE ϵ 4 status, concomitant antithrombotic use, and underlying CAA status. Furthermore, for measures of association, capture of these covariates would be important especially if prescribing was differential by these covariates. However, current labeling does not contraindicate use in any of these subpopulations, so it is unknown if these factors would lead to differential prescribing practices and possible confounding. As a result, although these covariates are important for the subpopulation analyses given the potential for interaction and/or effect modification, they are not as critical for the broad, overall population analysis.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The study would require descriptive analysis and covariate adjusted estimates of risk stratified by subpopulations.

6.2 Is Active Risk Identification and Analysis sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, the Active Risk Identification and Analysis system is sufficient to conduct descriptive analysis, analysis adjusted for multiple covariates, and stratified analysis.

7 NEXT STEPS

On December 15, 2023, DEPI-I communicated via email (in lieu of a live Safety Assessment Meeting [SAM]) to representatives from the Office of Surveillance and Epidemiology (OSE) and the Office of New Drugs (OND), that DEPI-I had determined that the Active Risk Identification and Analysis system is insufficient to assess the risk of ARIA and intracerebral hemorrhage >1cm in 1) a broad, overall population of Alzheimer's disease patients, and 2) the three subpopulations of interest— ApoE ϵ 4 homozygotes, patients with concomitant exposure to antithrombotics, and patients with underlying CAA. Concurrence with the insufficiency determination was obtained from DN1 on the same day and no OSE or OND representatives expressed disagreement. Upon approval, DN1 will issue a FDAAA Post-Marketing Requirement (PMR) for two studies with the following draft language:

PMR 4605-1: Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with donanemab, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ϵ 4 homozygotes, and/or exposed to antithrombotics or thrombolytics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA- hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to



estimated background rates in an appropriate comparator population.

PMR 4605-2: Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage > 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4605-1 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer disease untreated with donanemab. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with donanemab.



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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 1, 2024

To: Justine Kankam, PharmD
Regulatory Health Project Manager
Division of Neurology I (DN1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Samuel Fasanmi, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (Medication Guide (MG))

Drug Name (established name): KISUNLA (donanemab)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761248

Applicant: Eli Lilly and Company

1 INTRODUCTION

On June 11, 2023, Eli Lilly and Company submitted for the Agency's review a Class II resubmission of an Original New Biologic Drug Licensing Application for KISUNLA (donanemab-azbt) injection, for intravenous use. The purpose of this application is to seek approval for the use of KISUNLA (donanemab-azbt) injection, for intravenous use to treat Alzheimer's disease (AD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on June 16, 2023 and June 15, 2023, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KISUNLA (donanemab-azbt) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft KISUNLA (donanemab-azbt) MG received on June 11, 2023, and received by DMPP and OPDP on January 18, 2024.
- Draft KISUNLA (donanemab-azbt) Prescribing Information (PI) received on June 11, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 18, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Pre-decisional Agency Information

Memorandum

Date: January 30, 2024

To: Justine Kankam, Regulatory Project Manager, Division of Neurology Products 1 (DN1)
Kevin Krudys (DN1)
Tracy Peters, Associate Director for Labeling, (DN)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for Kisunla (donanemab-azbt) injection, for intravenous use

BLA: 761248

Background:

In response to DN1's consult request dated June 15, 2023, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the NDA submission for Kisunla.

PI:

OPDP's review of the proposed PI is based on the draft labeling received by electronic mail from DN1 on January 18, 2024, and our comments are provided below.

Medication Guide:

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the Sponsor to the electronic document room on June 12, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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Clinical Inspection Summary

Date	12/6/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Justine Kankam, Pharm.D., M.S., Regulatory Project Manager Kevin Krudys, Ph.D., Clinical Reviewer Ranjit Mani, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	BLA #761248
Applicant	Eli Lilly and Company
Drug	Donanemab
NME	Yes
Proposed Indication	Treatment of Alzheimer's disease
Consultation Request Date	7/31/2023
Clinical Inspection Summary Goal Date	11/10/2023, extended to 12/8/2023
Action Goal Date	3/12/2024
PDUFA Date	12/13/2023, extended to 3/12/2024 (major amendment)

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bergeron (Site #603), Lee (Site #108), and Norton (Site #253) were inspected in support of this BLA covering Protocol 15T-MC-AACI. Based on the inspection results, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The primary efficacy data, integrated Alzheimer's Disease Rating Scale (iADRS), was derived from the secondary efficacy data, Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog13) and Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL). Therefore, efficacy data verification focused on those secondary efficacy data as well the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), an additional secondary efficacy endpoint. No meaningful data discrepancies were identified. There was no evidence of under-reporting of adverse events.

II. BACKGROUND

Donanemab injection for intravenous use is being developed under IND 109157 for the treatment of Alzheimer's disease (AD). The sponsor submitted BLA #761248 in 5/2022 that included the results of a Phase 2 study, Protocol 15T-MC-AAAG, to support efficacy and safety in slowing disease progression of AD. The sponsor sought approval under the accelerated approval pathway based on the biological endpoint, reduction in amyloid beta plaques. Three clinical investigator inspections and a sponsor inspection were conducted during that review cycle. A Complete Response (CR) Letter was issued in January 2023.

In response to the CR and to support a traditional approval pathway, the sponsor has submitted the results of the Phase 3 confirmatory study, 15T-MC-AACI, to support the efficacy and safety of donanemab for the treatment of AD. The review division requested clinical investigator inspections covering this Phase 3 study.

Protocol 15T-MC-AACI (TRAILBLAZER-ALZ 2)

Title: "Assessment of safety, tolerability, and efficacy of donanemab in early symptomatic Alzheimer's disease"

Subjects: 1727

Sites: 244; North America (186 [US 170]), Asia/Pacific (24), Eastern Europe (19), Australia (8), Western Europe (7)

Study Initiation and Completion Dates: 6/19/2020 – 4/14/2023 (primary outcome last participant visit in double-blind phase)

Database Lock: 4/28/2023

This is a randomized, parallel-group, double-blind, placebo-controlled study of donanemab in subjects with early symptomatic Alzheimer's disease (AD). The double-blind extension phase of this protocol is ongoing.

Main inclusion criteria were:

- Male or female, 60 to 85 years of age
- Gradual and progressive change in memory function reported by the participant or informant for ≥ 6 months
- Mini-Mental State Examination (MMSE) score of 20 to 28 (inclusive)
- Meets flortaucipir F18 and florbetapir F18 scan criteria
- Have adequate literacy, vision, and hearing for neuropsychological testing
- Stable concomitant symptomatic AD medications and other medications that may impact cognition for at least 30 days prior to randomization
- Have a study partner who will provide written informed consent to participate, is in frequent contact with the subject (at least 10 hours/week), and will accompany the subject to study visits

Exclusion criteria included screening MRI showing evidence of significant abnormality that would suggest another potential etiology for progressive dementia; centrally read MRI demonstrating presence of amyloid-related imaging abnormalities edema/effusions (ARIA-E); >4 cerebral microhemorrhages; more than 1 area of superficial siderosis; any macrohemorrhage or severe white matter disease; poor venous access; or contraindication to MRI or PET.

The study was comprised of 4 phases: Screening Phase, Double-Blind Phase, Extension Phase, and a Follow-Up Phase.

Screening Phase

The screening phase was divided into two periods – an optional Lead-In Screening Visit (Visit 601) and a Complete Screening Visit (Visit 1). The optional Lead-In Screening Visit could be done at any time prior to the Complete Screening. Study procedures conducted during the Lead-In Screening Visit included abbreviated or full informed consent (subject and study partner), demographics, MMSE, P-tau, ApoE, and pharmacogenetics sample.

The Complete Screening Visit occurred up to 49 days (Day -49 to Day -1) prior to randomization. Study procedures conducted during the Complete Screening included, but were not limited to, full informed consent, physical/neurological examination, safety assessments (labs, ECG), and screening PET scans and MRI.

Double-Blind Phase (76 Weeks; Visits 2 to 21)

Subjects were randomized (1:1) to one of the following arms:

- Donanemab IV infusion: 700 mg every 4 weeks (Q4W) for 3 doses, then 1400 mg Q4W for up to 72 weeks
- Placebo IV infusion Q4W for up to 72 weeks

Subjects whose amyloid plaque reduction [as measured by florbetapir F18 PET scans at Visit 8 (Week 24), Visit 15 (Week 52), and Visit 21 (Week 76)] met criteria had a double-blind dose reduction of donanemab to placebo for the remaining duration of the study.

Extension Phase (78 Weeks; Visits 22 to 41)

The extension phase is double-blind and ongoing. Subjects were evaluated for amyloid plaque reduction by PET scan at Visit 21:

- Subjects randomized to donanemab who did not meet dose reduction criteria at Visit 21 continued to receive donanemab
- Subjects randomized to donanemab who did meet dose reduction criteria at Visit 21 were assigned to receive placebo beginning at Visit 22
- Subjects randomized to placebo were assigned to receive donanemab starting at Visit 22

Subjects whose amyloid plaque reduction [as measured by florbetapir F18 PET scans at Visit 28 (Week 102) or Visit 35 (Week 130)] met criteria had a double-blind dose reduction of donanemab to placebo for the remaining duration of the study.

Follow-up Phase (Up to 44 Weeks; Visits 801 to 804)

The Follow-up Phase began 12 weeks after the final dose of investigational product (IP). Subjects continued to have quarterly immunogenicity and safety follow-up visits until the subject completed Visit 804 or the site was notified that the subject was not required to complete all follow-up visits.

The **primary efficacy endpoint** was the change from baseline to Week 76 in the integrated Alzheimer's Disease Rating Scale (iADRS). Secondary measures included the Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog13), Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL), and Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) scales.

III. RESULTS

1. Richard Bergeron, M.D., Ph.D.

Site #603

The Memory Clinic of Ottawa
160 Blvd. De L'Hopital Suite 30
Gatineau, Quebec J8T 8J1
Canada

Inspection Dates: 10/16/2023 – 10/20/2023

At this site for Protocol 15T-MC-AAI, 185 subjects were screened, 28 subjects were randomized, and 17 subjects completed the double-blind phase of the study and continued in the ongoing extension phase. Eleven subjects discontinued the study due to withdrawal of consent (n = 5), physician decision (n = 5), and serious adverse event (SAE) (n = 1). Subject (b) (6), randomized to donanemab, experienced amyloid-related imaging abnormalities hemorrhage/hemosiderin deposition (ARIA-H) on Study Day (b) (6) and died (b) (6) days later. The narrative for this subject is included in the BLA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were randomized. An audit of the study records for 14 of 28 (50%) randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB and sponsor communications, financial disclosure, investigational product accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy data (Alzheimer Disease Assessment Scale-Cognition [ADAS-Cog13], Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living [ADCS-iADL], and Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB]), and primary efficacy data (integrated Alzheimer's Disease Rating Scale

[iADRS]).

The primary efficacy data, iADRS scores, are calculated from the ADAS-Cog13 and ADCS-iADL secondary efficacy data via an algorithm. Therefore, data verification focused on secondary efficacy data. All rating scale data were entered into an electronic tablet provided by the vendor, (b) (4). An information request was sent to the sponsor requesting the rating scale source data. The sponsor submitted pdf files to the BLA, including audit trails obtained directly from the (b) (4) system. Data verification for the ADAS-Cog13 and ADCS-iADL focused on comparing responses to each rating scale question in the source data to the corresponding SDTM dataset as adequate sponsor data line listings were not available. CDR-SB scores were reviewed and could be compared to sponsor data line listings. This reviewer reviewed rating scale data for 8 of 28 (28.6%) randomized subjects for Visits 2 and 21. No discrepancies were noted in the ADAS-Cog13 or CDR-SB data. Some discrepancies in responses to ADCS-iADL questions were identified in 4 of 8 subjects reviewed as described below. There was no evidence of under-reporting of adverse events.

Several items on the ADCS-iADL include a main question and several sub-questions related to the main question. If the subject answered “yes” to the main question, the sub-questions were asked; if the subject answered “no” to the main question, the sub-questions were not asked. For four subjects, the SDTM dataset included a “no” response rather than a missing response when the source indicated that the sub-questions had not been asked.

Reviewer comments: In discussions with the review division, the “no” response to sub-questions appeared to be logically consistent with the main question that was asked and answered by the subject.

There was one instance in which the treatment assignment was unblinded at this site. As noted above, Subject (b) (6), randomized to donanemab, experienced ARIA-H on Study Day (b) (6) ((b) (6)) and died (b) (6) days later. The site was notified of the subject’s death on (b) (6). The subject’s treatment assignment was unblinded through IWRS on (b) (6) by the clinical investigator (CI) due to a request from the subject’s spouse. Per protocol, emergency unblinding at a subject level for adverse events could be performed through the IWRS if the subject’s well-being required knowledge of the subject’s treatment assignment. A Note-to-File (NTF) dated (b) (6) documented the decision to unblind the treatment assignment for ethical reasons and for the CI to be able to have a comprehensive discussion with the subject’s family members. The CI noted that his decision to unblind treatment assignment was not according to protocol. The sponsor and IRB were notified of this event after it had occurred. The NTF stated that in any similar cases in the future, the CI would notify the sponsor to obtain the necessary approval prior to unblinding. This unblinding incident was reported as a protocol deviation in the sponsor’s data line listing.

Reviewer comments: The CI deviated from the protocol regarding circumstances in which unblinding were allowed. The CI noted that, in the future, he will obtain approval from the

sponsor prior to unblinding. This subject had completed only baseline assessments prior to the serious adverse events and unblinding; therefore, it is unlikely that efficacy analyses would be impacted.

2. Elly Lee, M.D.

Site #108

Irvine Clinical Research
2515 McCabe Way
Suite 350
Irvine, CA 92614

Inspection Dates: 8/7/2023 – 8/16/2023

At this site for Protocol 15T-MC-AACI, 203 subjects were screened, 26 subjects were randomized, and 20 subjects completed the double-blind phase of the study and are continuing in the ongoing extension phase. Six subjects discontinued the study due to withdrawal of consent.

An audit of the study records for 23 of 26 (88%) randomized subjects was conducted. Records reviewed included, but were not limited to, informed consent forms, source documents, monitoring documents, IRB and sponsor communications, financial disclosure, investigational product accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy data (ADAS-Cog13, ADCS-iADL, CDR-SB), and primary efficacy data (iADRS).

The primary efficacy data, iADRS scores, are calculated from the ADAS-Cog13 and ADCS-iADL scales via an algorithm. Therefore, data verification focused on the secondary efficacy data as detailed above (Site #603 inspection summary). This reviewer reviewed rating scale data for 8 of 26 (30.8%) randomized subjects. No discrepancies were noted in the ADAS-Cog13, ADCS-iADL, or CDR-SB data. There was no evidence of under-reporting of adverse events.

3. Jeffrey Norton, M.D.

Site #253

Charter Research
1025 Lake Sumter Landing
The Villages, FL 32162

Inspection Dates: 9/11/2023 – 9/15/2023

At this site for Protocol 15T-MC-AACI, 132 subjects were screened, 32 subjects were randomized, and 25 subjects completed the double-blind phase of the study and continued in the ongoing extension phase. Six subjects discontinued the study, and one subject was transferred to another clinical site. Discontinuation reasons included SAEs (n = 2), withdrawal of consent (n = 2), withdrawn by physician (n = 1), and withdrawal due to caregiver circumstances (n = 1). Subject # [REDACTED] (b) (6), randomized to donanemab, discontinued due to the SAE of

cerebral vascular accident. Subject # [REDACTED] (b) (6), randomized to placebo, discontinued due to worsening of Alzheimer's disease and death. Narratives for these discontinuations due to SAE are included in the BLA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were randomized. An audit of the study records for 12 of 32 (37.5%) randomized subjects was conducted. Records reviewed included, but were not limited to, informed consent forms, source documents, monitoring documents, IRB and sponsor communications, financial disclosure, investigational product accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy data (ADAS-Cog13, ADCS-iADL, CDR-SB), and primary efficacy data (iADRS). There was no evidence of under-reporting of adverse events.

The primary efficacy data, iADRS scores, are calculated from the ADAS-Cog13 and ADCS-iADL secondary efficacy data via an algorithm. Therefore, data verification focused on the secondary efficacy data as detailed above (Site #603 inspection summary). This reviewer reviewed rating scale data for 9 of 31 (29%) randomized subjects for Visits 2 and 21. No discrepancies were noted in the ADAS-Cog13 or CDR-SB data. Some discrepancies in ADCS-iADL data were identified in 4 of 9 subjects reviewed. The main discrepancies were similar to that described above (Site #603 inspection summary).

Reviewer comments: In discussions with the review division, the responses to sub-questions appeared to be logically consistent with the main question that was asked and answered by the subject.

{See appended electronic signature page}

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Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Central Document Room/BLA #761248
Division of Neurology 1/Division Director/Teresa Buracchio
Division of Neurology 1/Deputy Division Director/Emily Freilich (Acting)
Division of Neurology 1/Medical Team Leader/Ranjit Mani
Division of Neurology 1/Clinical Reviewer/Kevin Krudys
Division of Neurology 1/Medical Officer/Natalie Branagan
Division of Neurology 1/Project Manager/Justine Kankam
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OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	September 18, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761248
Product Name, Dosage Form, and Strength:	Kisunla (donanemab-azbt) injection, 350 mg/20 mL (17.5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	June 12, 2023
TTT ID #:	2022-2422-2
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

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1 REASON FOR REVIEW

As part of the approval process for Kisunla (donanemab-azbt) injection, the Division of Neurology 1 (DN 1) requested that we review the proposed Kisunla prescribing information (PI), medication guide (MG), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant originally submitted BLA 761248 on May 18, 2022. During that review cycle, we reviewed the PI, MG, carton labeling, and container label, and we provided our recommendations to the Division and the Applicant.^a Subsequently, we reviewed revised container label and carton labeling in response to our recommendations, which we found acceptable.^b However, on January 18, 2023, the Agency issued a complete response (CR) letter to the Applicant for BLA 761248 due to an insufficient safety database.

Thus, on June 12, 2023, the Applicant submitted a Class 2 Resubmission to respond to the deficiency outlined in the January 18, 2023 CR letter for BLA 761248.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

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^a Morris, C. Label and Labeling Review for Kisunla (BLA 761248). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 NOV 17. RCM No.: 2022-2422.

^b Morris, C. Label and Labeling Review MEMO for Kisunla (BLA 761248). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 JAN 11. RCM No.: 2022-2422-1.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The purpose of the resubmission is to provide the unblinded controlled safety and efficacy data from the Phase 3 Study AACI. The submission includes revised PI, MG, carton labeling and container label. We note, there are no changes to the product information. Our recommendations from the last review cycle were incorporated into the currently proposed PI and MG. The applicant is proposing additional revisions to the PI and MG to update the description of the clinical trial experience of Kisunla and associated data, which includes revisions to applicable sections of the labeling. We did not identify any new risks for medication errors in the revised PI and MG.

The current versions of the carton labeling and container label contain only one difference from those we previously found acceptable on January 11, 2023: the web address [REDACTED]^{(b) (4)} was replaced with www.kisunla.com. We do not object to this change.

Therefore, the PI, MG, carton labeling, and container label are acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed PI and container labels did not identify any new areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kisunla received on June 12, 2023 from Eli Lilly and Company.

Table 2. Relevant Product Information for Kisunla	
Initial Approval Date	n/a
Nonproprietary Name	donanemab-azbt
Indication	treatment of Alzheimer’s disease
Route of Administration	Intravenous infusion
Dosage Form	injection
Strength	350 mg/20 mL (17.5 mg/mL)
Dose and Frequency	(b) (4)
How Supplied	Carton containing one single-dose vial
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep the vial in the outer carton to protect from light. Do not freeze or shake. If refrigeration is not available, may be stored at room temperature (20°C to 25°C [68°F to 77°F]) for up to 3 days.
Container Closure^c	Type (b) (4) glass vial

^c Container closure specifications available at: <\\CDSESUB1\evsprod\bla761248\0003\m3\32-body-data\32p-drug-prod\donanemab-solution-for-infusion-all-01\32p7-cont-closure-sys\32p7-container-closure-v001.pdf>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 17, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Kisunla, donanemab, and BLA 761248. Our search identified two previous reviews as noted in Section 1.1, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Kisunla labels and labeling submitted by Eli Lilly and Company on June 12, 2023.

- Container label
- Carton labeling
- Prescribing Information (Image not shown), available from <\\CDSESUB1\EVSPROD\bla761248\0104\m1\us\proposed-uspi.docx>
- Medication Guide, available from <\\CDSESUB1\EVSPROD\bla761248\0104\m1\us\proposed-medguide.docx>

F.2 Label and Labeling Images

(b) (4)

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^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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JOHN C MORRIS
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

Pre-decisional Agency Information

Memorandum

Date: January 11, 2023

To: E. Andrew Papanastasiou, Regulatory Project Manager, Division of Neurology 1 (DN1)

Natalie Branagan, Clinical Reviewer, DN1

Tracy Peters, Associate Director for Labeling, DN1

From: Aline Moukhtara, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for KISUNLA (donanemab-azbt) injection, for intravenous use

BLA: 761248

Background:

In response to DN1's consult request dated May 25, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original BLA submission for KISUNLA (donanemab-azbt) injection, for intravenous use (Kisunla).

Medication Guide:

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide and comments were sent under separate cover on January 6, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft carton and container labeling submitted by the sponsor to the electronic document room on December 9, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Aline Moukhtara at 301-796-2841 or Aline.Moukhtara@fda.hhs.gov.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 11, 2023
Requesting Office or Division: Division of Neurology 1 (DN 1)
Application Type and Number: BLA 761248
Product Name and Strength: Kisunla (donanemab-azbt) injection,
350 mg/20 mL (17.5 mg/mL)
Applicant/Sponsor Name: Eli Lilly and Company
TTT ID #: 2022-2422-1
DMEPA 2 Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader: Stephanie DeGraw, PharmD

---

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 9, 2022 for Kisunla. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Kisunla (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations, and we have no additional recommendations at this time.

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^a Morris, C. Label and Labeling Review for Kisunla (BLA 761248). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 NOV 17. RCM No.: 2022-2422.

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JOHN C MORRIS
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 6, 2023

To: E. Andrew Papanastasiou
Regulatory Project Manager
Division of Neurology I (DN1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Aline Moukhtara, RN, MPH
Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): KISUNLA (donanemab-azbt)

Dosage Form and Route: injection, for intravenous use

Application Type/Number: BLA 761248

Applicant: Eli Lilly and Company

1 INTRODUCTION

On May 18, 2022, Eli Lilly and Company submitted for the Agency's review a rolling submission of an Original New Biologic Drug Licensing Application for KISUNLA (donanemab-azbt) injection, for intravenous use. The purpose of this application is to seek approval for the use of KISUNLA (donanemab-azbt) injection, for intravenous use to treat Alzheimer's disease (AD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I (DN1) on May 26, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for KISUNLA (donanemab-azbt) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft KISUNLA (donanemab-azbt) MG received on May 18, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 23, 2022.
- Draft KISUNLA (donanemab-azbt) Prescribing Information (PI) received on May 18, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 23, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 17, 2022
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761248
Product Name and Strength:	Kisunla (donanemab-azbt) injection, 350 mg/20 mL (17.5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	May 18, 2022
TTT ID #:	2022-2422
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

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1 REASON FOR REVIEW

As part of the approval process for Kisunla (donanemab-azbt) injection, the Division of Neurology 1 (DN 1) requested that we review the proposed Kisunla prescribing information (PI), medication guide (MG), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Example of Proposed Preparation and administration Table	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, MG, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Eli Lilly and Company.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The duration of infusion is presented inconsistently	Inconsistent presentation of administration information may increase the risk for	We recommend either defining a specified duration or range of duration of infusion, or specify

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	throughout the PI (Section 2.1 states 30 minutes; Section 2.5 states (b) (4)). Additionally, the Medication Guide states, "about (b) (4)".	wrong rate medication errors.	recommended rates or max rates of infusion.
Highlights of Prescribing Information			
1.	The duration of infusion is not presented.	Incomplete administration information may increase the risk for wrong rate medication errors.	If there is a specified duration of infusion (for example, 30 minutes) or range (for example 30 minutes to (b) (4)), we recommend adding this to the dosage statement.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2.1 "Dosing Instructions" is unnecessarily wordy.	This may be revised for brevity and readability to ensure key information is not overlooked.	We recommend revising to read "The recommended dose of Kisunla is 700 mg every four weeks for three doses, then 1,400 mg every four weeks (See Table 1)."
2.	Section 2.3 does not define when the missed dose should be administered.	Unclear missed dose instructions may increase the risk for dosing errors.	We recommend stating whether the missed dose should be administered as soon as possible or at next scheduled infusion.
3.	The first bullet point in Section 2.4 contains the sentence "(b) (4)".	This does not follow the sequence of steps to prepare the product.	We recommend moving the sentence "(b) (4)" between the "Withdraw required..." and "Gently invert..." bullets.
4.	Section 2.4 "Dilution Instructions" contains the sentence "(b) (4)".	This is an administration instruction.	We recommend relocating to Section 2.5 "Administration Instructions".

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
5.	Dilution instructions in Section 2.4 are unclear and the details are suitable to be presented in tabular format.	Unclear dilution instructions may increase the risk for wrong preparation/concentration errors.	We recommend using a table to present Kisunla dose in mg, final concentration in mg/mL, Kisunla volume in mL, diluent volume in mL, and total volume to be infused in mL. See Appendix E for an example.
6.	It may not be practical to (b) (4) as currently described in Section 2.4.	This may increase the risk for preparation errors.	We recommend replacing the statement (b) (4) " with "mix to the recommended total volume (See Table X)". Table X is the table we propose in the recommendation above.
7.	The infusion duration statement in Section 2.5 is open-ended and inconsistently stated throughout the labeling.	This may increase the risk for wrong rate medication errors.	We recommend defining the infusion duration as either a specified time (for example, 30 minutes), range of duration times (for example, 30 minutes to (b) (4)), or adding a maximum infusion rate.
8.	The line maintenance protocols are driven by the type of infusion access and may allow for flushing with other solutions.	This may increase the risk for incompatibility medication errors.	We recommend revising the flush statement (fourth bullet point in Section 2.5) to read "Flush the line only with 0.9% Sodium Chloride injection at the end of the infusion per access specific line maintenance protocol."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Post dilution storage and handling instructions are not present in Section 16.2.	This may increase the risk for degraded drug medication errors.	Add agreed upon post dilution storage and handling instructions to Section 16.2.
2.	The phrase "(b) (4)" in the first bullet	Unnecessary words may detract from more important information.	Delete the phrase "(b) (4)" from the refrigeration statement.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	point in Section 16.2 is unnecessary.		
3.	Conditions for unrefrigerated storage are not stated in Section 16.2.	This may increase the risk for unnecessary room temperature storage when refrigeration is preferred and available.	Add the following phrase "If refrigeration not available", or similar to the beginning of the room temperature storage statement.
Full Prescribing Information – Section 17 Patient Counseling			
1.	The method of distribution for the Medication Guide (MG) is not stated.	Patients should be made aware of how they will receive or can obtain a MG.	We recommend stating how the MG will be provided, such as, via company website or provided with each carton.
Medication Guide			
1.	The infusion duration statement does not align with similar statements in the PI.	Inconsistent administration information may increase the risk for patient confusion.	We recommend revising the infusion duration statement "Each infusion will last about (b) (4) " to align with the language agreed upon for the PI.

5 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The proprietary name, proper name, and dosage form are less readable (gray vs black or bold font) than other displayed information (such as, strength, Rx only statement, and Medication Guide statement).	This is critical information that should be the most prominent information on the label. For more information, see our guidance document at: https://www.fda.gov/meda/158522/download	We recommend improving the readability of the proprietary name, proper name, and dosage form in a manner consistent with FDA regulations, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The format for the expiration date is not defined.	A clearly defined expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. Please specify whether alphabetical or numerical characters will be used to represent the month.
3.	The (b) (4) statement can be improved.	This is inconsistent with Prescribing Information language.	To ensure consistency with the Prescribing Information, revise the statement, “(b) (4) to read “Dosage: See prescribing information.” Delete

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			redundant " (b) (4) ".
4.	The storage statement is incomplete.	Users are not made aware of acceptable storage conditions if refrigeration is unavailable.	We recommend replacing the statement " (b) (4) " with "If refrigeration not available, may be stored at room temperature (20°C to 25°C [68°F to 77°F]) for up to 3 days.
5.	The nonproprietary name suffix is represented with the placeholder "xxyy".	We refer to our Nonproprietary Name Suffix Advice Letter dated August 4, 2022, which states we found the nonproprietary name "donanemab-azbt" conditionally acceptable for your proposed product.	Replace the nonproprietary name suffix placeholder "xxyy" with the conditionally approved nonproprietary name suffix "azbt".
Container Label			
1.	The principal display area of the container label is visually cluttered.	Important information may be difficult to read or overlooked by some users.	We note that the (b) (4) is displayed prominently on the principal display panel (PDP) of the carton labeling in accordance with (b) (4). Therefore, in this instance, consider moving this statement and the (b) (4) to the secondary display area on the side panel under the recommended dosage statement. This will create more space between the lines of text on the PDP, improving readability.
Carton Labeling			

Table 3. Identified Issues and Recommendations for Eli Lilly and Company (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The translations of variable data box for serialization displays the expiration date and (b) (4) in close proximity.	This may increase the risk for misinterpretation of the expiration date.	If you intend to include a (b) (4) on the carton, we recommend reordering the variable data so the expiration date and (b) (4) are not in close proximity, and the expiration date is listed before the (b) (4) to make it more prominent.
2.	A placeholder for the product identifier 2-D barcode is not displayed.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes.	Please identify where the 2-D barcode portion of the product identifier will be displayed.
3.	As currently presented, there is no net quantity statement.	Per 21 CFR 201.51, the label of a prescription drug in package form shall bear a declaration of the net quantity of contents.	Revise "Single-Dose Vial" to read "One Single-Dose Vial".

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Kisunla that Eli Lilly and Company submitted on May 18, 2022.

Table 4. Relevant Product Information for Kisunla	
Initial Approval Date	n/a
Active Ingredient	donanemab-azbt
Indication	(b) (4) of Alzheimer's disease (AD)
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	350 mg/20 mL (17.5 mg/mL)
Dose and Frequency	(b) (4)
How Supplied	Carton containing one single dose vial
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) (b) (4). Keep the vial in the outer carton to protect from light. DO NOT FREEZE OR SHAKE. May be stored (b) (4) for up to 3 days at room temperature (20°C to 25°C [68°F to 77°F]).
Container Closure^a	Type (b) (4) glass vial

^a Container closure specifications available at: <\\CDSESUB1\evsprod\bla761248\0003\m3\32-body-data\32p-drug-prod\donanemab-solution-for-infusion-all-01\32p7-cont-closure-sys\32p7-container-closure-v001.pdf>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 2, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, BLA 761248 and donanemab. Our search did not identify any previous reviews.

APPENDIX E. Example of Proposed preparation and administration table

Kisunla dose (mg)	Final concentration (mg/ml)	Kisunla volume (ml)	0.9 % Sodium Chloride volume (ml)	Total volume to be infused (ml)
700	4	40	135	175
	5		100	140
	6		77	117
	7		60	100
	8		48	88
	9		38	78
	10		30	70
1400	4	80	270	350
	5		200	280
	6		154	234
	7		120	200
	8		96	176
	9		76	156
	10		60	140

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Kisunla labels and labeling submitted by Eli Lilly and Company, received on May 18, 2022.

- Container label
- Carton labeling
- Medication Guide (Image not shown), available from <\\CDSESUB1\evsprod\bla761248\0002\m1\us\proposed-medguide.docx>
- Prescribing Information (Image not shown), available from <\\CDSESUB1\evsprod\bla761248\0002\m1\us\proposed-uspi.docx>

F.2 Label and Labeling Images



1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JOHN C MORRIS
11/17/2022 10:38:57 AM

STEPHANIE L DEGRAW
11/17/2022 11:31:18 AM

Clinical Inspection Summary

Date	11/14/2022
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. (Acting) Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Emilios (Andrew) Papanastasiou, M.S, Pharm.D., Regulatory Project Manager Kevin Krudys, Ph.D., Clinical Reviewer Ranjit Mani, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
BLA #	761248
Applicant	Eli Lilly and Company
Drug	Donanemab
NME	Yes
Proposed Indication	(b) (4) of Alzheimer's disease
Consultation Request Date	6/13/2022
Summary Goal Date	11/18/2022
Priority/Standard Review	Priority
Action Goal Date	1/18/2023
PDUFA Date	1/18/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Concha, Solomon, and Vandersluis as well as the sponsor, Eli Lilly and Company, were inspected in support of this BLA, covering Protocol 15T-MC-AACG. This study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

During the inspection of the sponsor, it was noted that Site #189 was terminated due to good clinical practice (GCP) issues. The sponsor had previously informed FDA of this site closure in a communication submitted to the IND in 2019; however, this information was not included in the clinical study report for the BLA submission. Some study data was collected for the three subjects enrolled at this site. All three subjects were discontinued from the study and did not transfer to other sites (per subject preference). Based on the GCP issues that were discovered, we recommend that the review division perform a sensitivity analysis regarding this site.

The sponsor also described one instance of unintentional unblinding due to the local imaging center inadvertently sending a PET report to the clinical site, which was reviewed by the clinical investigator. Due to this unblinding, the subject was discontinued from the study. This unblinding event was not included in the clinical study report. We recommend that the review division consider asking the sponsor if other intentional or unintentional unblinding events occurred during the conduct of Protocol 15T-MC-AACG.

II. BACKGROUND

Donanemab injection for intravenous use is being developed under BLA 761248 (IND 109157) (b) (4) of Alzheimer's disease (AD). The sponsor has submitted the results of a Phase 2 study, Protocol 15T-MC-AACG, to support efficacy and safety for this indication. The sponsor is seeking approval under the accelerated approval pathway based on the biological endpoint of reduction in amyloid beta plaques. A Phase 3 confirmatory clinical study is ongoing.

Protocol 15T-MC-AACG

Title: "Assessment of safety, tolerability and efficacy of LY3002813 alone and in combination with LY3202626 in early symptomatic Alzheimer's disease" (Note: LY3002813 is donanemab)

Subjects: 271

Sites: 56 sites in North America (52 United States, 4 Canada)

Study Initiation and Completion Dates: 12/28/2017 to 12/04/2020

Database Lock Date: 1/5/2021

This was a Phase 2, double-blind, placebo-controlled study in subjects with early symptomatic Alzheimer's disease (AD). Major inclusion criteria were men or women 60 to 85 years of age; gradual and progressive change in memory function reported by subjects or informants for >6 months; CogState Brief Battery (CBB) learning/working memory score of 82 to 90; meet both centrally read 18F flortaucipir scan and 18F florbetapir scan criteria; and Mini-Mental State Examination (MMSE) score of 20 to 28 (inclusive) at Visit 1 or an acceptable historical flortaucipir PET scan within 6 months prior to Visit 1 that meets the central read criteria (added with Amendment C). Concomitant use of acetylcholinesterase inhibitors and/or memantine were allowed if the medication was given for at least 4 months and the dose was stable for at least 2 months before randomization.

The study was comprised of three phases: screening, double-blind treatment, and immunogenicity/safety follow-up phase.

Screening Phase: Week -9 to Week -1/Visit 1

Study procedures to determine subject eligibility including, but not limited to: MMSE, CBB, safety assessments (labs, ECG), and screening PET scans and MRI.

Double-blind Treatment Phase: Week 0/Visit 2 to Week 76/Visit 21

Subjects were randomized (1:1) to one of the following arms:

- Donanemab IV infusion: 700 mg every 4 weeks (Q4W) for 3 doses, then 1400 mg Q4W for up to 72 weeks
- Placebo IV infusion Q4W for up to 72 weeks

Subjects whose amyloid plaque reduction as measured by PET scans at Week 24/Visit 8 and/or Week 52/Visit 15 met specific criteria had a double-blinded dose reduction of donanemab to 700 mg or placebo for the remaining duration of the double-blind phase. This dose reduction was based on the specific level of PET signal at that visit.

Investigational product (IP) was prepared by an unblinded pharmacist (or other qualified unblinded personnel) and administered by a blinded nurse (or other qualified blinded personnel). Infusions were to be administered over a minimum of 30 minutes. If subjects experienced an infusion reaction, rescue medications could be administered, and subjects could be premedicated for subsequent infusions. Subjects were to be observed for approximately 2 hours following each IP infusion for the first 6 infusions; observation time was then reduced to 1 hour.

Note that under previous versions of the protocol, subjects were randomized to a third treatment arm consisting of donanemab administered in combination with oral LY3202626 (an inhibitor of β -site amyloid precursor protein cleaving enzyme 1). This treatment arm was discontinued as of Protocol Amendment D (10/9/2018).

Immunogenicity/Safety Follow-up Phase: 48 weeks (Week 88/Visit 801 to Week 124/Visit 804)

Subjects were to return to the site at Week 88 for collection of blood samples for anti-drug antibody (ADA) measurements, assessment of adverse events, and concomitant medications. Subject stopped immunogenicity follow-up visits when they either completed 3 additional quarterly visits (up to Week 124) or completed a visit in which their ADA returns to baseline, whichever occurs first.

The *primary efficacy endpoint* was the change from baseline to Week 76 in the integrated Alzheimer's Disease Rating Scale (iADRS). The *biological efficacy endpoint* on which accelerated approval is being sought is the change from baseline to Week 76 in brain amyloid as measured by florbetapir F18 PET scan.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the BIMO clinical investigator site selection tool (CISST), numbers of enrolled subjects, numbers of subjects with adequate PET data, and prior inspectional history.

III. RESULTS

1. Mauricio Concha, M.D

Site #132

Intercoastal Medical Group
2650 Bahia Vista Street
Suite 305
Sarasota, FL 34239-2634

Inspection Dates: 8/30/2022 – 9/7/2022

At this site for Protocol 15T-MC-AACG, 30 subjects were screened, 11 were randomized, and 10 subjects completed the study. Subject # (b) (6), randomized to placebo, experienced the SAE aspiration pneumonia resulting in death. Two subjects discontinued investigational product (IP) but continued to participate in the study and study-related procedures (e.g., MRIs, PET scans, labs, cognitive testing). Subject # (b) (6), randomized to placebo, discontinued IP due to the adverse event (AE) “systemic inflammatory reaction”; however, the sponsor’s category of discontinuation was “other”. Subject # (b) (6), randomized to donanemab, discontinued IP due to the serious adverse event (SAE) of symptomatic amyloid-related imaging abnormality edema/effusion (ARIA-E). The narratives for Subjects # (b) (6) and # (b) (6) are included in the BLA submission, but the narrative for Subject # (b) (6), who discontinued due to an AE, was not.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 11 randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, biological efficacy data (Positron Emission Tomography [PET] amyloid), secondary efficacy data (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB]), and primary efficacy data (integrated Alzheimer’s Disease Rating Scale [iADRS]).

Upon request, and after the inspection was announced, certified copies of PET amyloid quantitative data were sent to the sites by the vendor, (b) (4). The sponsor also submitted these data to the BLA. Data for the PET parameter “SUVR Cerebellum Longitudinal (b) (4) Analysis” was verified against sponsor data line listings for screening, Week

24, Week 52, and Week 76 time points for all randomized subjects. No discrepancies were identified.

iADRS scores are calculated from the Alzheimer Disease Assessment Scale-Cognition (ADAS-COG13) and Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL) scales. Therefore, the ADAS-COG13 and ADCS-iADL scores were verified against the sponsor data line listings. The CDR-SB scores were also verified against sponsor data line listings. The data for these rating scales were entered into electronic tablets and transmitted electronically to the vendor, (b) (4). A thumb drive containing these data were provided to the clinical site, and data were verified against the sponsor data line listings for all randomized subjects. No discrepancies were identified.

There was no evidence of under-reporting of adverse events. As noted above, the narrative for Subject # (b) (6), who was randomized to placebo and discontinued IP due to AE "systemic inflammatory reaction", was not included in the BLA submission. According to the CI, this subject experienced a fever to 103.2° F and a swollen face the day after receiving the Visit 12 infusion. Dr. Concha advised that the subject be taken to the emergency room, where the subject was administered acetaminophen for the fever. The AE recurred one week later, and the subject was treated at home with diphenhydramine and acetaminophen. No further information was available at the site.

Reviewer's comment: The narrative for Subject # (b) (6), who was randomized to placebo and discontinued IP due to the AE "systemic inflammatory reaction", was not included in the BLA submission since the discontinuation was categorized as "other". Omission of this narrative is unlikely to impact the overall assessment of safety.

2. Paul Solomon, Ph.D.

Site #104

Boston Center for Memory
180 Wells Avenue, Suite 304
Newton, MA 02459

Inspection Dates: 9/20/2022 – 9/28/2022

At this site for Protocol 15T-MC-AACG, 50 subjects were screened, 20 were randomized, and 15 subjects completed the study. Five subjects discontinued the study due to withdrawal by subject (1), other (1), and adverse events (3). Subjects # (b) (6) and # (b) (6), both randomized to donanemab, discontinued the study due to cerebral microhemorrhage. Subject # (b) (6), randomized to donanemab, discontinued the study due to symptomatic ARIA-E. Narratives for these discontinuations due to adverse events are included in the BLA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 20 randomized subjects was

conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, biological efficacy data (Positron Emission Tomography [PET] amyloid), secondary efficacy data (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB]), and primary efficacy data (integrated Alzheimer's Disease Rating Scale [iADRS]).

Upon request, and after the inspection was announced, certified copies of PET amyloid quantitative data were sent to the sites by the vendor, (b) (4). The sponsor also submitted these data to the BLA. Data for the PET parameter "SUVR Cerebellum Longitudinal (b) (4) Analysis" was verified against sponsor data line listings for screening, Week 24, Week 52, and Week 76 time points for all randomized subjects. No discrepancies were identified.

iADRS scores are calculated from the Alzheimer Disease Assessment Scale-Cognition (ADAS-COG13) and Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL) scales. Therefore, the ADAS-COG13 and ADCS-iADL scores were verified against the sponsor data line listings. The CDR-SB scores were also verified against sponsor data line listings. The data for these rating scales were entered into electronic tablets and transmitted electronically to the vendor, (b) (4). A CD containing these data were provided to the clinical site, and data were verified against the sponsor data line listings for all randomized subjects. No discrepancies were identified. Additionally, there was no evidence of under-reporting of adverse events.

3. Joel Vandersluis, M.D.

Site #146

240 W. Elmwood Drive

Suite 1000

Dayton, OH 45459-4248

Inspection Dates: 8/1/2022 – 8/12/2022

At this site for Protocol 15T-MC-AACG, 76 subjects were screened, 12 were randomized, and 10 subjects completed the study. Two subjects discontinued the study due to withdrawal by subject (1) and a SAE (1). The SAE occurred in Subject # (b) (6), randomized to placebo, who died secondary to cardiac arrest. One subject discontinued IP due to the SAE symptomatic ARIA-E (Subject # (b) (6)/donanemab) but continued to participate in the study and study-related procedures (e.g., MRIs, PET scans, labs, cognitive testing).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all 12 randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article

accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, biological efficacy data (Positron Emission Tomography [PET] amyloid), secondary efficacy data (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB]), and primary efficacy data (integrated Alzheimer's Disease Rating Scale [iADRS]).

Upon request, and after the inspection was announced, certified copies of PET amyloid quantitative data were sent to the sites by the vendor, (b) (4). The sponsor also submitted these data to the BLA. Data for the PET parameter "SUVR Cerebellum Longitudinal (b) (4) Analysis" was verified against sponsor data line listings for screening, Week 24, Week 52, and Week 76 time points for all randomized subjects. No discrepancies were identified.

iADRS scores are calculated from the Alzheimer Disease Assessment Scale-Cognition (ADAS-COG13) and Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living (ADCS-iADL) scales. Therefore, the ADAS-COG13 and ADCS-iADL scores were verified against the sponsor data line listings. The CDR-SB scores were also verified against sponsor data line listings. The data for these rating scales were entered into electronic tablets and transmitted electronically to the vendor, (b) (4). A thumb drive containing these data was provided to the clinical site, and data were verified against the sponsor data line listings for all randomized subjects. No discrepancies were identified. Additionally, there was no evidence of under-reporting of adverse events.

4. Eli Lilly and Company

839 S. Delaware Street
Indianapolis, IN 46225-1782

Inspection Dates: 9/26/2022 – 9/30/2022

This inspection covered sponsor practices related to Protocol 15T-MC-AACG and focused on the three clinical investigator sites chosen for inspection.

Records reviewed during the inspection included, but were not limited to, SOPs, organizational charts, electronic trial master file (eTMF), monitoring plan and reports, site selection/qualification, monitor qualification and training records, vendor operational plans, investigator agreements and 1572s, investigator compliance/corrective actions, IRB approvals, data management, financial disclosure forms, audit certificates, IP shipments/receipts/returns, safety reporting to FDA, IWRS use/testing/validation, and investigational product accountability.

The vendor, (b) (4), was responsible for all aspects of PET scan management for Protocol 15T-MC-AACG. (b) (4)

Documents provided during

the inspection included the (b) (4) Blinding Procedure, (b) (4) Flortetapir Longitudinal Analysis Workflow, and a High-Level Process Summary to show the flow of information from the imaging site to (b) (4).

According to the (b) (4) Blinding Procedure document, data that was to remain blinded, with no access included the treatment the subject was randomized to. Data that was to remain blinded with restricted access included MRI scans and PET scans (including change in dosing based on scans, standard uptake value ratio [SUVr], centiloid values, longitudinal analysis data).

According to the sponsor, there was one instance of unintentional unblinding regarding PET data. For Subject # (b) (6), randomized to donanemab, a locally read flortetapir PET scan result from Visit 15 was inadvertently sent to the site by the PET imaging center. The site study coordinator and clinical investigator viewed the results. (b) (4) confirmed that the results included in the report were considered unblinding, and the subject was discontinued from the study. In the sponsor's subject disposition line listing, it is noted that this subject discontinued due to a protocol deviation described as "subject discontinued due to V15 PET scan results read in error"; this listing also notes that the subject had discontinued investigational product at Visit 11 due to an adverse event. This event was not included in the sponsor's protocol deviation line listing. This unblinding event was also not included in the clinical study report.

The CRO, (b) (4), reviewed site qualifications and provided clinical monitoring for Protocol 15T-MC-AACG. For this protocol, 56 sites enrolled subjects. One site, Site #189, was terminated due to noncompliance. Issues identified at this site included significant staff turnover, lack of investigator oversight, failure to obtain and review medical records in a timely manner to confirm subject eligibility prior to randomization, incomplete or late source data, discrepancies between eCRF and source data, deficiencies in informed consent and re-consenting process, failure to report a SAE in a timely manner, and MRI scans for a study subject were not completed every 4 to 6 weeks for follow-up of moderate ARIA-E. Both (b) (4) and the sponsor implemented a plan to bring the site back into compliance, which included increased monitoring visits, but the site was ultimately terminated in September 2019. The sponsor informed FDA of the site termination. Three subjects were enrolled at this site at the time: Subject #'s (b) (6). The subject disposition line listing included in the BLA submission indicates that these three subjects discontinued at Visit 9 (study day 190-197) due to "withdrawal by subject," with the reason provided as "site closing, and subject chose not to continue at another site". Of note, Subject # (b) (6), randomized to placebo, had discontinued IP at Visit 5 due to an AE (non-Hodgkin's lymphoma) and Subject # (b) (6), randomized to donanemab, had discontinued IP at Visit 4 due to an AE (symptomatic ARIA-E). Narratives for both of these subjects were included in the BLA submission.

Reviewer comments: The sponsor described one case of unintentional unblinding during the conduct of Protocol 15T-MC-AACG. This event was not included in the clinical study report. The

review division may consider asking the sponsor if there were other instances of either intentional or unintentional unblinding that occurred during the study.

Site #189 was terminated due to GCP issues as described above. We recommend that the review division conduct a sensitivity analysis regarding this site.

{See appended electronic signature page}

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