UNDERSTANDING ApoE ε4 AND RISK OF ARIA

ApoE ε4 is a key factor when considering the risks and benefits of amyloid-targeting therapies (ATTs) for the treatment of Alzheimer's disease (AD)[1]

ApoE ε4 Prevalence[1,2-4,a]

ApoE ε4 is a gene variant that may increase a person's risk for developing AD.
The worldwide frequency of the ApoE ε4 allele in the general population is 13.7%.

In patients with diagnosed or suspected AD

~44% are **ApoE ε4 heterozygotes** (carry 1 copy of ApoE ε4)

~15% are **ApoE ε4 homozygotes** (carry 2 copies of ApoE ε4)

ApoE ε4 and ARIA Risk With ATTs[3,4]

ARIA is
more common
in ApoE ε4 carriers vs noncarriers and also more common in ApoE ε4 homozygotes vs ApoE ε4 heterozygotes

ApoE ε4 homozygotes have a
higher incidence
of symptomatic and serious ARIA compared to heterozygotes and noncarriers

[a]Estimated prevalence according to a meta-analysis of patients with diagnosed or suspected AD. The ApoE ε4 allele is a genetic risk factor for AD, with disease prevalence varying by age, gender, and ancestry.[2,5]

ApoE ε4=apolipoprotein E type 4 allele; ARIA=amyloid-related imaging abnormalities.

Lilly

TRAILBLAZER-ALZ 2 TRIAL DESIGN[3,6]

ASSESSED IN 2 POPULATIONS[3,6]

Overall population (N=1736)

Low-medium tau population (N=1182)
Subset of overall population

TRAILBLAZER-ALZ 2 had dual primary analysis populations. The study was powered to test the results of Kisunla in the low-medium tau (low tau to medium tau=earlier neuropathology) population. It also allowed enrollment of high tau participants so Kisunla could be tested in the overall population (the low-medium tau population plus high tau participants).[3,6]*

ELIGIBILITY[3]

- Confirmed presence of amyloid pathology
- AD with MCI or mild dementia

PRIMARY ENDPOINT[3]

- Change in iADRS score from baseline to 76 weeks (impact on cognitive and functional decline)

TREATMENT PERIOD[3]

- 1:1 randomization to Kisunla (n=860) or placebo (n=876) treatment arms at week 0
- Treated until amyloid plaques reached a minimal level† (assessed with amyloid PET scans at 24, 52, and 76 weeks), discontinuation, or study completion (76 weeks)[6]

DOSING AND ADMINISTRATION[3]

- Administered via once-monthly (Q4W) IV infusion (for up to 72 weeks)
- Kisunla: Q4W 700 mg, increased to 1400 mg at fourth infusion
- Placebo: Q4W
- ARIA-monitoring MRI before infusions 1, 2, 3, 4, and 7

*There were 2 primary analysis populations based on tau PET imaging with flortaucipir: 1) low-medium tau level population (SUVR of ≥1.10 and ≤1.46), and 2) combined population of low-medium plus high tau (SUVR >1.46).[3]

†In the protocol, if the amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on 2 consecutive PET scans, the patient was eligible to be switched to placebo.[6]
For reference, <24.1 Centiloids on an amyloid PET scan is consistent with a negative visual read.[7]

iADRS=integrated Alzheimer's Disease Rating Scale; IV=intravenous; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; PET=positron emission tomography; SUVR=standardized uptake value ratio.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.

ApoE ε4 Homozygotes: Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes treated with this class of medications, including Kisunla, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.

Consider the benefit for the treatment of Alzheimer's disease and risk of ARIA when deciding to treat with Kisunla.

ARIA INCIDENCES AND ApoE ε4 CARRIER STATUS

ARIA Incidences From TRAILBLAZER-ALZ 2[3]

	Kisunla		Placebo	
	%	n/N	%	n/N
Any ARIA	36	307/853	14	122/874
ARIA-E	24	201/853	2	17/874
ARIA-H[a]	31	263/853	13	111/874
Intracerebral hemorrhage >1 cm	0.5	4/853	0.2	2/874

ARIA Incidences and ApoE ε4 Carrier Status[3]

ApoE ε4 status % Kisunla patients (no. of patients)	Noncarriers 30% (255/850)	Heterozygotes 53% (452/850)	Homozygotes 17% (143/850)
Incidence of ARIA	25% Kisunla vs 12% placebo	36% Kisunla vs 13% placebo	55% Kisunla vs 22% placebo
Incidence of Symptomatic ARIA-E	4% Kisunla	7% Kisunla	8% Kisunla

[a]ARIA-H most commonly manifests as microhemorrhage and/or superficial siderosis. There was no increase in isolated ARIA-H (ie, ARIA-H in patients who did not also experience ARIA-E) for Kisunla compared to placebo.[3]

ARIA=amyloid-related imaging abnormalities; ARIA-E=amyloid-related imaging abnormalities-edema; ARIA-H=amyloid-related imaging abnormalities-hemosiderin deposition.

INDICATION

Kisunla is indicated for the treatment of Alzheimer's disease (AD). Treatment with Kisunla should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.

SELECT IMPORTANT SAFETY INFORMATION

Risk Factors for ARIA and Intracerebral Hemorrhages (ICH)

- **Radiographic Findings of Cerebral Amyloid Angiopathy (CAA):** Neuroimaging findings that may indicate CAA include evidence of prior ICH, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for ICH. The presence of an ApoE ε4 allele is also associated with CAA.
- In Study 1, the baseline presence of at least 2 microhemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, were identified as risk factors for ARIA. Patients were excluded from enrollment for findings on neuroimaging of prior ICH >1 cm in diameter, >4 microhemorrhages, >1 area of superficial siderosis, severe white matter disease, and vasogenic edema.

Please see additional Important Safety Information and full Prescribing Information, including Boxed Warning regarding ARIA, and Medication Guide for Kisunla.

kisunla™ (donanemab-azbt) injection for IV infusion 350 mg/20 mL

TESTING FOR ApoE ε4 STATUS

- **Testing for ApoE ε4 status should be performed prior to initiation of treatment with amyloid-targeting therapies—like Kisunla—to inform the risk of developing ARIA[3,4]**
- **Prior to testing, prescribers should discuss with patients the risk of ARIA across ApoE genotypes and the implications of genetic testing results to patients and their loved ones[3,4]**
- **Prescribers should inform patients that if genotype testing is not performed, they can still be treated with Kisunla. Without testing, it cannot be determined if they are ApoE ε4 homozygotes and at a higher risk for ARIA[3,4]**

Talk to your patients about ApoE ε4 genetic testing when considering initiation of Kisunla

SELECT IMPORTANT SAFETY INFORMATION

- **Hypersensitivity: Kisunla is contraindicated** in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients. Reactions have included anaphylaxis.

Amyloid-Related Imaging Abnormalities (ARIA)

Kisunla can cause ARIA-E, which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H generally occurs with ARIA-E. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages (ICH) >1 cm in diameter have occurred in patients treated with Kisunla.

Please see additional Important Safety Information and full Prescribing Information, including Boxed Warning regarding ARIA, and Medication Guide for Kisunla.

kisunla™ (donanemab-azbt) injection for IV infusion 350 mg/20 mL

AVAILABLE ApoE ε4 BLOOD TESTS[8-13,a]

Company	Test Name	Contact Information	Order test
Genotype tests ApoE **genotype** tests can distinguish an individual's alleles—ε2, ε3, or ε4—and if they are homozygous, heterozygous, or non-carriers			
Labcorp	APOE	(336) 436-7089 cgservices@labcorp.com	Order test
Athena Diagnostics®	ADmark® ApoE Genotype Analysis and Interpretation (Symptomatic)	(800) 394-4493 genetics@athenadiagnostics.com	Order test
Mayo Clinical Labs	APOE Genotyping	(800) 533-1710 mcl@mayo.edu	Order test
Proteotype tests The APOE gene produces the ApoE4 protein, and some laboratory tests determine ApoE status by assessing the patient's **proteotype**. Please confirm with the testing lab or manufacturer the test capabilities to distinguish between homozygous, heterozygous, and noncarriers			
Quest Diagnostics®	Quest AD-Detect® Apolipoprotein E (ApoE) Isoform	(866) 697-8378	Order test
C_2N Diagnostics	Precivity-ApoE™	(877) 226-3424 info@c2n.com	Order test
C_2N Diagnostics	Precivity-AD™	(877) 226-3424 info@c2n.com	Order test
Randox Laboratories Ltd.	ApoE4	(866) 472-6369	Order test

There is currently no available FDA-approved test for detection of ApoE ε4 alleles to identify patients at risk of ARIA if treated with Kisunla. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design.

[a]Certain tests can provide information about the combination of ApoE alleles (eg, differentiate ApoE ε4 heterozygotes vs homozygotes). Please see the intended use for the test, or contact the laboratory to ensure your test can detect ApoE alleles.

This list is intended for informational purposes and your consideration only, and is based on publicly available information as of April 30, 2024, for these organizations. Eli Lilly and Company (Lilly) makes no representations regarding the clinical or analytical validity, manufacturing quality, or design of the testing offered by the vendors included on this list. Inclusion on this list does not represent an endorsement, referral, or recommendation by Lilly. Contact the vendor for more information.

IMPORTANT SAFETY INFORMATION FOR Kisunla™ (donanemab-azbt)

WARNING: AMYLOID-RELATED IMAGING ABNORMALITIES

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid-related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.

ApoE ε4 Homozygotes: Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including Kisunla, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with Kisunla; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of Kisunla for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with Kisunla.

Kisunla is **contraindicated** in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients. Reactions have included anaphylaxis.

Amyloid-Related Imaging Abnormalities (ARIA)

Kisunla can cause ARIA-E, which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and ARIA-H, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease (AD), particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H generally occurs with ARIA-E.

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages (ICH) >1 cm in diameter have occurred in patients treated with Kisunla.

Incidence of ARIA

Symptomatic ARIA occurred in 6% (52/853) of patients treated with Kisunla. Clinical symptoms associated with ARIA resolved in approximately 85% (44/52) of patients.

Including asymptomatic radiographic events, ARIA was observed with Kisunla: 36% (307/853); placebo: 14% (122/874). ARIA-E was observed with Kisunla: 24% (201/853); placebo: 2% (17/874). ARIA-H was observed with Kisunla: 31% (263/853); placebo: 13% (111/874). There was no increase in isolated ARIA-H for Kisunla vs placebo.

Incidence of ICH

ICH >1 cm in diameter was reported in 0.5% (4/853) of patients after treatment with Kisunla vs 0.2% (2/874) on placebo. Fatal events of ICH have been observed.

Risk Factors for ARIA and ICH

ApoE ε4 Carrier Status

The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. 17% (143/850) of patients in the Kisunla arm were ApoE ε4 homozygotes, 53% (452/850) were heterozygotes, and 30% (255/850) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes (Kisunla: 55%; placebo: 22%) than in heterozygotes (Kisunla: 36%; placebo: 13%) and noncarriers (Kisunla: 25%; placebo: 12%). Among patients treated with Kisunla, symptomatic ARIA-E occurred in 8% of ApoE ε4 homozygotes compared with 7% of heterozygotes and 4% of noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, 2% of heterozygotes, and 1% of noncarriers.

The recommendations for management of ARIA do not differ between ApoE ε4 carriers and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. An FDA-authorized test for detection of ApoE ε4 alleles is not currently available. Currently available tests may vary in accuracy and design.

Radiographic Findings of Cerebral Amyloid Angiopathy (CAA)

Neuroimaging findings that may indicate CAA include evidence of prior ICH, cerebral microhemorrhage, and cortical superficial siderosis. CAA has an increased risk for ICH. The presence of an ApoE ε4 allele is also associated with CAA.

The baseline presence of at least 2 microhemorrhages or the presence of at least 1 area of superficial siderosis on MRI, which may be suggestive of CAA, were identified as risk factors for ARIA. Patients were excluded from enrollment in Study 1 for findings on neuroimaging of prior ICH >1 cm in diameter, >4 microhemorrhages, >1 area of superficial siderosis, severe white matter disease, and vasogenic edema.

Concomitant Antithrombotic or Thrombolytic Medication

In Study 1, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed. The majority of exposures to antithrombotic medications were to aspirin. The incidence of ARIA-H was 30% (106/349) in patients taking Kisunla with a concomitant antithrombotic medication within 30 days vs 29% (148/504) in patients who did not receive an antithrombotic within 30 days of an ARIA-H event. The incidence of ICH >1 cm in diameter was 0.6% (2/349) in patients taking Kisunla with a concomitant antithrombotic medication vs 0.4% (2/504) in those who did not receive an antithrombotic. The number of events and the limited exposure to non-aspirin antithrombotic medications limit definitive conclusions about the risk of ARIA or ICH in patients taking antithrombotic medications.

One fatal ICH occurred in a patient taking Kisunla in the setting of focal neurologic symptoms of ARIA and the use of a thrombolytic agent. Additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (eg, tissue plasminogen activator) to a patient already being treated with Kisunla.

Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla. Advise patients to carry information that they are being treated with Kisunla.

Caution should be exercised when considering the use of Kisunla in patients with factors that indicate an increased risk for ICH and in particular for patients who need to be on anticoagulant therapy or patients with findings on MRI that are suggestive of CAA.

Radiographic Severity

The majority of ARIA-E radiographic events occurred early in treatment (within the first 24 weeks), although ARIA can occur at any time and patients can have more than one episode. The maximum radiographic severity of ARIA-E in patients treated with Kisunla was mild in 7% (59/853), moderate in 15% (128/853), and severe in 2% (14/853). Resolution on MRI after the first ARIA-E event occurred in 63% of patients treated with Kisunla by 12 weeks, 80% by 20 weeks, and 83% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with Kisunla was mild in 17% (143/853), moderate in 4% (34/853), and severe in 5% (40/853). The maximum radiographic severity of ARIA-H superficial siderosis in patients treated with Kisunla was mild in 6% (47/853), moderate in 4% (32/853), and severe in 5% (46/853). Among patients treated with Kisunla, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 3% (4/143) vs heterozygotes 2% (9/452) or noncarriers 0.4% (1/255). The rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 22% (31/143) vs heterozygotes 8% (38/452) or noncarriers 4% (9/255).

Monitoring and Dose Management Guidelines

Baseline brain MRI and periodic monitoring with MRI are recommended. Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with Kisunla. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.

Recommendations for dosing in patients with ARIA-E and ARIA-H depend on clinical symptoms and radiographic severity. Depending on ARIA severity, use clinical judgment in considering whether to continue dosing, interrupt treatment, or permanently discontinue Kisunla. See Prescribing Information for additional dosing considerations.

There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data for dosing patients who experienced recurrent episodes of ARIA-E.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients who were treated with Kisunla. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy.

Infusion-Related Reactions (IRR)

IRRs were observed with Kisunla: 9% (74/853); placebo: 0.5% (4/874); the majority (70%, 52/74) occurred within the first 4 infusions. IRRs typically occur during infusion or within 30 minutes post-infusion. IRRs were mostly mild (57%) or moderate (39%) in severity. IRRs resulted in discontinuations in 4% (31/853). Signs and symptoms of IRRs include chills, erythema, nausea/vomiting, difficulty breathing/dyspnea, sweating, elevated blood pressure, headache, chest pain, and low blood pressure.

In the event of an IRR, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Pretreatment with antihistamines, acetaminophen, or corticosteroids prior to subsequent dosing may be considered.

Adverse Reactions: The most common adverse reactions reported in ≥5% of patients treated with Kisunla (n=853) and ≥2% higher than placebo (n=874): ARIA-H microhemorrhage (25% vs 11%), ARIA-E (24% vs 2%), ARIA-H superficial siderosis (15% vs 3%), headache (13% vs 10%), IRRs (9% vs 0.5%).

Please see full Prescribing Information, including Boxed Warning regarding ARIA, and Medication Guide for Kisunla.

DN HCP ISI APP

kisunla™ (donanemab-azbt) injection for IV infusion 350 mg/20 mL

ARIA MANAGEMENT WITH KISUNLA

DOSING RECOMMENDATIONS FOR PATIENTS WITH ARIA-E[3]

Clinical Symptom Severity[a]	ARIA-E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[b]	Suspend dosing[b]
Mild	May continue dosing based on clinical judgment	Suspend dosing[b]	
Moderate or Severe	Suspend dosing[b]		

[a]Mild: discomfort noticed, but no disruption of normal daily activity; Moderate: discomfort sufficient to reduce or affect normal daily activity; Severe: incapacitating, with inability to work or to perform normal daily activity.[3]
[b]Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.[3]

DOSING RECOMMENDATIONS FOR PATIENTS WITH ARIA-H[3]

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing at current dose and schedule	Suspend dosing[a]	Suspend dosing[b]
Symptomatic	Suspend dosing[a]		

[a]Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.[3]
[b]Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment when considering whether to continue treatment or permanently discontinue Kisunla.[3]

In patients who develop intracerebral hemorrhage >1 cm in diameter during treatment with Kisunla, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Resumption of dosing should be guided by clinical judgment.[3]

Please see additional Important Safety Information and full Prescribing Information, including Boxed Warning regarding ARIA, and Medication Guide for Kisunla.

References: 1. Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-3821. **2.** Farrer LA, Cupples LA, Haines JL, et al; for APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *JAMA*. 1997;278(16):1349-1356. **3.** Kisunla (donanemab-azbt). Prescribing Information. Lilly USA, LLC. **4.** Leqembi (lecanemab-irmb). Prescribing Information. Eisai R&D Management Co., Ltd. **5.** Emrani S, Arain HA, DeMarshall C, et al. APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. *Alzheimers Res Ther*. 2020;12(1):141. doi:10.1186/s13195-020-00712-4 **6.** Sims JR, Zimmer JA, Evans CD, et al; for TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-527. **7.** Navitsky M, Joshi AD, Kennedy I, et al. Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale. *Alzheimers Dement*. 2018;14(12):1565-1571. **8.** Labcorp. *APOE* Alzheimer's disease risk. Accessed August 29, 2024. https://www.labcorp.com/tests/125536/i-apoe-i-alzheimer-s-disease-risk **9.** Quest Diagnostics™. Quest AD-Detect® Apolipoprotein E (ApoE) Isoform, Plasma. Accessed May 23, 2024. https://testdirectory.questdiagnostics.com/test/test-detail/12563/quest-ad-detect-apolipoprotein-e-apoe-isoform-plasma?q=12563&cc=MASTER **10.** Athena Diagnostics®. ADmark® ApoE genotype analysis and interpretation (symptomatic). Accessed May 23, 2024. https://www.athenadiagnostics.com/view-full-catalog/admark-apoe-genotype-analysis-and-interpretation-symptomatic1 **11.** Mayo Clinic Laboratories. Apolipoprotein E genotyping, blood. Accessed May 23, 2024. https://www.mayocliniclabs.com/test-catalog/overview/35358 **12.** Precivity™ By C_2N Diagnostics. ApoE – Genetic Testing. Accessed May 23, 2024. https://precivityad.com/apoe-genetic-testing-healthcare-providers **13.** Randox. Randox ApoE4 Array (EV4113). Accessed May 23, 2024. https://www.randox.com/alzheimers-disease array/

kisunla™ (donanemab-azbt) injection for IV infusion 350 mg/20 mL