Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

donanemab (TBC)

(Eli Lilly Canada Inc.)

Indication: Donanemab is indicated for the treatment of Alzheimer's disease. Treatment with donanemab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease. In controlled clinical trials, donanemab was found to slow the decline in cognition and function in a clinically meaningful manner and demonstrated significant amyloid plaque removal.

August 12, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Donanemab
Indication: To slow the clinical decline associated with Alzheimer's disease (AD) progression in patients with early AD or mild cognitive impairment (MCI) due to AD
Name of Patient Group: Alzheimer Society of Canada
Author of Submission: Luca Pisterzi

1. About Your Patient Group

The Alzheimer Society of Canada is the leading nationwide health charity supporting people living with all forms of dementia, including Alzheimer's disease, as well as their caregivers and their families. We work to identify, develop and facilitate national priorities that enable our members to effectively alleviate the personal and social consequences of Alzheimer's disease and other dementias.

Active in communities across Canada, the Society offers information, programs and support services, fundraises to advance research, advocates for policy change and increases public awareness of Alzheimer's disease and other dementias.

We rely on individual and corporate donors, communities and health-care partners to help us deliver on our mission. Additionally, we do not receive donations from pharmaceutical companies.

The Research, Knowledge Translation and Exchange, Partnerships and Programs department at the Alzheimer Society of Canada contains staff with expertise from many different perspectives. Our staff bring with them extensive experience in dementia research, aging and health care, data analysis and evaluation, project management, care coordination, and knowledge translation and exchange practices.

We are proud of the co-design approach we take in creating materials, programs and throughout all research processes. This is done through our robust and active National Advisory Group consisting of over 70 members. The Advisory Group of People with Lived Experience of Dementia is the heart of the Alzheimer Society of Canada. Our members make a significant impact on our work, including dementia research, education and advocacy.

alzheimer.ca/en | alzheimer.ca/fr

2. Information Gathering

Online surveys were conducted between May 24th, 2024 - June 10th and June 24th - July 31st, 2024. Two different surveys were developed and conducted: one for patients and one for caregivers. Surveys were conducted in English and French. Patients and caregivers were asked questions about the impact of Alzheimer's disease or Mild Cognitive Impairment (MCI) on the lives of patients and the effect of current treatments as well as questions directed to people with donanemab experience.

Additionally, staff at the Alzheimer Society of Canada provided their professional expertise within this submission. This included providing relevant research to consider as well as experiences gathered through working with people living with dementia and their caregivers.

A multimedia strategy was launched between May 2024 – July 2024 that utilized the Alzheimer Society of Canada website, social media channels, mailing lists, provincial and local newsletters, researcher and clinical networks, and broader partner organizations. A targeted approach was taken in reaching out to all clinical/sites that participated in donanemab trials (publicly available data) in Canada to share information about the survey with their patients and caregivers.

Overall, 283 people completed the surveys. A total of 63 people completed the patient survey. 60 English respondents who responded to the patient survey consented for their data to be used. 2 English respondents live in Quebec and therefore were referred to INESSS to submit a response. 1 French respondent lives in Quebec, and therefore were referred to INESSS to submit a response.

A total of 220 people completed the caregiver survey. 206 English respondents who responded to the caregiver survey consented for their data to be used. 6 English respondents live in Quebec and therefore were referred to INESSS to submit a response. 7 French respondents live in Quebec, and therefore were referred to INESSS to submit a response. All respondents except for three are from Canada (representing Alberta, British Columbia, New Brunswick, Nova Scotia, Ontario, Saskatchewan, Manitoba, Newfoundland and Labrador and Prince Edward Island). The other three respondents live in the United States, Austria and Australia.

Patients		Caregivers	
English	French	English	French
60	1	206	7

A total of 9 people completed the survey specific to donanemab treatment: 4 patients and 5 caregivers; 9 in English and 0 in French. The respondents live in Ontario.

Patients		Caregivers	
English	French	English	French
4	0	5	0

3. Disease Experience

Patients

- 23 have MCI
- 21 have early-stage Alzheimer's disease
- 6 have middle-stage Alzheimer's disease
- 0 have late-stage Alzheimer's disease
- 6 do not know
- 1 preferred not to answer

Memory loss was the most commonly reported symptom of Alzheimer's disease or MCI by patients (90% n=54), followed by anxiety (60% n=36), becoming withdrawn (50% n=30) and depression (45% n=27).

Caregivers

- 43 people they cared for had MCI
- 61 people they cared for had early-stage Alzheimer's disease
- 56 have middle-stage Alzheimer's disease
- 19 people they cared for had late-stage Alzheimer's disease

- 25 do not know
- 0 preferred not to answer

For caregivers, memory loss was the most reported symptom observed in the person they are supporting (96% n=198), followed by changes in behaviour (64% n=131), anxiety (63% n=129), disorientation/getting lost (56% n=115), becoming withdrawn, (48% n=99) and personality changes (48% n=99).

If the person with Alzheimer's disease or MCI progressed from MCI to Alzheimer's disease, for a small number of patients and caregivers this did not change the health and social care services that patients and caregivers accessed. However, for the majority of patients and caregivers it did change the health and social care services that they accessed.

Accessing programs and services

Patients reported there was a lack of services offered in their region or had difficulty finding them or reported receiving respite services or attending day programs.

- Have been referred to a neurologist who specializes in the disease. I am not accessing social care services at this time.
- There are not any services for early onset in my province.
- Have caregiver support. Attend day program and Alzheimer's groups. Have excellent care from geriatrician and memory clinic.

Caregivers reported an increase in the home care or respite services accessed, such as having assistance from personal support workers. Many reported not having enough support. Some caregivers also reported that the person they cared for had moved into long-term care.

- Required admission into a long-term care facility for 24/7 care quite early on due to symptom progression and perceived lack of community supports.
- Additional services required, including Continuing Care services, Personal Support Workers, meal preparation services, therapists; Alzheimer Society support groups.
- Our doctor is much more involved with the progression of the disease. We need help to provide self-care on a regular basis. We also need help getting some respite once in a while.
- Just getting an answer as to where he is on the spectrum of cognitive illness is very difficult. Getting access to any kind of support is challenging. The message we hear most often is, I wish we could do more. Goodbye.

Impact of progression of condition/disease on the person with MCI or Alzheimer's disease

- It's been awful for me and my family. I have four children, four granddaughters and another on the way. My thought processes are slow. I want to be able to play games with them and I get confused when trying to play.
- It has impacted me with my friends and family. As well, I have trouble in groups, meeting new people, or simply just trying to remember everything.
- Memory lapses and remember names, places and things.
- I gave up my driver's licence and sold my car.
- I forget more and more. And I feel it. As if part of my brain is blank.
- Minimal difference in symptoms.
- I am only 57 so the progression is scary
- Difficulty in doing everyday chores
- Memory has gotten worse - I have lost my drivers license.
- I get very confused most of the time.
- Can no longer read, write and speak with trouble.

- I remember the past in detail, but not very recent happenings. This annoys my wife and friends. I have difficulty remembering friends names.
- Significantly. Total short term memory loss. Cannot stay alone.
- I find myself incapable of doing many tasks that were easy for me to do.
- Mostly with communication. I no longer can remember lots of common words and items. My vocabulary is much smaller. I have trouble following shows on TV, and I frequently do not understand conversations. I find this depressing. So far my ability to care for myself has not been affected to a great extent, except that I am unable to plan meals on my own.
- Devestating

Changes to caregiving role due to symptom progression of the person supported

- Caregivers (35% n=72) increased the overall amount of care they provide.
    - Caregivers (28% n=57) increased the assistance they provide with instrumental activities of daily living (such as: shopping, cooking, cleaning, transportation, finances, decision making and medications).
    - Caregivers (10% n=21) are unable to leave the person they support at home alone.
    - Caregivers (6% n=13) are experiencing caregiver burnout.
    - Caregivers (4% n=7) increased the amount assistance they provide with activities of daily living (such as: eating, personal hygiene, grooming, dressing, bathing, toileting, transferring etc.).
    - Caregivers (2% n=4) needed to quit their jobs or move to part-time work to provide care.
    - Caregivers (1% n=3) also provide care to others such as children.
    - Caregivers (0.97% n=2) have given up their social life.

General information about the disease experience

Alzheimer's disease is a chronic neurodegenerative disease that eventually affects all aspects of a person's life. Due to the progressive nature of most dementias, people with dementia who live at home will eventually need increasing levels of medical and social support (to the point where the person needs 24-hour care), which may ultimately present challenges to their family and friends who act as caregivers. Canadian statistics (CIHI, 2018b) have shown that for people living with dementia:

- 1 in 4 require a lot of help for activities of daily living (e.g., eating, dressing, personal hygiene)
- 1 in 4 experience behavioural changes (e.g., anger, delusions, getting lost, restlessness, hallucinations, paranoia)
- 1 in 4 have symptoms of depression
- 1 in 4 were admitted to hospital at least once in the last three months
- 1 in 5 have been to an emergency room in the last three months

According to Nimmons et al. (2023), dementia leads to multiple issues, including difficulty in communication and increased need for care and support. Additionally, their study suggests that discussions about advance care planning often happen late in the process, or not at all. It is suggested that this may be due to reluctance, fear or stigma. Maintaining the person's identity and social connections, as well as living well with dementia, may help health-care providers have advance care planning conversations with patients.

There are many different challenges that caregivers for people with dementia experience. Here are some examples from the Canadian Institute for Health Information (2018b):

- 26 mean hours a week of informal care are provided to seniors with dementia, compared to other seniors.

- Unpaid caregivers of seniors with dementia are more likely to experience distress (45%) than caregivers of other seniors (26%). Some drivers of distress among caregivers are higher cognitive impairment, mood and behavioural symptoms of people receiving care (e.g., moderate to severe cognitive impairment, depression, anger/confusion, delusions, wandering and responsive behaviours) that occurred at least once in the last 3 days.
- $1.4 billion was the estimated total out-of-pocket costs paid for by caregivers of people with dementia in Canada in 2016.
- Financial challenges for caregivers of people with dementia consist of but are not limited to: home modifications, professional health care or rehabilitation services, hiring people to help with daily activities, transportation, specialized aids and/or prescription or non-prescription drugs. Depending on stage of life, caregivers may have to leave work to care for the person with Alzheimer's disease or MCI. This impacts their financial stability and ability to participate fully in life.

The goal of treating Alzheimer's disease is to manage and alleviate the symptoms and increase quality of life/wellbeing for both the person living with dementia and caregivers. However, some symptoms of Alzheimer's disease may be more important to manage than others, if they put the person or others around them at harm. For example, the person with dementia demonstrating physical aggression or irritability may put caregivers at harm, which could lead to physical or emotional abuse. Additionally, if a person living with Alzheimer's disease frequently leaves secure areas, like the home, and becomes lost, this is both a risk to the person with dementia as well as others around them. Another term for this is called "wandering," and research suggests that this occurs in approximately 15 to 60% of people living with dementia (Cipriani, Lucetti, Nuti & Danti, 2014). Search and rescue missions can be costly for governments and emotionally distressing for family and friends.

General comments from patients about the disease experience:

- It is a terrible disease that takes away a large part of you.
- I hate the very thought of having this disease which my Mom had my twin brother has now and oldest sister
- Frustration in not having the ability to cope as I used to. Planning things is more difficult.
- My experience with MCI has convinced me that any medication that would reduce the amyloid beta plaques in my brain is well worth any risk.
- I feel that when I received this diagnosis that I was punched! I was shocked and frightened. Even though I knew something was wrong, I still never expected to hear I had Alzheimer's at age 67. Like many other diseases, this diagnosis is heartbreaking. When told to "get your affairs in order", it makes you think life is almost over.
- It is concerning to me for sure. I am only 67 years old.
- Access to Geriatric Specialists has been a major problem. In order to receive early diagnosis we need to have the right health care. Our family doctor is very supportive.

General comments from caregivers about the disease experience:

- Memory is awful. Gets angry if anyone disagrees with him or if he believes that they are wrong.
- Very difficult with the memory loss and confabulation that the person experiences. Trust between the person and others has been eroded due to this making it even more difficult to care for them.
- Comments from doctors telling us that they do not even know if the drug she is taking is doing any good.
- Maintaining a schedule & making life as simple as possible for the person seems to keep he/she calm & stress free.
- Progression of the disease has been steady.
- I always keep in my mind, she did not ask for this. This is a terrible disease that takes away your memories, then your dignity. I will do whatever I can to help her through this journey.
- This disease is not only horrific for the individual but is difficult for the whole family.
- After years of caregiving, I grudge not getting on with my own life and projects.
- It has been a very slow process of loss of mental capability over the past 10 years and it is heart breaking to see my intelligent capable partner slowly lose his sense of mastery (the only word that encompasses the scope of his losses.
- Would love to see more research and hoping for a cure for alzheimers of course. Late for us now but for others.
- Her disease has evolved very gradually and it is difficult to see how much she regresses each day or month. So far, except for memory loss which seems to be getting worse, we are both coping very well.
- My father has always been a very active person. At this point, he doesn't want to go anywhere that there are people as he doesn't think he'll remember them. My mother still wants to be an active person, they used to travel frequently and meet

with friends. at this point, my parents are not travelling as my mother can't care for my father on her own. As a daughter is very sad to watch what is happening to my father.
- This is not a journey I would wish for anyone. Life has become very difficult and the future is bleak.
- I found it has impacted my life by not being able to do the things i once done such as walking every day. I have to do all the work at home which I just had to do a part of before. It has cut down on my ability to be able to relax even when I am gone for a short period. I am worried about leaving her alone for long periods of time.
- I wish there were more resources available that specialize in dementia care.
- I would like to help my father gain some independence again.
- I am overwhelmed and burned out. I retired to take care of my mother and am now losing both myself and my mother.
- I was lucky. I could afford to pay for the services he needed. But it was still exhausting.
- Just been real hard and if there is something that can help it would be greatly appreciated.
- My dad chose to participate in clinical trials for years when he had MCI and mild AD as he hoped it would help others and it gave him a way to make meaning from his experiences and contribute to something hopeful. I'm so proud of how he faced such a daunting prognosis. His involvement in research also provided him and his family/ caregivers with support in monitoring and understanding his symptoms and disease progression, which was a great comfort. Finally, he was accepted into a medication trial that could improve his symptoms and the hope we felt was indescribable. Unfortunately his disease had progressed too fast and his symptom severity disqualified him from the trial. But, that doesn't discount the value that hope for some improvement or disease progression delay held for all of us.
- Although there are lots of services available, I am at a loss as to how to best use those services. An example would be bathing- always a difficult task to accomplish but if I have someone come in to help with this I feel it would be a dignity issue for the patient. Most difficult times are trying to undress for bed, dressing in the morning and showering.
- It's frustrating when I ask about medications to help slow the progression of symptoms & mom's memory dr (who is also her family practitioner) says "nope, there's nothing"... she tells us the only meds out there have serious side effects & are for people who are much worse/slide from mildCI to dementia
- Her biggest problem is communicating orally, cannot find words, helpless feeling when trying to communicate
- It has been a confusing and largely unsupported experience.
- Support through the cognitive memory clinic, where we are involved in a clinical drug trial, and more recently the Alzheimer's Society, has been invaluable for me as caregiver
- My mom is still highly functional, cleans and cooks, and self hygiene. As a result we don't qualify for help. I need guidance , how to approach all of this. Direct her on here course. Took 2 yr to get the assessment. And now at least 9months for an assessment to confirm dementia. In the mean time no more specialize doctor visits Just counselling and home visit. Seems very limited resources and help. Everyone's hands tied.
- Each day gets more difficult.
- Very tiring
- The diagnosis was not directly communicated with the person with dementia, which has created a lot of confusion and anxiety as to why medications are being prescribed (and the need for a driving evaluation). This in turn has put a tremendous amount of stress on the family - creating a lot of caregiver burden for the primary caregiver.
- My person's presentation is extremely fast progression coupled with Primary Progressive Aphasia. She has lost almost all basic functions for self care in three years. I would wish to prolong this for anyone. It's absolute hell for both of us.
- It is very challenging to work, have a young family and care for an older adults living with dementia, I do not know how to help families in our position, but we were very lucky that our circumstances allowed us to be as successful as we were.
- This is the most difficult disease to deal with. Your spouse becomes a monster and you cannot get away until they qualify for a Nursing home. No wonder the incidence of dementia increases in caregivers
- My husband was also on respiridone for anxiety, they DR in long term care also removed that, shortly after removing galantimine.the Dr put him on olanzapine- to me this was the drug that progressed his disease in a very negative way. Behaviours issues, and total loss of any comprehension. He died 4 months after going on this drug, 9 months after going into LTC.
- Heart wrenching disease that effects the quality of life for both the person suffering from dementia and the care givers
- Overwhelming responsibility caring for Alzheimer patient. Need more supports for caregivers.
- This is a horrific disease and takes a huge toll (mentally & physically) on all involved in getting care assistance for your loved one. For those with Alzheimer's everyday is a new struggle and the suffering is inhumane, & not well managed by the healthcare system
- It is so hard to get help.
- It's the pits.
- This is a sad depressing disease. There is uncertainty everyday. You have no time line as everyone is different. As a careperson you are on 24/7, eventually it becomes very emotional and physically challenging.
- Caregivers need caregivers. The services offered by the CCAC/LINH/HCCSS are completely insufficient. don't give us the advice that we caregivers need to take care of ourselves. get public money so we have time to do that.

- Her condition is progressing slowly.
- My father is getting great medical care which is enabling him to stay in their home with my mother, who unfortunately is now showing signs of cognitive impairment herself. On the negative side, it is sometimes frustrating, depressing, sad and exhausting for the caregiver. If I am diagnosed, I would want MAID immediately to not put my family through this. My husband has been in long term care for 5 years with dementia, other than financing the home, there is no purpose to his life.
- One of the hardest things has been withdrawal from our lives of friends.
- My personal experience is that Long Term Care Homes choose to overmedicate people because they don't have the knowledge to help work with patients with Dementia or Alzheimers.
- Getting a diagnosis is very frustrating. We can't seem to get testing as the system is overwhelmed. He had a diagnosis of mbi over a year ago and then a couple of visits from a nurse but the last visit was 7 months ago and there have been changes. No one will listen.
- Supports are lacking! Tax credits are a joke, disability is a joke. Home care is based on their availability not the timing of our needs. PEI needs an equivalency of Behavioral Supports Ontario program. The nursing homes in this province greatly lack the education and knowledge to provide best practice care for dementia residents. When we utilize respite care the interventions we use at home are not enacted during respite.
- It is difficult to see my wife struggle to be herself and for me to watch it. I would like to be able to her her more.
- Caregiving for my dad and I is very exhausting
- It is very challenging and I am a nurse. The care is very intimate at times. Not everyone can cope with this.
- Sunset effect occurs fairly regularly, sometimes there are emotional downs for both of us, degree of short term memory loss varies day to day hour to hour
- Alzheimer's sucks. It's a horrible disease. Not only for the individual but their family. Everyday I see more and more progression.
- More things should be taken into consideration ie with the moca test not everyone has the ability to draw, math is not always a good test.

4. Experiences With Currently Available Treatments

- 260 respondents provided information about the treatments that they or the person for whom they are caring has received since their diagnosis.

- 21 different drugs were discussed by respondents.

Treatments Received	n
Aducanamab	1
Aricept (donepezil)	140
Atorvaststatin	1
Citalopram	3
Estradiol	1
Exelon (rivastigmine)	17
Souvenaid supplements	1
Fluoxetine	1
Lion's mane	1
Listrinopril	1
Lorazepam	1
Melatonin	2
Mirtazapine	2
Olanzapine	1
Paroxetine	1

Quetiapine/ Seroquel	3
Razadyne or Reminyl (galantamine)	26
Risperidone	3
Trazadone	1
Sertraline	7
SSRI	1
I don't know	16
Prefer not to answer	3

Patient and caregiver comments about the benefits of currently available treatments were split between people who reported positive benefits and those who reported no improvements. Current treatments do not consistently meet the medical needs of all individuals.

For example, some medications were reported to slow memory loss, but the person with dementia still inevitably worsened/will worsen over time. Additionally, many people reported that they do not know if the treatments are helping due to the progressive nature of the disease.

The following are some positive experiences with some the above treatments:

Aricept

- It's help me with the stress and second guessing everything.
- Since my taking medications I have a relatively the progress it seem.
- I am thinking more clearly and am less anxious.
- The drug removed the majority of the forgetfulness. I am on a half dose as the full dose resulted in significant side effects.
- I think it has helped with my memory.
- Has helped me feel slightly more clear and improved fine motor skills.
- I seem to be able to think more clearly and have not observed any worsening of my symptoms.
- Delayed progression of symptoms. Improved scores on testing.
- When first prescribed saw amazing improvement…not so much now.
- I scored slightly better one year after starting.
- Better memory.
- Hasn't seemed to be progressing.
- Feel better after about an hour.

- Much less anxiety and depression. I've become more active now that I'm taking the pill, but not as much as I used to be.
- I don't know how much more progressed my mom would be without it. We'll never know if it's truly helped or not.
- My husband went on this medication almost a year ago and it did make a difference at first but I can't say that it is as effective as it once was at this point.
- Not sure whether there is a stabilizing effect but there may be some improvement in memory
- I think it may have helped slightly with the decline. My mother is aware she is more forgetful and says she feels she is retaining more since starting on the pills 7 months ago.
- When started taking it noticed a increase in memory remembering things a bit more clearly.
- I've noticed that she is more aware since she started.
- Seemed to help some, when she could be persuaded to take the medicine while still at home - paranoia and irritability often caused her not to take the medicine. For the 16 months before she went into hospital, she could not be persuaded to take the meds at all.
- Condition seems stable.
- Dramatically improved ability to focus and memory. It also had a calming effect, reducing incidences of paranoia and delusions.
- Seems to have improved his mood and motivation.
- There seems to have been less symptom progression since she has been taken it.
- Her medication seems to have slowed the onset of the disease, but I do not know for sure because I have nothing to measure it by.
- This medication has been amazing for my husband.
- I feel it has helped her in slowing down the progression.
- Seems to have slowed progression of the condition.
- May have helped slow the progression, it's hard to know, but it gave us a sense of doing everything we could to improve the situation knowing we were facing a devastating.
- Seemed to help with focus in the early stages, more "with-it".
- Calms aggression.
- When initially prescribed, person seemed more alert.
- Appeared to help with his memory, ability to set the table, play some card games. You don't know till you stop taking it, if it is helping.
- He is still capable to attend to most of his personal hygiene.
- Positive effect early on when first started. Helped with confusion. As AD has progressed not sure if it is helping or not.
- Helped with delusions, paranoia, depression.
- Some improvement to mood
- Apparently slowed the disease.

- Help settled to concentrate and remember a bit more.
- Anxiety seem to be under control until late in the day.
- My husband started immediately and we did notice a considerable improvement early on. Also, we see his neurologist every six months, and he has remained fairly steady in the Alzheimers progress and his Dr. is pleased with that. We don't know how much to attribute to Aricept.

Citalopram

- Helped somewhat with anxiety.
- Sleeps better and less depressed.
- Eased delusional behaviour.

Exelon (rivastigmine)

- Helps somewhat in household duties.
- Mental acuity improvements using transdermal patch. Oral not as effective.
- Improved mood and sociability.
- Seems to slow down the disease.
- Seemed to stabilize function/memory for more than a year.
- Seems that rivastigmine has stabilized their condition — meaning there is more calmness and less confusion overall than without the medication.

Galantamine

- Slowing the dementia.
- Improved ability to be able to read books and remember plots and themes of the books.
- Sleeps better.
- Seems to have slowed the progression.
- Galantimine seemed to help for a # of years.
- Slowed the process for about three years.
- Feels more relaxed.

Memantine

- Stabilization.
- Slowed down the progression of cognitive decline.
- Perhaps an improvement in the MOCA test.
- He can still drive in our small town, takes care of his personal needs, dressing, toileting, has a good attitude and is happy.
- Slight improvement in restlessness as she appeared more relaxed.
- The beginning it was doing its job however at this stage. What see no positives.

Quetiapine/Seroquel

- This really helps with anxiety, and since adding one dose of long acting, he has been much more stable.
- Quetiapine can settle the individual for a period of time.

Sertraline

- Meds brought BP into normal range and anti-anxiety has helped being more engaged with life.

Patients reported the following negative experiences with the above treatments:

- Dizziness (16.7% n=10)
- Nausea/Vomiting (10% n=6)
- Confusion (8.3% n=5)
- Flu-like symptoms (8.3% n=5)
- Allergic reactions (rash, swelling, difficulty breathing) (5% n=3)
- Vision changes (5% n=3)
- Bleeding in the brain (1.7% n=1)
- Cough (1.7% n=1)
- Difficulty walking (1.7% n=1)
- Seizures (0%, n=0)
- Changes in heart rate/chest is pounding (1.7% n=1)
- No negative side effects (36.7% n=22)
- I don't know (5% n=3)
- Prefer not to answer (3.3% n=2)
- Other
    - Leg cramps
    - Migraine
    - More bowel movements than usual
    - Diarrhea, stomach aches
    - Insomnia
    - Lethargy, extremely tired; listless
    - Head is cloudy and heavy
    - Vertigo
    - Strange dreams

Patients found the following side effects most difficult to tolerate:

- Dizziness (15% n=9)
- Confusion (8.3% n=5)
- Nausea/Vomiting (6.7% n=4)

- Flu-like symptoms (5% n=3)
- Vision changes (5% n=3)
- Difficulty walking (5% n=3)
- Allergic reactions (rash, swelling, difficulty breathing) (3.3% n=2)
- Changes in heart rate/chest pounding (3.3% n=2)
- Bleeding in the brain (0% n=0)
- Cough (0% n=0)
- Seizures (0% n=0)
- No negative side effects (8.3% n=5)
- I don't know (5% n=3)
- Prefer not to answer (1.7% n=1)
- Other (please specify)
    - Leg cramps
    - Migraine
    - Tired
    - Insomnia
    - Balance
    - Digestive issues
    - All of them

Caregivers described some negative experiences they observed as the person with Alzheimer's disease or MCI received the treatments above:

- Dizziness (8.3%% n=17)
- Nausea/Vomiting (6.8% n=14)
- Confusion (5.8% n=12)
- Difficulty walking (4.4% n=9)
- Cough (3.4% n=7)
- Changes in heart rate/chest pounding (2.4% n=5)
- Vision changes (1.9% n=4)
- Allergic reactions (rash, swelling, difficulty breathing) (0.97**%** n=2)
- Flu-like symptoms (0.97**%** n=2)
- Bleeding in the brain (0.49% n=1)
- Seizures (0.49% n=1)
- No negative side effects (34% n=70)
- I don't know (15% n=31)
- Prefer not to answer (1.5% n=3)

- Other (please specify)
    - Fatigue
    - Agitation
    - Anxiety
    - Insomnia / sleep disturbances
    - Facial swelling
    - Increase urination
    - Headaches
    - Diarrhea
    - Fainting spells
    - Leg muscle cramps
    - Nausea
    - Lethargic
    - Depressed
    - Heart rate under 48
    - Coughing (but not sure if it was from the medication)
    - Digestive
    - Speech
    - Mobility
    - Sleepiness
    - Left branch bundle block during donepezil use
    - Overstimulated which caused anxiety and agitation
    - Keeps going to the washroom multiple times an hour
    - Confusion
    - Forgetfulness
    - Dizzy
    - Put person on edge, difficulty relaxing
    - Lack of motivation
    - No energy
    - Violent behaviour, aggression

Caregivers reported that for the person they supported, the medication side effects found most difficult to manage included:

- Nausea/Vomiting (6.8% n=14)
- Confusion (6.3% n=13)
- Dizziness (5.8% n=12)
- Difficulty walking (4.4% n=9)
- Cough (2.4% n=5)
- Flu-like symptoms (1.5% n=3)
- Vision changes (1.5% n=3)
- Allergic reactions (rash, swelling, difficulty breathing) (0.97**%** n=2)
- Bleeding in the brain (0.49% n=1)
- Changes in heart rate/chest pounding (1.9% n=4)
- Seizures (0.49% n=1)
- No negative side effects (26.2% n=54)
- I don't know (12.1% n=25)

- Prefer not to answer (2.4% n=5)
- Other (please specify)
    - Left branch bundle block with donepezil
    - Fatigue
    - Headaches
    - Diarrhea
    - Fainting spells
    - Sleep disturbances
    - Digestive

5. Improved Outcomes

The Alzheimer Society of Canada asked patients and caregivers to evaluate the importance of different outcomes for their treatment or the treatment of the person they support, on a scale of 1 (not important) to 5 (very important).

Patients reported that the top five most important outcomes of a treatment were:

- maintaining the ability to think clearly (85% n=51)
- preventing memory loss (81.7% n=49)
- maintaining the ability to care for themselves (81.7% n=49)
- maintaining quality of life (81.7% n=49)
- slowing the worsening of symptoms (78.3% n=47)

Caregivers reported that the top five most important outcomes of a treatment for the person were:

- slowing the worsening of symptoms (94.6% n=192)
- maintaining the person's quality of life (93.1% n=189)
- maintaining the person's ability to think clearly (87.1% n=175)
- preventing memory loss of the person (84.2% n=170)
- maintaining the ability of the person to care for themselves (78.2% n=158).

Most Important Outcomes for Patients

Importance of outcome	1 - not important	2	3	4	5 – very important
Slowing the worsening of symptoms	3.3% 2	1.7% 1	1.7% 1	8.3% 5	78.3% 47
Managing side effects of the medication	6.7% 4	16.7% 10	16.7% 10	15% 9	36.7% 22
Maintaining the ability to care for myself	1.7% 1	1.7% 1	0% 0	6.7% 4	81.7% 49
Preventing memory loss	1.7% 1	3.3% 2	5% 3	3.3% 2	81.7% 49
Maintaining my ability to think clearly (reducing confusion)	3.3% 2	0% 0	1.7% 1	3.3% 2	85% 51
Reducing disorientation (getting lost)	6.7% 4	3.3% 2	8.3% 5	6.7% 4	66.7% 40
Maintaining emotions	1.7% 1	6.7% 4	15% 9	6.7% 4	60% 36
Maintaining quality of life	1.7% 1	1.7% 1	1.7% 1	3.3% 2	81.7% 49
Ability to work	28.3% 17	10% 6	16.7% 10	5% 3	23.3% 14
Ability to sleep	1.7% 1	3.3% 2	10% 6	13.3% 8	55% 33
Ability to drive	15% 9	1.7% 1	8.3% 5	10% 6	55% 33
Ability to perform household tasks	1.7% 1	3.3% 2	11.7% 7	25% 15	45% 27
Ability to care for others who depend on me	13.3% 8	6.7% 4	11.7% 7	15% 9	36.7% 22

Patients were also asked if they would be willing to tolerate new side effects from therapies that can **delay disease progression**. On a scale of 1 (will not tolerate side effects) to 5 (will tolerate significant side effects):

- 41.6% (n=25) patients said they would tolerate new side effects for therapies that can delay the progression of Alzheimer's disease and mild cognitive impairment.

Patients were also asked if they would be willing to tolerate new side effects from therapies that can **reduce the symptoms** of Alzheimer's disease and mild cognitive impairment. On a scale of 1 (will not tolerate side effects) to 5 (will tolerate significant side effects):

- 43.3% (n=26) of patients said they would tolerate new side effects for therapies that can reduce the symptoms of Alzheimer's disease and mild cognitive impairment.

Access to medication that could delay the progression of Alzheimer's disease or mild cognitive impairment - Patients

Many patients felt that access to medication to delay the progression of their Alzheimer's disease or MCI was significant. Comments included words like "hope" and "life changing" as well as many examples of retaining aspects of quality of life such as independence, living at home for longer, engaging in daily activities and more meaningful time with family. Comments also included reducing fear, anxiety and stress or adding happiness or confidence. There is also a relatively small minority of patients who felt the medication would negatively impact their life or were uncertain.

- Provide hope
- Be life changing
- Allow them to maintain an active/normal/independent/productive/meaningful life and sense of self for longer
- Increase their quality of life and happiness
- Allow them to take part in daily activities (driving, working, household tasks)
- Give them more time to engage with family, friends and their community
- Decrease their stress/anxiety/fear
- Allow them to live at home for longer

Patient comments:

- Hope
- My family and I have been hoping and praying there could be some drug that will help delay Alzheimer's.
- It would help immensely in maintaining an active/normal life involving family, friends, daily activities, and travel.
- Would change my life and my children's.
- Would stop stressing.
- It would extend meaningful life and allow me to continue to be active longer.
- Give me confidence.
- Less anxiety, the ability to continue to engage in multiple activities and to travel.
- It would allow me to live more normally enjoying my loved ones and activities.
- This is a moot point because I think I delay my progression of Alzheimer's by keeping very busy and stretching my brain capacity and by having a purpose in my life.
- I'd have no cloudy, heavy brain - thus more confidence and ability to do, for example, math in my head. I would be more social - less tired thus have people to my house. I would cook and eat better.
- Depends on the side effects and actual efficacy of the medications. Not worth the risk of 30% brain bleed for no meaningful difference.
- Then I could return to being myself and even though it is not the most important thing, I'd like to get my license back.
- My life and its quality would continue more like they were before I was diagnosed with MCI. I want to continue being the person I was before.
- Continue to live a more normal life a little longer.
- I would keep working and enjoy life more. These drugs should be approved ASAP.
- Future independence.
- It would feel like I was getting a gift! I would get to spend more time with my spouse and my children. I could continue to live in my home, continue to be part of a family, part of friendships, part of a community. I would feel it would be an opportunity to appreciate and truly value life; which previously, I just took for granted.
- Would improve the quality of my life.
- It will reduce the feeling of a slippery slope, that I have no control over.

- Right now I can do everything except that I am not allowed to drive. I feel that I could drive but my doctor told me to stop driving so I don't drive.
- Decrease fear of the future.
- Wouldn't need to rely on caregiver to same extent. Life would be more pleasant and productive.
- It would mean the world to me.
- Hopefully it would give me more years of independent living. I have told my family that when I cannot live independently, I want MAID.
- My life!
- It would give me a chance to continue to have a life and fully participate in my life with my children and husband. It would delay my becoming dependent on others for my care.
- Would allow me to continue to do the things that I am doing.
- I'd be very happy.
- Huge difference- being able to function close to what I would think of as « normal » would allow me to maintain my quality of life.
- It would mean everything. My boys are under the age of 12, and every moment together counts.
- It would take a lot of speculation out the equation.
- If the medication works, it could be very impactful in improving quality of life in the long term.
- It could prolong normalcy in my life.
- It would be important so that I could continue to drive and travel and care for my home and myself and my family.
- I am 86. So it is hard to say!
- Give some hope. Positive impact on my daily life.
- It would mean that I can continue to be productive and enjoy my family.
- Wonderful. A gift.
- Anything to slow down the disease would be great.
- It would be wonderful to be the normal ME.
- I need it.
- Big impact.
- I would feel more competent.
- Clearly it would be amazing. Quality of life. Right?

Most important outcomes for caregivers

Importance of outcome	1 - not important	2	3	4	5 – very important
Slowing the worsening of symptoms	0.99% 2	0% 0	0% 0	4.4% 9	94.6% 192
Managing side effects of the medication	2.6% 5	5.1% 10	20.4% 40	27.6% 54	44.4% 87
Maintaining the ability for the person to care for themself	2.0% 4	0.5% 1	7.4% 15	11.9% 24	78.2% 158
Preventing memory loss of the person	1.5% 3	0.5% 1	4.5% 9	9.4% 19	84.2% 170
Maintaining the person's ability to think clearly (reducing confusion)	0.5% 1	0% 0	4.0% 8	8.5% 17	87.1% 175
Reducing the person's disorientation (getting lost)	2.5% 5	2.0% 4	8.0% 16	15.9% 32	71.6% 144
Maintaining the person's emotions	0.5% 1	1.5% 3	9.9% 20	17.3% 35	70.8% 143
Maintaining the person's quality of life	0% 0	0% 0	1.5% 3	5.4% 11	93.1% 189
Maintaining the person's ability to work	42.6% 84	10.2% 20	25.4% 50	9.6% 19	12.2% 24
Maintaining the person's ability to sleep	2.0% 4	2.0%	16.2% 32	26.8% 53	53% 105
Maintaining the person's ability to drive	42.4% 84	8.6% 17	16.2% 32	12.6% 25	20.2% 40
Maintaining the person's ability to perform household tasks	9.4% 19	12.4% 25	26.2% 53	24.8% 50	27.3% 55
Maintaining the person's ability to care for others	37.2% 74	13.6% 27	22.6% 45	14.6% 29	12.1% 24

Access to medication that could delay the progression of Alzheimer's disease or mild cognitive impairment - Caregivers

The vast majority of caregivers expressed that access to medication that would delay the progression of Alzheimer's disease would have a significant impact on them as caregivers using words like "hope" "great" "wonderful" and heartfelt comments on the positive impact of their relationship with the person with dementia. Comments also included factors such as financial (e.g. reduced care needs and cost, ability to retain employment levels), emotional (reduced stress, worry and family friction) and quality of life for both the person and caregiver (e.g. independence, ability to live at home longer, improved sense of self, less required time and energy demands). There were also a relatively small number of caregivers who thought that medication access could have a negative impact on themselves or the person they care for.

- Provide hope
- Reduce the need for paid care
- Reduce the need for caregiver (unpaid care)
- Reduce financial costs
- Allow the person they support to live at home for longer
- Allow the person they support to maintain a sense of purpose and a sense of self

- Allow the person they support to increased independence for daily activities (be safe alone, personal care, driving, household tasks)
- Maintain their life partner relationship versus having a caregiver/person with the condition relationship
- Increase in quality of life and happiness (for both the person living with the condition and the caregiver)
- Allow the person they support and caregiver to take part in activities such as travel and social events
- Give the person they support more time to engage with family, friends
- Decrease stress/anxiety (for both the person living with the condition and the caregiver)
- Allow caregivers to stay in the workforce
- Allow the person and caregiver to be able to plan for the future
- Reduce crisis situations, transitions in care support

Caregiver comments:

- This would lessen the caregiving burden and allow me to have more of a life myself, including continuing to work full time (instead of having to go to part time). It would also push off the inevitable decision to place the person in care.
- Not on duty 24/7.
- Would help to maintain some independence and more self worth. Much less anxiety and depression.
- This would've made a life altering improvement for the individual affected and all the loved ones around them in a positive way. Unfortunately, we are past that point, but hopefully a future drug will help others in a similar situation!
- There would be less confusion for me, as he changes his mind daily. He would be able to live alone longer.
- My child would have a proper grandma. I would still have a mom and not another dependent.
- It would provide a better quality of life and more independence.
- It would reduce my anxiety on a daily basis. Slowing progression would relieve the burden on my other parent as well.
- I could rest easy knowing her quality of life is given it's full potential. I feel so helpless and only want the best for my mother.
- Caring for someone at the beginning of the disease is not too difficult. Once the disease progresses it because a very stressful and difficult experience for all family members in addition to the primary caregiver. Even a delay of 5 to 10 years would greatly reduce the need for outside care, as the person gets closer to dying of natural causes besides that of Alzheimer's.
- We would be able to keep them home with us longer without having to move them to a long term care facility (probably outside of their hometown) where the decline would be even faster.
- Very much so - if his cognitive ability and memory loss would improve - I am all in favour of a new medication. I might not have to look after him as much as I do now and he could hopefully continue to drive and take care of himself.
- As this is my partner it would enable us to continue in a life partnership rather than becoming a surrogate mother.
- It would improve the quality of life or at least prolong the ability for the person to maintain the current quality of life. Also helps to reduce the friction between family members.
- She can remain active in the home and have a continued sense of purpose and contribution to the family wellbeing.
- It would make my family happy.
- It would provide the opportunity for a better quality of life.

- I believe he would take this drug. He won't take the other meds because he says they will do nothing to stop the process of the development of this.
- Less stress and less anxiety.
- Access to a medication which would slow the progression of the disease would enable us to have a more social lifestyle.
- This would keep her as she was. Confident, sociable, carry a conversation, dependent.
- Less time and energy demands for me.
- This would depend on his/her quality of life. If it prolonged before getting to bad great, but if it prolonged on a down side would not support the drug.
- It would make it less stressful and, ideally, mean that she'd require less of my time (or that less of our time together would be dealing with stressful topics).
- It would be less stressful caring for the person as he/she could live more normally and be able to care for themselves.
- Would let me continue in the caregiver role for longer.
- Not much. She is already in need of care. Now, if it could reverse the disease, that would be a different answer.
- Would pay any price to slow this disease down.
- It changes how you live, how you plan. If I could count on it maintaining her at this point in her illness, well it's an absolute game changer.
- Allow her to engage more with friends and family.
- I expect that it would stress of having to take on responsibility for daily tasks that the person can now perform.
- No impact, disease has progressed to far already.
- It would help immensely.
- Freedom for us both.
- I wouldn't be worried about her hurting herself or getting disoriented.
- We would be able to enjoy more & different things in our daily routine which makes for a happy, healthy retirement with all our loving family & friends.
- It would reduce the stress and anguish that is a part of experiencing my wife's cognitive decline and loss of autonomy.
- Improve my quality of life and help keep the person effected more like the person I knew.
- Hard to say, in many ways I suppose.
- It would change everything and give us hope.
- It is difficult watching someone you love slowly lose control of their life. It also causes anxiety and distress to them and their families.
- Lengthening caregiving duration.
- My husband is otherwise physically very healthy, so slowing down his cognitive decline would allow him to maintain a higher quality of life.
- In almost every way. I would not worry so much about leaving him alone, I would not have to always have an awareness of what he is trying to do and support him doing my best to not be intrusive.
- Decrease my time spend caregiving.

- This would be wonderful and amazing.
- This would provide hope and hopefully more time before symptoms get worse - very important to us as he is only 52 and our children are still only 18 and 20.
- They would be easier to care for - the paranoia and anxiety makes my father very difficult or impossible to reason with or to care for.
- Would provide hope and permit her to have a higher quality of life for a longer period.
- If it maintained her current abilities I could live with that although it would be a miracle to see her improve.
- It would depend on if it worked or not.
- It would simplify my life and lessen the stress for sure.
- We could continue to travel, play golf, swim, enjoy dinners out
- A great deal.
- This would be great and a relief.
- Make me happier for her.
- Significantly her happiness is good for my health and also the health of others who adore and love her.
- The person could be safely left without supervision.
- We could ensure that it doesn't get worse and it gives us hope that my dad will be around for longer to see his grandchildren grow up.
- Would ease the work time & cost burden.
- Positively
- This type of medication would be life-changing. My mother cares for my 87-year-old father who has Alzheimer's. Her life has changed very much as she is caring for my father. We have to consider my dad for everything we do in the day. In order to make him, comfortable, we want to explain what activities are going on. If there was a medication to change this reality or slow it down, our lives would be free to hopefully restore some enjoyable daily living activities.
- Maintain her independence and living in her own home.
- Continue to feel self worth.
- It would change our sense of helplessness. It would improve almost every aspect of our life.
- Positively, as it would reduce the stress of the daily not knowing what is going to happen next.
- It will make my life easier; I'll have time to take care myself.
- It would provide some hope of keeping my partner with me longer.
- Would improve confidence & quality of life.
- Make like easier for my mom.
- I have to say that postponing the ALZH Terminal Journey does not excite me; this is a long Palliative Care Journey & it is not apparent that drugs are a solution. Quality of life has to be a Benefit.
- Make things easier to cope with.
- By hopefully slowing down the progression of the disease.
- Every body will happy with the progress and be benefitted.

- It would help me have to do less. It would give me more peace of mind.
- I'd like to keep my life partner, for as long possible. His maintenance of the outside of our house (gardening, snow removal etc) is still pretty good. He will assist inside, if I ask him. The new drug may keep us in our home a little bit longer.
- If it would improve his current quality of life he may be able to go home and enjoy family life again.
- If we could slow of maintain his current mental status, that would be extremely welcomed and appreciated.
- I would be less burdened and sad. I would have time to take care of myself and family members. I would have time to enjoy pastimes and friends.
- Relationship maintenance. Improve personal care.
- I would feel less anxious about being there to oversee and make decisions.
- Reduce a lot of worry about the future. Enable us to plan for the future without worry about mental deterioration.
- It would immensely reduce the emotional stress and worry that we as a family go through. Seeing him decline mentally has taken a huge toll on all of us.
- He now requires almost constant supervision, where earlier in the disease he could be on his own and seek support, if needed. For family activities that are not of interest to him or would be too taxing on him, one family member often stays behind to care for him and also misses out on the family activity. The financial costs of care are also a burden on my parents which means they don't access as much support as they need. Having more time where my dad could be independent and contribute more fully to decisions about his care would be a relief, not to mention how priceless it would be having more moments where my dad is himself and contributing to the conversation and sharing his experiences.
- Less to have to do to support them.
- Slowing Alzheimer's in my spouse would be HUGELY IMPACTFUL. My spouse has exhibited short-term memory loss for 2 years which is very noticeable to others. To maintain her ability to function and have meaningful relationships is very important to me. Her future prospects are frightening, so even delaying Alzheimer's symptoms would be a huge win.
- Game changer
- We would both get our lives back.
- It would allow us to carry on as we have for nearly sixty years.
- I feel it would reduce the agitation and depression of feeling they no longer have control of their lives.
- I would be a new person. Caregiver for an Alzheimer's patient is not easy. It's like caring for a baby all over again except you can soothe babies when they are upset. The stress level can be extreme on certain days.
- Having a medication that slows the progress of dementia would relieve some of the worries our family has about Dad's quality of life.
- He would feel more confident and be able to care for himself better.
- It would allow me to spend more time enjoying the things I love, taking care of my own responsibilities at home, and knowing that she is comfortable and content in her life that's all I want, I would love to see something positive happen so that my mom and dad could both live their best life.
- It would make me way more attentive to other things and able to do more with my life. My grandmother would not be going on her last trip ever in September.
- It would reduce all of our anxiety about our mom's/grandma's future. Preventing her from becoming worse off than she is, it would mean the world to us all. And to her as well.
- It would improve our relationship and thereby improve our quality of life.
- I think it would be wonderful

- It would assist in maintaining our current quality of life.
- Reduce my own anxiety and stress managing my parent, plus stress about getting the disease myself.
- Make things much calmer more relaxed.
- Reduce stress.
- Small effect today but huge benefit if Alzheimer's impact could be stopped or delayed.
- I wish I had this access when my father was diagnosed. It's so important to me and I will do what I can to help in order for others not to suffer the way my family did.
- It would be the greatest blessing. She would feel better about herself, feel in control again. It would keep me calmer. Knowing I've got more time with her.
- It would lessen or delay caregiving responsibilities, as already have others to care for.
- I would do anything.
- Best thing possible.
- At this stage, slowing the progression would not impact the care I already provide but would help maintain some QOL for my partner and myself.
- More time to prepare for the future, adjust with the changes. They know the drug should help, so maybe overall more positive mentally to the person, they are being "treated".
- It's too late in the disease to make a difference now unless a new drug could reverse Alzheimer's.
- Allow more quality time to enjoy each others company.
- It would be wonderful to slow down and give her more time.
- This would (potentially) allow them to continue living at a certain level of independence. In addition, it would alleviate some of the anxiety they are experiencing in relation to their diagnosis.
- Some independence for both of us, sharing of the household load, social interaction.
- This would allow the person living with dementia to maintain their abilities and independence for a longer period of time, which is significantly important for both the person and their care partner. This, however, would need to be balanced with potential side effects of the medication, as well as the ongoing assessment, diagnostic testing, and availability of testing equipment.
- It would mean he would be able to do things without having to constantly ask me what we are doing that day. He would be able enjoy his day to day life more.
- Current situation is okay, except for partner's distress at progressing symptoms. Something that would slow progress to more serious difficulties would be hugely welcome.
- I can't imagine it would help. The rate of progression is so staggeringly fast and she has already lost so much basic function.
- I would have been happy to have a drug option, but I think that the stigma of dementia and the denial of certain family members may have prevented access to the treatment when it could have had the most impact.
- We have a wonderful life and are young at heart, spending three months at a time in each other's countries and it would mean the world to us both if we could maintain this for longer.
- Being able to have a drug that sold the progression would have made life easier and perhaps he wouldn't need to have someone with him all the time telling him what to do all the time making sure he's fed bathed it's like looking after a child.
- I would not agree to a medication that slowed the disease it needs to cure the disease.

- Of course, it would have been alot easier on me! It is extremely important to try to slow down this horrific disease. It totally destroys the person! it's extremely sad to watch someone so vibrant, fade away and forget everything! Please try any drug that might help!!!
- Already has access to Aricept - seemed to slow the progression of the disease at first and this allowed the person to continue to do things that allowed some sense of independence (e.g., preparing a sandwich, bathing, getting dressed.)
- It would have meant a lot.
- It would mean that long term care may not be the only viable option.
- Everything. I've already loss 3 family members to this horrid disease.
- I cannot describe how happy I and my family would be.
- Tremendous
- Great perhaps be easier.
- It would relieve the worry when he is alone and not knowing day to day the mood he may be in.
- Slowing the progression of impairment would have allowed more time for thoughtful and informed advance care planning, arrangement of supports and transition to care at a comfortable pace (rather than on an emergency basis due to rapid disease progression). This would reduce anxiety and worry of family members and caregivers and improve overall quality of life for the entire family unit.
- It would be a major break through, life would be so much better for all involved in regards to their quality of life and helping to make the disease more manageable.
- I would get sleep and could work and be less suicidal.
- We could have conversations again share things in our lives.
- What does slowing mean? We in a slow downward spiral, slowing doesn’t mean much what work be better would arresting symptom for some meaningful period of time even if mean faster decline later.
- It would give us quality days instead of quantity.
- Obviously this would make everyone's life easier.
- What it would mean to me would be not to see her decline as fast as she is now. Maybe get more history of her early life and the first few years when my mom and dad got married. I have so many questions now with no answers.
- If any new drug becomes available it would help my loved and also help myself so that we both can live a better life.
- Any drug that slows the progression is great. Expands the normal functions of our life together.
- I would have loved this for my father, so he could have had lived more fulfilled after his diagnosis.
- That may have been important in the beginning but we didn't know what was going on in the early stages. Mom was helping him, and then she got sick, so his diagnosis took much longer.
- It would mean she would need less support from me and others - less coordinating efforts on my part as well.
- We'd have finished our home renovation, got our own taxes in on time, my husband her brother gave up work opportunities in order to get her house sold, plus less grief and fear.
- It would be ideal but not essential.
- It would be easier for the person, having less confusion and loss of self, and maintain their dignity being able to take care of some of their needs.

- Would mean everything. Our lives have basically been destroyed by AD. We cope but not in a happy way. Our retirement years have been devastated.
- It would provide hope in a disease that feels very hopeless.
- The 2 medications he takes seem to be slowing his progression, he has had the diagnosis for 8 yrs and still drives.
- Quality of life well into their 80s.
- It would allow me to get her the care she deserves. Better quality of life.
- It would have given us more quality time together, with less focus on caregiving.
- If the medication would slow down the disease with no huge side affects, it would be great for the recipient as well as the caregiver.
- If the drug works well and doesn't have serious side affects it would be a beacon of hope.
- This means little to our current situation but provides hope for his descendants who may have inherited this disease.
- This would have a huge impact - more time spent with our children who are in university and quality time with others as well as less impact on me and my ability to continue working.
- Give us more quality years to spend together independently.
- It would take a lot of stress off the family.
- It would be great as it may prevent her from needing a nursing home in near future.
- It might offer a better quality of life for my mom! It would be wonderful to have her interact with me as she used to do!
- I would take it if there weren't any a high chance of complications.
- Allegedly that is what Galanatime and similar drugs are supposed to do. Whether they actually work is another matter. The research is not particularly positive. Expeditious research that would result in better medications would be life altering.
- It would be amazing to slow the progress and be able to carry on longer with a more normal life.
- It would be fantastic for my mom and dad and myself.
- It will allow a bit of relaxation.
- Mom has had a slow decline. I am always on alert regardless of progression.
- Any drug that can do this is terrifically beneficial to both of us worry of having constant increase of responsibilities decreased.
- It is extremely important. How could it not be.
- It would be wonderful as it might lessen her dependence on me and allow her/us to remain in our home longer.
- It would make the life of caregiver easier.
- Wont impact my daily life but wont drastically impact his.
- When he was first diagnosed or prior it would have meant everything to me. I would be able to have my spouse and relationship and he could enjoy his grandchildren. Daily life would not be like it is now.
- It would mean everything...I wouldn't be worrying about her all the time.
- It would allow that person to have their freedom. In our case the person retired one and then diagnosed with this disease. At the same time covid hit and worsened the fear of dying for that person.
- Would prolong the time before extra services are needed, or having to quit my independent life/work.

- Very important, it would maintain our quality of life.
- Obviously there would be less pressure on me to provide support, and we would be able to communicate easier.
- It would allow me peace of mind knowing that the person's cognitive decline can be delayed and add to overall well-being which would allow me some comfort.
- It would be lovely to share crafting projects with my mom again!

Experience With Drug Under Review

- 4 patients with donanemab treatment experience completed the survey.
- 5 caregivers supporting a person with donanemab treatment experience completed the survey.
    - All respondents are living in Ontario.

- 1 patient has MCI
- 1 patient has early-stage Alzheimer's disease
- 2 patients have middle-stage Alzheimer's disease
- 1 caregiver provides care to a person with MCI
- 1 caregiver provides care to a person with early-stage Alzheimer's disease
- 2 caregivers provide care to people with middle-stage Alzheimer's disease
- 1 caregiver provides care to a person with late-stage Alzheimer's disease

- 4 patients were diagnosed in 2021 or earlier
- Caregivers are providing care for people diagnosed in 2021 or earlier

- 1 patient reported also taking galantamine and experiencing benefits
- 3 patients reported also taking Aricept, one experiencing positive benefits
- 3 caregivers reported that the person they cared for were also taking Aricept. They reported that some positive effects were experienced early on when the medication was first started.
- 1 caregiver reported that the person they cared for were also taking Serataline and saw a positive benefit.

Patient Experience of Treatment

- 3 patients had no trouble accessing donanemab
- 1 patient reported having trouble accessing donanemab.
- All 5 caregivers had no trouble having the person they care for access donanemab.

Quality of Life of Treatment

Both patients and caregivers of people with donanemab treatment experience reported that they (or someone they cared for) participated in the donanemab trials as they "thought it was important to participate in the study to help the research and hopefully help find a cure" and "to slow progression" of MCI or Alzheimer's disease.

- 2 patients found that taking donanemab delayed the progression of their Alzheimer's disease or mild cognitive impairment
- 1 patient did not believe that donanemab delayed the progression of their Alzheimer's disease or mild cognitive impairment
- 1 patient was unsure if taking donanemab delayed the progression of their Alzheimer's disease or mild cognitive impairment

- 2 patients found that taking donanemab slowed the worsening of symptoms of their Alzheimer's disease or mild cognitive impairment
- 1 patient did not believe that taking donanemab slowed the worsening of their symptoms
- 1 patient was unsure if taking donanemab slowed the worsening of their symptoms

- 1 caregiver found that taking donanemab delayed the progression of Alzheimer's disease or mild cognitive impairment in the person they care for
- 2 caregivers did not believe that donanemab delayed the progression of Alzheimer's disease or mild cognitive impairment in the person they care for
- 2 caregivers were unsure if taking donanemab delayed the progression of Alzheimer's disease or mild cognitive impairment in the person they care for

- 1 caregiver found that taking donanemab slowed the worsening of symptoms of Alzheimer's disease or mild cognitive impairment of the person they care for
- 1 caregiver did not believe that taking donanemab slowed the worsening of symptoms of Alzheimer's disease or mild cognitive impairment of the person they care for
- 3 caregivers were unsure if taking donanemab slowed the worsening of symptoms of Alzheimer's disease or mild cognitive impairment of the person they care for

Patients reported that taking donanemab impacted their daily life in the following ways:

- It improved my daily life.
- Not any effect.
- In the clinical trial I was blinded so I don't know if initially I received the drug.
- I thought my memory was better. My mood was better.
- I truly believe that Donanemab improved my symptoms for the period of time that I was taking it.

Caregivers responded that the person they care for taking donanemab affected the person's daily life in the following ways:

- Caused brain swelling and bleeding. Produced stroke like symptoms and aphasia. Never recovered from this side effect.
- Gave him a real sense of purpose to his life. He is able to contribute to making the world a better place for many in the future.
- Didn't notice much benefit, as my husband has appeared to decline rapidly. It is a blinded trial, so it may be that the first 18 months he was on a placebo. Now ending second 18 months of receiving Donanemab, decline is still occurring faster than hoped.
- Aside from attending the necessary appointments, there was really no affect on her life.

Caregivers reported some changes to their caregiving role, as a result of the person they care for taking donanemab:

- Adverse reaction causing rapid decline in the disease. I have total care 24/7 for this individual now.
- My husband gave up driving early in his diagnosis. Taking Donanemab meant driving 2.5 hours monthly for treatment. Additionally there is the added burden of MRI and PET scans, located far from our place of residence. Added burden to my daily life.
- Aside from taking her to the necessary appointments, there was really no affect on my life.
- Sharpened my sense of responsibility.
- Increased my responsibility as I am sole driver. I also worried about interaction with his diabetes.

Overall assessment

The following are some positive experiences patients had with taking donanemab:

- I experienced clearer thinking and problem solving. Also it was great to get to know the clinical research team.
- I had this so early that I have no idea.
- I was in a blinded trial for 18 months. I am now in the second 18 mos receiving donanemab, but my disease has progressed to the point where we are not seeing much benefit.
- I thought my memory was better. My mood was better.
- I thought that my condition was improving while taking Donanemab, but I started to get worse after I was taken off the drug.

The following are some positive experiences caregivers had with the person they care for taking donanemab:

- Being involved for 3 years in the study we have made good friends with the clinicians and staff at the clinic. We have also been able to explain to our friends how much we have learned and the positive outlook we have been able to maintain.
- Care at the clinic where Donanemab is administered has been exceptional. Monthly follow-ups are reassuring. New community of friends at the clinic has been very positive.
- She was in a better mood when taking the drug because she thought it was improving her condition.
- Being able to contribute has made our lives feel valuable.
- Positive experience with care.

The following are some negative experiences patients had with taking donanemab:

- None really.
- None.
- Having to travel long distances to receive the drug, and even longer distances to have MRI and PET scans.
- None, except depression after I was taken off the drug and my condition began to get worse.

The following are some negative experiences caregivers had with the person they care for taking donanemab:

- Caused brain swelling and bleeding. Produced stroke like symptoms and aphasia. Never recovered from this side effect.
- Long travel distances.
- We understood that it would be made available to study participants off label at the end of the study. That does not appear to be the case.
- She became somewhat depressed when she as taken off the drug.

7. Companion Diagnostic Test

N/A

8. Anything Else?

Recommendation from patients about donanemab:

- 4 patients would recommend taking donanemab to other people with Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease.

Patient comments associated with the above statement:

- It works!
- Perhaps it works. So there is no reason not to use it.
- Research showing it has helped others. It is such a devastating disease anything that helps is worth it.
- I personally had no negative side effects, and felt that it helped my condition.

General comments from patients:

- I would have liked to have know, based on a subsequent scan, whether the plaques were starting to build up in my brain again after I was taken off the drug. For some reason, the drug company would not provide me with this information.
- I wish I was still receiving it.

Recommendations from caregivers about donanemab:

- 4 caregivers would recommend taking donanemab to other people with Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease.
- 1 caregiver would not recommend taking donanemab to other people with Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease.

Caregiver comments associated with the above statements:

- Any hope
- In her case there were no negative side effects, and she believed that it helped her symptoms.

General comments from patients:

- Being able to contribute has made our lives feel valuable.
- Positive experience with care.
- We understood that it would be made available to study participants off label at the end of the study. That does not appear to be the case.
- The hardest decision I have had to make in this caregiving journey is to place my partner (the person I support) in long term care. Any medication that would have slowed the progression of the disease would have allowed me to continue to care for my partner at home, which is the best place for her.
- My dad says “that having gone through this and living through this with somebody you love and you’ve been married to for 68 years is extremely difficult and painful to see a loved one go through that. If health Canada can approve a medication that would help slow down the progression of this Horrendous disease that would be the humane thing to do. Lack of support and education for me is what I'm lacking. It's all hard. More help for caregivers, more help at sooner stages is so necessary.
- Alzheimer's is a long, grueling and sad existence for the entire family. The chance to delay or prevent this disease would benefit future generations and the medical system.
- We’ll try anything that may help.
- Happy to get on a trial of any kind that might help our Mother or others in the future.
- People with Alzheimer's don't have a lot of time. Many would be willing to risk adverse effects to find medications that could work.
- Please approve asap. We don’t have time to lose. Everyday is worse and non reversible.
- It seems to me that Drugs are not the answer. Lifestyle change involving Nutrition, Exercise & Environment seems to be the best course of action.
- Hope this medicine could treat.
- I really wish this was available in mom’s earlier stages. She has progressed quite quickly and I do not think this will help at the stage she is in.
- I deal with residents daily who could benefit sooooo much as well. The quality of life it would give is indescribable.
- Some of these new drugs might have some side effects, but Alzheimer's Disease is going to kill you anyway, so I personally would try anything! My Mom would of tried anything to help slow down the disease!!!
- I don't understand the importance of this as obvious that anything that slows, helps, is important to both the subject and the caregiver.
- I believe all the new drugs that are being tested these days for early Alzhiemer's disease should also be available for people that have had Alzhiemer's disease. Maybe a MRI done to determine if the drug may help.

General feedback from people living with dementia and caregivers on treatment and health-care system use

Below is general feedback gathered (prior to the donanemab surveys) about treatment/medication needs and issues, and health-care system use of people living with dementia and caregivers.

Medication costs

It is important to take into account the financial strains that many caregiver of people with dementia experience. The following information may be helpful to consider, when thinking about the importance of accessing affordable treatments.

In our analysis of the interviews [The Impact of First Link® across Canada Report, 2023], it became clear that one of the major factors impacting the quality of life of caregivers is finances. Those that were living with financial security (e.g. secure housing, food security, **ability to afford medications**), and in particular those who were able to afford private care (e.g. private homecare support, adult day programs, higher-end assisted living), described a **significantly higher quality of life than those that were living in poverty,** despite the same level and quality of services being offered by the Alzheimer Society (Alzheimer Society of Canada, 2023, p. 52).

Interviewed key stakeholders identified a number of resources and supports that are either limited or not available, but that would improve the quality of life and/or care of persons with dementia and their caregivers; these **included improved coverage from the Ontario Drug Formulary so that all relevant medications are covered and everyone has equal access to medication** (Alzheimer Society of Canada, 2010, p. 101).

Medication side effects/health-care system use

Some people with dementia will experience side effects from medications that can send them to hospital emergency rooms. This information may be helpful when thinking about some of the risks that may come with new treatments.

A number of participants indicated that the person they cared for attended the emergency room due to a fall, several due to **medication side effects** or issues, and several due to extreme behavioural issues that the caregiver could not manage (Alzheimer Society of Canada, 2023, p. 58). **About 44% of participants reported an emergency department visit within the last year,** which is nearly double the 2015 CIHI population estimate from 2015 of 25% emergency room usage among dementia patients (Alzheimer Society of Canada, 2023, p. 10). **Approximately 28% of participants reported at least one overnight stay in hospital within the past year,** which is higher than the 20% reported in the dementia population by CIHI in 2015 (Alzheimer Society of Canada, 2023, p. 11).

Benefits of medication/treatment – Delaying dementia progression and advancing research

Secondary prevention treatments that delay the disease process before too much permanent damage is done have the potential to reduce the progression of dementia. Delaying the progression of dementia for those diagnosed will make a significant impact to Canada's health-care system and caregivers as we know that by the year 2050, more than 1.7 million Canadians are expected to be living with dementia (Alzheimer Society of Canada, 2022). The use of secondary prevention treatments that delay dementia symptoms early on can allow people living with dementia to live independently for longer and caregivers to provide care at home (McDade et al. 2020). Delaying progression of dementia allows for people to live at home, reducing the number of people living in long-term care homes and potentially saving governments in Canada money.

Providing access to disease modifying drugs could also advance treatment research. Access to these drugs could allow researchers to continue to learn about the potential benefits or risks of this type of treatment for people with MCI or Alzheimer's disease. These treatments, while not perfect, are very important in establishing a baseline on which to achieve incremental improvements; much like cancer chemotherapeutic regimens, what is considered frontline therapy will soon be surpassed in effectiveness, safety and ability to access by novel candidates. This too, will also be the case for Alzheimer's disease and dementia, and these treatments provide that baseline on which to measure future treatments.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   N/A

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Some donanemab clinical trial locations in Canada shared the surveys with their clients.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

N/A

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Luca Pisterzi
Position: Vice President, Research
Patient Group: Alzheimer Society of Canada
Date: August 12, 2024

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Donanemab (Kisunla®)
Indication: Treatment of Alzheimer's disease
Name of Patient Group: Alzheimer Society of Ontario
Author of Submission: Adam Morrison, Senior Director of Public Policy and Partnerships; and Jessica Hogle, Public Policy Coordinator, Alzheimer Society of Ontario

1. About Your Patient Group

The Alzheimer Society of Ontario represents a federation of 26 frontline health and community support service providers, operating in every community across Ontario, and is part of a national federation of Alzheimer Societies across Canada. We supported over 84,000 clients last year, including both care partners and people living with dementia. We provide education and training to physicians and other health and social care professionals, as well as to the general public, and work to reduce the stigma that is far too often associated with dementia. As a health service provider, we offer system navigation, care partner respite, adult day programs, therapeutic recreation, and so much more at little or, for nearly all of our programs, no cost to families. With hundreds of staff and thousands of volunteers we seek to alleviate the personal and social consequences of Alzheimer's disease and related dementias, and to promote research into a cure. Learn more and find an Alzheimer Society near you: https://alzheimer.ca/on/en/about-us/find-your-local-alzheimer-society.

2. Information Gathering

Three focus groups were held, one in-person and the other two virtually. The in-person focus group was held in London, Ontario on August 7, 2024. The first virtual focus group was held on August 6, 2024, and the second on August 7, 2024. All focus groups were hosted by Alzheimer Society of Ontario staff and the in-person group was held the Alzheimer Society Southwest Partners' office in London, Ontario. The in-person focus group included seven participants (four care partners, three individuals living with Alzheimer's disease) who had direct experience with Alzheimer's disease but were not involved in a clinical trial for donanemab. The virtual focus groups were hosted by the Alzheimer Society of Ontario with recruitment supported by the Toronto Memory Program, a clinical trial site for donanemab. The Toronto Memory Program was not involved in the focus group process except for recruiting eligible participants. Virtual focus groups included four participants (two care partners and two people living with Alzheimer's disease), all of whom had personal experience with donanemab. Participants had experience with three of the three drugs approved for prescription for Alzheimer's disease in Canada and publicly funded in Ontario, being Aricept (donepezil), Reminyl ER (galantamine), and Exelon (rivastigmine).

Participants were asked to self-report their connection to Alzheimer's disease, including diagnosis (if any). All participants in the virtual focus groups who were receiving donanemab had a confirmed diagnosis to verify eligibility to enroll in the clinical trial by PET scan. Participants in the in-person focus group did not necessarily have a confirmed diagnosis (being differentiated from a probable diagnosis, which is given without confirmation of amyloid plaque presence in the brain); their feedback is nevertheless of equal importance, due to their interactions with health care

providers being more typical to what Canadians will experience should the drug being considered be approved for use outside of a clinical trial environment. Participants with later-stage Alzheimer's disease, who would not be eligible for the drug being considered, also bring firsthand experience of disease progression and are thus able to speak to the importance of delayed progression—the desired outcome of donanemab.

Participant ages ranged from 67 to 83, including six men and five women.

Focus group participants were asked a series of questions, included as Appendix B. Focus groups were recorded to ensure participant sentiment was accurately captured in this submission. Participants received a $25 gift card as thanks for their time; this was presented to all participants regardless of their feedback. The Alzheimer Society of Ontario also offered to reimburse expenses associated with attending the focus groups; no participants requested reimbursement.

3. Disease Experience

Focus group participants were unanimous in declaring that Alzheimer's disease has upended their day-to-day lives, disrupting hobbies, goals, life-long plans, and redefining their relationships. The most common and difficult reality faced by all groups was the loss of companionship and partnership, with several noting they would rather have received a diagnosis of cancer because at least they "still have their mind" – a heartbreaking truth experienced by many people affected by dementia. Several care partners have experience supporting others with different chronic conditions and stated that providing care for someone living with dementia is more time consuming and stressful than any other care they have provided before.

Participants experienced their lives changing overnight, including leaving behind the lives they planned with their spouse in exchange for a life full of ongoing grief and stress. All groups emphasized the lack of support available for care partners and the toll that it takes on them both physically and emotionally, with one participant sharing stories of continued sleep deprivation and physical harm caused by her loved one unknowingly while he sleeps. Care partner participants were in mutual agreement that there is a lack of support in the community – financial, emotional, social, and respite – to help care for their loved one, leaving them to feel inadequate, frightened, trapped and alone in their caregiving role.

A lack of uncertainty and control was noted by numerous participants, with several care partners unsure about how much longer they can manage to care for their loved one. One care partner in a virtual focus group said, 'I have changed our happy retirement plan for travel and time with family to one where I map out how much money I will need for supports at home and an inevitable move to a memory care floor in a retirement home or long-term care home.' This care partner remarked that she and her husband both worked and saved for a comfortable retirement, but now she was unsure how long their financial resources would be able to support her husband's increasing care needs.

The words of participants themselves best summarize their experiences with Alzheimer's disease:

> "A life that looked like happy retirement is gone. It was gone overnight. Now there is stress, grieving, lack of independence, and decline." - Care partner to husband living with dementia
>
> 'His world is getting harder, his social circle is getting smaller, and this is hard to see…' 'Financially as well, as he can't practice his craft, can't continue to contribute.' - Care partner to husband living with dementia
>
> "It destroyed my life without really knowing why, except knowing that there is this word 'Alzheimer's.' My wife – I hope that she can have a life... It's never going to stop until I die, which is very hard." - Person living with dementia

"You are frustrated all the time with everything you have to deal with, as well as caring for the patient. It just doubles everything. And the anticipatory grief – you are just losing that person every day, and you have to face that and deal with that every day. It's all consuming." - Care partner to mother living with dementia

"My whole lifestyle changed to provide care, to provide a routine, to provide stability, and single-handedly trying to preserve my husband's dignity. All plans, activities, and future expectations for my life have been taken away from me the moment he was diagnosed. I feel trapped as a caregiver, I'm trapped in this role, and I can't fix anything. I feel inadequate, I feel frightened, and I feel alone. I'm broken hearted for my husband. And at the same time, I am exceedingly resentful, and I'm grieving the losses—all the big losses, the little losses, and the biggest loss is my companion. I'm sleep deprived. I've received accidental injury in the form of bruises at his hand during his nightmares because they can't bring this under control with any drugs. My own physical health is impacted by stress. In my life experience, it is much easier to look after a helpless newborn baby 24/7, 365 days all by yourself than it is to look after an individual who is suffering from this condition. That's how it's changed my life." - Care partner to husband living with dementia

"I wish he'd been diagnosed with cancer or something else… not dementia. If I got diagnosed, I'm not sure how long I would want to live, knowing that I would lose my mind." - Care partner to husband living with dementia

"I just feel sad all the time. I want my husband back. Not like this. I'm depressed, I know I am. [redacted] You know, when you're younger you think when it's your time to go you will probably get cancer or something like that. I never thought about this. It was such a shock." - Care partner to husband living with dementia

4. Experiences With Currently Available Treatments

Participants had experience with all four available medications in Ontario, including Aricept (donepezil) and Reminyl ER (galantamine), Exelon (rivastigmine), and Ebixa (memantine). These medications, among other cholinesterase inhibitors, aim to reduce symptom severity but their effects are temporary and do not stop or fix damage caused in the brain by Alzheimer's disease. Despite treatments currently being available for prescription for Alzheimer's disease, these are not comparable in outcome to the drug being considered which could alter the clinical progression of Alzheimer's disease.

Some of the focus group participants with experience accessing one of the above drugs reported difficulty quantifying their benefit, if any. One of the participants living with dementia stated that, "It is hard to say the effects because I don't know what the norm would be," and another participant stating it is, "Hard to know if [the medication] is working as [my husband] has always progressed slowly." All participants who had experience with these medications were recommended by their medical practitioner, with one participant noting, "I take what they give me, and I don't know if they work or not." Another participant said, "Any time we ask the doctor about medication, they said there were too many side effects," deterring them from wanting to receive more information. No participants in our focus groups thought the currently available medications were of noticeable benefit and had either discontinued them or kept taking them as a matter of course, but not with an expectation of symptom improvement.

The majority of participants who used either Aricept and Reminyl reported minimal benefits, again expressing difficulty judging if their supported person's cognitive decline was lessened by the drug being prescribed. One participant offered that her husband was prescribed Aricept for two and a half years which initially, "Helped him plateau with very little change the first year." However, this participant experienced adverse side effects after one year, stating her husband, "Was wound up so tight on this drug and would have wicked tantrums and be very argumentative." Since then, he has stopped taking the medication. Another care partner discussed her husband being prescribed Exelon, which was easy to access and affordable for their financial situation. This care partner stated that her husband is now, "More interactive

[since being prescribed this medication]," though it did not help much with memory, "... but certainly in mood and attitude."

When asked whether or not these medications met the needs of the care recipient and the care partner, there was a general consensus that these medications are not sufficient to meet their needs. At the in-person focus group, one care partner effectively captured the perspective of the rest of the group: "I can't identify a need that is realistic. We all want our lives back, but that's not realistic. There are huge gaps both in drugs and services offered."

5. Improved Outcomes

Participants expressed a unanimous desire for a cure, or disease-reversing treatment, signalling the importance of further research to meet patient need. In the absence of a disease-reversing treatment, participants expressed optimism for a disease-modifying treatment: a drug that can slow the clinical progression of Alzheimer's disease, which is not currently available in Canada. One person living with dementia said, "'I want a drug that keeps me where I am, not get worse. If there was a drug that slowed it down, [I would take it]." Another participant living with dementia expressed their desire for disease modifying therapies, stating, "I would accept this, how I am now. Life goes on and I could accept that, being where I am now." Others in the focus group from London, Ontario agreed that a "cure and prevention" would be the best outcome of new treatments, while another participant who is currently in clinical trials for donanemab said they would like for a drug, "That gave things back," suggesting a partial reversal of symptoms of Alzheimer's disease or halting the disease progression.

Trade-offs that participants would need to consider primarily focused on accessibility, cost, and quality of life for both the care partner and person living with dementia. A care partner and person living with dementia who is currently involved in a clinical trial for donanemab expressed the importance of accessibility: "Access might be something we consider. It can't be administered near where we live so going forward, having easier access to the drug is important." Additionally, many participants emphasized that "cost would be a major factor," not only referring to the drug itself but also costs associated with diagnostic testing (i.e. travel, time away from home, etc.). Quality of life was a common and heavily emphasized theme for all participants. They expressed a strong desire to make an informed choice with respect to risks of side effects, with one participant saying she would want to, "Compare benefits with the prognosis of other health issues my husband has already. So, I want to know what the impact of the drug has on other various conditions, not just dementia." Further to this, another care partner said a new therapy would need to provide an "equal balance between the masking of the symptoms and the alteration of the personality. It's a Catch-22 to take anything. You can stabilize some confusion and smooth out language skills, but you're going to cash in some other lovely thing about them. So ideally if a drug could reach a balance of being helpful and not too destructive, that would be great."

When evaluating risk and trade-offs, participants expressed the desire for new therapies to also consider quality of life, with one participant stating, "The quality of life for both the person with dementia and the caregiver are paramount". Another participant who is a care partner for her mother living with dementia expressed her frustration with the lack of support currently offered for care partners in Ontario and said, "We need to take into the considerations the mental load of the caregivers. What are we imposing with the side effects? Are we lessening the load of the caregiver or are we adding to the mental load of the caregiver..." suggesting that the introduction of new therapies should help to reduce the burden on care partners, not add to it.

6. Experience With Drug Under Review

Summary statement on values: Donanemab brings hope, and the most important values that need to be considered for this review are: access to the treatment (both financial and ease of access for diagnostic tests and infusions);

effectiveness in halting the progression of Alzheimer's (and participants were willing to risk side effects if progression could be halted); and a supportive ecosystem for patients and their care partners to take the treatment and be supported during their dementia journey.

Out of the eleven participants, only two people living with Alzheimer's disease and two care partners had direct experience with donanemab, which was accessed through a clinical trial at the Toronto Memory Program.

One of the two participants with direct experience receiving donanemab reported possible side effects of the drug, however, this individual is still unclear if they are taking donanemab or the placebo. As stated by their care partner, "Now he is directionally and spatially challenged. He has agnosia very badly. When diagnosed it was less so, but he has progressed a lot [since the clinical trial started]. I am not sure if this is from the drug or just the progression of the disease."

The other participant who had direct experience with donanemab said they had experienced, "... No negative impacts or side effects" since taking the drug. Their overall experience was positive, stating that, "The connection with staff was very good during the trial. We felt supported all the way through. Knowing there's somebody there watching the progress, being honest, and they would tell us if anything changed – good or bad," highlighting the importance of transparency and support when starting a new drug therapy. Both the person living with Alzheimer's disease and their care partner agreed that entering the clinical trial for donanemab gave them a sense of hope and empowerment, if not for them but for others: "It was somewhere to go that was hopeful. Anything [redacted] was doing, it may not have any impact on his life, but it might help people in the future and their kids," and "... this stuff never bothered him anyways, and if it helps someone else then he is fine with that."

While participants could not, nor could they be expected to, determine to what extent donanemab altered the clinical progression of their Alzheimer's disease (especially in cases where donanemab was administered alongside currently approved non-disease-modifying drugs), one participant's self-observation concluded that the drug had either halted or slowed their cognitive decline thus far. They were pleased with these results and had hope for others who could have access to donanemab in the future, if approved.

Of the four participants with direct experience with donanemab (two persons living with Alzheimer's disease and their care partners), their attitudes differed towards the trade-offs necessary to participate in the donanemab trial. As an infused product, participants were required to make monthly visits to an infusion centre. One care partner shared that they had a positive experience and enjoyed the time spent together, saying, "We are both retired. It was a great 'date day' for the two of us. We would bring our reading material, or I would knit. But really, it was somewhere to go where there was hope—it was hopeful." Conversely, the other care partner to her husband living with Alzheimer's disease was hesitant to say if she found their experience to be as positive: "I don't know if it was beneficial. In part because we don't know what it would have looked like without the treatment, even whether he was taking the drug or a placebo." In part, the care partner's experience and involvement in the process and their caregiving role, coupled with lack of support weighed heavy on their experience, with her stating, "If I knew then what I knew today about [redacted] progression, would I still have taken this drug in a clinical trial? Maybe. But I'm just not sure. I don't know how much longer I can manage on my own and take care of him." This care partner's experience and thoughts suggest the need for more support for care partners relating to access and time commitments for new drug therapies.

7. Companion Diagnostic Test

Donanemab requires confirmation of amyloid plaque buildup in the brain prior to commencement of treatment. For the near future, this necessitates one of two procedures: a PET scan, or a lumbar puncture followed by cerebrospinal fluid analysis. Participants were asked about their experiences, if any, with these two procedures.

This was the area with the greatest divergence between participants with experience receiving donanemab, and those without. Participants receiving donanemab reported positive experiences with diagnostic procedures, with one person living with Alzheimer's disease saying his experience receiving a PET scan, "Didn't bother [him] at all," and another stating, "The PET scan provided some certainty, some comfort [to us]." None of the participants received a lumbar puncture as part of diagnosis. No participants paid for the procedures, as this cost was covered in the clinical trials.

However, participants expressed an understanding that PET scans and lumbar punctures/CSF analysis for the purposes of diagnosing Alzheimer's disease are not publicly funded in Ontario. Patients not involved in clinical trials would need to pay out of pocket for diagnostic tests, or have them covered by other sources, without policy change in Ontario. One participant noted, "PET scans are $3000-5000, which is too expensive. If this drug is approved, the government will need to cover PET scans as part of the funding for treatment.' None of the participants connected with a clinical trial for donanemab expressed anxiety or stress about the results of their PET scans. Instead, they found the results of diagnostic testing to be settling: "At least we know for sure what this is, so we can get on with our planning," a care partner of a patient in the donanemab trial stated.

Participants not involved in a clinical trial (i.e. the control group) reported a lack of awareness of diagnostic options, and a lack of conversation about these procedures with medical providers. There was confusion among participants in the control group who had received a test but did not know for what: multiple participants mentioned receiving a "brain scan" but did not know if it was a PET scan, and for what purpose the test was conducted. Some participants were unaware testing beyond cognitive assessments existed and reported no proactive discussion with their primary care provider. One participant was told by their physician that a PET scan will not confirm a diagnosis, "So no point in getting one," and the only way to be sure is through a lumbar puncture. Another participant said such diagnostic tests were mentioned, but not recommended for their needs, so there was no further discussion with their physician.

Were a diagnostic procedure to be required to access treatment, participants raised a number of concerns they would need to be addressed before consenting, including: what preparations, if any, are necessary; what are the potential side effects of the testing; and a clear explanation of the results of testing. These comments suggest a strong desire for clear medical advice and consultation on diagnostic procedures.

Another particular concern was the cost and length of wait times for these diagnostic tests. For all the participants involved in the in-person focus group, they said it was hard to justify how much money they would have been comfortable paying for such tests if this was available to them years ago because they are now well into their disease trajectory. There was also a group consensus among the control group that if wait times for a diagnostic test was more than a year, they may be "too far gone," with one care partner saying, "I would not want to stall this disease where we are now. At this point, I am willing to face the natural course of this and see where it goes... I wouldn't want him to be stuck like this forever," suggesting that wait times must be short and testing should be conducted early in the trajectory of the disease and how much people living with dementia will progress as they wait for a confirmed diagnosis.

The differing levels of knowledge between participants in the focus groups highlights the varying degrees of knowledge practitioners have about dementia care, and their subsequent willingness and ability to discuss treatment and testing options with patients. One care partner whose husband is in the donanemab trial said, "We didn't know lab tests could be done to confirm dementia until getting connected to a geriatrician, who did cognitive testing. The geriatrician then referred him for other scans, which led to being connected with a clinical trial at Toronto Memory Program." Participants connected to the Toronto Memory Program, a clinic with specialized knowledge in dementia care, were well informed and confident about their treatment options, with one care partner sharing they "felt supported all the way through." Those not connected to the Toronto Memory Program reported less confidence and awareness of available procedures.

8. Anything Else?

The Alzheimer Society of Ontario wishes to emphasize, on behalf of the clients we have the honour to serve, the unmet need that the drug under review fills for Ontarians living with Alzheimer's disease. No other product available in Canada can alter the clinical progression of Alzheimer's disease, the single most important unmet need expressed by focus group participants. A treatment for Alzheimer's disease, of which there are four approved in Canada, cannot be compared to a disease-modifying treatment, of which there are none. Participants in our focus groups stressed that current medications are not sufficient support, and they provide little to no comfort that dementia is being managed. The ability to retake control, to regain time, and to delay dementia has long been hoped for by Canadians affected by dementia. For those who are too far along in their disease progression, their hope is that such treatments can be available for hundreds of thousands who will be diagnosed in the future. That possibility is now within reach, as one participant said hopefully:

> "It's too late for most of the folks in this room to benefit from anything that is going to come out of this focus group, but hopefully, we can push for some improvements to access across the country at every level of health care to ensure that when our children, who are very likely to develop this disease, find themselves in the early stages, and then maybe they will stand a fighting chance to live a cognitive life to the end." - Care partner to husband living with Alzheimer's disease

Appendix A: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. **Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.**

   Yes. The Toronto Memory Program led outreach for recruitment of participants for the virtual focus groups, with all participants also being associated with the Toronto Memory Program. The Alzheimer Society Southwest Partners, which is a legally distinct entity from but part of the same province-wide federation as the Alzheimer Society of Ontario, hosted and recruited participants for the London focus group. Neither the Toronto Memory Program nor the Alzheimer Society Southwest Partners were involved in the drafting of questions or facilitation of the focus groups. Neither organization had any input into this submission, which was written solely by Alzheimer Society of Ontario staff.

2. **Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.**

   No.

3. **List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.**

Table 1: Financial Disclosures

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Biogen Canada				X
Eisai Canada				X
Eli Lilly Canada				X
Novo Nordisk Canada				X
Roche Canada				X
Ministry of Health, Ontario				X
Ministry for Seniors and Accessibility, Ontario				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Adam Morrison
Position: Senior Director, Public Policy & Partnerships
Patient Group: Alzheimer Society of Ontario
Date: August 12, 2024

Appendix B: Questions Asked to Focus Group Participants

Participants in the London, Ontario focus group were asked the following questions:

1. Describe your connection to, and experience with, Alzheimer's disease. How has it changed your life? In what way(s) have you found it to be most impactful?
2. There are three medications funded for treatment of Alzheimer's disease in Ontario: Aricept (donepezil), Reminyl ER (galantamine), and Exelon (rivastigmine). A fourth, Ebixa (memantine), is approved for use in Canada but not publicly funded in Ontario. Thinking only of these four currently available treatments:
    a. Do you have any direct experience with them? If so: have you noticed any improvements and/or side effects? If not: were there any barriers (cost, access, etc.) that prevented you from accessing them?
    b. Did your health care provider(s) mention treatment options to you, and/or did you research them yourself? Do you feel existing treatment options meet your needs, or are there gaps?
3. What is, to you, the most important outcome not offered by currently available treatments?
4. Thinking of the outcome(s) you mentioned in the last question, how would your life change if there were a treatment available that could offer this? What risks would you take and what trade-offs would you make (such as acceptable side effects, time to access the treatment, etc) to get this outcome?
5. Still thinking of the same outcome(s), what else would you consider when deciding whether or not to access a treatment that might offer this?
6. The drug being considered, donanemab, requires a confirmed diagnosis of mild cognitive impairment or early Alzheimer's disease. This diagnosis can currently only be obtained in Canada through a PET scan or a lumbar puncture, followed by CSF analysis (a lab test). Do you have any experience with one or both of these diagnostic tests? If so: how easy or difficult was it to obtain? Did you encounter any barriers, such as wait time or cost? Were you confident going into the experience, or did you have unaddressed concerns? If not: were you aware that these options existed to seek a confirmed diagnosis? Did you discuss them with your care provider? Were there specific barriers that prevented or discouraged you from seeking a confirmed diagnosis?
7. Based on what you know today of PET scans and lumbar punctures, would you be confident and comfortable accessing one of these options if it was required prior to beginning treatment? Do you feel the results would give you more certainty before deciding on treatment options? What would you want to know about these diagnostic options before agreeing to proceed?
8. Is there anything else you would like the people who will decide whether or not Canadians have access to disease-modifying treatments for Alzheimer's disease to know? What values do you think are most important to be considered by those evaluating donanemab?

In addition to the above eight questions, participants in the virtual focus groups, who all had direct experience with donanemab, were also asked the following questions:

9. During the time you were receiving treatment with donanemab, what benefit(s) if any did you notice? How would you say these benefits impacted your life, and the lives of your family and care partner(s)?
10. During the time you were receiving treatment with donanemab, what negative impact(s) if any did you experience? How would you say these negative impacts affected your life, and the lives of your family and care partner(s)?
11. During the time you were receiving treatment with donanemab, what side effects did you experience if any? How did you manage these side effects?
12. Thinking back to any other medications you have tried that were prescribed for Alzheimer's disease, did you find donanemab easier, about the same, or more difficult to tolerate? In what way(s)?

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: D**onanemab**

Indication: **Donanemab is indicated for the treatment of Alzheimer's disease. Treatment with donanemab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease. In controlled clinical trials, donanemab was found to slow the decline in cognition and function in a clinically meaningful manner and demonstrated significant amyloid plaque removal.**

Name of Patient Group: Dementia Network Calgary

Authors of Submission: Diane Rennie and Kim Brundrit

1. About Your Patient Group

Dementia Network Calgary is a growing group of knowledgeable, capable, and passionate individuals from across the public (including those living with dementia and their family care givers), private and nonprofit sectors in Calgary and area with an interest in Alzheimer's disease and related dementias. Created in 2013, it is based on a collective impact model, an innovative approach to tackling complex social and systemic issues, which requires the coordinated efforts of cross-sector stakeholders. For more information, please visit: www.dementianetworkcalgary.ca

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Information for this submission has been gathered from people with lived experience over the last six years through community gatherings, surveys and focus groups. Recently, two focus groups were held in November 2023, one with caregivers and one with people living with a diagnosis, to discuss the impact of dementia on daily living. A purpose-designed survey was also completed in May/June 2024. Another study, completed over the last year, focused on the challenges faced by caregivers who are asked to support decision-making for people living with MCI or a type of dementia.

The vast majority of this data was collected in Calgary and the surrounding area, but some of the surveys reached a broader audience across Alberta and Canada. The demographics of community gatherings and focus groups are typically a mix of genders with adults between the ages of 30 and 85. Everyone who attends has lived experience with dementia either as a person with a diagnosis or as a caregiver/family member. We do not collect ethno-cultural data. Community gatherings are held approximately four times per year but less during the pandemic.

We have engaged with over 6000 people impacted by dementia over the last six years. We have used their contributions and quotes directly in this submission.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients 'and caregivers 'day-to-day life and **quality of life**. Are there any aspects of the illness that are more important to control than others?

When asked about how dementia impacts their day-to-day life and quality of life, both people living with dementia and their care partners described the loss of independence, decreased ability to accomplish tasks that were once easy to complete as well as financial, physical and emotional stress and exhaustion. Providing care can impact all aspects of day-to-day life.

The following quotes paint a picture of the challenges:

"It has meant I experience almost daily stigma and discrimination - and zero disability support to live independently apart from what I self manage."

"Managing my parent's care, both personally and financially, is a strain physically and emotionally."

"I am always on call and never feel like I can truly relax. The calls come at anytime, day or night. I live with constant stress and anxiety and worried about what's going to happen next."

"My children and my spouse don't get the best of me because I have no "best" left."

"We can't go on vacation for more than 5 days and I'm always worried if my phone is out of sight."

"I spend every day with my mother at her care home. It is heartbreaking."

"Emotionally this disease is completely draining. Visits are hard, especially those as she continues to deteriorate."

"I developed anxiety and depression due to exhaustion and mom's verbal abuse."

"Day to day there is always a heaviness in knowing what is happening with our mom."

"Loss of spousal relationship, time spent looking for lost items, doing tasks that were once his, accompanying him to appointments etc., ongoing frustration with having to repeat myself, loss of retirement plans and travel, financial concerns for the future, sadness and depression (now being treated for same)."

"The disease took hold of my mother who was a very independent, outgoing individual. She at 85 began losing her memory, lost her ability to drive safely, was easily confused.

She was diagnosed with Alzheimer's at 88 years. I became her caregiver, monitoring her life to keep her physically and financially safe. I was devastated to see how the disease was taking away hers and my livelihood. I still, even with her being in a facility, visit with her daily."
"My health has declined since her diagnosis, as a result of stress, putting her needs before mine. My quality of life has definitely deteriorated in terms of social involvement with friends and relatives. My physical capabilities too have dramatically changed since my mom's diagnosis. I have not had the time, effort or desire to exercise like I used to or eat as well. My relationship with my husband has been tense since having to constantly look in on my mother."

"I'm beyond exhausted, and I have no life outside of medical appointments, pharmacy runs, and trips to the grocery store. Friends and family do not understand the extent this level of care takes."

"I'm afraid I'll get in an accident or I'll get sick, and then I won't be able to provide care. I'm always in a state of being on the edge waiting for the next emergency or fire to be put out. My life is chaotic. I wouldn't have it any other way if it means keeping my parents in their own home as they age."

"It feels that all my physical and mental energy is drained by the end of the day. I wake up exhausted as it seems that I have to be on the alert even at night. I have no life of my own. Everything we do revolves around her dementia and Alzheimer's."

Financial burdens:

"I miss a lot of work now and when I do not work, I do not get paid."

"I miss work at least once a week, often more. I pay out of pocket for private help and additional items like technology aids and special programs."

"I have had to take a leave of absence from my job. I no longer have an income."

"I am draining what little retirement savings I had worked for over the years."

"There is always a part of my brain worrying about mom. During her diagnostic process, I missed at least a half-day of work, each week, for about 3 months, to get to appointments."

Care partners observations of the impact dementia has on the person living with the disease at 2023 focus group and 2024 survey.

“There is a loss of independence and personhood for both the person living with mild dementia and their care partner. Roles shift dramatically even in the early phases of disease detection and presentation.”

“He has lost confidence in his ability to manage finances and behave appropriately in social situations so he relies on me to be there to fill in any gaps.”

“She has no independence whatsoever. She lives in a near constant state of fear, anxiety and paranoia.”

“He is quite dependent on me for cooked meals, remembering what he has to do each day, where to store things and where to find things, going to appointments with him, doing all our finances.”

“My mom is now in a care facility for Alzheimer’s. She is not the same person she once was - she ran a business with hundreds of employees, and now she can't even toilet herself. The declines have been so very sad, especially at the start when she could sense it was happening. It always scared her to have Alzheimer’s, so she kept saying "oh this scares me - I hope it's not that". She said this even after we were told she had Alzheimer’s. Basically everything that she had built her life to be has been taken away”.

“My father can’t do the things he loved to do such as grocery shop, garden, cook and eat delicious foods. He is now confined to a bed or chair watching tv or sleeping. He was active and vibrant, and always on the go. Now everything he does from walking to feeding himself to dressing to going to the toilet can no longer be done with privacy or dignity. He can no longer eat/chew the foods he loves to eat. He can no longer whip up gourmet meals with ingredients from his garden. He can no longer email his friends or do his online banking. He gets confused using the tv remote and the telephone. It’s heartbreaking to watch him struggle. His anger and frustration is palatable and understandable. He needs 24/7 assistance with all his life tasks. What kind of “life” is this? We enter the world with such flourish and fanfare, yet we leave the world joyless, without dignity.”

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Comments around current treatments typically focused on social or community "treatments" such as adult day programs or support groups. Caregivers find these services to be helpful in providing them with some relief from their daily caregiving tasks and peer support. While there are some medications designed to treat symptoms (Aricept), we did not hear from anyone who has access to a treatment for MCI or dementia.

5. Improved Outcomes

CADTH is interested in patients 'views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

When people living with dementia were asked about how daily life and quality of life might be improved, there comments were simply a "better quality of life" and "it would be greatly improved!"

From the focus group with care partners in 2023 as well as the survey in 2024, there was discussion around the hope that the future feeds scientific progress for a disease modifying therapy to halt or slow disease progression. Comments included:

"improvement in the ability to diagnose and treat people living with mild dementia with confidence and competence"

"..the advancement of a medication that preserves memory, enables engagement, and extends independent function."

"A medicine that combats the fidgeting and pacing associated with sundowning."

When asked if there would be value in a treatment that would delay progression of the disease, following comments were made:

"It would allow more enriched time with the person living with dementia as well as more time to prepare."

"More years of better quality of life. Perhaps the individual might pass away from some of other cause prior to dementia slowly stealing their life."

"Personally, I would do anything to delay the progression of the disease if I were to be diagnosed. Because there is no "cure" and I've cared for 2 parents with dementia, I would choose to enact MAID so any delay would literally prolong my life."

Finally, one care partner explained it this way “the more time one could have with capacity is a gift.”

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

We have not engaged with anyone who has experience with the drug under review.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

As per the previous question, we have not engaged with anyone who has experience with the drug under review. Clinical trials for this treatment were not offered in Calgary. Without knowing what companion diagnostic tests might be required, it’s difficult to comment, other than to say that caregivers often need to attend these types of tests to ensure the person with the diagnosis is able to find their way, understand the process and provide consent.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

No

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of

Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Kim Brundrit
Position:Collective Impact Lead
Patient Group: Dementia Network Calgary
Date: August 15, 2024

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Donanemab

Indication: To slow the clinical decline associated with Alzheimer's disease (AD) progression in patients with early AD or mild cognitive impairment (MCI) due to AD

Name of Patient Group: International Federation on Ageing

Author of Submission: Elizabeth Lewis

1. About Your Patient Group

The International Federation on Ageing fondly known as "IFA" is an international non-governmental organization (NGO) whose members are government, NGOs, academia, industry, and individuals in nearly 80 countries. Together these organizations represent over 80 million older people. IFA believes that all these members working together are essential to help shape and influence policy and good practices. IFA stands to drive the agenda for the world's population ageing. We are proud to have general consultative status at the United Nations. The International Federation on Ageing is a non-State actor in official relations with the World Health Organization (WHO).

IFA began its operations in 1973 at a time when population ageing, and its social and economic consequences of population ageing were only just beginning to be realised by certain governments. Its origins lie in the organisation of AARP who in the early 1970s sought to find a useful role it could play internationally. IFA has several active portfolios, including : Addressing Inequality; Age-Friendly Environments; Applied Technologies; Combating Ageism; Decent Work for All; Fostering Healthy Ageing; Long-Term Care; Vision Health; IFA in The Decade of Healthy Ageing; and Hearing in Later Life.

2. Information Gathering

Following an in-depth review of Canada's National Dementia Strategy and existing literature on the Canadian caregiving context, a 15-minute, ~50 question survey was created by the International Federation on Ageing (IFA) in collaboration with Eli Lilly Canada Inc. The survey was supported by QuestionPro, which allowed for a variety of question formats to be asked, including multiple choice, Likert scale and rankings, and written responses.

To ensure fair and consensual participation in the survey, a consent statement outlining the topics covered, length of time, and confidentiality of responses was shared with participants. The survey was disseminated using non-probability sampling, with the support of the market research and analytics company, Leger, who shared the survey to their pre-existing network of Canadian caregivers to people living with dementia. The survey was completed by 397 respondents who identify as caregivers for a person with dementia. To our knowledge, no respondents have experience with Donanemab. Furthermore, the survey did not include responses from those who provide care for anything other than dementia, limiting the ability to compare the experiences of dementia care providers with other types of caregivers. The survey was made available from roughly May 1st-June 1st, 2024.

Canadian caregivers for people with dementia responded to the International Federation on Ageing's (IFA) survey on the experiences and perspectives of being a caregiver for a person with dementia. The survey was completed by 397 people. Of the 397 respondents, 108 identified as men (27%), 286 as women (72%), and two as non-binary or gender diverse (0.5%). The reported sexual orientations of respondents varied across the spectrum, with 84.4% of respondents identifying as heterosexual or straight, and nearly 16% identifying as a member of the LGBTQ+ community (including those who are asexual, bisexual, gay, lesbian, pansexual, queer, and demisexual).

The age of respondents varied, with 27% reporting to be between the ages of 56-65 years of age, 20% between 66-75, 18.4% between 46-55, 12.6% between 26-35, 12% between 36-45, 5% between 76-85, and 4% between 18-25, and 0.5% over 86 years of age.

Most respondents reported being of White or European descent at 82.4% of respondents, followed by 5.3% of East Asian descent, and 2.8% of Southeast Asian descent. Those of Middle Eastern, Indigenous, Latin American, Black, or African American, and South Asian descent were all significantly underrepresented composing 0.76%, 1%, 1%, 2.5% and 2.3% respectively.

Following the survey requirements, 96% of respondents reported to be Canadian citizens, with approximately half of all respondents currently residing in Ontario (46%). Following Ontario, the most frequently reported province of residence was British Columbia at 14%, followed by 12% in Alberta, and 10% in Quebec.

The total income of respondents was dispersed across the range of responses, with the highest frequency of respondents (18.9%) making between $80,000- $99,999 before taxes annually, followed by 15.4% making $100,000 - $149,999, 15% making $40,000- $59,999, 10% making $20,000 - $39,999, 9% making $60,000 - $79,999, 8% making $150,000 - $199,999, 4% making $19,999 or less, 4% making $200,000 - $249,999, and 3% making $250,000 or higher annually.

3. Disease Experience

Canadian caregivers' lives are profoundly impacted by the cognitive decline of those they provide care for. IFA's Canadian national survey revealed the significant impact that caregiving has on their daily activities, healthy behaviors, and finances and savings. The following findings highlight the burden experienced by caregivers:

Responsibilities Associated with Caregiving:

- Approximately three quarters of caregivers (74%) spend more than 5 hours a week providing in-person care, with 31% of caregivers indicating that they spend between 5-15 hours a week providing in-person care for a person with dementia.
- More than half of caregivers' state that they are sometimes, often, or always the only person who is available to provide care (63%).
- The most reported task that caregivers provide support with is transportation; transporting the person they care for to medical appointments, leisure activities and social events (77.3% of respondents indicated they perform this task).
- The second most performed task (68%) for caregivers is assisting with domestic duties, including meal preparation, dish washing, grocery shopping, cleaning the home, doing laundry, and cleaning shared spaces.

- The third most frequently reported task (61%) was assisting with medical treatments such as taking medications, engaging in mind-stimulating activities, and engaging in therapeutic practices.
- Almost half of all caregivers (43%) also indicated that they provide support with personal care, including bathing and showering, nail care, foot care, genital care, dental care, grooming, and dressing. Through their written responses caregivers also indicated that companionship, and simply spending quality time together was also a common and important task.

Most respondents (89%) indicated that their responsibilities and tasks as a caregiver have increased in intensity since they have begun caregiving, with nearly half of all respondents marking this increase as moderate or significant (44%).

Impact of Caregiving on Caregivers' Lifestyle:

Dementia caregiving had a range of impacts on the lifestyle choices of Canadian caregivers.

- Half of caregivers (50%) affirmed that their role as a caregiver for a person with dementia has impacted their ability to eat regularly and well.
- Following similar trends 64% of respondents indicated that being a caregiver had impacted their ability to be physically active and over three quarters of respondents (76%) indicated that being a caregiver had impacted their duration and quality of sleep.
- Two thirds of respondents (66%) indicated that being a caregiver had impacted their ability to have meaningful social connections and nearly half of respondents (46%), indicated that being a caregiver had impacted their sexual relationship.
- Most respondents (79%) indicated that being a caregiver had impacted their ability to take vacations, with 26.5% of respondents stating that their ability to take a vacation had been significantly impacted.
- Nearly half of all respondents (49.5%) positively indicated that being a caregiver had impacted their ability to attend their own medical appointments, including doctor, dental, massage therapy, physiotherapy, or a psychologist.

Financial Impact of Caregiving

- 30% of respondents agree, or *strongly* agree that their role as a caregiver has conflicted or impeded their success at work.
- 28% of caregivers agree, or *strongly* agree that their role as a caregiver impacts their ability to gain or hold employment.
- Nearly half of caregivers indicated that they have felt impacted (49%).
- 13% of caregivers stated that their savings have been moderately or significantly impacted by their role as a dementia caregiver.
- 68% of respondents indicated that their out-of-pocket expenses have increased since they started caregiving.

As further supported by the finding that caregiver responsibilities, tasks, and out-of-pocket expenses have increased in intensity since first becoming a caregiver, the introduction of a drug capable of slowing the clinical decline associated with Alzheimer's disease (AD) progression in patients with early AD or mild cognitive impairment (MCI) due to AD, would have a considerable positive impact on caregivers, ideally decreasing the burden of care.

4. Experiences With Currently Available Treatments

There are no currently available treatments that can comparably alter the clinical progression of Alzheimer's disease. While questions regarding the use of therapies or treatment plans for persons living with dementia and their caregivers

was outside of the scope of IFA's research, several written responses highlighted the lack of adequate support and treatment options available to persons living with dementia, and the subsequent impact on caregivers:

- "As dementia becomes more common, I would have expected an "emergency network" would exist to provide support to the caregivers. I remember a situation whereas I spent 90 minutes to get someone to come home to calm down my partner - no emergency help was available except "911". Although reluctant to call, I did because that was the only recourse. I feel that was a misuse of an important resource. What is required, in my humble opinion, is a "24/7 emergency dementia crisis resolution network" to help out caregivers. Sometimes, caregivers get overwhelmed and family members are not always available!"

- "Have to fight for provincial healthcare support, and then, in rare circumstance when support is available, I am generally disappointed with the quality of service provided."

- "Some days are really hard and I don't know where to turn. People listen but they don't actually help. I need help and not words."

- "It is a very vulnerable place for a person to have this disease and they are often immobile. Without proper machines it is very hard to move or transport the person or dress or bathe them. The patient does not always know what is happening so they can get angry or not want to participate."

- " It's VERY expensive. I'm currently paying almost 10K a month for my mothers care. Money will run out soon. Then what? Kick her to the curb? There are no services available. Waiting lists for long term care is a joke."

Ultimately, despite treatments currently being available for prescription for Alzheimer's disease, these are not comparable in outcome to the drug being considered which would alter the clinical progression of Alzheimer's disease

5. Improved Outcomes

A drug that alters the clinical progression of dementia can significantly benefit caregivers by helping to reduce their physical and emotional burdens. Improved patient functioning and cognitive abilities enable patients to maintain independence longer, decreasing the need for consistent care, including hygiene care, eating, transportation, and time spent supervising. Furthermore, a drug like Donanemab can increase caregivers' emotional well-being, offering a sense of hope and relief, and decreasing the anxiety associated with cognitive decline. Delaying further cognitive decline and maintaining function and partial independence can reduce the hours associated with caregiving, providing caregivers with more time and energy to maintain their own social networks and enhance their well-being. Finally, a drug like Donanemab can ideally provide come financial relief for caregivers. Reducing cognitive decline can reduce the costs associated with an increased burden of care, such as home modification, transportation, respite care, and long-term care facilities. Further, caregivers may be able to continue their employment or work more hours, balancing their caregiving responsibilities with their professional lives.

6. Experience With Drug Under Review

The survey conducted by the International Federation on Ageing did not include questions inquiring patient or caregiver experience with Donanemab. Thus, commenting on user's experience with Donanemab is beyond the scope of the IFA.

7. Companion Diagnostic Test

While the patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with Donanemab are beyond the scope of IFA's survey, it is worth noting that caregivers, who are not providing care for a person on Donanemab, highlight the significant burden that providing care has for on their finances, and time. Thus, additional requirements associated with accessing testing facilities must consider the financial and resource-based hardship that caregivers are already experiencing.

8. Anything Else?

The International Federation on Ageing wishes to advocate on behalf of Canadians, and specifically those who provide care for a person with dementia, that the introduction of a drug like Donanemab has the potential to radically improve the lives, networks, and communities of those with cognitive decline and dementia. Alzheimer's disease and dementias impact the mobility, autonomy, financial status, and well-being of those who provide care. Currently, caregivers feel under supported, under resourced, under paid, and overwhelmed. Any initiative that has the potential to significantly and meaningfully improve the conditions of those living with dementia and their care providers, ought to be supported and taken seriously.

Appendix: Patient Group Conflict of Interest Declaration

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   Yes. Eli Lilly contributed to the funding of the project, and Leger contributed to the participant recruitment.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No. All data analysis was completed by the International Federation on Ageing.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Eli Lilly				X
Pfizer Canada and Pfizer Global				X

GSK				X
Cochlear				X
Moderna				X
Sanofi				X
MSD				X
Bayer				X
Biogen				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Elizabeth Lewis
Position: Project and Policy Coordinator
Patient Group: The International Federation on Ageing
Date: **August 9, 2024**

Appendix B: Questions Asked Survey Participants

1) Do currently provide, or recently have provided, care for a person with diagnosed with dementia?
2) What type of dementia does the person with dementia that you provide care for have?
3) How would you best describe the current stage of dementia of the person you provide care for?
4) For the stage of dementia that the person you care for has, do you believe there are adequate resources and treatment options accessibly available for them?
5) Which of the following best describes your Sex?
6) Which of the following best describes your Gender?
7) Which of the following age ranges do you fit in?
8) Which of the following best describes your Sexual Orientation?
9)Which of the following best describes your racial background?
10) Which of the options below applies to your status in Canada?
11) What province or territory do you currently live in?
12) Among the following categories, which best reflects the TOTAL INCOME before taxes, of all the members of your household? Income includes any retirement savings, pension, assets, earnings, public assistance etc.
13) What is your relationship to the person with dementia that you have provided care for in the past 12 months?
14) Where does the person you care for with dementia reside?
15) Rank the sources that have taught you the most about dementia from most informative (1) to least informative (4)?
16) Which of the following best describes your current employment status as a caregiver?
17) How many hours a week do you spend providing in-person care for a person with dementia?

18) If you have employment in addition to caregiving responsibilities- do you feel like your role as a caregiver has conflicted with or impeded your success at work?
19) If you do not have employment in addition to caregiving responsibilities- do you feel like your role as a caregiver impacts your ability to gain or hold employment?
20) Do you feel adequately mentally supported by your employer?
21) Are you satisfied with the time off from work your employer provide you with? (Including vacation days, sick days, family and personal days)
22) How many sick or mental health days are you afforded by your employer annually?
23) How often do you take time off from your paid employment to fulfill your role as a dementia caregiver?
24) Does your employer provide additional benefits or financial support for employees with adult dependents who are critically ill, injured, or in need of end-of-life care?
25) In the past 12 months, rank which tasks you have done from greatest frequency (1) to least frequency (6)
26) In the past 12 months, how frequently are you the only person who is available or able to provide care:
27- 46) Please answer the following questions regarding the severity of impact that caregiving for a person with dementia has had on you as a caregiver:

Questions Regarding Use of Funds	Amount Respondents Spend Annually				
	0$	Less than 500$ annually	Between 500-2000 dollars annually	Between 2000- 3500 dollars annually	More than 3500 dollars annually
As a caregiver, the out-of-pocket money that I have used towards necessary home modifications to accommodate the person with dementia that I provide care for has been:					
As a caregiver, the out-of-pocket money that I have used towards professional health care or rehabilitation services for the person with dementia that I provide care for has been:					
As a caregiver, the out-of-pocket money that I have used towards hiring additional help services for the person with dementia that I provide care for has been:					

As a caregiver, the out-of-pocket money that I have used towards transportation, travel, and accommodations because of caregiving responsibilities has been:					
As a caregiver, the out-of-pocket money that I have used towards prescription or non-prescription drugs for the person with dementia that I provide care for has been:					

Questions Regarding Impacts of Caregiving:	Likert Scale of the Severity of Impact on Caregivers				
	None	Very Mild	Mild	Moderate	Severe
As a caregiver for a person with dementia, my savings or retirement funds have been impacted:					
As a caregiver, my out-of-pocket expenses have increased since I began caregiving					
My responsibilities and tasks as a caregiver have increased in intensity since I began caregiving:					
My hours spent as a caregiver have increased in intensity since I began caregiving: My knowledge of dementia has increased since I began caregiving:					

The resources and community support I access as a caregiver have increased in intensity since I began caregiving:					
My time spent with friends and family has increased in intensity since I began caregiving:					
My time taken away from paid employment has increased in frequency since I began caregiving:					
Being a caregiver has impacted my ability to eat regularly and eat well.					
Being a caregiver has impacted my ability to be physically active.					
Being a caregiver has impacted my duration and quality of sleep.					
Being a caregiver has impacted my ability to have meaningful social connections.					
Being a caregiver has impacted my ability to take vacations.					
Being a caregiver has impacted my sexual relationship(s).					
Being a caregiver has impacted my ability to attend my own medical appointments, including doctor, dental, massage therapy, physiotherapy, psychologist etc.					

Being a caregiver has impacted my ability to attend commitments for religious or spiritual reasons.					

47) In the past 12 months, what coping methods have helped you deal with your caregiver responsibilities (select all that apply):
48) In the previous 12 months, have any of the following sources provided support for you (Please select all that apply):
49) The supports that you receive as a caregiver considers your racial, cultural, or religious needs; provide translators or information in other languages?
50) If it were an available option, I would want to spend less time caregiving?
51) Do you feel adequately supported in your role as a caregiver? Please explain your response:
52) What kinds of support would you like to have more of?
53)What does the public not understand about dementia caregiving:

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0822-00
Generic Drug Name (Brand Name): Donanemab
Indication: people with Mild Cognitive Impairment (MCI) or Mild dementia due to biomarker confirmed Alzheimer's disease (AD)
Name of Clinician Group: Consortium of Canadian Centres for Clinical Cognitive Research (C5R)
Author of Submission: Dr. Michael Borrie, Past President C5R and current executive member, with the executive members of C5R.

1. About Your Clinician Group

Organization Purpose and Website Link:

C5R is a not-for-profit research network that facilitates collaboration and partnerships between pharmaceutical companies and Canadian dementia researchers. C5R research sites conduct clinical trials in the desire to research developing treatments for patients with Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD) as well as other forms of dementia.

C5R - Consortium of Canadian Centres for Clinical Cognitive Research

2. Information Gathering

The information included in this submission is from

1. Publicly available published scientific literature from the randomized controlled trial (RCT) with Donanemab (JAMA 2023;330(6):512-527)

2. Some of the Directors have participated in Advisory Boards to Eli Lilly

3. The Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTDs). For over 30 years C5R members have contributed to the CCCDTDs and the resulting published clinical practice guidelines.

4. The current Directors of C5R have also drawn from their extensive clinical experience, particularly when commenting on section 3, Current Treatments and Treatment Goals, 4, Treatment Gaps, 5 Place and Therapy.

The first draft of the document was written by Dr. Borrie. Dr. Michael Borrie is a clinician researcher and site investigator, with the Cognitive Clinical Trials Group (CCTG), Parkwood Institute, London, Ontario. The CCTG conducts investigator initiated observational studies and pharma sponsored RCTs in people with Mild Cognitive Impairment (MCI) and mild dementia due to Alzheimer's disease (AD). The draft was then read and edited by directors of the executive committee of C5R, who are also clinician researchers or clinician scientists in AD.

3. Current Treatments and Treatment Goals

Canadian Context

The Canadian context has been shaped by five CCCDTDs 1-5, 1989 -2019 and the resulting published clinical practice guidelines. See additional information section for references to the published guidelines.

Non-drug treatments for MCI and Mild dementia

Clinical recommendations and advice to patients and caregivers recommended by the CCCDTD guidelines

1. Regular aerobics/resistive weight exercise
2. Mediterranean style diet
3. Mental stimulation approaches
4. Socialization
5. Attention to restorative sleep practices/sleep hygiene
6. Alcohol or drug reduction/cessation

Drug treatments recommended by the CCCDTD guidelines

The Acetyl Cholinesterase Inhibitors (AChEIs) are indicated for symptomatic treatment for people who have:

- mild to moderate dementia, clinically diagnosed as due to AD
- mixed Alzheimer's and vascular dementia or primary Lewy Body disease (LBD) or mixed AD and LBD
- They are not indicated for frontotemporal dementia.
- The three AChEIs are donepezil, rivastigmine and galantamine.

Memantine is indicated either

- as monotherapy
- combined with an AChEI for moderate/severe clinical AD
- clinical mixed dementia.

The AChEIs and memantine are for symptomatic treatment only. They are not disease modifying in their mechanisms.

There are no treatments available through special access programs at this time.

Ideal Treatment Scenarios

An ideal treatment should target the mechanisms of AD when it is detectable using one or more recognized biomarkers of AD. These biomarkers include cerebrospinal fluid (CSF), positron emission tomography (PET), amyloid imaging and emerging blood biomarkers (eg, p-tau181, p-tau217)

People with No Cognitive Impairment but at Risk

An ideal treatment would be effective to stop progression of the disease in asymptomatic people with biomarker confirmed AD.

People with Cognitive Impairment

An ideal treatment should stop the progression of clinical symptoms of asymptomatic biomarker proven AD and reverse any cognitive symptoms if they arise. An ideal treatment should stop progression of patient's symptoms of subjective cognitive decline (SCD) or symptoms of MCI in people who have biomarker proven AD as the underlying neurodegenerative process for their symptoms.

Slowing of Cognitive Impairment

A less than ideal treatment should slow progression of biomarker proven AD in people at risk without symptoms, or people with SCD or MCI or mild dementia due to AD.

Each of these ideal treatment scenarios with decreasing ability to stop, reverse, or slow the disease, would still reduce the severity of symptoms. They would increase the likelihood of maintaining employment for longer, maintaining independence in instrumental activities of daily living (IADLs) and self-care activities of daily living, reducing burden on caregiver and the likelihood of the eventual need for long-term care

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There are no treatments approved in Canada at this time that stop, reverse or even slow the progression of AD.

The three AChEIs and memantine have modest effects.

From clinical experience, beyond the original 6-month RCTs for each of these compounds, about 40% of patients started on an AChEI alone or in combination with memantine, or memantine alone, have a positive response or stabilization of their progression of the disease, as evaluated by caregivers. This is not blinded information and is potentially biased by positive expectations by caregivers.

Using clinical experience estimates, the side effects to the AChEIs, occur in about 10-15% of people and include, nausea, vomiting, diarrhea and urinary urgency leading to the discontinuation of the medication or the reduction in dose from the maximum recommended dose.

Using clinical experience estimates, the side effects to memantine, occur in 10-15% of people experiencing side effects and include increased confusion, agitation, or constipation leading to the discontinuation or dose reduction from the maximum dose.

A symptomatic response, based on clinical experience can be anticipated for 6-12 months. Following these 6-12 months of improvement, or stabilization of symptoms, there usually will be progressive cognitive decline reported by a family member subjectively and objectively on cognitive tests.

Functional decline measured on Instrumental Activities of Daily Living (IADLs) scales occurs in a parallel manner to what might be expected for the natural course of AD.

There are no treatments at this time to stop, reverse or even slow the course of the disease.

Treatments are needed that will stop and potentially reverse the disease, or slow the disease particularly if it is detected when a person has no symptoms, meets the clinical criteria for SCD or the clinical criteria for MCI.

Adherence to the three AChEIs and memantine would be improved if they were less likely to cause side effects. The current formulations of the three AChEIs and memantine are relatively convenient, either being once a day or twice a day by mouth. Rivastigmine has been manufactured as a topical patch, and applied once a day may reduce side effects and improve adherence.

The provincial drug plan coverages of the above 4 medications vary by province. For instance, in Ontario, memantine is not covered and costs about $4 per day. It's also not covered in BC and it's about the same price, $4/d or $120/month. The rivastigmine patch is also not covered and costs about $4.75/day, $143/month in ON and $6.20/day and $186 month in BC.

Limitations

The main limitation with the above treatments are the occurrence of side effects mentioned above with only modest symptomatic benefits. They do not alter the underlying neurodegenerative process.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Mechanism of Action

Donanemab is an immunoglobulin G1 monoclonal antibody directed against insoluble modified, N-terminal truncated form of β-amyloid and aids plaque removal through microglial mediated phagocytosis.

In the published RCT, the serial amyloid PET scans showed rapid clearance of amyloid from the brain and the p-tau217 plasma biomarker improved in a normalizing direction. The biomarkers analyses showed that Donanemab modifies in a positive manner the biomarkers of AD.

With this confirmation of the mechanism of action, Donanemab will complement the other available treatments which are symptomatic treatment in their actions. If approved in by Health Canada, Donanemab could be one of the first disease modifying treatments (DMTs) for AD in Canada.

Donanemab is one of two DMTs to demonstrate slowing of the underlying disease process with robust randomized clinical trial evidence thus far.

The CCDTD guidelines recommend the AChEI drugs be initiated in people with mild dementia but not be initiated in people with MCI.

Donanemab could be one of the first two approved in Canada DMTs indicated for people with MCI due to biomarker proven AD and could be one of the first-line DMTs treatments for MCI due to AD.

Donanemab will be indicated for people with MCI or mild dementia due to biomarker proven AD. It will be given to patients with MCI or mild dementia due to biomarker proven AD, regardless of whether or not patients were intolerant to an AChEI or whether AChEIs were contraindicated.

Donanemab is expected to cause a shift in the current treatment paradigm. The approval of a disease-modifying therapy will highlight the incredible gaps in care that exist for early assessment and treatment of Alzheimer's disease in Canada. Whereas other leading causes of death and disability such as stroke or cancer have well-organized provincial agencies and clinical care pathways, 12/13 Canadian provinces and territories do not have a dementia care pathway. The paradigm shift includes not only a drug that can modify the disease course but requires the health care system to become better organized around dementia diagnosis and management from early recognition of symptoms and risk factors to long-term care planning.

Donanemab treatment will not preclude treatment with AChEI. This is a therapy that can work in concert with the four existing symptomatic therapies.

Lecanamab is another DMT that is being reviewed by Health Canada. Since there are no other drugs for people with symptomatic treatment Lecanamab and Donanemab are the 2 DMTs for MCI due to biomarker proven AD, There is no other treatment to recommend before recommending Donanemab or Lecanemab for people with MCI. For patients who have already progressed to mild dementia due to biomarker proven AD, there is no advantage to the patient to be recommended AChEIs before initiating Lecanemab or Donanemab since their AD pathological process will continue to progress. Lecanemab and Donanemab could slow the progression of their MCI and mild dementia to moderate or severe dementia.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Based on the current Donanemab RCT data - Most Likely to Respond:

Patients with MCI due to biomarker proven AD and secondly patients with mild dementia due to biomarker proven AD are most likely to respond to Donanemab. With the current RCT evidence, these patients with MCI and mild dementia due to biomarker proven AD are the ones most in need of an intervention.

Stage of Disease

A trial of Donanemab (Trailblazer 3) conducted in the US and Japan in cognitively unimpaired people (Preclinical AD) will end in 2027/2028. The RCT will determine whether beginning Donanemab even earlier in people with beta amyloid pathology and no cognitive impairment, but who are at risk of AD, might benefit.

The most recent RCT evidence for Donanemab did not inform whether Donanemab would be a benefit to people who have moderate or severe dementia due to biomarker proven AD. It is generally considered that slowing of AD pathology in the moderate to severe stage is too late to make a clinically important difference.

Issues Relating to Diagnosis

The clinical diagnosis of MCI or mild dementia needs to be made by a physician with expertise in the field of neurodegeneration/ dementia.

Patients best suited for the treatment with Donanemab need to be identified clinically first, as meeting the established clinical criteria for MCI or the established clinical criteria for mild dementia. Because of long waiting lists for qualified physicians, a triage system for rapid referral may need to be established.

Patients with MCI have a history of progressive cognitive decline, most commonly involving short-term memory.

Objective evidence of this progressive decline is confirmed by a common Canadian neurocognitive screening test called the Montreal Cognitive Assessment (MOCA). A score of less than 26/30 would be in the range for a diagnosis of MCI.

Repeated administration of the MOCAs or similar instruments can confirm objective evidence of improvement, stabilization or progressive decline.

Corroborated information obtained from a caregiver, indicating that a patient's cognitive impairment, compromising their independence for one or more of their known performance on IADLs, meets the criteria for dementia. Generally, it would be considered mild dementia if the standardized mini-mental state exam (SMMSE) is 20/30 or higher.

A patient being considered as a possible patient to receive Donanemab must have MRI-based neuroimaging. Specifically, a baseline MRI scan is necessary if Donanemab is a treatment that a patient and their caregiver is considering with their physician who is knowledgeable and willing/able to prescribe Donanemab therapy. The MRI with susceptibility weighted images (SWI), or equivalent sequences, is to rule out the presence of significant silent brain haemorrhage (more than 4 microbleeds or evidence of macro haemorrhage should be an exclusion from treatment due to bleeding risk).

Because of the risks for adverse events, initiation of treatment should be made by a physician with expertise in the field of neurodegeneration/dementia. The baseline MRI needs to be completed to rule out more than 4 microbleeds, macrobleeds superficial siderosis or severe white matter disease.

The presence of amyloid pathology (≥37 Centiloids) was assessed with F-floretapir[13] or ^{18}F-florbetaben positron emission tomography(PET), and presence of tau pathology was assessed by F-florau cipir PET imaging with central image evaluation.

Amyloid PET scans are expensive and have not been clinically available in most provinces. Hopefully blood biomarkers for beta amyloid 42 or phosphorylated-tau217 will become recognized and accepted as a proxy for Amyloid PET scanning or Lumbar puncture. (i.e. Precivity AD, not yet approved in Canada)

Cerebral Spinal Fluid (CSF) is likely to become more clinically available. It is dependent on specialists who have the expertise to do a lumbar puncture (LP) to obtain the CSF for analysis. More specialists are being trained to perform LPs. A national reference lab for the analysis of CSF biomarker is available in Vancouver. It is anticipated other centres will be approved in the future.

The future approval of and clinical availability of one or more blood biomarkers for AD might reduce the future need for expensive PET amyloid scans and time-consuming lumbar punctures. Until such an approval of one or more blood biomarkers and clinical availability is widely available, determination of AD pathology at baseline will be dependent on amyloid PET scans or CSF analysis.

Companion Diagnostic Tests

The companion diagnostic tests required highlight as above – MRI, brain using SWI sequences or equivalent sequences to rule out more than 4 microbleeds, and/or macrobleeds, plasma p-tau181 or p-tau217 as a screening test to inform whether to proceed to amyloid PET scan or lumbar puncture with CSF analysis. Plasma, p-tau217 has been shown to be more sensitive and specific than p-tau181. Regularly scheduled and as required urgent MRI must also be available to monitor potential side effects of ARIA which tend to occur in the first 6 months of treatment.

Genetic testing for ApoE status has been recommended. Patients with the E4 allele of the ApoE gene are at higher risk of Amyloid Related Imaging Abnormality (ARIA) and are also at higher risk of progression to dementia if diagnosed with AD pathology. ApoE genetic status will need to be accounted for to tailor patient discussions about benefits and risks of donanemab therapy. ApoE testing is available in Canada.

Under Diagnosis

Cognitive impairment in older individuals is generally underdiagnosed. It is sometimes unrecognized or not acknowledged by the person who may have lack of insight to their impairment.

There is a stigma against dementia diagnosis. Caregivers may dismiss the onset of short-term memory impairment as being “just due to old age”.

Some family physicians are uncomfortable doing the clinical assessments and screening neurocognitive tests such as the MOCA. The MOCA assessment takes at least 10 minutes and not easily accommodated in family physician’s short appointment times.

A diagnosis requires additional input, quite separately, from a knowledgeable partner/spouse, daughter or son, or other family member or friend who knows the person well.

There are ongoing subgroup analyses from the RCT to determine whether some subgroups are more likely to exhibit a response than others.

There is also a lack of evidence on patients outside of the clinical trial criteria. For instance, patients with young onset dementia under the age of 60 (which was the cutoff for the inclusion criteria for the published trials). There is no data on atypical presentation of Alzheimer's disease, such as logopenic progressive aphasia, or posterior cortical atrophy, which often have underlying Alzheimer's pathology. Specific studies tailored to these populations will be needed to guide application of DMTs for AD.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcome Measures

The outcome measures used in clinical practice are usually briefer, less in-depth assessments, than those used in RCTs particularly as it applies to measures of cognition. In Canadian clinical practice, the MOCA is the most common cognitive outcome measure used in primary care and specialist practices, such as Memory Clinics.

The total score on repeated MOCA over months and years can be followed between primary care and specialist memory clinics to confirm cognitive improvement, stability or decline. The MOCA correlates with the more in-depth instruments used in clinical trials.

There are various clinical functional measures, including the Lawton-Brody Instrumental Activities of Daily Living Scale, the Disability Assessment for Dementia (DAD). The ADCS MCI-ADL scale is often used in clinical trials and could be also used in clinical practice to measure functional change over time with repeated measurements. However, the administration of this scale time-consuming and may not be practical in everyday clinical practice. A simplified scale that assesses daily function will be very useful in monitoring patients on treatment.

The frequency of monitoring of clinical response is probably once every 6 months with one of the above scales (i.e. MOCA plus DAD) while monitoring for side effects may need to be more frequent , especially the first 6 months after initiation of treatment.

Clinically Meaningful Response Findings

Clinically meaningful responses based on the RCT would include, slowing of cognitive decline, slowing of functional decline and maintenance of independence in IADLs over time.

There will be some variability between physicians as to what they consider a clinically meaningful response. However, when considering an individual patient, there is no comparator to know what that person's natural progression of AD might have been in the absence of treatment.

If the physician (family physician or specialist) following a person over time, using repeated questionnaires or other objective measures, they may be able to determine a plotted slope of decline on these scales. Continued, repeated measures after initiation of treatment, might show a shallower trajectory of decline on the cognitive scale(s) and IADL scale(s) suggesting slower decline or stabilization of decline.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Discontinuation/Endpoints

From the Donanemab RCT, clearance of amyloid on repeat amyloid PET scan was confirmed. Early significant changes on both brain amyloid PET scans and P-tau217 blood test results could be used for clinical monitoring of therapy. However, for clinical practice this is not practical at present because the cost and lack of availability of amyloid PET scans.

Progression from MCI or mild dementia due to biomarker proven AD to moderate or severe dementia could be another endpoint. Progression of disease with increasing dependence in IADLs and later dependence in self-care ADLs could be a further treatment endpoint. Admission to long-term care facility could be an endpoint.

A clinical endpoint-based termination criterion, or a time-based criterion could be a practical solution. However, long-term outcome data will be needed to better guide the decision on treatment duration.

Treatment Pause/Discontinuation

Adverse events such as asymptomatic or symptomatic Amyloid Related Imaging Abnormality – edema (ARIA-E) or asymptomatic or symptomatic Amyloid Related Imaging Abnormality-hemorrhage (ARIA-H) are detected on urgent MRI done at the time of onset of acute new neurological symptoms. ARIA-E and ARIA-H while on treatment, would be a reason to pause treatment. Once ARIA-E and ARIA-H and any acute symptoms have resolved and repeat MRI have confirmed radiographic resolution of ARIA-E and ARIA-H, resumption of treatment can be considered with the patient and caregiver. The resumption of treatment can be considered with the patient and caregiver. This was the study protocol within the clinical trial and other RCTs with other similar DMT compounds. ARIA-E and ARIA-H are more likely to occur within the first 6-months of initiation of treatment and less likely to occur after one year on treatment.

Objective confirmation of ARIA-E and ARIA-H is by MRI scan done urgently at the time of the onset of symptoms. New microbleeds while on treatment and particularly macrobleeds could be additional reasons for discontinuing treatment. Appropriate Use Guidelines for the US are being drafted and will be published.

5.5 What settings are appropriate for treatment with donanemab? Is a specialist required to diagnose, treat, and monitor patients who might receive donanemab ?

Specialists required

Specialists are required for assessing patient's suitability for Donanemab therapy. They include neurologists, geriatricians, geriatric psychiatrists who have a special interest, training and experience in making the clinical diagnosis of MCI and mild dementia and who have training in the interpretation of the Alzheimer's disease biomarkers (e.g. p-tau181/p-tau217, CSF interpretation and amyloid and tau PET interpretation), and have the knowledge to appropriately manage people experiencing side effects of ARIA-E and/or ARIA-H

Initially confirmation of diagnosis by a specialist experienced with the interpretation of appropriate Alzheimer's disease biomarkers is important. Family physicians working in dementia assessment clinics who have acquired added competency in management of dementia could be included.

The Donanemab RCT required 6 additional scheduled MRI's for safety over 18 months, particularly monitoring of ARIA. Centres giving Donanemab must be able to access MRIs reliably.

Radiologists trained in identifying microbleeds on the baseline MRI susceptibility weighted images are necessary before proceeding to treatment. Neuroradiologists and community radiologists trained and educated in recognizing ARIA-E and ARIA-H are necessary as part of the team managing patients initiated on Donanemab. Trained neurologists, geriatricians, geriatric psychiatrists, anesthetists and possibly nurse practitioners able to perform LP for CSF collection in an outpatient setting need to be available, particularly when PET imaging in not available.

Where PET imaging is available, nuclear medicine physicians will need to be trained in the interpretation of amyloid PET scans as to whether amyloid PET scans meet the threshold for being positive or negative on the centiloid scale or equivalent scale.

Radiologists, educated on and able to quickly interpret baseline MRI scan susceptibility weighted images for microbleeds, need to be in place. They also need to be able to read subsequent urgent MRI scans for patients on treatment who develop new neurologic symptoms which might be due to ARIA-E or ARIA-H.

Infusion Centres

Donanemab is administered intravenously every 4-weeks. From the RCT it was for a period of 76 weeks.

Infusion centres need to be available either in the hospital or outpatient setting with nursing staff educated to observe for local infusion reactions or systemic reaction, particularly with or after the first few infusions.

There will need to be linkages between the specialist diagnosing people with MCI or mild AD due to biomarker proven AD and a prescribing specialist if it is not the same as the diagnosing specialist. The trained radiologist for the baseline MRI and the infusion centre should be linked if there are any adverse reactions with the infusion. As well, the patient's primary care physician, and prescribing physician need to be linked in if there are any new neurologic symptoms after or between infusions.

Additionally, prescribing physicians must have some mechanism for after-hours care. For example, if part of a call group, then members of the call group will need to be aware of Donanemab and ARIA E and ARIA-H.

6. Additional Information

Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer's Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512–527. doi:10.1001/jama.2023.13239

CCCDTD4 *Canadian geriatrics journal : CGJ* vol. 15,4 (2012): 120-6. doi:10.5770/cgj.15.49

CCCDTD5 - Alzheimers Dement. 2020;16(8):1182-1195. doi:10.1002/alz.12105

MOCA - mocacognition.com

Disability Assessment in Dementia; Gelinas et al, Am J Occup Ther 1999

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Mr. William Jagger, C5R in collaboration with Dr. Michael Borrie assisted to collate the responses from the executive committee members of C5R.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

   C5R has received financial payments over the last 2-years from the following pharmaceutical companies for completing scientific reviews of study protocols

   Facilitating connections between potential C5R clinical trial site and pharmaceutical companies.

   Supporting recruitment of participants to clinical trials.
   Supporting regular telephone calls with participating C5R site in a trial for recruitment and retention of participants
   Clinical trials funding to conduct clinical trials, under contract, are paid to affiliated research organizations and managed to support the clinical trials research team at the research site.
   Immediate from pharma companies.

Sponsor	Protocol
AbbVie	M22-721 (HARBOR)
Acumen Pharmaceuticals	ACU193-201 (ALTITUDE-AD)
Alector	AL002-02
Alector	AL002-LTE
Alzheon Inc	ALZ-801-AD301 (APOLLOE4)
Alzheon Inc	ALZ-801-AD351 (APOLLOE4-LTE)

Anavex	2-73-AD-004
Anavex	2-73-AD-EP-004
Otsuka Pharmaceuticals Inc.	20-AVP-786-307 (ASPECT)
Biogen	221AD305 (ENVISION)
Biogen	221AD304 (EMBARK)
Biogen	247AD201 (CELIA)
Cerevel	CVL-871-2001
Eisai Inc	BAN2401-G000-201
Eli Lilly	15T-MC-AACH (TRAILBLAZER EXT)
Eli Lilly	15T-MC-AACI (TRAILBLAZER-ALZ 2)
Eli Lilly	I9X-MC-MTAE
Eli Lilly	J1G-MC-LAKD (TRAILRUNNER-ALZ 2)
Eli Lilly	J1G-MC-LAKF (TRAILRUNNER-ALZ 3)
GlaxoSmithKline Inc.	219867 (PROGRESS-AD)
Greenvalley	GV971-007 (GREEN MEMORY)
Hoffmann-La Roche Limited	BP44745 (GABriella)
Hoffmann-La Roche Limited	WN41874 (OpenRoad OLE)
Hoffmann-La Roche Limited	WN42171 (POSTGRADUATE)
Hoffmann-La Roche Limited	WN42444 (Skyline)
IGC Pharma LLC	IGC-AD1-P2 BIDAG
IntelGenx	IGX-CLI-2017-001 (BUENA)
Janssen	63733657ALZ2002 (AUTOMONY)
Novo Nordisk, Canada Inc.	NN6535-4725 (EVOKE Plus)
Novo Nordisk, Canada Inc.	NN6535-4730 (EVOKE)
Cassava	PTI-125-06 (REFOCUS-ALZ)
Cassava	PTI-125-10 (OLE)
WAVE Life Sciences UK Limited	WVE-004-001

Declaration for Clinician 1

Name: Dr. Michael Borrie
Position: Past president and current Director, C5R
Date: Aug 8, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai (as a consultant)			X	
EISAI (paid to the institution as a clinical trials site investigator)				X
Eli Lilly (as a consultant		X		
Biogen (as a consultant)		X		
Biogen (paid to the institution as a clinical trials site investigator)				X
Roche		X		
Janssen (paid to the institution as a clinical trials site investigator)				X
Alector (paid to the institution as a clinical trials site investigator)				X

* Place an X in the appropriate dollar range cells for each company.

Clinical Trials funding, from pharma companies to conduct clinical trials under contract with the Cognitive Clinicial Trials Group at Parkwood Institite' is paid to the Lawson Health Research Institute.

Declaration for Clinician 2

Name: Robin Hsuing
Position: President, C5R
Date: 08-08-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai (as a consultant)		X		
Eli Lilly (as a consultant)		X		
Roche (as a consultant)	X			
NovoNordisk (as a consultant)	X			

Cassava (paid to the institution as a clinical trials site)				X
Biogen (paid to the institution as a clinical trials site)				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Andrew Frank
Position: Secretary/Treasurer
Date: Aug 8, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Lilly Canada		X		
Eisai Canada		X		
Roche Canada	X			
Novo Nordisk	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Stephen Pasternak
Position: Chair, Protocol Review
Date: Aug 8, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eli Lilly (Consultant)	X			

Cassava (to the institution as a clinical trials site investigator)			X	
Zywie Bio LLC (to the institution as a clinical trials site investigator)				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: John Marotta
Position: Member Finance Committee, Protocol Assessment and Review Committee
Date:
Aug 8, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eli Lilly (as a consultant)		X		
Biogen (clinical trials paid to institution only)			X	
Cassava (clinical trials paid to institution only)			x	
Optina Diagnostics clinical trials paid to institution only)			x	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Alex Henri-Bhargava
Position: Director at Large
Date: Aug 8, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Eisai (Consulting)		X		
Eli Lilly (Consulting)	X			
Roche (Consulting)	X			
NovoNordisk (Clinical trial funding)*				X*
Canadian Coalition for Seniors' Mental Health (Clinical Guidelines Development)	X			
Intelgenx (Clinical trial funding)*				X*
Cerevel (Clinical trial funding)*				X*
Anavex (Clinical trial funding)*				X*
Green Valley Shanghai (Clinical trial funding)*				X*
Canadian Consortium on Neurodegeneration in Aging				X*
Centre on Aging and Brain Health Innovation (Research grant)			X*	

* Clinical trials funding from pharmaceutical companies and non-governmental agencies to conduct clinical trials and research under contract with the Clinical Trials Unit at the Royal Jubilee Hospital is paid to the Vancouver Island Health Authority. Compensation for Dr. Henri-Bhargava's involvement is paid to him by the Health Authority and not directly by funders.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0822-000
Generic Drug Name (Brand Name): Donanemab
Indication: Alzheimer's disease
Name of Clinician Group: Canadian Consortium on Neurodegeneration in Aging
Author of Submission: Eric Smith, MD

1. About Your Clinician Group

The Canadian Consortium on Neurodegeneration in Aging (**CCNA**), a CIHR-funded network with collaborating partners such as the Alzheimer Society of Canada and Brain Canada, was formed in 2014 by more than 350 clinicians and researchers throughout Canada who came together to accelerate progress in research on age-related neurodegenerative diseases (ccna-ccnv.ca). CCNA's scientists are often referred to the key scientific experts and opinion leaders in all aspects of dementia research CCNA's leading vision is to significantly reduce the burden of age-related neurodegenerative diseases of Canadians by accelerating the discovery, innovation, and the adoption of new knowledge. We aim to position Canada as a global leader in increasing our understanding of neurodegenerative diseases, working towards prevention, and improving the quality of life of those living with dementia.

To achieve the CCNA's vision, it has been conducting high quality research to understand and prevent dementia as early as possible, and to improve the quality of life and care of those living with dementia while understanding the various related ethical, legal, and social issues. The CCNA works to effectively translate significant findings in order to reach out to the public, interesting organizations, and people with lived experience, and disseminate knowledge to these various audiences. CCNA has received international peer review and been renewed by the Canadian government twice. It has now begun its phase 3 (2024-2029).

2. Information Gathering

In April 2024 the CCNA commissioned an initiative on Preparedness for Alzheimer Disease Modifying Therapies in Canada, to synthesize information on the Alzheimer's disease (AD) modifying therapies lecanemab and donanemab, with the goal of identifying gaps in knowledge about application of these treatments, preparedness of the Canadian health system, and areas for future investigation with an emphasis on research that will be most applicable to the Canadian health system. A Steering Committee was formed, and working groups were created to examine clinical effectiveness, patient selection, subgroup effects, diagnosis and management of amyloid-related imaging abnormalities (ARIA), the number of potentially eligible patients by province, and equitable access to the potential benefits of therapy.

This clinician and researcher input to CDA has been prepared by the CCNA Steering Committee for Canadian Preparedness for Alzheimer Disease Modifying Therapies, and reviewed and approved by the CCNA Research Executive committee. Input from the working groups of this initiative is expected by September 2024. The results of our initiative will be posted on the CCNA website, released to the public for comment, published on a preprint server, and submitted for publication in a Canadian peer-reviewed medical journal.

The information in this document is based on Canadian expert opinion, review of the TRAILBLAZER-ALZ 2 trial publication and appendix (Sims et al. JAMA 2023;330:512-527), TRAILBLAZER-ALZ 2 trial protocol, a consensus statement on appropriate use of donanemab published by a group of American investigators (Cummings J et al. J Prev Alzheimers Dis 2023;10:362-377), a report by the RAND corporation on dementia care in Canada (Liu JL et al, RAND Research Report 2019), and a peer-reviewed publication on the preparedness of Canada for AD disease-modifying therapies (Black SE et al, Can J Neurol Sci 2023:1-8).

The CCNA Steering Committee for Canadian Preparedness for Alzheimer Disease Modifying Therapies is chaired by Dr. Eric Smith, MD, MPH, a dementia neurologist with expertise in vascular dementia and cerebral amyloid angiopathy. The Vice Chair is Dr. Howard Chertkow, MD, dementia neurologist and the Scientific Director of the CCNA. Other Steering Committee members include Dr. Natalie Philips, PhD (neuropsychologist with expertise in cognitive assessment and diagnosis), Dr. Howard Feldman, MD (dementia neurologist and expert in designing and conducting trials for AD).

3. Current Treatments and Treatment Goals

AD is a progressive neurodegenerative disease that is marked by accumulation of senile plaques, composed of beta-amyloid, and neurofibrillary tangles, composed of aggregated tau.

Currently, there are two approved medication classes for AD in Canada: the cholinesterase inhibitors and memantine.

The cholinesterase inhibitors are donepezil, galantamine, and rivastigmine. These drugs act to increase the concentration of acetylcholine in the synapse. They are believed to have a cognitive enhancing effect, but do not modify the course of the disease. In other words, the rate of cognitive decline is not altered by these medications. Once treatment is stopped symptomatic benefits are lost. They do not have sustained benefits or significant evidence that they modify the underlying disease biology. Clinically, this class of drugs is felt to provide modest symptomatic benefits. The primary outcome for trials of the cholinesterase inhibitors was the change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). According to Cochrane reviews, treatment with cholinesterase inhibitors for six months “produced improvements in cognitive function, on average -2.7 points (95%CI -3.0 to -2.3), in the midrange of the 70 point ADAS-Cog Scale”. Cholinesterase inhibitors are covered by drug insurance programs for older Canadians, but most provinces require that a special authorization form be completed for their use. The Consensus Canadian Conference on Dementia Diagnosis and Treatment of Dementia (CCCDTD) guidelines, 4th edition, addressed the use of cholinesterase inhibitors, stating that they “recommend a trial of a cholinesterase inhibitor for most patients with AD (Grade 1A)” (Gauthier S, et al. Can Geriatrics Journal 2012;15:120-126).

The other medication approved by Health Canada for the treatment of dementia due to AD is memantine. Memantine blocks NMDA receptors. Like the cholinesterase inhibitors, memantine is thought clinically to have a modest symptomatic benefit in more advanced AD without modifying the course of the disease. According to a Cochrane systematic review, “high-certainty evidence from up to 14 studies in around 3700 participants consistently shows a small clinical benefit for memantine versus placebo: Clinical global rating (CGR): 0.21 CIBIC+ points (95% confidence interval (CI) 0.14 to 0.30); cognitive function (CF): 3.11 Severe Impairment Battery (SIB) points (95% CI 2.42 to 3.92); performance on activities of daily living (ADL): 1.09 ADL19 points (95% CI 0.62 to 1.64); and behaviour and mood (BM): 1.84 Neuropsychiatric Inventory (NPI) points (95% CI 1.05 to 2.76)” (McShane R, et al. Cochrane Database Syst Rev 2019;3:CD003154). Memantine is not covered by most provincial formularies, the exception being Québec. Therefore, according to our expert knowledge this drug is not widely used in Canada. The Canadian Consensus CCCDTD, 4th edition, recommends that “combination therapy of a cholinesterase inhibitor and memantine is rational (as the medications have different mechanisms of

action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B)" (Gauthier S, et al. Can Geriatr J 2012;15:120-126).

Some medications are used to off label to treat behavioural complications of dementia, including antidepressants and antipsychotics. However, these medications not labelled for the treatment of AD, and do not modify the course of functional and cognitive decline in AD.

Non-pharmacological treatments for dementia include supportive care, advance care planning, and cognitively stimulating therapies (such as art therapy and recreational therapy). However, none of these therapies have been shown to modify the accumulation of senile plaques and neurofibrillary tangles in AD.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The main limitation of current pharmacological and nonpharmacological treatments for AD is that they treat symptoms but do not modify the course of the disease. The cholinesterase inhibitors and memantine improve cognition, as demonstrated by higher mean scores on the ADAS-Cog in clinical trials, but the rate of decline over the longer term is not altered. The lack of a disease modifying therapy is a major unmet need. AD is a common disease. According to the 2024 Alzheimer Society of Canada Landmark Report #2, in 2020 there were more than 650,000 persons living with dementia and 123,800 new cases per year (https://alzheimer.ca/en/the-many-faces-of-dementia-in-canada-landmark-study-volume-2), of which a majority were diagnosed clinically with AD. Addressing the unmet need for a disease modifying therapy for AD could improve the lives of hundreds of thousands of Canadians.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The approval of donanemab would shift the current treatment paradigm. There are no current Health Canada approved drugs that modify the course AD.

The mechanism of action of donanemab is unique compared to other Health Canada approved treatments for AD. Donanemab is a monoclonal antibody that binds to a form of beta-amyloid found in senile plaques, triggering the immune system to remove them from the brain. This is complementary to the mechanism of action of the cholinesterase inhibitors, which increased levels of the neurotransmitter acetylcholine, and memantine, which blocks NMDA receptors.

Donanemab would be used as a complement to existing therapy with cholinesterase inhibitors. In the TRAILBLAZER-ALZ 2 trial, most patients were concurrently taking cholinesterase inhibitors. Based on their very different mechanisms of action, there is no reason to believe that there would be drug interactions between donanemab and the cholinesterase inhibitors.

Donanemab has only been proven to be effective in patients in the early stages AD. In the TRAILBLAZER-ALZ 2 trial, participants were required to have a diagnosis of mild cognitive impairment or mild dementia due to AD, the presence of cerebral beta-amyloid based on a positive amyloid PET scan (with the ligands florbetapir or flobetaben), the presence of cerebral tau as diagnosed on flortaucipir-PET, and a Folstein MiniMental Status exam score of 20 to 28. An MRI was required to demonstrate the absence of severe white matter, disease, >4 cerebral microbleeds, more than 1 area of superficial siderosis, or any macrohemorrhage.

Prescribing donanemab in clinical practice will require substantial changes in Canadian dementia systems of care. In the CCNA Preparedness for Alzheimer Disease Modifying Therapies In Canada Initiative, Work Groups will be reviewing these changes in order to synthesize current information and provide a Canadian agenda for research on adaptations in care paradigms, with plans for a full report to be released in fall 2024. Based on our current review of the literature, we anticipate that the most impactful changes to Canadian clinical practice will be:

- Testing to confirm the presence of brain beta-amyloid: Currently, AD is diagnosed clinically based on a compatible clinical syndrome (cognitive impairment identified by clinical history and objective cognitive assessment, that interferes with functioning in work or usual activities, and that represents a decline from previous levels of functioning) which is not explained by other neurologic, medical, psychiatric disorders, usually informed by the results of routine laboratory testing for metabolic or endocrine mimicking conditions (e.g., hypothyroidism, vitamin B12 deficiency) and a brain CT or MRI scan to exclude a mass lesion or significant cerebrovascular disease. Thus, AD is a clinical diagnosis made after excluding other conditions. To prove that beta-amyloid, the target for the drug, is present in the brain would require Canadian patients to have increased access to either amyloid PET imaging or lumbar puncture with CSF analysis of beta-amyloid and tau. Currently, these AD tests are only rarely used in clinical practice. There is limited capacity in Canada for amyloid PET testing, due to the small number of PET scanners and high expense. A research paper found that there would be higher capacity in Canada for CSF testing than PET (Black SE, et al. Can J Neurol Sci 2023:1-8); however, capacity for CSF testing is still probably less than what would be needed to test all Canadians who could potentially benefit from the drug. There is fast paced development of blood-based sensitive measures of amyloid and phospho-tau that are highly correlated to amyloid PET results. Their promise may help address this need by providing more accessible non-invasive testing alternatives (Hansson O, et al. Nat Aging 2023;3:506-519).
- Testing to confirm the presence of brain tau: Confirming the presence of brain tau is not routinely done in Canada when making the diagnosis of AD. In the TRAILBLAZER-ALZ 2 trial, flortaucipir-PET was used to diagnose cerebral tau. However, in Canada neither flortaucipir nor other tau ligands have been approved by Health Canada for use. Tau can also be detected in the CSF, but the capacity for lumbar puncture for CSF testing would likely need to be increased. There has been rapid progress in blood markers of tau, which may become ready to enter clinical practice in the near future (Hansson O, et al. Nat Aging 2023;3:506-519).
- Requirement for more frequent MRI scans: In the TRAILBLAZER-ALZ 2 trial, patients had 5 MRI over 18 months, not including a diagnostic and baseline MRI before treatment, to monitor for radiological signs of ARIA, the most common complication of donanemab therapy. ARIA can cause serious brain edema or hemorrhaging. In the US the prescribing information calls for similarly intensive MRI followup to identify this problem as patients may be asymptomatic or symptomatic with this complication and management depends on its identification. In current dementia practice in Canada, only one brain image (most commonly CT rather than MRI) is needed diagnostically to exclude conditions other than AD. Even though followup MRI scans may be shorter (average 10-15 minutes acquisition time, depending in the scanner model) compared with diagnostic scans (15-20 minutes acquisition time), this requirement for multiple MRIs will strain Canadian capacity for MRI scans, resulting in decreased access to donanemab therapy or longer wait times for MRIs for other conditions.
- Requirement for drug infusion every 4 weeks: This will require access to a clinic or day medicine program for infusions, or arrangement for home intravenous infusion.

The requirement for access to beta-amyloid testing, MRI scans, and intravenous infusions will probably require treatment in specialized centers in larger urban areas, and this has the potential to exacerbate geographic and other disparities in access to care in Canada.

We are aware that another drug that removes beta-amyloid, lecanemab, is also under review by the Canadian Drug Agency. Like donanemab, lecanemab is a monoclonal antibody that is designed to remove beta-amyloid from the brain in patients with Alzheimer's disease. Most patients that could be treated with donanemab would also be eligible for treatment with lecanemab. Because both drugs have a similar mechanism of action, patients should be treated with one drug or the other, not both. The clinical benefit of each drug seems similar. Although the clinical trials of donanemab and lecanemab used different primary outcomes, when the effect is expressed as a percentage of decline compared with the placebo group the magnitude of benefit was close to the same: donanemab slowed progression by 22.3% versus placebo in the combined group (across all levels of brain tau) on the integrated Alzheimer's Disease Rating Scale (iADRS), while lecanemab slowed progression by 27.1% versus placebo on the Clinical Dementia Rating Sum of Boxes (CDR-SB) (CLARITY-AD trial; van Dyck et al NEJM 2023;388:9-21). The TRAILBLAZER-ALZ 2 trial reported change in CDR-SB as a secondary outcome; on that measure, which matches the primary outcome of the CLARITY-AD trial of lecanemab, donanemab slowed progression by 28.9% compared with placebo. However, the risk of side effects of amyloid-related imaging abnormalities (ARIA; see section 5.4 for more information on ARIA) may be higher with donanemab. In the TRAILBLAZER-ALZ 2 trial of donanemab, ARIA with edema (ARIA-E) was detected on magnetic resonance imaging (MRI) in 24.0% and ARIA with hemorrhage (ARIA-H) was detected in 31.4%), while in the CLARITY-AD trial of lecanemab ARIA-E was detected in 12.6% and ARIA-H in 17.3%. Some caution is needed when comparing these numbers because, even though definitions of ARIA and MRI screening frequency were similar across the trials, the drugs were not directly compared to each other and many cases of ARIA are asymptomatic or only mildly symptomatic. Donanemab is infused once every 4 weeks, while lecanemab must be infused more frequently, once every 2 weeks. The lower infusion frequency of donanemab compared with lecanemab will likely be attractive to patients and would also reduce costs for the health system. More research is needed to compare ARIA rates and outcomes between these drugs, and to better understand how patients and physicians would choose between them. A post-marketing registry could contribute to this research.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Donanemab has only been proven to be effective in the early stages of AD. The view of our Steering Committee is that donanemab is not appropriate for patients that do not meet the essential elements of the TRAILBLAZER-ALZ 2 inclusion criteria: a diagnosis of mild cognitive impairment or mild dementia due to AD, Folstein MiniMental Status Exam score of 20 to 28, and evidence of beta-amyloid in the brain as shown by amyloid PET or lumbar puncture with CSF analysis. It would be helpful to provide specific prescribing information as, for example, is included in the US FDA package insert. Some of the assessments used to determine eligibility for TRAILBLAZER-ALZ 2 are not done in routine clinical practice in Canada, such as tau PET. A Working Group commissioned by the Steering Committee for the CCNA Initiative on Preparedness for Alzheimer Disease Modifying Therapies in Canada will examine criteria for eligibility in detail.

To be equitable, our view is that all patients in need of an intervention--which would be all patients with mild cognitive impairment or mild dementia due to AD--should be offered the opportunity to choose therapy if they meet eligibility criteria for treatment. A working group commissioned by the CCNA Steering Committee will review evidence for the number of potentially eligible patients across Canada, with separate estimates by province. A previous publication (Black SE, et al. Can J Neurol Sci 2023:1-8) estimated that less than 2% of patients in Canada had access to the resources required to receive AD disease modifying therapy similar to donanemab. However, emerging evidence suggests that the denominator eligible population is smaller than previously believed. It is important to note that most patients with AD will not be eligible for this therapy, predominately because they have later stage disease. It is also the case that many patients with mild AD will have other contraindications to treatment aside from the core criteria, such as need for

anticoagulation. Finally, we anticipate that some patients will choose not to receive therapy, given the requirement for frequent infusions and potential risks of side effects. It will be important to engage patients and their care partners in patient centered decision-making to help them decide whether this therapy is appropriate for them. The CCNA steering committee will commission a group on Clinical Effectiveness that will include persons with lived experience of dementia and their care partners to explore the patient and family focused considerations for whether to choose therapy or not. A report from this committee is expected in fall 2024.

AD is underdiagnosed in the community, particularly in the earliest stages preceding dementia, such as when only mild cognitive impairment is present. To offer equitable treatment to all potentially eligible Canadians, improvements in systems of care for evaluating cognitive symptoms will be needed. This includes increased training for primary care providers in methods for evaluating patients with cognitive concerns. At minimum, this would include that primary care providers would need expertise in assessing cognitive function and cognitive related activities of daily living. The Montréal Cognitive Assessment (MoCA) is a cognitive assessment tool developed in Canada that can be administered in 10 to 15 minutes and is sensitive for detecting mild cognitive impairment or dementia. Increased access to specialists, including allied health professionals such as clinical neuropsychologists, will likely also be necessary. The complex decisions on eligibility and management of donanemab will need to be taken by expert clinicians with considerable expertise in dementia care who are familiar with protocols for use of the drug.

The TRAILBLAZER-ALZ 2 trial stratified patients into low/medium tau and high tau, and then reported results separately in the low/medium group and the combined group (high/low/medium). (The term “low” was used by the trial investigators to describe patients in whom tau was elevated compared to normal, but only mildly so). There were 1,182 patients randomized and analyzed in the low/medium tau group, and 1,736 in the high tau group. The primary study outcome was the change over time in the integrated Alzheimer Disease Rating Scale (iADRS). The difference in change in iADRS the low/medium group, compared with placebo, was +3.25 (95% CI 1.88 to 4.62), representing a 35.1% slowing of disease progression. The difference in change in iADRS the combined low/medium/high group, compared with placebo, was +2.92 (95% CI 1.51 to 4.33), representing a 22.3% slowing of disease progression. A post-hoc analysis of the high tau group alone showed that the difference in change, compared with placebo, was not significant on the iADRS (+1.26, 95% CI -1.77 to 4.28, p=0.42) but was significant on a secondary outcome that is commonly used in AD trials, the Clinical Dementia Rating Sum of Boxes (CDR-SB) (-0.69, 95% CI -1.19 to -0.20; on this scale, negative numbers indicate better outcomes). This raises the possibility that treatment may be less effective in patients with high tau, which correlates with later stage disease with more clinical symptoms and dysfunction. In our review, more research is needed on the relationship between amount of tau and response to therapy. However, the FDA package label for patient selection does not recommend confirming the presence or amount of tau, only that the presence of beta-amyloid be confirmed.

Review of the effects of donanemab in patient subgroups suggests that caution may be warranted in treatment of patients who carry two copies of the apolipoprotein E epsilon 4 allele (APOE4). According to eTable 8 of Supplement 3 of the TRAILBLAZER-ALZ 2 main publication, the incidence of ARIA-E was much higher in APOE4 homozygotes (40.6%) compared with APOE4 heterozygotes (22.8%) or non-carriers (15.7%). (The incidence of ARIA-E in the placebo arm was 2.1%). The incidence of ARIA-H was higher in APOE4 homozygotes (50.3%) compared with APOE4 heterozygotes (32.3%) or non-carriers (18.8%). (The incidence of ARIA-E in the placebo arm was 13.6%). An analysis of effect modification of the primary study outcome was presented in eTable 9 of supplement 3. For both the low/medium group and the combined group, the point estimate for the primary outcome was closer to neutral for APOE4 carriers, and the confidence limits were wider and crossed 1 in the APOE4 homozygote subgroup. The US FDA Package label recommends that APOE be tested prior to treatment, and that the risk should be discussed with patients.

Analyses of the effect of donanemab by baseline subgroups was presented in eTable 9 of Supplement 3. The effect of treatment appears very similar in men and women. However, there is a suggestion that treatment may be less effective in people of Black race or Hispanic ethnicity. The point estimate in Asians was similar to White, but the confidence limits were wider, consistent with low enrollment of Asian participants (Table 1).

A Work Group of the CCNA will comprehensively review information on effects and subgroups, with a plan to publish our results in fall 2024. Post-marketing surveillance of clinical benefits and risk of ARIA could shed more light on risks and benefits of treatment in important subgroups including APOE4 carriers and people who are not White ethnicity.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

In the TRAILBLAZER-ALZ 2 trial, the iADRS at 18 months was used as the primary endpoint. The difference in change in iADRS the combined low/medium/high group, compared with placebo, was +2.92 (95% CI 1.51 to 4.33), representing a 22.3% slowing of disease progression. The iADRS is a combination of scores from two widely used measures in AD trials: the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog; a battery of neuropsychological tests) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living scale (ADCS-iADL). However, these scales are not used in clinical practice. Clinicians are more likely to follow treatment response using a clinical interview, bedside cognitive assessment such as the Folstein MMSE or MoCA, and an assessment of activities of daily living. The clinical meaning of the difference in iADRS is controversial. The difference observed in the trial, +2.92, is lower than the previously derived minimum clinically important difference for MCI (5 points) and AD with mild dementia (9 points) (Wessels et al, Alzheimer's & Dementia 2022;8:e12312). It is uncertain whether patients and clinicians will notice this difference. More research is needed to understand the clinical relevance of this treatment, and its effects on other aspects of living with dementia including activities of daily living, behavioural symptoms, ability to live safely at home, and overall quality of life. A Work Group commission by the CCNA is expected to issue a report on the clinical meaning of the effects of donanemab treatment in fall 2024.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

In TRAILBLAZER-ALZ 2, individuals whose amyloid-PET signal was normalized, suggesting that their excess amyloid had been successfully removed, were no longer treated with donanemab. This is an attractive feature of the donanemab treatment program, as it shortens the duration of treatment for some patients, reducing patient burden and costs. In the trial, amyloid PET was repeated at 24 weeks and at trial end at 76 weeks. Amyloid clearance was achieved in 29.7% of participants at 24 weeks and in 76.4% at 76 weeks. More research is needed to understand whether the effect of drug persists beyond 76 weeks, whether more treatments after 76 weeks can achieve amyloid clearance, and whether patients with clearance should be re-scanned to screen for amyloid re-accumulation and, if it has re-accumulated, whether to give another round of donanemab therapy. In the Canadian health system, there is currently insufficient access to amyloid-PET to test for amyloid removal in all provinces (Black et al, CJNS 2023;1-8). In contrast to PET, CSF and blood assessments of beta-amyloid probably reflect the ongoing balance of amyloid production and clearance rather the total burden of deposited amyloid in the brain. Therefore, it is not clear whether CSF and blood markers can substitute for amyloid PET in determining whether amyloid has been successfully removed from the brain. More research is needed on more accessible, lower cost biomarkers of brain amyloid removal. A Work Group commissioned by the CCNA will synthesize existing literature and offer suggestions for research on ways to monitor patients on donanemab therapy. A report from this group is expected in fall 2024.

The occurrence of amyloid -related imaging abnormalities (ARIA) or infusion reactions are expected to be the main adverse events that would prompt premature interruption or discontinuation of treatment.

ARIA are thought to result from excessive immune system reaction to treatment, leading to perivascular inflammation with resulting vasogenic edema, brain hemorrhage, or both. Symptoms of ARIA can include headache, delirium, seizure, focal neurological deficits, or hemorrhagic stroke. Serious complications can result, including hospitalization and death. In the TRAILBLAZER-ALZ 2 trial, serious adverse events were reported in 17.4% of patients on donanemab and 15.8% of patients on placebo. Treatment discontinuations due to adverse events occurred in 13.1% of donanemab and 4.3% of placebo participants. Deaths occurred in 3/853 on donanemab and 1/874 patients on placebo. Symptomatic ARIA with edema occurred in 19.7% of donanemab and 7.4% of placebo participants. The TRAILBLAZER-ALZ 2 trial protocol included frequent MRI scans to screen for asymptomatic ARIA, which, when present, required modification of the donanemab dosing protocol. In total, five MRI scans were required over an 18 month period including one end study MRI; however, in the presence of imaging evidence of ARIA (which occurred overall in 36.8% of donanemab treated patients) extra MRIs were required. The burden of doing multiple MRIs per patient adds to the system impacts of therapy (see our response to 5.1).

In the TRAILBLAZER-ALZ 2 trial, infusion reactions occurred in 8.7% of donanemab and 0.5% of placebo participants. Infusion reactions may require treatment with antihistamines or, for more serious reactions, referral to an Emergency Department.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Given the need for access to beta-amyloid testing, MRI scanning, and intravenous infusions, we anticipate that treatment would be provided more safely and effectively in specialized centers such as dementia specialty clinics. Monitoring for safety and freedom from ARIA requires MRI scanning with expert radiological interpretation, that is probably only available in larger care centers in urban areas. Due to the complexity of donanemab therapy, it is probably most safely and effectively provided by specialists with expertise in dementia. This could include neurologists, geriatric psychiatrists, geriatricians, and family physicians with a practice focus on geriatrics or dementia.

However, identifying patients who should be offered treatment will require coordination with primary care providers, as dementia care in Canada is predominately centered in family practice. This will require more primary care providers to be skilled in assessment and diagnosis of mild cognitive impairment and dementia.

The Steering Committee for the CCNA Preparedness for Alzheimer Disease Modifying Therapies in Canada Initiative has commissioned a Working Group to synthesize existing information on provision of care and equitable access to care, with reports expected in fall 2024.

6. Additional Information

None.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

   The CCNA is funded by a grant from the Canadian Institutes of Health Research,

Declaration for Clinician 1

Name: Eric Smith
Position: Professor of Neurology, Department of Clinical Neur
Date: 16-06-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

Declaration for Clinician 2

Name: Howard Chertkow
Position: Professor of Medicine (Neurology), University of Toronto>
Date: 16-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	x			
Biogen	x			
Eli Lilly	x			
Hoffman-La Roche Limited	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Natalie Phillips, Ph.D.
Position: Professor of Psychology, Concordia University; Associate Scientific Director, CCNA
Date: 16-06-2024

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
No conflicts of interest				

Declaration for Clinician 4

Name: Howard Feldman
Position: Professor, Department of Neurosciences; Director, Alzheimer's Disease Cooperative Study at UC San Diego
Date: 16-06-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vivoryon Therapeutics				x
Novo Nordisk, Inc.		x		

Arrowhead Pharmaceuticals	x			
Roche/Genentech Pharmaceuticals	x			
Tau Consortium				x
Janssen Research & Development, LLC			x	
Association for Frontotemporal Degeneration (AFTD)	x			

CADTH Reimbursement ReviewCADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0857-000

Generic Drug Name (Brand Name): Donanemab

Indication: Mild cognitive impariment due to Alzheimer's and mild Alzheimer's dementia

Name of Clinician Group: <Geriatricians at Trillium Health Partners>

Author of Submission: < Drs. Shiv Khosla, Jason Kerr, Amina Jabbar, Ahmad von Schlegell, Shanojan Thiyagalingam>

1. About Your Clinician Group

We are part of a group of 16 community-based geriatricians in Mississauga, Ontario with academic appointments at a large academic center. We practice inpatient and outpatient geriatrics with a large portion of our clinical visits being for dementia and its complications

2. Information Gathering

Information was gathered through a literature review including the following:

- Study Details | A Study of Donanemab (LY3002813) in Participants With Early Alzheimer's Disease (TRAILBLAZER-ALZ 2) | ClinicalTrials.gov
- Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial | Dementia and Cognitive Impairment | JAMA | JAMA Network
- Study Details | A Donanemab (LY3002813) Prevention Study in Participants With Alzheimer's Disease (TRAILBLAZER-ALZ 3) | ClinicalTrials.gov
- Study Details | A Follow-On Study of Donanemab (LY3002813) With Video Assessments in Participants With Alzheimer's Disease (TRAILBLAZER-EXT) | ClinicalTrials.gov
- Amyloidosis in Alzheimer's Disease: Pathogeny, Etiology, and Related Therapeutic Directions - PMC (nih.gov)
- Expected and diagnosed rates of mild cognitive impairment and dementia in the U.S. Medicare population: observational analysis - PMC (nih.gov)
- Psychosis linked to higher misdiagnosis rates in dementia patients, study suggests - Unity Health Toronto
- Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants | Alzheimer's Research & Therapy | Full Text (biomedcentral.com)
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3487532/
- https://www.nejm.org/doi/suppl/10.1056/NEJMoa2212948/suppl_file/nejmoa2212948_protocol.pdf

- https://link.springer.com/article/10.1186/1471-2377-14-101
- untitled (jamanetwork.com)
- https://pubmed.ncbi.nlm.nih.gov/37490245/
- Hannson, et. Al., 2022
- van Dyck et al., 2023a
- Arrighi et al., 2016
- Adhikari et al., 2022
- Sims et al., 2023a

3. Current Treatments and Treatment Goals

Currently, in Canada, dementia is a terminal diagnosis. The most common cause of dementia, Alzheimer's disease, is slowly and gradually progressive over an average of 8-12 years from symptom onset to death. Medications for Alzheimer's that are currently in circulation are cholinesterase inhibitors (donepezil, galantamine and rivastigmine) for mild, moderate and severe disease, and a N-methyl-D-aspartate (NMDA) receptor antagonist (memantine) for severe dementia. The classes of medications can either be used independently or combined. These medications have a modest effect in treating some symptoms of Alzheimer's disease but do little to slow the progression and nothing to modify the underlying disease mechanism.

The costs of cholinesterase inhibitors are covered by the Ontario Drug Benefit up to a certain point in the disease trajectory - until the Mini Mental Status Examination (MMSE) score falls below 10. Memantine is not covered and can cost patients between $100-130 per month depending on which pharmacy they use.

Ultimately, in the current state, patients with dementia decline and ultimately need assistance from caregivers for their basic activities of daily living, which include bathing, dressing, grooming, feeding, toileting and transferring. Caregivers are either family members, friends or community members, personal support workers (PSWs) from Homecare and Community Support Services (HCCSS) or hired privately. Caregivers shoulder a significant burden of care, which lead to economic costs with a decrease in work hours and/or inability to work, inability to look after their own families, and worsening of their own medical conditions such as depression, anxiety and stress related diseases such as hypertension among many other diseases. Over time, dementia can lead to severe impairment in quality of life for both those with the disease and their care partners.

Donanemab differs from currently available treatments in that it is a monoclonal antibody that significantly decreases the number of amyloid deposits in the brain. This is important as the amyloid hypothesis suggests that deposition of beta-amyloid in the brain leads to toxicities causing Alzheimer's disease. Although amyloid plaques may or may not be thought of as the underlying cause of the disease, there is indisputable evidence that brain Aβ protein accumulation plays a key pathophysiological role in large part backed by evidence from recent advanced imaging techniques such as amyloid PET scans. Decreasing the amyloid in the brain is theorized to modify the underlying disease mechanism, thus delaying the progression of the

disease leading to prolonging life, delaying functional decline, improving health-related quality of life, maintaining independence and decreasing caregiver burden. Delaying disease progression is also theorized to delay the need for admission to long-term care.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Cholinesterase inhibitors and memantine are currently widely available treatments for people with Alzheimer's dementia. These medications do not modify the underlying pathology of the disease. Thus, a patient with Alzheimer's dementia will progress to functional dependency whether they take these medications or not. Newer treatments that sustainably modify the way that Alzheimer's dementia progresses are needed to maintain functional independence, improve quality of life and decrease caregiver stress. Caregiver burden and indirect costs associated with Alzheimer's disease are significant healthcare drivers for this presently incurable disease.

No medications are currently approved for Mild Cognitive Impairment (MCI) due to Alzheimer's disease. Literature suggests that earlier interventions in progressive cognitive decline lead to a slower disease trajectory, projecting a slower loss of function.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Anti-amyloid drugs are arguably the first disease modifying therapies (DMT) for Alzheimer's disease (Cummings et al., 2023). If approved, Donanemab can modify Alzheimer's dementia by reducing the amount of amyloid in the brain. It would be used first line in patients with MCI due to Alzheimer's disease and mild Alzheimer's disease. In the TRAILBLAZER-ALZ 2 trial, Donanemab was given to patients who were taking a cholinesterase inhibitor, memantine, or both. Data showing differences in response to patients taking a currently available medication with and without Donanemab is not available. This trial stratified patients with Alzheimer's pathology into 2 groups. The first with low/medium levels of tau, and the second combined low/medium/high levels of tau. Tau is an important protein in Alzheimer's as it is liked to the development of memory loss. In patients with low/medium tau, dementia progression was slowed by 35.1%. In the combined tau group, it was slowed by 22.3%.

Donanemab has the potential to cause a shift in the current treatment paradigm of dementia patients. It would not be appropriate for patients to try currently available treatments prior to treatment with Donanemab, as the disease will continue to progress in severity leading to worsening cognition and function for the patient. Delaying treatment with Donanemab will allow the disease to progress past the mild stages, making them ineligible for treatment. Donanemab should be given earlier in the disease course to further prevent the decline associated with Alzheimer's dementia.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The patients who would be best suited for treatment with Donanemab would reflect the patient population in the TRAILBLAZER-ALZ 2 trial. These include MCI due to Alzheimer's disease and mild Alzheimer's disease. The trial also shows that patients with a low to moderate tau burden are more likely to have a favorable response to donanemab. People with MCI due to other causes, Alzheimer's disease with a severity greater than mild, or a diagnosis of other forms of dementia would not be eligible for Donanemab.

Eligible patients would be identified from the referral pool to specialists including geriatricians, neurologists, geriatric psychiatrics, and memory clinics. The encounter would involve a detailed cognitive history, with focus on cognitive domains, a functional inquiry, ruling out other potentially contributing factors, cognitive testing and a physical exam. The cognitive domains are memory and learning, speech and language, executive function, motor perception, complex attention, social attention, and motor functions. The functional inquiry includes a review of basic and instrumental activities of daily living. On history, potentially reversible causes of cognitive decline such as a stroke, depression, anxiety, other neurological conditions such as Parkinson's disease, and head trauma are ruled out. Cognitive testing may include the Standardized Mini Mental Status Examination (MMSE) with published use criteria of 22-30,

In addition to routine guideline-based screening to rule out potentially reversible causes of dementia, the presence of amyloid must be proven. In the trial for Donanemab, this can be completed with an amyloid PET scan of the brain. Other disease modifying therapies, for example, lecanemab allowed for either an amyloid PET scan and/or p-tau/AB42 cerebrospinal fluid (CSF) biomarkers. It is unclear at this time if positive CSF biomarkers would qualify for donanemab eligibility. In the current state, in Mississauga, amyloid PET scans are only available for research purposes, not for assisting with dementia diagnosis. CSF biomarkers are not available in the public payor system. In the future, plasma biomarkers may become available. Recent research presented at AAIC in June 2024, has shown that PrecivityAD2 test (known as "APS2"), a blood biomarker, was 90% accurate in predicting Alzheimers disease. The Alzheimer's association has also produced guidelines for appropriate use recommendations for blood biomarkers.

There are several issues related to diagnosis. In the current state, mild cognitive impairment (MCI) is under-diagnosed. Potential reasons for under-diagnosis include patients and families feeling that the cognitive changes they are experiencing are normal due to aging, front-line primary care physicians not being aware of the difference between normal aging and MCI, and patients not having access to a family doctor or specialist in memory care. This under-diagnosis is more prevalent in the non-white population.

Misdiagnosis of MCI due to Alzheimer's disease and Alzheimer's dementia does occur in clinical practice as there are many symptoms, particularly hallucinations and delusions, that overlap with other forms of dementia, for example, lewy body dementia and Parkinson's disease dementia. The introduction and utilization of biomarkers to the standard of care for diagnosis of

Alzheimer's disease will allow for an earlier, more accurate diagnosis for patients, and allow for personalized treatment to be tailored to their disease subtype.

Based on current data available, it is not possible to predict which patients with MCI due to Alzheimer's disease and mild Alzheimer's disease will exhibit a response to Donanemab.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcomes used in clinical practice include cognitive tests such as the Montreal Cognitive Assessment (MOCA) and Standardized Mini Mental Status Examination (MMSE). Given the progressive nature of the disease with current unavailability of disease modifying medications, it is anticipated that all patients with dementia, whether they are on currently available treatments or not, will have a gradual decline in their cognitive scores. Given that all patients progress at a different rate, and their baseline scores are heterogenous, we cannot compare one person's baseline score and rate of decline to another. Introduction of a disease modifying medication could result in a meaningful slowing of the decline in cognitive testing scores. Literature suggests that over a longer duration of therapy, there may be larger differences in the rates of cognitive and functional decline.

Another way progression is assessed is through a detailed history from the patient with dementia and someone who can provide accurate collateral history. Through this, a reliable functional history can be obtained, and the disease trajectory can be followed on the Global Deterioration Scale. The trajectory of a patient on treatment can be compared to current anticipated norms.

Using standardized cognitive tests and the Global Deterioration Scale ensures homogeneity in the assessment regardless of the assessor.

In research, scales commonly used include the ADAS-Cog and the Clinical Dementia Rating Scale, which can take 40 and 90 minutes to administer respectively. This is not practical for use in day-to-day practice.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

When to stop Donanemab in the trajectory of dementia has not been adequately studied. The Trailblazer-EXT study is looking at the progression of dementia after patients completed the Trailblazer-ALZ 2 study. In addition, the Trailblazer-3 study is investigating the effects of Donanemab administered over a longer time period (45 months). There are no current guidelines dictating that Donanemab should be discontinued if Alzheimer's progresses past the mild stage.

Other reasons to consider stopping Donanameb would be the development of any of the exclusionary criteria used in the clinical trial. These are:

- Significant neurological disease affecting the central nervous system other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infections of the brain, Parkinson’s disease, multiple concussions, or epilepsy or recent seizures (except febrile childhood seizures).
- Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion could interfere with the analysis in this study, or has a life expectancy of <24 months.
- History of cancer within the last 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, nonprogressive prostate cancer, or other cancers with low risk of recurrence or spread.
- Participants with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant’s ability to complete the study. Participants with a history of schizophrenia or other psychosis are excluded.
- Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
- History of alcohol or drug use disorder (except tobacco use disorder) within 2 years before the screening visit.
- History of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).
- Have any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia.
- Screening MRI which shows evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the participant’s ability to safely participate in the study
- Have any contradictions for MRI including claustrophobia or the presence of contraindicated metal implants/cardiac pacemaker
- Have a centrally read MRI demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease at screening.
- Sensitivity to florbetapir F18 or flortaucipir F18.
- Poor venous access.
- Contraindication to PET.
- Present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds the local recommended exposure limits.

- LFT results with ALT, AST >2.5x ULN, total bilirubin > 1.5x ULN and/or alkaline phosphatase >2x ULN
- Have received active immunization against beta-amyloid in another study.
- Have known allergies to donanemab, related compounds or any components of the formulation.

In the Trailblazer-ALZ 2 study, adverse events leading to discontinuation were:

eTable 7. Summary of adverse events leading to treatment discontinuation in ≥0.5% participants in the donanemab group during the placebo-controlled period.

AEs Leading to Treatment Discontinuation, n (%)	Donanemab (N = 853)	Placebo (N = 874)
Participants with treatment discontinuation due to AEs	112 (13.1)	38 (4.3)
IRR	31 (3.6)	0
ARIA-E	21 (2.5)	3 (0.3)
ARIA-H	7 (0.8)	2 (0.2)
Hypersensitivity	4 (0.5)	0

In the setting of ARIA, patients were discontinued and monitored further as follows:

Table 2: Dosing Recommendations for Patients With ARIA-E

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.

[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.

ARIA-H
The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 3.

Table 3: Dosing Recommendations for Patients With ARIA-H

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]	Suspend dosing[a]	

- **5.5 What settings are appropriate for treatment with Donanemab? Is a specialist required to diagnose, treat, and monitor patients who might receive Donanemab?**

Donanemab can be administered in a hospital setting, infusion center or specialty care clinic that has first-aid capabilities and is well equipped to treat transfusion reactions. Specialists, including Geriatricians and Neurologists are required to diagnose, treat and monitor patients who might receive Donanemab.

6. Additional Information

Side effects for anti-amyloid therapy can be broadly categorized into Amyloid Related Imaging Abnormalities (ARIA) and drug-related infusion reactions.

ARIAs are further classified into two subgroups: edema (ARIA-E) and hemorrhage (ARIA-H) subtypes. ARIA-E are brain imaging findings of sulcal effusions and parenchymal edema; ARIA-H are brain imaging findings of microhemorrhage, macrohemorrhage, and superficial siderosis. It is thought that ARIA-E and ARIA-H occur due to drugs targeting the extracellular Aβ in the brain also remove amyloid in blood vessels, impairing the vascular integrity. However, the exact mechanism is not well known, and research is ongoing . For example, one research group showed evidence for a neuronal hypersensitivity reaction to the drug as a potential mechanism (Adhikari et al., 2022).

The most common symptoms in those who were symptomatic were primarily headaches, confusion, vertigo, nausea/vomiting, visual disturbances, and rarely more serious side effects such as seizures or focal neurologic deficits. The prevalence of ARIA across the different anti-amyloid drugs is shown in table 2.

In Donanemab, only a small portion of those with ARIAs were symptomatic. For instance, ARIA-E was only symptomatic in 6.1% of those receiving Donanemab. Interestingly, the majority of ARIAs identified in these clinical trials resolved without intervention and a minority of cases resolved after treatment adjustment or discontinuation. It is unclear whether or not there are long term consequences of having asymptomatic, resolved ARIAs. .

Only a minority of participants had serious adverse events in the treatment group compared to placebo groups. Serious adverse events were defined as death, a life-threatening outcome requiring inpatient hospitalization or disability. Serious adverse events occurred in 17.4% of those receiving Donanemab versus 15.8% in placebo group.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate

or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Shiv Khosla

Position: Geriatric Physician

Date: Aug 9, 2024

X **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Jason Kerr

Position: Geriatric Medicine Specialist

Date: 09-08-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Shanojan Thiyagalingam

Position: Geriatric Medicine Specialist

Date: 09-08-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: <Ahmad von Schlegell>

Position: <Enter currently held position> Geriatric Medicine Specialist

Date: <DD-MM-YYYY> 08-09-2024

X I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Amina Jabbar

Position: Geriatric Medicine Specialist

Date: 09/08/2024

sho **X** I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.