A study of evaluating the efficacy between a new drug (Donanemab) compared to an established treatment (Galantamine) in Alzheimer's disease

By

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A thesis submitted to the School of Pharmacy in partial fulfilment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled **"**A study of evaluating the efficacy between a new drug (Donanemab) compared to an established treatment (Galantamine) in Alzheimer's disease**"** submitted by Farhana Yasmin (20146044) in Summer 2024 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy (B.Pharm.) on March 1, 2026.

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Ethics Statement

Through this project, no animal is used or harmed, and no human trials have been conducted.

Abstract/ Executive Summary

A combination of symptomatic and disease-modifying therapy approaches are necessary for Alzheimer's disease (AD), a progressive neurological illness. This thesis examines the safety, pharmacokinetics, and clinical effectiveness of galantamine, a well-known cholinesterase inhibitor, and donanemab, a new anti-amyloid monoclonal antibody, in the treatment of AD. Major biological databases were used to perform a thorough narrative review of long-term randomized studies and Phase I–III clinical trials. Despite manageable safety concerns, such as amyloid-related imaging abnormalities, the results show that donanemab significantly reduces amyloid plaque and is linked to a clinically meaningful slowing of cognitive and functional deterioration in early AD. Galantamine, on the other hand, has a proven safety profile, preserves cognition and everyday functioning, and exhibits consistent long-term symptomatic improvements without changing illness. Overall, this study emphasizes how new disease-modifying medications and conventional symptomatic treatments complement one another, underscoring the significance of tailored therapeutic approaches in the changing management of Alzheimer's disease.

Keywords: donanemab; galantamine; anti-amyloid monoclonal antibody; clinical trial; amyloid plaque clearance; cholinesterase inhibitor

Dedication

I am dedicating my efforts and work to my beloved parents.

Acknowledgement

First and foremost, I want to express my gratitude to Almighty Allah, without whose mercy the journey would not have been possible. I would want to express my appreciation and honor to my most respected supervisor, Mohd. Raeed Jamiruddin, PhD, associate professor, BRAC University. The chance to work under his guidance and supervision was a fantastic experience. His encouragement never fails to motivate me to finish this endeavor. Additionally, I want to thank all of the great faculty members of BRAC University's School of Pharmacy. I also want to express my gratitude to my parents for providing me with unwavering moral support during the whole process.

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ARIA-E: Amyloid-related imaging abnormalities with edema.

CLcr: Calculated creatinine clearance.

PK: Pharmacokinetic

MMSE: Mini-mental state examination.

SD: Standard deviation.

Chapter 1

Introduction

The primary cause of dementia, Alzheimer's disease (AD), has been identified as a global public health priority. In the United States, AD affected around 5.8 million people in 2020; by 2060, that number is expected to quadruple to 14 million. By 2050, it is anticipated that there would be 152.8 million cases worldwide. The last 20 years have seen a number of clinical trials for AD that attempted to provide an effective disease-modifying medication fail. One treatment option for AD is to remove the extracellular amyloid-β (Aβ) plaques in the brain (Ashraf et al., 2024) (**1**). Moreover, Alzheimer's disease is a degenerative neurological condition that mainly impacts behavior, memory, and cognitive functions. Drugs for Alzheimer's disease can help with memory issues and other cognitive disorders. The way that drugs of the cholinesterase class work is by boosting cell-to-cell communication. The drugs keep the brain's chemical messenger, which Alzheimer's disease depletes, intact. Cholinesterase inhibitors are commonly prescribed, including donepezil (Aricept, Adlarity), galantamine, and rivastigmine transdermal patch (Exelon).

Among all medications, Donanemab slows the course of Alzheimer's disease. It is a more recent medicine that works by assisting the body in removing amyloid plaques from the brain. It is a drug that targets amyloid plaque and uses a novel therapeutic approach.
However, by raising acetylcholine levels in the brain, galantamine, an acetylcholinesterase inhibitor, helps treat Alzheimer's disease by enhancing memory and cognitive performance. By increasing levels of acetylcholine, a crucial neurotransmitter, galantamine, a type of cholinesterase inhibitor, is a well-known drug that enhances memory and brain function. The indications, mechanism of action, contraindications, and adverse effects of galantamine are reviewed in this activity. It's an older process with a fantastic Alzheimer's disease mode of action.

No country currently markets donanemab, a novel molecular entity (NME). Kisunla is the idea for the proprietary name. On January 18, 2023, the first application for donanemab's expedited approval was granted a Complete Response (CR) letter due to the safety database being. Inadequate in describing donanemab's long-term safety in treating Alzheimer's disease. The results of the key clinical trial (Study AACI) are included in this resubmission application, which aims

for conventional approval and aims to rectify the shortcomings mentioned in the CR letter (*761248Orig1s000MedR*, n.d.) (**2**). Donanemab is a humanized IgG1 monoclonal antibody which mainly targets N-terminal pyroglutamate Aβ, a modified type of β-amyloid that is primarily present in plaques. In early-stage Alzheimer's disease (AD), which includes mild cognitive impairment from AD or mild AD with verified brain amyloid pathology (Dodel & Frölich, 2025) (**3**). Also, known as "N3pE-Aβ," donanemab identifies an N-terminally shortened version of Aβ that has cyclized pyro-glutamate (pE) as its third amino acid and is devoid of aspartate-1 and alanine-2. About 1-3 percent of the Aβ peptides in AD brain tissue are this changed form of Aβ. Instead of being found in aqueously diffusible Aβ oligomers and protofibrils, N3pE-Aβ is insoluble and thought to be found only in fibrous amyloid plaques and cerebrovascular deposits. Like antibodies to the natural N-terminus (like lecanemab), donanemab binds to N3pE-Aβ in plaques and blood vessels after crossing the blood-brain barrier via intravenous injection. Over time, it is thought that antibody attachment to any form of Aβ will cause local microglial cells to phagocytose the Aβ-antibody complexes, destroying and clearing amyloid plaques. It is believed that the activated microglia also phagocytose the far more prevalent Aβ peptides that start with aspartate-1, a process known as "bystander clearance," because the N3pE variation makes up less than 3% of Aβ peptides in most AD brains. Since N3pE-Aβ is not abundant in the AD brain, the donanemab clinical trial design allowed for the possibility of stopping treatment if the antigen had probably been eliminated, that is, if plaques were no longer detectable by amyloid PET (Rabinovici et al., 2025) (**4**). Basically, Donanemab was created using the amyloid cascade theory to treat Alzheimer's disease (AD). This treatment uses antibodies to target amyloid, which is only found in brain plaques. Donanemab can significantly lower amyloid plaque levels in patients with early-stage AD, according to the phase 2 clinical trial TRAILBLAZER-ALZ. Two The accumulation of amyloid plaques is thought to contribute to the following: tau, as indicated by plasma phosphorylated tau 217 (p-tau217), and neurofibrillary tangles in the brain and neuroinflammation, as indicated by plasma glial fibrillary acidic protein (GFAP), a marker for astrocytic activation or proliferation (Gueorguieva et al., 2023) (**5**). Assisting doctors with the safe and appropriate administration of this innovative treatment is the aim of the donanemab AUR (Appropriate Use Recommendations). With a focus on optimising patient safety, the AUR aims to supplement sponsor-generated marketing materials, FDA prescribing information, and clinical trial publications by offering an unbiased, scholarly viewpoint on the proper use of donanemab. The

AUR takes expenses and reimbursement into account, does not recommend treatments, and does not assess meaningfulness in relation to efficacy or effectiveness. They are suggestions rather than rules, specifications, or demands. As new information becomes available to support the practical application of donanemab, the AUR is meant to be a "living document" of those changes. Clinical judgement should always be given priority over the AUR when determining whether a patient is suitable to receive or continue this innovative therapy (Rabinovici et al., 2025) (**6**).

One reversible acetylcholinesterase inhibitor used to treat Alzheimer's disease is galantamine. In about an hour for instant release (IR) tablets and four hours for extended release (ER) capsules, galantamine is quickly absorbed after oral administration and achieves Cmax. The absorption of galantamine is not clinically affected by food (Huang & Fu, 2010) (**7**). It is found in a review that Galantamine was sold commercially in Bulgaria under the brand name "NIVALIN." Galantamine's anticholinesterase action was originally documented in early from an in vivo investigation on a cat under anaesthesia in the 1960s. Eventually, pre-clinical development got underway, and scientists looking for new ways to treat Alzheimer's disease began looking into galantamine's potential benefits. 9-11. By the 1990s, galantamine had been licensed for Alzheimer's. In 1996, Sanochemia Pharmazeutika received the first patent on the synthesis method of galantamine, and the drug was initially approved for use as a treatment for Alzheimer's disease in Iceland, Ireland, Sweden, and the United Kingdom (Upadhyay et al., 2020) (**8**). Actually, galantamine is a naturally occurring alkaloid belonging to the Amaryllidaceae family. Soviet scientists initially isolated it from the Caucasian snowdrop plant in the 1950s. Later, they isolated it from the bulbs of various Amaryllidaceae species. Traditional herbal therapy has been using these herbs for ages. The primary active ingredient was discovered to be galantamine, which acts on the cholinergic system through two different mechanisms. It is a nicotinic receptor for acetylcholine allosteric modulator and a selective, reversible, competitive inhibitor of acetylcholinesterase (AChE) with central action. Compared to plasma BuChE, it is 50 times more selective for human erythrocyte AChE (AChE IC50 = 0.35 μM; BuChE IC50 = 18.6 μM) (Cheng et al., 2024) (**9**). Benzazepine alkaloid galantamine is a competitive, reversible inhibitor of acetylcholinesterase. It does not have a structure comparable to other inhibitors of acetyl cholinesterase. According to the suggested mechanism of action of galantamine, acetylcholinesterase is reversibly inhibited, preventing acetylcholine from being hydrolysed and increasing acetylcholine concentration at cholinergic

synapses. The effect of agonists (like acetylcholine) at nicotinic acetylcholine receptors may be enhanced by galantamine's allosteric binding with these receptors. Glucuronidated by hepatic cytochrome P450 enzymes, galantamine is eliminated unaltered in the urine. Moreover, long-term galantamine therapy for AD patients lowers behavioural symptoms and slows down cognitive and overall loss; this effect is particularly pronounced in people with intermediate or severe stages of the illness. Additionally, PET measurements show similar long-term benefits (Bhattacharya et al., 2014) (**10**).

Chapter 2

Methodology

2.1 Study Design

The purpose of this systematic narrative literature review was to compare the clinical outcomes, pharmacokinetics, safety profile, and efficacy of galantamine, a well-known cholinesterase inhibitor, and donanemab, a disease-modifying anti-amyloid monoclonal antibody, in the treatment of Alzheimer's disease (AD). The review concentrated on data from long-term randomized controlled trials, population pharmacokinetic/pharmacodynamic (PK/PD) research, Phase I–III clinical trials, and highly regarded review papers.

2.2 Search Strategy and Search Engines

Several digital scientific databases were used in a thorough literature search to guarantee that all pertinent published evidence was covered. The databases and search engines listed below were thoroughly investigated:

- PubMed
- Scopus
- Google Scholar
- ClinicalTrials.gov
- Web of Science

In order to find any more appropriate research that was not found through database searches, the reference lists of important review articles and clinical trial publications were also manually examined.

2.3 Search Keywords

The search was made reproducible by using a predetermined set of keywords and Boolean operators. Apparently, the primary keywords were:

- Donanemab
- Galantamine
- Alzheimer's disease
- Cholinesterase inhibitor
- Anti-amyloid monoclonal antibody
- Amyloid plaque clearance
- MMSE, CDR-SB, ADAS-Cog
- ARIA-E, ARIA-H
- Clinical trial
- Pharmacokinetics" OR "PK/PD modeling
- Cognitive outcomes

Each database's search strings were slightly modified to meet indexing specifications.

2.4 Search Results Acquired

The approximate number of records found in the primary database search was as follows:

- PubMed: ~73 records
- Scopus: ~31 records
- Google Scholar: ~102 records
- ClinicalTrials.gov: ~22 registered trials
- Web of Science: ~56 records

Additional screening was applied to the remaining articles after duplicated records from other databases were eliminated.

2.5 Inclusion Criteria

The following criteria had to be completed for a study to be included in the review:

- Published in journals with peer review.
- Composed in English.
- Human subjects were involved.
- Researched on galantamine or donanemab in Alzheimer's illness.
- Clinical effectiveness, pharmacokinetics, pharmacodynamics, safety results, or endpoints related to cognition or function.
- Phase I–III clinical trials, long-term randomized controlled trials, and population PK/PD assessments were included.
- Published within a most relevant and current time span, with studies published after 2010 for galantamine and after 2018 for donanemab being given preference.

2.6 Exclusion Criteria

Based on the following standards, studies were not included:

- Studies using just animals or in vitro.
- Case series or reports with extremely tiny sample sizes.
- Conference abstracts lacking complete published data.
- Research with unclear results or methods.
- Publications that are written in languages other than English.
- Papers centered on Alzheimer's disease excluding assessments of donanemab or galantamine.

2.7 Data Extraction and Synthesis

Seventeen resourceful papers were chosen for data gathering and in-depth analysis after the inclusion and exclusion criteria were applied. Among them were:

- Phase I–II donanemab clinical trials.
- The Phase II TRAILBLAZER-ALZ trial.
- Population PK/PD modeling studies.
- Long-term randomized controlled trials of galantamine.

- Pharmacokinetic and safety studies of intranasal galantamine (Gln-1062).

Important information acquired from every study was:

- Study design and phase
- Sample size
- Safety and adverse event profiles
- Primary and secondary outcome measures
- Drug dosage and administration route
- Cognitive and functional assessment results

2.8 Screening and Selection Process

Three steps were included in the screening process:

i. **Title screening**: To exclude research that isn't relevant.
ii. **Abstract screening**: To determine eligibility according to inclusion and exclusion standards.
iii. **Full-text review**: To extract essential information and verify relevance.

17 papers were chosen for in-depth data extraction and comparative analysis after passing all screening phases and meeting the eligibility requirements. The discussion and result tables in this thesis were derived from these investigations.

Chapter 3

Result

Table 1: Overview of Pharmacokinetic, Safety, and Amyloid-Clearing Results from Donanemab Phase I–II Clinical Trials (Gueorguieva et al., 2023) (**11**).

Study	Sample Size	Drug	Outcome Measure	Result Summary
Phase I Donanemab Trial (NCT02624778)	46 participants	Donanemab (q2w/q4w regimens; 10–40 mg/kg single or repeated)	ADA response, amyloid PET decreases, and PK profile.	Significant amyloid reduction is seen, two-compartment pharmacokinetics, an 11.8-day half-life, and an increased incidence of ADA with little effect on efficacy.
Phase II TRAILBLAZER-ALZ (NCT03367403)	131 on PK, 254 in ARIA model, 304 in exposure-response analysis	Every four weeks, donanemab 700 mg → 1400 mg	ARIA-E safety, the exposure-response connection, and amyloid plaque elimination (PET)	Many subjects cleared their amyloid by 52 weeks; the required threshold concentration is 4.43 μg/mL; carriers of APOE ε4 are four times more likely to develop ARIA-E; exposure is unrelated to ARIA-E.
Combined Population PK/PD Model	Total pooled: 304 participants	Donanemab	PK, response to exposure, ADA influence, and amyloid elimination	PK is affected by weight and ADA; the half-life of plaque elimination is 10.2 years; the clearance duration is predicted by baseline amyloid; the impact of ADA is negligible.

Legends

- **ARIA-E**: Amyloid-related imaging abnormalities with edema.
- **CLcr**: This defines calculated creatinine clearance.

- **n**: Number of participants.
- **PK**: PK defines Pharmacokinetic.

Table 2: Comprehensive Analysis of Phase I–II Donanemab Trials' Effectiveness, Safety, and Cognitive Results (Rashad et al., 2022) (**12**).

Study	**Sample Size**	**Drug**	**Outcome Measure**	**Result Summary**
Lowe et al., 2021 (Phase 1)	N = 63 (51 Donanemab, 12 placebo)	IV dosages, one or several (0.1–10 mg/kg)	Amyloid PET, MMSE, FCSRT-IR, ADAS-Cog14	10 mg/kg decreased amyloid (−44.4 CL); mild infusion responses; some ARIA-H; no serious incidents
Lowe et al., 2021 (Phase 1b)	N = 61 (46 Donanemab, 15 placebo)	Various 10–20 mg/kg; one-time 10/20/40 mg/kg every 2 weeks and every 4 weeks	NTB, MMSE, ADAS-Cog14, ADCS-MCI-ADL-24, and Amyloid PET	ARIA-E 26.1%, ARIA-H 21.7%, complete clearance of 23.9%, and swift amyloid reduction (to −58.4 CL)
Mintun et al., 2021 (Phase 2 TRAILBLAZER-ALZ)	N = 272 (131 Donanemab, 126 placebo)	700 mg to 1400 mg every 4 weeks	iADRS, MMSE, CDR-SB, ADAS-Cog13, and PET amyloid/tau	84.13% reduction in CL amyloid; 32% decline in progression; ARIA-H 30.5%, ARIA-E 26.7%

Legends

- **AD:** AD represents Alzheimer's disease.
- **ADCS-IADL:** The Instrumental Activities of Daily Living Inventory from the Alzheimer's Disease Cooperative Study.
- **ARIA-H:** Amyloid-related imaging abnormalities because of hemosiderin deposition and hemorrhage.
- **CDR-SB:** Clinical Dementia Rating Scale-Sum of Boxes.
- **MMSE:** MMSE represents mini-mental state examination.
- **SD:** Standard deviation.

- **SUVR:** Standardized uptake value ratio.
- **TE-ADA:** Treatment-emergent anti-Donanemab antibodies.

Table 3: Summary of Safety, Pharmacokinetic, and Pharmacodynamic Results for Intranasal Gln-1062 (Bakker et al., 2020) (**13**).

Study	Sample Size	Drug	Outcome Measure	Result Summary
Bakker et al., 2020 – Safety, PK & PD of Gln-1062	48 healthy elderly patients	Placebo; oral galantamine 16 mg for PK comparison; Gln-1062 (intranasal) 5.5 mg, 11 mg, and 22 mg b.i.d. × 7 days	PK (Cmax, AUC, Tmax), PD (Adaptive tracking, N-back, EEG, VAS, VVLT), Safety (TEAEs)	Safe and well tolerated; frequent nasal adverse events; fewer gastrointestinal side effects compared to oral galantamine; dose-linear PK; notable improvement in sustained attention at 22 mg (+1.95%, p=0.0055)

Legends

- **PK**: PK defines Pharmacokinetic.
- **PD**: Pharmacodynamics.
- **Cmax**: Peak Concentration (The greatest concentration of a medication in the blood or target tissue following a dose)
- **AUC**: Area Under the Curve (The overall exposure of the body to a medication during a specified time frame, determined from the concentration-time graph)

Table 4: Overview of Major Clinical Trial Details for the 2-Year Galantamine Study in Alzheimer's Disease (Baseman et al., 2014) (**14**).

Study	Sample Size	Drug	Outcome Measure	Result Summary
Effects of Galantamine in a 2-Year Randomized, Placebo-Controlled Study in Alzheimer's Disease	2,045 patients received treatment (1,024 galantamine; 1,021 placebo).	Galantamine (8–24 mg/day, ER)	MMSE (cognition), DAD (function), TEAEs, and mortality	Death rate = 42% (HR = 0.58). Cognitive decline decreased (−1.41 vs. −2.14). The function declined more slowly (−8.16 vs. −10.81). TEAEs that are mild (nausea is most common).

Legends:

- **TEAE:** Treatment-emergent adverse event.
- **N:** Total number of patients in the treatment group.
- **n (%):** Number of patients reporting the event (n) and the percentage of patients in that group (%).

Chapter 4

Discussion

4.1: **Outcome domains in Alzheimer's disease using donanemab**

From the result section, tables 1 and 2 describes the overall results from the Phase I–II clinical studies of donanemab, which show a continuously growing body of evidence confirming the antibody's ability to dramatically lower the burden of amyloid plaque while maintaining a constant

yet manageable safety profile. Donanemab's basic pharmacokinetic (PK) behavior was determined by early Phase I research (NCT02624778), which revealed a predictable two-compartment model with a half-life of roughly 11.8 days. Mainly, instead of the frequent emergence of anti-drug antibodies (ADA), these early trials showed strong amyloid clearance across a variety of dosage regimens; these antibodies did not significantly reduce efficacy. Donanemab, a monoclonal antibody that targets amyloid, has biological proof-mechanism. Appreciation goes to the Phase I PET imaging results, which also verified quantifiable decreases in amyloid burden.

Constructed on this basis, the TRAILBLAZER-ALZ trial (NCT03367403) advanced into Phase II by improving dose-response relationships and demonstrating variables influencing safety outcomes, such as amyloid-related imaging abnormalities (ARIA). The study found that an approximate threshold value of 4.43 μg/mL was associated with enough amyloid clearance. It also showed that carriers of APOE ε4 were approximately four times more likely to acquire ARIA-E. Exposure levels did not directly correlate with ARIA occurrence, despite the prevalence of ARIA incidents, indicating that biological sensitivity is more important than dosage intensity. Moreover, baseline amyloid burden significantly predicts clearance duration, although the presence of ADA has little effect on clinical or biochemical response, according to population-level PK/PD modeling. By establishing a defined safety framework and mechanistic confidence, the experiments that are used earlier helped shape trial designs for subsequent testing.

These observations are further supported by the results published by Lowe et al. (2021), which show consistent amyloid decrease across several Phase 1 and 1b cohorts utilizing different intravenous dosage regimens. A 10 mg/kg dose significantly reduced CL by about −44 in the Phase 1 trial, with low ARIA-H and primarily moderate infusion-related responses but no significant clinical effects. With up to −58.4 CL decrease and 23.9% of patients reaching full amyloid clearance, the Phase 1b data demonstrated even more significant effects. The ARIA-E and ARIA-H rates (26.1% and 21.7%, respectively) continued to be consistent with previously documented risk patterns, highlighting the significance of baseline cerebral amyloid load and genetic susceptibility. Donanemab's quick and effective amyloid-removing action is highlighted by this group consistency, which also supports its biological efficacy at various dosage levels.

The most compelling evidence of the potential clinical benefit of donanemab comes from the pivotal Phase II TRAILBLAZER-ALZ data from Mintun et al. The antibody resulted in a

remarkable 84% reduction in amyloid and a 32% slowing of clinical decline compared to placebo across primary and secondary endpoints, including iADRS, MMSE, CDR-SB, and ADAS-Cog13. Despite the high ARIA rates (ARIA-E 26.7%, ARIA-H 30.5%), most of them were controllable and in line with expectations for anti-amyloid monoclonal antibody therapy. Significantly, improvements in clinical progression markers were closely correlated with the degree of amyloid reduction, highlighting the mechanistic connection between plaque clearance and functional stabilization in early Alzheimer's disease.

An image appears across Tables 1 and 2: In early-stage Alzheimer's disease, donanemab shows quick, strong, and frequently near-complete amyloid clearance. Its pharmacokinetic profile is appropriate for monthly dosing, and the production of ADA has little functional impact. Although significant, safety concerns—particularly ARIA events—fall within the anticipated range for amyloid-targeting antibodies and seem to be more closely related to baseline risk variables than to drug exposure levels alone. Crucially, significant amyloid reduction can result in a clinically significant slowing of cognitive and functional deterioration, according to early and mid-stage trials.

The combined findings of these Phase I–II studies offer compelling clinical and mechanistic evidence for the therapeutic potential of donanemab. They support the idea that targeted amyloid clearance, in conjunction with patient stratification and cautious ARIA control, may provide a workable disease-modifying strategy for Alzheimer's disease. They also support the advancement into more sophisticated clinical trials.

The information compiled in tables 1 and 2 is shown graphically in the pie chart that follows the outcome domains of humanized IgG1 monoclonal antibody, donanemab. The information has been gathered from different review papers that are mentioned in the tables as well.

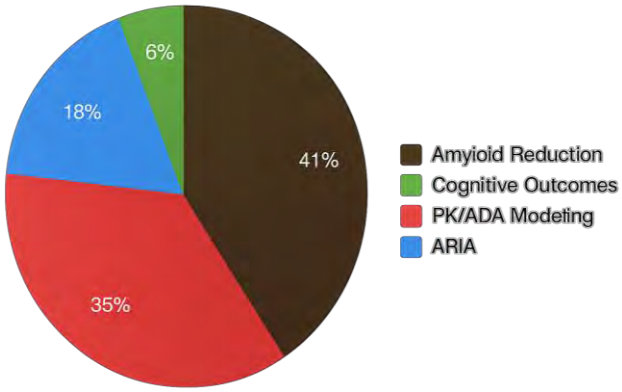

Figure 1: Distribution of outcome domains assessed in Phase I–II clinical studies of donanemab. Most published results are related to amyloid reduction, which is the main way that donanemab modifies illness. A significant amount is made up of pharmacokinetic and anti-drug antibody (PK/ADA) modeling, which emphasizes immunogenicity evaluation and exposure-response characterization.

The main focal areas of the data gathered during the clinical trials for the Alzheimer's drug donanemab are depicted in the pie chart. Amyloid Reduction, the drug's primary treatment mechanism as an anti-amyloid antibody that targets brain plaque, accounts for the greatest percentage of the data (41%). PK/ADA Modeling (Pharmacokinetics/Anti-medication Antibody Modeling) makes up the second-largest portion (35%), which is essential for comprehending how the medication is absorbed, transported, metabolized, and eliminated as well as how the body's immune system reacts to it. The ARIA (Amyloid-Related Imaging Abnormalities) data, which comprises 18% of the data, represents safety profile monitoring. ARIA is a well-known possible adverse effect of anti-amyloid treatments that need to be closely monitored, usually with MRI scans. Lastly, Cognitive Outcomes, which gauge the medication's effectiveness in reducing the rate of cognitive and functional deterioration, comprise the lowest portion (6%). While cognitive outcomes constitute the ultimate clinical aim, this distribution shows a strong emphasis on verifying the drug's mechanism (amyloid reduction), describing its profile and body reaction (PK/ADA), and addressing its principal safety risk (ARIA).

4.2: **Clinical endpoints in treatment evaluation using galantamine**

The outcomes shown in Tables 3 and 4 demonstrate two complementary therapeutic approaches for managing Alzheimer's disease: long-term assessment of well-known oral treatments like galantamine and innovative intranasal delivery of cholinergic drugs like Gln-1062. These studies

offer valuable information about maximizing pharmaceutical efficacy and tolerance in senior citizens. The Phase I–II study of intranasal Gln-1062 (Table 3) shows a promising reformulation approach intended to maximize exposure to the central nervous system while reducing systemic side effects that are frequently linked to oral cholinesterase inhibitors. While pharmacological evaluations—especially gains in sustained attention at the highest 22 mg dose—indicate real cognitive engagement early in development, the dose-linear pharmacokinetic profile shown in older participants suggests predictable absorption via the nasal route. Also, compared to the gastrointestinal side effects associated with oral galantamine, nasal adverse events were typically modest and far less bothersome. This distinction highlights the potential clinical value of intranasal formulations in terms of improving tolerability without compromising cognitive benefit. Gln-1062 is a unique therapeutic approach that may improve patient quality of life in Alzheimer's disease and solve adherence issues by achieving higher central medication concentrations with fewer systemic toxicity.

On the contrary, the extensive two-year galantamine experiment (Table 4) offers important long-term proof of the continued therapeutic benefit of conventional cholinesterase inhibition. With more than 2,000 patients recruited, the research produces reliable data that reflects safety and effectiveness in the real world. Galantamine showed significant preservation of functional abilities (DAD decline: −8.16 vs. −10.81) and delayed cognitive decline (MMSE: −1.41 vs. −2.14) over a two-year period, demonstrating its dual influence on cognition and everyday living skills. An unexpected but clinically significant result is the significant decrease in mortality (hazard ratio 0.58), which may indicate wider systemic advantages or potential neuroprotective processes linked to long-term cholinergic activation.

The effectiveness and safety of galantamine remained satisfactory and consistent with previous studies, supporting its dependability as a long-term treatment, even in the face of treatment-emergent adverse effects, most frequently moderate nausea. The long-term galantamine results offer a crucial benchmark when compared to the newly developed intranasal agent Gln-1062: established agents continue to provide measurable, sustained clinical benefit in large and diverse Alzheimer's populations, while newer delivery methods may improve tolerability and acute cognitive responses.

In conclusion, the combined data from Tables 3 and 4 shows how innovation and optimization are essential components of Alzheimer's medication. While long-term galantamine therapy continues to show reliable, significant therapeutic results, intranasal Gln-1062 reflects forward-looking developments targeted at enhancing medication delivery and lowering systemic toxicity. When taken as a whole, these results highlight the fact that future frameworks for treating Alzheimer's disease will probably depend on both the creation of new drugs and the improvement of current treatments to improve patient adherence, safety, and efficacy at various stages of the disease's progression.

The pie chart that follows clinical endpoints in treatment evaluation using galantamine graphically displays the data gathered in tables 3 and 4. The data was collected from various review publications that are also referenced in the tables.

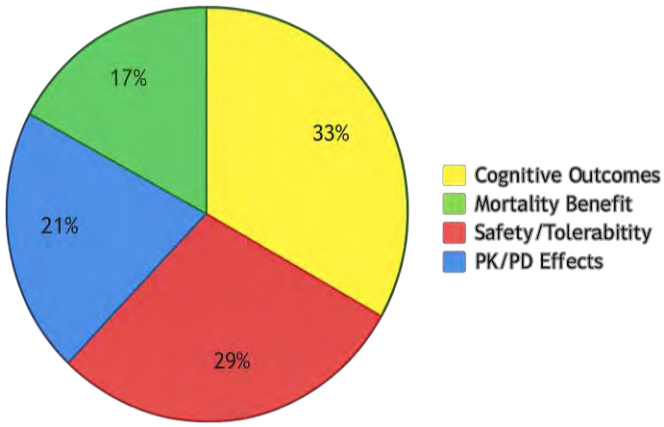

Figure 2: Distribution of clinical endpoints evaluated in galantamine-based Alzheimer's disease studies. The drug's principal symptomatic benefits are shown by the greatest proportions that correlate to cognitive function and global clinical status. One important factor that shows how galantamine affects patient independence is functional outcomes pertaining to everyday living activities.

The provided pie chart, which graphically depicts the distribution of results in galantamine studies for Alzheimer's disease, makes it evident that the medication's clinical usefulness is multifaceted. Positive results in Global Clinical Status and Cognitive Function, which together constitute the main therapeutic advantages, occupy the greatest sections of the chart. By improving cholinergic neurotransmission, galantamine—a reversible cholinesterase inhibitor and positive allosteric modulator of nicotinic acetylcholine receptors—addresses a major deficiency in Alzheimer's pathogenesis. The significant amount provided to Activities of Daily Living (ADL) and Functional

Improvement emphasizes that the medication's impact goes beyond mental state to practical, everyday abilities, which is essential for patient autonomy and lessening the burden on caregivers. Galantamine may also be helpful in treating the non-cognitive symptoms of dementia, such as agitation or psychosis, according to a smaller but substantial slice for behavioral symptoms. Lastly, the section on Adverse Events and Safety highlights the unavoidable adverse effects of cholinesterase inhibitors, mostly gastrointestinal, which are usually dose-dependent and controllable.

Chapter 5

Conclusion

Donanemab and galantamine, two pharmacologically different therapeutic approaches for the management of Alzheimer's disease (AD), are thoroughly compared in this thesis review, which reflects both the changing paradigm of disease modification and the ongoing significance of symptomatic treatment approaches. This study highlights the advantages, disadvantages, and clinical consequences of each therapeutic modality by methodically combining data from early- and mid-phase clinical trials, long-term randomized studies, and pharmacokinetic analyses.

Donanemab consistently reduces amyloid plaque in early Alzheimer's disease, as shown by the findings in Tables 1 and 2. This effect is reinforced by a consistent pharmacokinetic profile and strong biological confirmation of mechanism. Amyloid clearance was attained across several dosage regimens in Phase I–II trials with no effect from anti-drug antibodies and safety results, especially ARIA, remained controllable and mostly influenced by baseline risk factors rather than exposure alone. Crucially, a clinically significant slowing of cognitive and functional deterioration was strongly correlated with increased amyloid reduction. When taken as a whole, these results validate donanemab's advancement into advanced clinical trials and support it as a potentially effective disease-modifying treatment. Donanemab is expected to trigger an immune response against these harmful plaques and help the body eliminate them. This, in turn, is expected to slow Alzheimer’s progression (Jayaprakash & Elumalai, 2025). Although,

donanemab is an obvious example of excellent translational medicine and has already been acknowledged as a game-changer in the treatment of AD. Its creation offers Alzheimer's patients new hope by bridging the gap between basic research and therapeutic use. Treatment was found to be effective in removing amyloid plaques and to have mild adverse effects in earlier studies on animal subjects. (*Alzheimersnewstoday-Com-News-Donanemab-Slows-Cognitive-Functional-Decline-in-Early-Alzheimers-Trailblazer-Study-Shows-*, n.d.) (**15**)

On the other hand, galantamine is a well-known cholinesterase inhibitor that has been used in therapeutic settings for many years. By improving cholinergic neurotransmission, it consistently reduces symptoms. Long-term clinical trials attest to its capacity to improve everyday living activities, decrease cognitive and functional decline, and maintain an acceptable safety profile with mostly minor and controllable side effects. Although galantamine does not alter the underlying neuropathology of Alzheimer's disease, its long-term effectiveness, affordability, and ease of use support its continued usefulness, especially in moderate-to-late stages of the disease and in situations where more sophisticated biologic therapies might not be practical. New formulations that aim to maximize medication delivery and tolerance include intranasal galantamine (Gln-1062) (**16**). The effects of neuromuscular blockade have long been reversed by the acetylcholinesterase inhibitor galantamine. Numerous positive, therapeutic, and protective impacts on organ systems have been demonstrated by biological studies on galantamine. Consequently, galantamine is a phytochemical with a range of pharmacological characteristics that require more research to establish an efficient safety profile in humans and to provide therapeutic benefits (Kaur et al., 2022) (17).

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