INVENTION EVALUATION STUDY (SAMPLE REPORT)

An oral pharmaceutical composition comprising fasudil for improving cognition in a patient with Alzheimer's Disease

Qualevia ref no.:

Date: July 17, 2025

Confidential

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CONTENTS

EXECUTIVE SUMMARY

Alzheimer's disease (AD) is a rapidly growing global health concern, currently affecting over 55 million people and projected to rise steeply with aging populations. The Alzheimer's therapeutics market is expected to reach $11.34 billion by 2032, propelled by unmet clinical needs, increasing R&D investment, and a shifting regulatory landscape favouring innovative treatments.

Within this evolving ecosystem, Rho-associated kinase (ROCK) inhibitors are gaining momentum as promising disease-modifying agents, due to their roles in neuroinflammation, synaptic dysfunction, and neurodegeneration. The ROCK inhibitor segment alone is projected to reach $2.5 billion by 2033, underscoring its commercial and clinical relevance.

The invention under evaluation discloses an oral immediate-release formulation of Fasudil - a ROCK inhibitor - designed to improve cognitive function in patients with Alzheimer's disease. The composition involves a daily oral dose of 90–120 mg, divided into three equal portions. Fasudil benefits from a well-characterized clinical safety profile in other indications, demonstrates blood-brain barrier penetration, and modulates several AD-relevant pathways including amyloid-beta accumulation, tau phosphorylation, and oxidative stress. These attributes support its potential as a disease-modifying therapy in contrast to traditional symptomatic agents.

Patent landscape analysis indicates growing innovation activity in this field, led by institutions in the United States. Fasudil is currently the most advanced ROCK inhibitor in clinical trials for AD, with a Phase 2 study underway. While the invention aligns well with therapeutic needs and market trends, novelty risks exist: two patent publications fully disclose the invention's key features. This overlap will require strategic positioning and refinement to mitigate potential challenges to patentability.

A SWOT analysis reveals key strengths, such as multi-target efficacy, clinical tolerability, and cost-effectiveness. Opportunities include regulatory fast-track designations, combination therapy potential, and alternative delivery systems. At the same time, academic and commercial stakeholders must navigate competition from anti-amyloid agents, evolving regulatory benchmarks, and payer constraints.

Conclusion

For the academic institution holding this patent, the invention offers a strong foundation for translational development - provided the potential novelty risks are carefully managed. The institution can leverage its position by refining claim scope, exploring differentiated delivery methods, and initiating academic-industry partnerships.

With a favourable safety profile, unmet market need, and ongoing clinical validation, this asset holds tangible potential for licensing, collaborative development, or spin-off formation. Strategic next steps through the tech transfer office can help unlock its value in the growing Alzheimer's therapeutics market.

UNDERSTANDING THE INVENTION

Summary

The invention relates to an oral pharmaceutical composition comprising a Rho kinase inhibitor for enhancing cognitive function in patients with Alzheimer's Disease. Specifically, the composition features an immediate-release formulation of Fasudil. Fasudil is administered orally in a total daily dose ranging from 90 mg to 120 mg. A preferred regimen involves dividing the daily dose into three equal portions administered throughout the day. This targeted approach aims to optimize drug availability and therapeutic effect. The formulation addresses cognitive decline through Rho kinase pathway modulation.

Features and Benefits

Features: The following are important features of the invention:

Sr. No.	Feature
Feature 1	An oral pharmaceutical composition comprising rho kinase inhibitor for improving cognition in a patient with Alzheimer's Disease.
Feature 2	Rho kinase inhibitor of key feature 1 is immediate release formulation comprising Fasudil.
Feature 3	Fasudil of Feature 2 is typically administered orally in a total daily dose of between 90 mg and 120 mg per day.
Feature 4	A preferred dosing regimen of Feature 3 involves administering the daily dose in three equal portions throughout the day.

Benefits:

- Enhanced Cognitive Function in Alzheimer's Patients
- Convenient Oral, Immediate-Release Dosing
- Optimized Dosing Regimen for Sustained Efficacy

Target Market Segment

- Pharmaceuticals for Neurodegenerative Disorders
- Central Nervous System (CNS) Therapeutics Market

NOVELTY ASSESSMENT

Objective

The objective of this novelty search is to identify potentially relevant granted patent, published patent application or non-patent literature that disclose or overlap with the key features of the invention related to the use of Rho kinase inhibitors for treating Alzheimer's Disease. The search would be performed without any date range or jurisdictional limitation.

Summary of Findings

A total of 2 patent references and 4 non-patent references were identified as potential relevant to the features of the invention. Both patent references fully disclosed all key features (Feature 1 to 4). Among the non-patent references, only non-patent result 1 disclosed a majority of features (Features 1–3) but not the dosing regimen (Feature 4), while others showed partial relevance for one or more features. These partial disclosures may indicate background knowledge.

Search Results

Table 1 and Table 2 below show our mapping of references against the feature of the invention. 'Y' indicates presence of a feature in the reference. 'N' indicates that we could not find enough evidence of presence of the feature in the reference.

Table 1: Patent References

S. No.	Publication number	Feature 1	Feature 2	Feature 3	Feature 4
1	US12329761B2	Y	Y	Y	Y
2	US20250134906A1	Y	Y	Y	Y

Table 2: Non-Patent References

S. No.	Publication number	Feature 1	Feature 2	Feature 3	Feature 4
1	Non-patent result 1	Y	Y	Y	N
2	Non-patent result 2	Y*	Y*	Y*	N
3	Non-patent result 3	Y*	Y*	N	N
4	Non-patent result 4	Y*	Y*	N	N

Notes:

Y indicates the reported reference partially discloses the key feature of the invention*

Relevant Patent References

Patent result 1: US12329761B2

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Publication Number	US12329761B2
PDF Copy	Link
Publication date	2023-06-22
Filing date	2021-01-08
Earliest Priority date	2021-01-08
Assignee	Woolsey Pharmaceuticals Inc
Inventor name	Thomas MacAllister, Sven Jacobson
Title	Methods of using rho kinase inhibitors to treat Alzheimer's disease
Abstract	Disclosed are methods of treating patients with AD using a rho kinase inhibitor. A preferred rho kinase inhibitor used according to the invention is fasudil, which is typically administered orally in a total daily dose of 70-140 mg. A preferred dosing regimen involves administering the daily dose in three equal portions throughout the day. Preferred methods continue for more than one month and typically at least 2 or 3 months. Some preferred methods do not treat mild cognitive impairment and patients have and MMSE score of ≤23 and/or a CDR-SOB score of ≥4.5.
Relevant Excerpts	Relevant excerpts from specifications: The invention contemplates **treating patients with AD using a rho kinase inhibitor**. A preferred rho kinase inhibitor used according to the invention is **fasudil**, which is typically administered **orally in a total daily dose of 70-140 mg**. A preferred dosing regimen involves administering the **daily dose in three equal portions throughout the day**. Preferred methods continue for more than one month and typically at least 2 or 3 months. EXAMPLE Eighty patients diagnosed with probable AD with at least one positive AD biomarker (aβ and/or tau abnormality) are recruited. Patients with VaD, DLB, bvFTD, or semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia are excluded, along with patients with another concurrent active neurological disease. Patients with a non-neurological comorbidity or who use medication that could adversely affect cognition are also excluded. Patients have a maximum MMSE score of 23 and a minimum MMSE score of 15. **Cohorts of 20 patients are treated orally with fasudil** or placebo in a dose escalating manner. Each group is randomized 10 patients each to placebo or drug and treated for 60 days. At the end of 30 days, based on assessment of adverse event, the next cohort with a higher dose is begun. At the end of 60 days, patients will be assessed for efficacy and safety and

	will be re-randomized into the next higher dose in the absence of dose-limiting side effects. **Oral dosing using 10 mg immediate release tablets** starts with the first cohort at 60 mg per day (administered in 3 equal doses throughout the day), the **second cohort at 90 mg per day (administered in 3 equal doses throughout the day), the third cohort at 120 mg per day (administered in 3 equal doses throughout the day)** and the third cohort at the maximum planned dose is 150 mg per day (administered in 3 equal doses throughout the day). No effect in cognition is observed with the 60 mg dose at 60 days, whereas each of the other doses show improvements at 60 days versus control. When the first cohort is escalated to 90 mg per day, a difference in cognition between treated and control in that cohort is observed. Cognition improves in a dose-dependent manner across all doses. A dose-dependent increase in creatinine, indicating possible kidney dysfunction are seen. Only 50% of the subjects who are escalated to the 120 mg per day dose are also escalated to the 150 mg dose and 25% of patients treated with 150 mg daily are dose-reduced due to elevated creatinine levels. It is determined that the **optimal dose for improving cognition in AD dementia is between 90 mg and 120 mg per day**. Below 90 mg, there is no efficacy and above 120 mg elevated creatinine becomes dose-limiting in many patients.

Patent result 2: US20250134906A1

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Publication Number	US20250134906A1
PDF Copy	Link
Publication date	2025-05-01
Filing date	2023-02-17
Earliest Priority date	2023-02-17
Assignee	Woolsey Pharmaceuticals Inc
Inventor name	Qicai LIU, Hemant Joshi, Thomas W. MacAllister
Title	Oral formulations of fasudil with ion exchange resin
Abstract	An oral pharmaceutical composition is provided that can comprise a rho kinase inhibitor, for example, fasudil, a pharmaceutically acceptable salt thereof, a hydrate thereof, a prodrug thereof, a substituted derivative thereof, or a metabolite thereof, or any combination thereof, the rho kinase inhibitor having a bitter taste; and an ion exchange resin. The ion exchange resin can partially or fully mask the bitter taste of the rho kinase inhibitor, making the composition more palatable. The composition can comprise a solid dosage form, and/or a liquid dosage form. The solid dosage form can comprise a powder, granules, a tablet, or a capsule, or any combination thereof. The composition can be present, for example, in a unit dose, in an amount sufficient to treat a neurodegenerative disease. A method of treating the neurodegenerative disease with the oral pharmaceutical composition is provided. The method can ameliorate a symptom of a neurodegenerative disease.
Relevant Excerpts	An oral pharmaceutical composition is provided that can comprise a rho kinase inhibitor, a pharmaceutically acceptable salt thereof, a hydrate thereof, a prodrug thereof, a substituted derivative thereof, or a metabolite thereof, or any combination thereof, the rho kinase inhibitor having a bitter taste; and an ion exchange resin. The rho kinase inhibitor can comprise, for example, fasudil, for example, hexahydro-1-(5-isoquinolinesulfonyl)-1H-1,4-diazepine monohydrochloride hemihydrate, or a metabolite thereof, or both. For example, the metabolite can be hydroxyfasudil. The ion exchange resin can partially or fully mask the bitter taste of the rho kinase inhibitor. The bitter taste can be accompanied by a numbing taste, or the numbing taste can be present in the absence of a bitter taste. The ion exchange resin can be similar effective with respect to masking the numbing taste. The ion exchange resin can be a first taste masking agent, and the oral pharmaceutical composition can further comprise a second taste masking agent. The first taste masking agent can be a bitterness masker and the second taste masking agent can be, for example, a taste masking agent that is not a bitterness masker. The second taste masking agent can comprise, for example, one or both of a sweetener and a flavoring agent. The oral pharmaceutical composition can comprise a coating. The oral pharmaceutical composition can comprise a solid dosage form, or a liquid

dosage form, or both. The solid dosage form can comprise a powder, granules, a tablet, or a capsule, or any combination thereof. Granules, powder, or both can be provided as sprinkles. Pharmaceutically acceptable taste-masking compositions comprising, for example, a rho kinase inhibitor, such as fasudil (including salts and hydrates), at least one resin present as a taste-masking agent, and at least one pharmaceutically acceptable excipient are disclosed.

An oral pharmaceutical composition of the present disclosure can be formulated such that the rho kinase inhibitor is present in an amount sufficient to treat a neurodegenerative disease. The neurodegenerative disease can comprise, for example, Alzheimer's disease, a vascular dementia, amyotrophic lateral sclerosis (ALS), motor neuron diseases (including amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), pseudobulbar palsy, progressive muscular atrophy (PMA), primary lateral sclerosis (PLS), spinal muscular atrophy (SMA) and monomelic amyotrophy (MMA), as well as some rarer variants resembling ALS), Parkinson's disease, Huntington's disease, multiple sclerosis, progressive supranuclear palsy (PSP), or corticobasal syndrome (CBS), or any combination thereof. A method of treating a neurodegenerative disease is provided by the present disclosure. The method can comprise administering to a patient an oral pharmaceutical composition of the present disclosure in an amount sufficient to treat the neurogenerative disease in one or more doses. A method is also provided comprising administering to a patient an oral pharmaceutical composition of the disclosure in an amount sufficient to ameliorate a symptom of a neurodegenerative disease in one or more doses. For example, the symptom can comprise wandering, agitation, cognitive impairment, anxiety, muscle weakness and/or degeneration, sleep disorders, troubles breathing, sleep apnea, depression, psychiatric issues, or the like, or any combination thereof. An oral pharmaceutical composition can be administered, for example, by mixing the composition with food, or beverage, or both.

A method of treating a neurodegenerative disease is provided, the method comprising administering to a patient a composition of the present disclosure in an amount sufficient to treat the neurogenerative disease. For example, the amount of rho kinase inhibitor per dose can be less than about 0.5 mg, from about 0.5 mg to about 250 mg, from about 5.0 mg to about 225 mg, from about 10 mg to about 200 mg, from about 20 mg to about 180 mg, from about 25 mg to about 170 mg, from about 30 mg to about 160 mg, from about 40 mg to about 150 mg, from about 50 mg to about 140 mg, from about 60 mg to about 120 mg, from about 75 mg to about 100 mg, or more than 250 mg, or any amount therebetween, or any range therebetween. These amounts can refer to the rho kinase inhibitor, a pharmaceutically acceptable salt thereof, a hydrate thereof, a prodrug thereof, a substituted derivative thereof, or a metabolite thereof, or any combination thereof. These doses can be delivered in a single dosage form

	or in multiple dosage forms. Multiple dosage units, for example, tablets or capsules, can be administered at the same time, or sequentially over a given time period, for example, a twenty-four hour day, or both, to achieve a target dose. Some examples of doses per day are set forth in Table A with respect to various therapeutic targets. Doses outside or overlapping these ranges can also be employed. Doses can be adjusted based on the weight, health, and other factors of a specific patient or a group of patients. The daily dose of fasudil can be 180 to 360 mg in an immediate release formulation administered 2-3 times per day. Thus, each individual dose would contain 60-180 mg of fasudil, for example, 60, 90, 120 or 180 mg.

Relevant Non-Patent References

Non-Patent result 1:

Click here to return to the search results table

Result number	Non-Patent Reference 1
Author	Andreas Wolff, Jörg Peine, Josef Höfler, Gabriela Zurek, Claus Hemker, Paul Lingor
Document Title	SAFE-ROCK: A Phase I Trial of an Oral Application of the ROCK Inhibitor Fasudil to Assess Bioavailability, Safety, and Tolerability in Healthy Participants
Website	Link
Publication Date	28 February 2024
Relevant excerpts	Objective The objective of this study was to assess the absolute **bioavailability of oral**, in comparison to IV, **application of the approved formulation of fasudil (ERIL®)** and to evaluate the safety and tolerability of the oral application of fasudil. Introduction In parallel with the vast physiological effects of ROCK, ROCK inhibition offers a wealth of pharmaceutical applications for various acute and chronic diseases. **ROCK inhibition promotes vasodilatation,** reduces vascular smooth muscle contraction, and preserves endothelial integrity, leading to alleviated cerebral vasospasm following subarachnoid hemorrhage [4], improved clinical outcome in ischemic stroke [5], ameliorated pulmonary hypertension [6], and increased ischemic threshold of angina patients during exercise [7]. In addition to implications in cardiovascular diseases, in some cancer entities, such as breast and bladder cancer, elevated expression of ROCK was observed, associated with late stages and metastasis, while **ROCK inhibition** reduced migration and tumor growth in animal models [8]. Furthermore, **preclinical work also indicates beneficial effects in neurodegenerative diseases such as Alzheimer's disease**, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [3, 9–11]. In the central nervous system, ROCK was shown to regulate axonal regeneration and neuronal survival [12]. ROCK inhibition resulted in beneficial effects on inflammation, survival, motor functions, and histological parameters in animal models of ALS and PD [13–24]. Results Fourteen subjects aged 30–70 years were included in this trial. After oral administration, fasudil concentrations in blood were mostly very low [1.4 g/L; coefficient of variation (CV) 41.0%]. After IV application, the peak concentration was 100.6 µg/L (CV 74.2%); however, a high variance in peak concentrations were assessed for both treatments. The maximal concentrations of hydroxyfasudil in blood were similar after oral and IV treatment [111.6 µg/L (CV 24.1%) and 108.4 µg/L (CV 19.7%), respectively]. Exposure of hydroxyfasudil (assessed as AUC0–tz) differed between both treatments, with

449 µg × h/L after IV treatment and 309 µg × h/L after oral treatment. Therefore, the absolute bioavailability of hydroxyfasudil after the oral treatment was approximately 69% of the IV treatment. **No serious adverse events (SAEs) occurred during this trial, and good tolerability of oral fasudil (90 mg/day) was documented**.

Discussion

This phase I, two-period crossover trial an absolute bioavailability of 69% was documented of the **oral application of the approved and commercially available formulation of fasudil (ERIL®)** in comparison to the reference IV application of fasudil. Additionally, **oral application of fasudil raised no safety concerns and gastrointestinal tolerability of the oral administration of 90 mg/day fasudil could be established**. To our knowledge this is the first published bioavailability study of the licensed formulation of fasudil comparing oral and IV administration. As described previously, fasudil is metabolized rapidly after IV administration, resulting in a serum half-life of 0.3–0.4 h [26, 32]. The precise etiology of the observed high inter-subject variability of Cmax after IV administration remains elusive. Internal quality control did not identify any analytic biases associated with the observed variability. However, fasudil undergoes swift hepatic metabolism with discernible inter-subject variability, suggesting that the observed variations may be attributed, in part, to differences in metabolization kinetics among subjects. Oral fasudil experiences an even more pronounced first pass effect, resulting in low concentrations and high variances of fasudil. Hinderling et al. [29] studied the bioavailability of investigational solutions, powder and **immediate-release tablets of fasudil hydrochloride** and found comparable systemic concentrations of hydroxyfasudil, the active metabolite of fasudil, independent of the release site in the intestine. Pharmacokinetics of fasudil were not addressed in this study. However, the peak concentration of hydroxyfasudil tended to be smaller after colonic release compared with oral or ileal administration. Additionally, aqueous solution and **immediate-release tablets displayed comparable systemic availability in this study** [29]. In the present study, the maximal concentrations and time to peak concentration of hydroxyfasudil in the blood were comparable between the oral and IV treatments. For hydroxyfasudil, an exposure (AUC) of 400–555 µg × h/L has been documented after IV applications (30 mg fasudil over 30 min) [26, 32] and 300 µg × h/L for investigational oral solution administration of 40 mg of fasudil hydrochloride [29]. Our findings using the licensed formulation of fasudil are in line with this, with AUC0–tz for hydroxyfasudil of 449 µg × h/L after IV treatment and 309 µg × h/L after oral treatment. Based on our findings, **the absolute bioavailability of hydroxyfasudil after the oral treatment was approximately 69% of the IV treatment. For studies employing oral fasudil, this must be considered, and the dosage must be adapted**.

Conclusions

	Oral fasudil was generally well tolerated in the studied population, and no safety concerns were identified. However, systemic bioavailability of oral hydroxyfasudil corresponded to 69%, and dose adjustments need to considered. **The results presented here lay grounds for future trials of fasudil in chronic diseases, which require an oral long-term application**. This trial was registered with EudraCT (no. 2019-001805-26).

Non-Patent result 2:

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Result number	Non-Patent Reference 2
Author	Jie-Zhong Yu, Yan-Hua Li, Chun-Yun Liu, Qing Wang, Qing-Fang Gu, Hui-Qing Wang, Guang-Xian Zhang, Bao-Guo Xiao, Cun-Gen Ma
Document Title	Multitarget therapeutic effect of Fasudil in APP/PS1 transgenic mice
Website	Link
Publication Date	2017
Relevant excerpts	Abstract Introduction: **Therapeutic strategies targeting Alzheimer's disease**-related molecule β- amyloid (Aβ), Tau protein and β-site amyloid precursor protein cleaving enzyme (BACE) have been recently explored. However, the treatment effect for single target is not ideal. **Based on multiaspect roles of Rho kinase inhibitor Fasudil on neuroprotection, neurorepair and immunomodulation, we observed therapeutic potential of Fasudil and explored possible mechanisms in amyloid precursor protein/ presenilin-1 transgenic (APP/PS1 Tg) mice, an animal model of Alzheimer's disease**. Methods: **APP/PS1 Tg mice were treated with Fasudil (25 mg/kg/day)** for 2 months by intraperitoneal injection. Mouse behavior tests were recorded every day. The expression of Aβ deposition, Tau protein phosphorylation, BACE and postsynaptic density 95 (PSD-95) in hippocampus was assayed. The levels in the brain of Toll-like receptors (TLRs)-nuclear factor kappa B/p65（NF-κB/p65)- myeloid differentiation primary response gene 88 (MyD88) inflammatory cytokine axis were measured. Results: Fasudil treatment ameliorated learning and memory deficits, accompanied by reduced Aβ deposition, Tau protein phosphorylation, and BACE expression, as well as increased PSD-95 expression in hippocampus. Fasudil intervention also inhibited TLR-2/4, p-NF-κB/p65, MyD88, interleukin-1beta, interleukin-6 and tumor necrosis factor-α for TLRs-NF-κB-MyD88 inflammatory cytokine axis and the induction of interleukin-10. Conclusion: Fasudil exhibited multitarget therapeutic effect in APP/PS1 Tg mice. The study provides preclinical evidence that Fasudil treatment ameliorated memory deficits in APP/PS1 Tg mice, accompanied by the reduction of Aβ deposition and Tau protein phosphorylation, the decrease of BACE and the increase of PSD-95, as well as inhibition of TLRs-NF-κB-MyD88 inflammatory cytokine axis. However, these results still need to be repeated and confirmed before clinical application.

Non-Patent result 3:

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Result number	Non-Patent Reference 3
Author	Hayder M. Al-kuraishy, Ghassan M. Sulaiman, Hamdoon A. Mohammed, Ali I. Al-Gareeb, Ali K. Albuhadily, Sohaib G. Mohammed
Document Title	Role of RhoA-ROCK signaling inhibitor fasudil in Alzheimer disease
Website	Link
Publication Date	27 April 2025
Relevant excerpts	**Alzheimer disease (AD)** is the most common neurodegenerative brain disease linked with the development of dementia. AD neuropathology is characterized by the progressive accumulation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles (NFTs). Different signaling pathways are involved in AD neuropathology through modulation of Aβ formation and tau protein hyperphosphorylation. One of these signaling is Rho-associated protein kinase (ROCK). RhoA-ROCK signaling boosts the production of Aβ through activation of β-secretase and augments the formation of NFTs. RhoA-ROCK signaling is also intricate in the development of oxidative stress and neuroinflammation. Consequently, **targeting RhoA-ROCK signaling by specific inhibitors, such as fasudil, may decrease AD neuropathology.** Therefore, this perspective aims to discuss the **role of RhoA-ROCK signaling in the pathogenesis of AD and how fasudil could be effective in its treatment**.

Non-Patent result 4:

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Result number	Non-Patent Reference 4
Author	Wenyue Wei, Yuyin Wang, Jing Zhang, Qingfang Gu, Xiaoqin Liu, Lijuan Song, Zhi Chai, Minfang Guo, Jiezhong Yu, Cungen Ma
Document Title	Fasudil ameliorates cognitive deficits, oxidative stress and neuronal apoptosis via inhibiting ROCK/MAPK and activating Nrf2 signalling pathways in APP/PS1 mice
Website	Link
Publication Date	31 March 2021
Relevant excerpts	Introduction Alzheimer's disease (AD) is a common neurodegenerative disease, characterized by senile plaques (SP), neurofibrillary tangles (NFTs) and memory deficits as well as behavioural disability [7]. According to the World Alzheimer Report 2016, an estimated 46.8 million individuals suffered from AD-related dementia worldwide and this figure may be forecasted to reach 131.5 million by 2050 [26]. With the coming of world population aging, AD, one disease closely related to aging, has become a serious health and economic burden in the society. Several decades of relevant observations have proved that various pathological changes have occurred during the progression of AD including oxidative stress, mitochondria dysfunction, and neuronal apoptosis, which are likely to have the prominent roles contributing the pathogenesis of AD [17]. Even today, some symptomatic treatments have been taken the clinically, but there is still no effective etiological therapy available [35]. Oxidative stress, as a characteristic of the aging progress, occurs when the level of oxidation exceeds endogenous antioxidant defence, and causes irreversible alternations to biomacromolecule. It is well known that oxidative stress plays a crucial role in pathogenesis of AD on account of its close correlation with the disease severity [27]. Additionally, brain is the most vulnerable region because of its high oxygen consumption and the relatively weak antioxidant system [9]. Particularly, hippocampus, a vital memory centre, would probably be the first brain area with cell death occurring in AD affected by the oxidative damage [25]. These studies provide a novel approach to attenuate neuronal apoptosis and slow down the course of AD by inhibiting oxidative stress response [18]. **The neural apoptosis in AD is regulated by various signalling pathways. Primarily, the important serine-threonine Rho-associated protein kinase (ROCK) participates in the regulation of various cellular activities**, including proliferation, adherence, contraction, secretion, and apoptosis. ROCK contains two isoforms, ROCK1 and ROCK2, and they share quite high homology. ROCK1 is expressed mainly in the non-neuronal tissue, while the expression of ROCK2 is mainly found in the nervous system [24]. There is considerable evidence indicating that ROCK2 overexpression contributes to the development and progression of neurodegenerative diseases, such as

multiple sclerosis (MS), Parkinson's disease (PD), and AD [6]. **Thus, inhibiting ROCK2 would be a novel therapeutic approach against neurological disorders** [28]. Next, the mitogen-activated protein kinase (MAPK) is another kind of serine-threonine kinase that generally exists in eukaryotic cells, and accumulating studies have shown that MAPK pathway activation is closely related with the physiological and pathological process of cells [1]. MAPK is mainly composed of p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular regulated protein kinases (ERK) [21]. Furthermore, insufficient activation of nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) in the nuclei has also been closely related to chronic neurological disorders such as AD [11]. Nrf2 is the most important redox-regulated transcription factor that plays a pivotal role in anti-oxidative stress via modulating the expression of a battery of endogenous redox-regulated enzymes such as hemeoxygenase-1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), and superoxide dismutase (SOD) [2].

Fasudil, a selective ROCK inhibitor, has been applied to relieve cerebral vasospasm in clinical practice since the last century [22]. Our previous results and other researchers' studies also provided several lines of evidence that ROCK inhibitors significantly improved cognition in amyloid precursor protein/presenilin-1 (APP/PS1) mice, combined with the reduction of pathological products in the whole brain, such as amyloid-b (Ab) deposits, p-Tau and b-site APP-cleaving enzyme (BACE). In addition, the administration of ROCK inhibitors boosted the synapse function and neurotrophic factors levels, as well as restrained the immune response in the central nervous system (CNS) by regulating the peripheral immune system [15,30,39]. And based on the above, **Fasudil may be a promising drug for CNS disorders including AD**. However, it is still unclear whether Fasudil has antioxidant effects on AD as well as its exact mechanisms. Few studies have focused on the molecular mechanism of Fasudil on AD in vivo involving modulation of MAPK and Nrf2 pathways. Therefore, in this study, we have aimed to investigate the antioxidant effects of Fasudil on the classic mouse model of AD, and explore its possible mechanisms.

Search Strategy

Patent and non-patent search strategies were designed based on the key features of the invention. These strategies were run in combination to perform a comprehensive search on the subject matter.

Patent Search Strings		
Search Concept	**Search strategy**	**Hits**
Rho Kinase + Alzheimer	("rho kinase" OR "ROCK inhibitor" OR fasudil) NEAR5 (cognition OR "cognitive function" OR memory OR "Alzheimer*" OR "neurodegenerative disorder*" OR dementia)	50
Fasudil + Formulation	(fasudil OR "rho kinase inhibitor") NEAR5 ("oral composition" OR "oral formulation" OR "immediate release")	20
Fasudil + Dosage	(fasudil NEAR3 ("90 mg" OR "120 mg" OR "daily dose" OR "three times a day" OR "divided dose*" OR "thrice daily"))	10

Non-Patent Search Strings
Google Scholar/Google Web
"rho kinase inhibitor" AND (cognition OR "cognitive function") AND (Alzheimer OR dementia OR "neurodegenerative disorder")
fasudil AND cognition AND Alzheimer
fasudil AND ("cognitive function" OR memory) AND (Alzheimer OR dementia OR "mild cognitive impairment")
fasudil AND "oral formulation" AND "immediate release"
fasudil AND ("90 mg" OR "120 mg") AND ("three times daily" OR "divided dose" OR "oral administration")

Data Coverage
• Patent searches were conducted using commercial and freely available patent databases (subject to availability of information on the platform) • Non-patent literature searches were carried out on Google Web and Google Scholar

Search Date
• The novelty search was performed on July 16, 2025

TECHNOLOGY LANDSCAPE

Objective

The objective of this technology patent landscape analysis is to assess the current state of the art **in the use of Rho kinase inhibitors for the treatment of Alzheimer's Disease**. The analysis is conducted at a broader scope than the novelty search, encompassing any Rho kinase inhibitor instead of Fasudil.

The goal is to identify key assignees, research institutions, and other active players contributing to innovation in this space. This includes mapping patent filing trends, technological focus areas, and the overall intensity of innovation.

Summary of Findings

Between 2014 and 2023, the Rho kinase–Alzheimer's patent landscape reveals a steady rise in innovation, with invention velocity peaking between 2020 and 2022, growing at a ~10.8% CAGR. The United States leads as the dominant innovation source, contributing nearly five times more than the next-ranked country, China. Woolsey Pharmaceuticals stands out as the top innovator, contributing over four times more inventions than any other entity, reflecting a strong lead in this niche. While the landscape is U.S.-centric, emerging contributions from Asia and Europe, alongside involvement from startups, academia, and global pharma, point to a diversifying and competitive innovation ecosystem.

Analytical Frameworks

To understand the broader innovation landscape, the patent dataset was probed using multiple analytical frameworks. These include, invention velocity, innovation source, top innovators, etc.

Invention Velocity

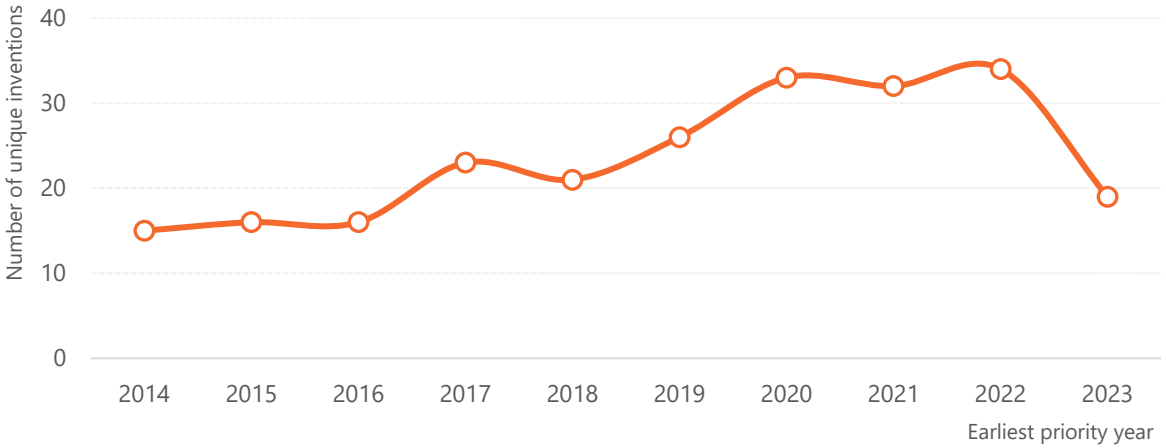
The line chart illustrates the year-wise trend in global patent filings related to **Rho kinase inhibition for Alzheimer's Disease**, based on the volume of unique inventions from 2014 to 2023.

The filing velocity for Rho kinase inhibition in Alzheimer's Disease showed a steady increase from 2014, peaking between 2020 - 2022 with over 30 unique inventions annually. Invention filings grew at a **CAGR of ~10.8% between 2014 and 2022**, indicating sustained innovation momentum. This reflects strong innovation interest and competitive activity during that period.

A sharp decline in 2023 is due to a lag between the filing and the first publication event at the PTOs.

Invention Filing Velocity in Rho Kinase Inhibition for Alzheimer's Disease

Based on global volume of unique patent families, (2014-Present)



Innovation Source

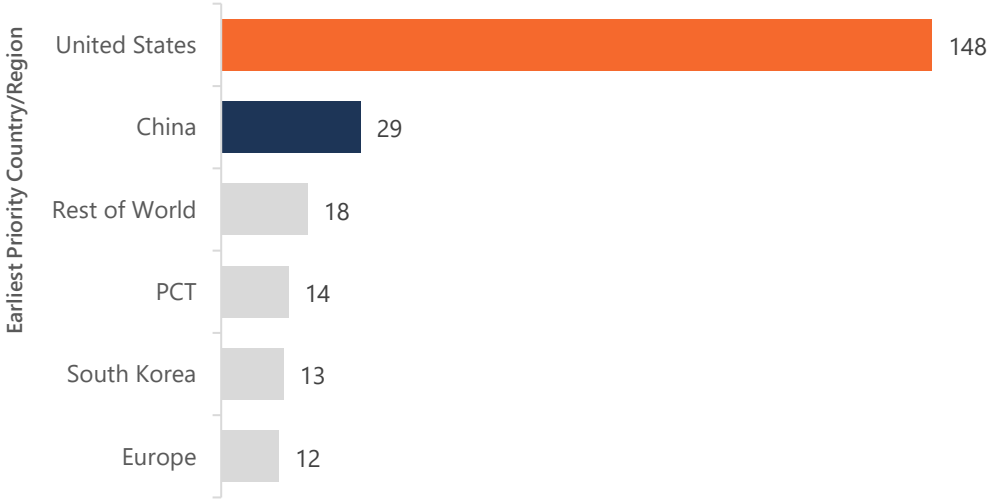
The bar chart illustrates the country of origin for inventions based on the earliest priority filings from 2014 to 2023.

The United States emerges as the leading source of innovation in this domain, with 148 unique inventions. China ranks a distant second, followed by contributions from other geographies. The presence of earliest priority filings via the PCT system also suggests international collaborations or multinational development efforts.

This distribution indicates that the U.S. has been the primary hub for early-stage innovation in this space, with limited but growing activity across Asia and Europe.

Source of Innovation in Rho Kinase Inhibition for Alzheimer's Disease

Based on volume of unique patent families, (2014-Present)



Top Innovators

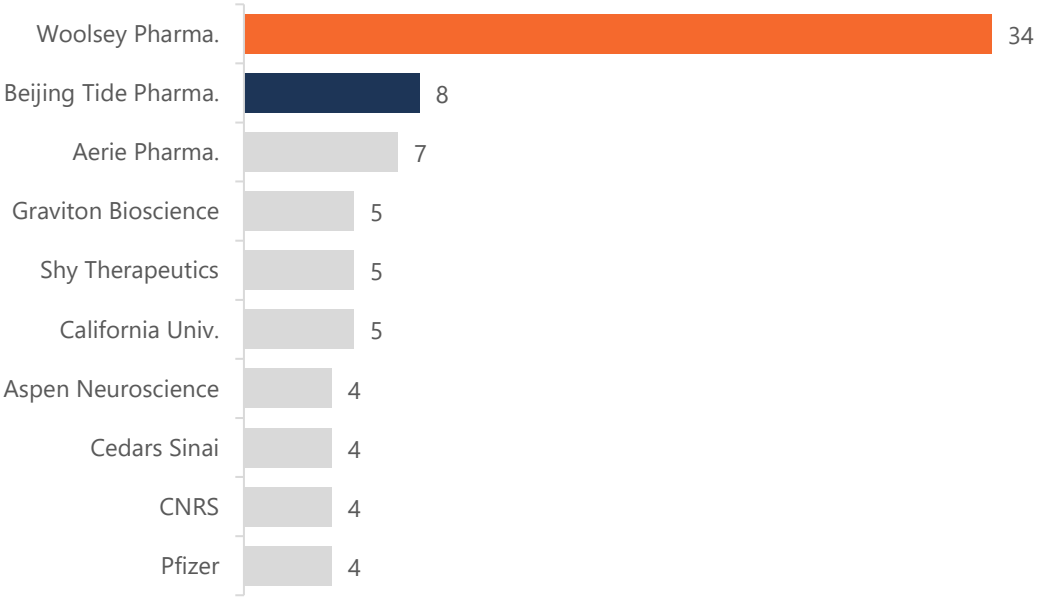
The bar chart highlights the top organizations driving innovation between 2014 and the present.

Woolsey Pharmaceuticals leads the field by a wide margin, with 34 unique inventions - over four times that of the next player. Beijing Tide Pharma and Aerie Pharma follow with 8 and 7 inventions, respectively. Other contributors include a mix of biotech firms, academic institutions, and pharmaceutical companies such as Graviton Bioscience, Shy Therapeutics, the University of California, and Pfizer.

This distribution underscores Woolsey Pharma's dominant position in this niche, while also reflecting a diverse innovation ecosystem involving startups, research institutions, and global pharma.

Top 10 Innovators in Rho Kinase Inhibition for Alzheimer's Disease

Based on volume of unique patent families, (2014-Present)



Search Strategy

Patent search strategies were designed based on a broader scope of **the use of Rho kinase inhibitors for the treatment of Alzheimer's Disease.** These strategies were run in combination to perform a comprehensive search on the subject matter.

Patent Search Strings		
Search Concept	**Search strategy**	**Hits**
Alzheimer + Any Rho Kinase	PRD>=(20140101) AND CTB=(Alzheimer* OR neurodegenerat* OR (neuro ADJ degenerat*) OR (neuro-degenerat*) OR cogniti* OR dementia*) AND CTB=((Rho NEAR2 kinas*) OR (rock ADJ inhibit*) OR fasudil* OR (rho NEAR3 inhibit*));	250

Data Coverage
• Patent searches were conducted using commercial and freely available patent databases

Search Date
• The technology landscape search was performed on July 16, 2025

MARKET ANALYSIS

Overview

The global Alzheimer's disease therapeutics market is experiencing significant growth, driven by an aging population and increasing disease prevalence. The market is projected to reach $11.34 billion by 2032, with a CAGR of 10.5%. Within this expanding landscape, Rho-associated kinase (ROCK) inhibitors represent an emerging therapeutic class with substantial potential for treating Alzheimer's disease and related neurodegenerative conditions.

ROCK inhibitors target the Rho/ROCK signalling pathway, which plays critical roles in neuronal function, synaptic plasticity, and neuroinflammation. Dysregulation of this pathway has been implicated in Alzheimer's pathophysiology, making ROCK inhibition a compelling therapeutic approach. The global ROCK inhibitor market is valued at $1.2 billion in 2024 and is projected to reach $2.5 billion by 2033, exhibiting a CAGR of 9.1%.

Market Potential and Drivers

The Alzheimer's therapeutics market is projected to reach **$11.34 billion by 2032**, with ROCK inhibitors positioned as a high-impact emerging class for disease modification. A successful CNS-penetrant ROCK inhibitor could achieve **peak sales of $2–5 billion**, with a near-term opportunity of **$500 million to $1 billion** for niche applications. As clinical data matures, particularly from the ongoing fasudil trial, the path is opening for first-mover therapies that differentiate from existing anti-amyloid approaches.

Alzheimer's disease currently impacts over 55 million people worldwide, with prevalence expected to rise sharply due to global population aging. Regional prevalence rates vary significantly, with Japan (2,637) and Italy (2,387 cases per 100,000) reporting the highest figures. The United States has 1,466 cases per 100,000, with the number of patients aged 65 and older projected to reach 7.2 million by 2025. Although China has a lower prevalence rate, it accounts for the largest absolute number of Alzheimer's patients.

Market growth is driven by aging demographics - projected to reach 2.1 billion people aged 60+ by 2050, alongside advances in diagnostic tools, a persistent lack of effective disease-modifying therapies, and a surge in pharmaceutical R&D investments.

Product in Market & Pipeline

While no ROCK inhibitors are currently approved for Alzheimer's Disease, several have regulatory approval for other indications (Fasudil, Ripasudil, Netarsudil, Belumosudil), establishing a precedent for safety and pharmacological relevance. Fasudil leads the Alzheimer's pipeline with an ongoing Phase 2 trial, while a growing wave of next-generation ROCK inhibitors are in preclinical development, targeting improved CNS delivery and ROCK2 selectivity (FSD-C10, Y-27632, BA-1049, NRL-1049). The delivery approaches researched include Oral tablets, Intranasal, Intravenous, and Transdermal patches.

Alternative Therapies

The Alzheimer's treatment landscape remains dominated by **anti-amyloid therapies**, led by FDA-approved drugs like Lecanemab and Donanemab, while Aducanumab continues to see limited adoption. Meanwhile, **tau-targeting therapies** are advancing through clinical trials, though results remain mixed. **Neuroinflammation** is gaining traction as a therapeutic focus, with several compounds

targeting microglial activity and inflammatory pathways. Traditional symptomatic treatments like **cholinesterase inhibitors** and **NMDA antagonists** still hold significant market share.

Regulatory Landscape and Clinical Development

ROCK inhibitors targeting Alzheimer's Disease must navigate complex regulatory pathways. Both the FDA and EMA offer fast-track and accelerated approval options for therapies addressing high unmet need, with growing acceptance of biomarkers as surrogate endpoints. Clinical development faces significant hurdles, including challenging patient recruitment, long timelines, and evolving approval standards. Despite this, compounds like fasudil benefit from a favorable safety profile and prior clinical use, supporting their advancement into Alzheimer's-specific trials.

Key Industry Players and Academic Activity

Both established pharmaceutical companies and emerging biotechs are actively advancing ROCK inhibitors for neurological and other indications. Helse Stavanger HF leads the ongoing fasudil Phase 2 trial, while companies like Aerie Pharmaceuticals, Avicenna Biosciences, and Kowa are investing in next-generation or repurposed compounds. Academic institutions, including the University of Alabama at Birmingham and Emory University, are at the forefront of ROCK2-focused Alzheimer's research. Biotechs such as Celon Pharma, RedX Pharma, and Bioaxone are driving innovation in targeted and CNS-penetrant ROCK inhibitor development.

SWOT ANALYSIS

The SWOT analysis reveals that fasudil-based ROCK inhibitors possess significant strengths in safety profile, cost-effectiveness, and multi-target mechanisms, but face substantial challenges from limited clinical data and competitive threats. Success will require strategic positioning, innovative delivery approaches, and careful market timing to capitalize on the expanding Alzheimer's therapeutics opportunity.

Strengths	Weaknesses
• Established Clinical Safety Profile • Proven Blood-Brain Barrier Penetration • Multiple Neuroprotective Mechanisms • Cost-Effectiveness • Strong Intellectual Property Position	• Limited Clinical Data in Alzheimer's Disease • Non-Selective ROCK Inhibition • Dosing and Administration Challenges • Cardiovascular Safety Considerations
Opportunities	**Threats**
• Expanding Alzheimer's Disease Market • Limited Disease-Modifying Alternatives • Regulatory Fast-Track Pathways • Combination Therapy Potential • Academic Technology Transfer • Intranasal Delivery Innovation	• Competition from Anti-Amyloid Therapies • Regulatory Approval Challenges • Patent Expiration Risks • Market Scepticism • Reimbursement Challenges

Strengths:

Fasudil benefits from a well-established clinical safety profile, with decades of use in Japan and China for cerebral vasospasm and favourable tolerability. It crosses the blood-brain barrier effectively, with high oral bioavailability - an advantage over infusion-based anti-amyloid drugs. Fasudil's multi-target neuroprotective effects, including anti-inflammatory and synaptic repair mechanisms, offer therapeutic breadth. Additionally, it is cost-effective relative to newer therapies and supported by a strong IP portfolio, making it an attractive candidate for further development and licensing.

Weaknesses

Despite its strengths, fasudil lacks large-scale clinical data in Alzheimer's Disease, which poses regulatory and adoption challenges. Its broad kinase activity may lead to off-target effects, contrasting with more selective next-generation ROCK inhibitors. The current dosing regimen - multiple oral doses per day - may reduce compliance, especially in cognitively impaired patients. Moreover, fasudil's vasodilatory effects raise cardiovascular safety concerns, particularly in elderly populations with comorbidities.

Opportunities

The growing Alzheimer's market and limited effectiveness of existing therapies create strong demand for novel disease-modifying treatments. Fasudil's unique mechanism and safety profile position it well for fast-track regulatory pathways. There is significant potential for combination therapies, especially with anti-amyloid drugs, and innovation in delivery methods like intranasal formulations could enhance CNS targeting. Academic research and technology transfer initiatives offer new licensing and partnership opportunities to advance ROCK inhibitor development.

Threats

Anti-amyloid therapies like lecanemab and donanemab have become the standard of care, backed by extensive data and strong commercial support. More selective, next-generation ROCK inhibitors under development may outperform fasudil in terms of safety and specificity. Regulatory approval for Alzheimer's drugs remains complex, with high trial failure rates and stringent endpoints. Additionally, patent expiration risks and payer resistance - especially in cost-constrained healthcare systems - could hinder fasudil's commercial viability, despite its affordability.

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