

# Finding the way forward

Citation for published version (APA):

Kerckhoffs, J. (2025). *Finding the way forward: Exploring post-stroke cognitive impairments and the therapeutic potential of the PDE4 inhibitor roflumilast*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20250214jk>

## Document status and date:

Published: 14/02/2025

## DOI:

[10.26481/dis.20250214jk](https://doi.org/10.26481/dis.20250214jk)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## Impact

Stroke is the second leading cause of death worldwide, with currently one in four individuals expected to have a stroke in their lifetime. Stroke survivors experience many challenges, and at the core of these challenges often lie the cognitive deficits they experience. These cognitive impairments which typically manifest between three to six months after a stroke are referred to as Post Stroke Cognitive Impairment (PSCI). PSCI prominently impacts daily functioning and imposes a large burden on the survivors and their caregivers. Additionally, it poses a substantial financial strain on healthcare systems and society. Problems with memory and thinking are often described as the primary concern. Currently, no pharmacological treatment options exist beyond acute stroke care. Therefore, any advancement in treatment would provide major benefits for *science, society, healthcare economics, and clinical practice*. A potential therapeutic approach currently being explored is the inhibition of the enzyme phosphodiesterase type 4 (PDE4). A promising PDE4 inhibitor is roflumilast. Consequently, the primary aim of this dissertation was to understand the nature of these cognitive impairments and explore the effects of roflumilast on PSCI. Additionally, prior research has shown that subjective and objective memory problems often do not align. Therefore, the second aim of this dissertation was to explore the relationship between subjective and objective memory complaints and to potentially bridge the gap between them through the use of virtual reality (VR).

## Main findings

First, the studies described in this research confirm that PDE4 inhibition with roflumilast enhances memory function in PSCI patients. This outcome aligns with initial expectations as previous research had shown the strongest effects of the drug on memory. Additionally, an effect on memory was anticipated based on the regions of the brain where the drug is believed to be most effective. We found that the participants who took roflumilast for three months, performed better on tests assessing memory function, compared to those in the placebo group. The participants did not experience significant side effects, as the type and frequency of complaints were similar between the placebo and roflumilast groups.

Thus, our studies confirmed the safety and tolerability of roflumilast at a dosage of 100 µg.

Second, we studied whether roflumilast also has an effect on other cognitive functions. While standard neuropsychological testing did not show treatment effects on other cognitive functions, analysis of daily digital home-based assessment indicated that roflumilast positively impacts psychomotor function and focused attention. Future studies should explore these effects in more detail.

Third, naturally, the main goal was to improve the daily lives of our participants. We used questionnaires to assess subjective memory performance, participation in daily life, and mood. However, we did not find much significant effects of the treatment on these questionnaires. Only in the OLE study, women experienced fewer subjective memory complaints after three months of roflumilast treatment. The participants and their caregivers did however spontaneously report subjective improvements.

Finally, this discrepancy between objective memory problems and subjective memory complaints was explored in this dissertation. As mentioned, these two aspects do not always align. To address this we aimed to bridge the gap by using virtual reality (VR) to assess memory performance in a sensory-rich environment. This study showed that a sensory-rich VR condition may help close this gap, considering that the stroke patients' performance on the sensory-rich VR memory task correlated with their subjective memory complaints. Notably, this was not the case in a neutral environment and among healthy controls.

### **Scientific impact**

The studies described in this thesis have been published or submitted to international peer-reviewed scientific journals. Additionally, the results have been presented at national and international conferences.

Our proof-of-concept study yielded the expected outcome: roflumilast improves memory function in stroke survivors and is safe and well-tolerated. The findings can inform other *researchers* to start future phase III studies, aimed at confirming the efficacy and effectiveness of roflumilast. Additionally, the results could serve as a basis for a health technology

assessment to evaluate the cost-effectiveness of this new treatment.

The integration of standard neuropsychological tests, questionnaires, and digital home-based daily assessments to evaluate cognitive function is a method that could be adopted by future *researchers* to obtain a more comprehensive view of cognitive abilities. This accounts for day-to-day variations complementing the traditional ‘snapshot’ provided by neuropsychological assessments conducted at fixed time points. Recognizing the importance of integrating multiple assessment modalities can enhance the design of studies investigating the effects of treatments on cognitive function in brain injury patients. The use of sensory-rich VR memory assessments could provide further insights by aligning subjective memory complaints with objective memory problems in future studies.

Furthermore, a method was demonstrated to deal with strong placebo responders or baseline imbalances. The analysis, which adjusted for baseline characteristics as recommended by EMA and FDA, was conducted by Cognivia and could serve as a valuable example for future *researchers*.

## Societal and clinical impact

Finding an effective treatment for PSCI would have significant implications for *patients*, their *caregivers*, *health care systems*, and *society*. As mentioned, many people will face the serious consequences of stroke, including cognitive impairments, which severely impact the quality of life of both the individual and their spouses or caregivers. Stroke survivors often struggle to reintegrate into society, with many not being able to go back to work. This creates a substantial societal burden. Additionally, the financial strains are considerable, affecting both *health care systems* and *government resources*. Therefore, the fact that current findings may contribute to the development of a treatment for these patients, holds importance for all these stakeholders.

The clinical trial presented in **Chapters 2** and **3** is an indispensable step in the process of demonstrating roflumilast’s therapeutic potential in order to get regulatory approval, ultimately facilitating its availability for *patients* who could benefit from its use. The presented studies provide the first proof that PDE4 inhibition could be a promising treatment for

PSCI patients and possibly even *other patients* dealing with traumatic brain injury or mild cognitive impairment. The Open-Label Extension (OLE) study in **Chapter 3** employs a method that reflects conditions that could be seen as more similar to clinical practice. This study showed further improvements in cognitive performance in PSCI patients who had previously received placebo treatment. However, as participants are aware that they will receive the active drug in an OLE study, this knowledge may influence their expectations. Therefore, the results will include medication effects as well as expectation effects as is the case in clinical practice.

During the trial, *General Practitioners* contacted us several times for advice. Several participants receiving roflumilast reported feeling significantly better after participating in the trial, prompting them to seek guidance from their GP. Since roflumilast is approved for the treatment of Chronic Obstructive Pulmonary Disease (COPD), the drug could be prescribed off-label. The fact that participants ask for this along with GPs being willing to help their patients, suggests that, despite the subjective questionnaires in the ROSTMEMA trial not showing improvements, roflumilast may indeed have a beneficial effect for PSCI patients. It also highlights the great unmet medical need in this patient group.

When the results of our study are shared with the general public (e.g. through organizations such as 'de Hersenstichting'), *physicians* might receive more requests for roflumilast. In this context, it would be necessary for the *physicians* to have access to information regarding dosage and potential side effects. Current results suggest a dosage of 100 µg, which does not seem to be associated with significant side effects. Therefore, we are planning to write an article for a Dutch journal aimed at GPs or host a webinar to disseminate this information.

*Clinicians* depend on past and ongoing research findings to formulate their advice and to select appropriate treatment options. Roflumilast may eventually be incorporated into post-stroke medication regimens, complementing psychological treatment and cognitive rehabilitation. By enhancing patients' memory and attention, roflumilast could improve the effectiveness of therapies designed to help individuals cope with cognitive and functional changes following a stroke, enabling them to better recall conversations with their *clinicians*.

The positive effects of roflumilast on memory performance, combined

with possible effects on psychomotor function and attention, could have great clinical implications. PSCI *patients* could greatly benefit from these effects and it may increase the likelihood of (partially) returning to work, and enable them to more actively participate in *society*. Thus, the current findings may guide future clinical practice, offering a possible path to improvement for PSCI patients.

## Dissemination activities

The findings of this thesis have been or will be disseminated within the scientific community through publication in open-access international peer-reviewed journals. **Chapter 5** has been published as open-access which makes it freely available to researchers across the world. **Chapters 2, 3, and 4** will also be made freely available once accepted for publication. Moreover, the datasets will be accessible upon request for future *research*. The published paper is easily accessible to anyone interested and has been actively promoted on social media platforms like LinkedIn, as well as the website [www.hersenletsellimburg.nl](http://www.hersenletsellimburg.nl). This will also be done for the other papers after publication. Moreover, the results have been presented at several international conferences, by means of oral presentations or posters including the Neuropsychological Rehabilitation Special Interest Group of the World Federation for NeuroRehabilitation (NR-SIG-WFNR), the Global Neuropsychology Congress, and the European Stroke Conference (ESOC). These conferences attract both *clinicians* (e.g. neurologists, neuropsychologists) and *researchers*. Additionally, the findings have been shared with *professionals* within the field through symposia and webinars organized by the Limburg Brain Injury Centre. Moreover, the protocol for the trial was presented at a regional conference for geriatricians. We have also shared our research and findings with the *general public*. This was achieved through presentations at informal public meetings organized for people with ABI and their partners, caregivers, and relatives such as the Brain Cafés in Kerkrade and Baarlo. Additionally, our work was featured in an interview in the local newspaper 'De Limburger'. Finally, a blog post on the results was written and shared on LinkedIn and the website of the Limburg Brain Injury Centre. For the chapters that remain to be published, we plan to share the findings with participants through the website of our sponsor 'De Hersenstichting' and via our website: [www.rostmema.nl](http://www.rostmema.nl).