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Original Research Article

A Randomised, Double-Blind, Placebo-Controlled Trial of Actovegin in Patients with Post-Stroke Cognitive Impairment: ARTEMIDA Study Design

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Key Words

Stroke · Vascular dementia · Cognitive impairment · Pharmacotherapy · Actovegin

Abstract

Background: No drug treatment to date has shown convincing clinical evidence of restoring cognitive function or preventing further decline after stroke. The ongoing ARTEMIDA study will evaluate the efficacy and safety of Actovegin for the symptomatic treatment of post-stroke cognitive impairment (PSCI) and will explore whether Actovegin has any disease-modifying effect by assessing whether any changes are sustained after treatment. ***Design:*** ARTEMIDA is a 12-month, multicentre trial in patients (planned a total of 500, now recruited) with cognitive impairment following ischaemic stroke. The study consists of a baseline screening (≤7 days after stroke), after which eligible patients are randomised to Actovegin (2,000 mg/day for up to 20 intravenous infusions followed by 1,200 mg/day orally) or placebo for a 6-month double-blind treatment period. Patients will be followed up for a further 6 months, during which time they will be treated in accordance with standard clinical practice. The primary study endpoint is change from baseline in the Alzheimer's Disease Assessment Scale, cognitive subscale, extended version. Secondary outcomes include: Montreal Cognitive Assessment; dementia diagnosis (ICD-10); National Institutes of Health Stroke Scale; Barthel Index; EQ-5D; Beck Depression Inventory, version II, and safety. ***Conclusion:*** There is a clear need for effective treatments for PSCI. ARTEMIDA should provide important insights into the use of a novel drug therapy for PSCI.

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Introduction

Cognitive dysfunction frequently occurs following stroke and is an important cause of stroke-related morbidity [1, 2]. The treatment of cognitive impairment and prevention of further decline are essential aspects of stroke rehabilitation. A variety of interventions have been assessed. However, there is only limited evidence to suggest beneficial effects of physical activity, cognitive training and risk factor reduction, and clearly more research is needed [3, 4].

Pharmacological therapy to enhance cognition may also theoretically lead to improved recovery. However, no drug treatment to date has shown convincing clinical evidence of preventing further cognitive decline or restoring cognitive function after stroke. The urgent need for robust, well-designed studies investigating the treatment of post-stroke cognitive impairment (PSCI) and prevention of cognitive decline is widely recognised [5].

Post-Stroke Cognitive Impairment

PSCI is a major cause of functional disability and is associated with impaired quality of life, depression, increased risk of progression to dementia and reduced long-term survival [6–8]. Although not well-defined, it is typically understood to refer to any cognitive deficit after a cerebrovascular event, ranging from mild cognitive impairment to frank vascular dementia. A restricted definition of vascular cognitive impairment excluding cases of dementia has been suggested (vascular cognitive impairment-no dementia) [9].

The pathology of PSCI is heterogeneous and involves a variety of processes. Large- and small-vessel cerebrovascular disease can cause cortical infarcts as well as strategic subcortical infarcts, resulting in cortical deactivation and direct neuronal damage. Silent small-vessel disease of the subcortical white matter also has a role [5, 10]. Furthermore, there is a close relationship between PSCI (as with vascular dementia) and Alzheimer's disease, the two often occurring together with additive negative effects on cognition [5, 11, 12].

PSCI is a part of the nosological syndrome of vascular dementia, for which several treatments have been investigated. However, drugs used to treat Alzheimer's disease, such as cholinesterase inhibitors or NMDA receptor antagonists, have been shown to have limited efficacy in vascular dementia and none have been approved by major regulatory agencies for this specific indication [13]. Pleiotropic drugs with multimodal mechanisms of action have shown some potential in vascular dementia studies [14] but, to date, there are no randomised controlled trials (RCTs) showing effective pharmacological treatment of PSCI using appropriate scales.

Actovegin

Actovegin (Takeda Pharmaceuticals, Zurich, Switzerland) is a deproteinised ultrafiltrate of calf blood composed of more than 200 biological substances. It has been used in clinical practice in a variety of indications including ischaemic stroke and brain injury, peripheral arterial and venous perfusion disorders, diabetic polyneuropathy and skin trauma conditions [15].

As a result of its large number of bioactive constituents, Actovegin affects numerous biochemical pathways and has pleiotropic neuroprotective and metabolic effects [16]. It has been reported to increase the number of neuronal cells and synaptic connections and to reduce apoptosis in a dose-dependent manner when added to freshly cultured primary rat neurons in vitro [17]. Recently, Actovegin has also been shown to activate the in vitro expression of NF-κB, a transcription factor that is believed to have neuroprotective properties [16]. This modulation of the NF-κB pathway may in part explain the neuroprotective and anti-apoptotic effects of Actovegin. In addition, Actovegin also has multiple metabolic

effects, including improved oxygen utilisation and uptake, enhanced cellular energy metabolism and increased glucose uptake [18–20]. These effects may enhance energy metabolism in the brain, as well as contribute to the beneficial effects seen in patients with diabetic complications (e.g. diabetic neuropathy) [21].

Previous trials have shown clinical efficacy and favourable tolerability of Actovegin in patients with mixed dementia. In a double-blind, placebo-controlled study of 60 patients with mild-to-moderate dementia (organic brain syndrome), intravenous Actovegin resulted in a significantly greater improvement in cognitive function (assessed by the Sandoz Clinical Assessment Geriatric Scale and the Clinical Global Impression Scale) than placebo after 4 weeks [22]. Similarly, oral Actovegin significantly improved the Syndrom Kurztest and the Clinical Global Impression Scale scores versus placebo in a study of 200 patients with mild-to-moderate dementia [23]. Actovegin was also effective in improving cognition (Syndrom Kurztest and Clinical Global Impression Scale) in a randomised, placebo-controlled study of 120 dementia patients, 77 of whom had vascular dementia [24].

More recently, two pilot studies have indicated that Actovegin significantly improves functional recovery and reduces neurological deficits when administered to patients in the acute period of ischaemic stroke. In the first study, Actovegin (n = 32) resulted in significantly greater improvements in the Mini-Mental State Examination (MMSE) and Gusev Skvortsova Scale than piracetam (n = 11) after 30 days [25]. In the other trial, intravenous Actovegin for 10 days significantly improved the Barthel Index score when given alone (n = 25) or in combination with citicoline (n = 25) compared with placebo (n = 26). The National Institutes of Health Stroke Scale (NIHSS) score was also improved with Actovegin, although this was only statistically significant in the group also receiving citicoline [26]. However, as yet, there are no data on the effects of Actovegin on post-stroke cognitive function from large-scale, long-term RCTs.

Design

ARTEMIDA is a 12-month, multicentre, randomised, double-blind, placebo-controlled trial to assess the effect of treatment with Actovegin in patients with PSCI (www.clinicaltrials.gov: NCT01582854). The planned total of 500 patients have been recruited at approximately 25 centres across Russia, Belarus and Kazakhstan, with enrolment completed 1 month before the end of the recruitment phase. The study protocol is approved by the relevant Competent Authorities and Ethics Committees and the trial will be conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and any applicable local regulations.

The study consists of baseline screening (≤7 days after stroke), at the end of which eligible patients will be randomised to add-on treatment with Actovegin or placebo for a 6-month period. Patients will then be followed up for a further 6 months, during which they will be treated in accordance with standard clinical practice but not including Actovegin (fig. 1).

The main objective of the study is to evaluate the efficacy and safety of Actovegin for the symptomatic treatment of PSCI. The study will also explore whether Actovegin has any disease-modifying effect by assessing whether the treatment effects on PSCI seen at 6 months are sustained during the post-treatment period. Stroke-related outcomes other than cognitive impairment will also be recorded.

The study will enrol men and women aged ≥60 years who have experienced a recent mild-to-moderate supratentorial ischaemic stroke, confirmed by computed tomography scan or magnetic resonance imaging. For inclusion, patients must be fully conscious, with symptoms and/or signs indicating cognitive impairment, an NIHSS score of 3–18 and a Montreal

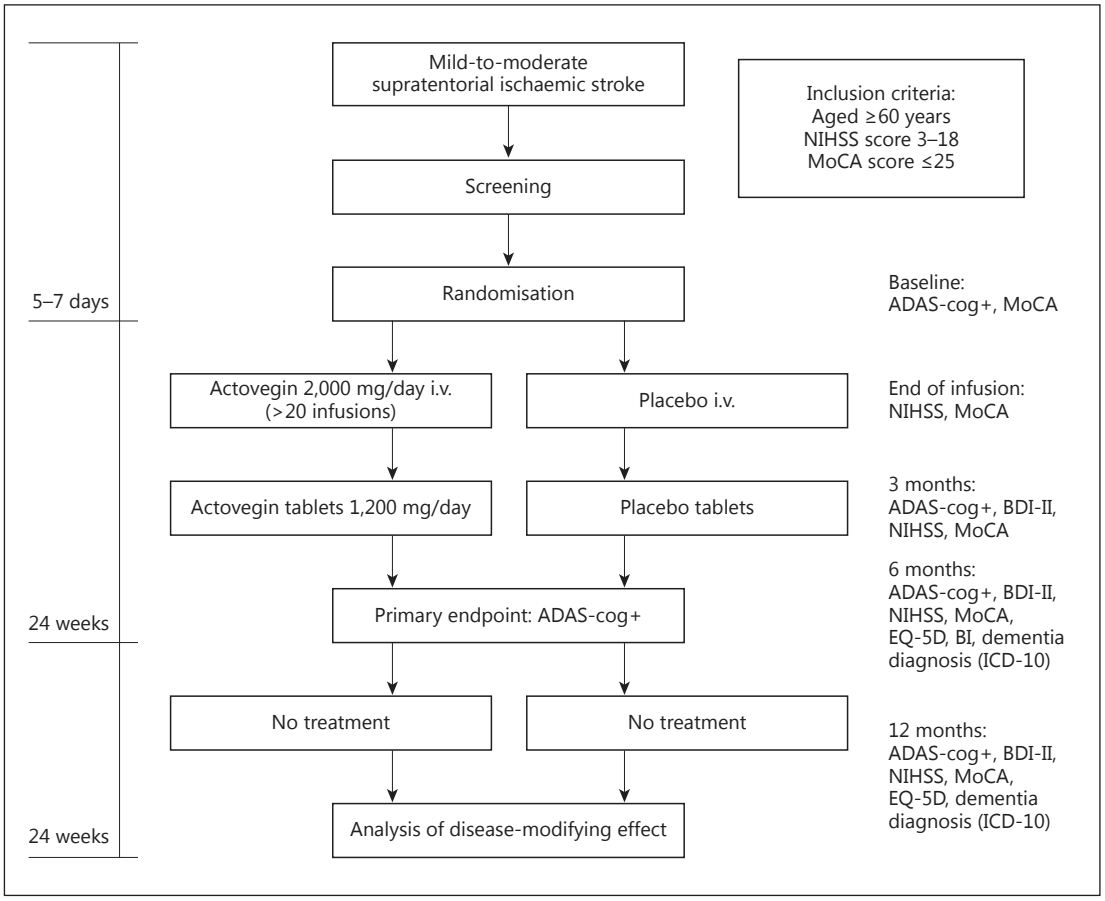

Fig. 1. Study design. BI = Barthel Index.

Cognitive Assessment (MoCA) score of ≤25 (adjusted for level of education). At randomisation, the patient must be able to complete the Alzheimer's Disease Assessment Scale, cognitive subscale, extended version (ADAS-cog+) and the MoCA scale. All patients must provide written informed consent.

Exclusion criteria include a medical history of dementia, major depression or psychotic disorder, any concomitant serious or life-threatening disease potentially resulting in death within 12 months, suspicion of cardioembolic stroke despite anticoagulant treatment, treatment with thrombolytics, carotid surgery or neurosurgery or the need for such treatment, or myocardial ischaemia. Patients will be excluded at randomisation if progressive stroke is suspected, blood pressure exceeds 220 mm Hg (systolic) or 140 mm Hg (diastolic), or if receiving any non-permitted medication.

Patients who experience a recurrent stroke during the study will be withdrawn from the trial but included in the analysis, given that the objective is to study the treatment effect on cognitive performance after an index stroke and that cognition in the period after a recurrent stroke would be expected to deteriorate with a highly variable impact on the primary endpoint. Patients will also be withdrawn from the study if they experience a transient ischaemic attack requiring hospitalisation or treatment, or use any non-permitted medication. Planned carotid angiography, carotid artery surgery or neurosurgery will also result in patients being withdrawn from the study.

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The patients will be randomised at a 1:1 ratio using an Interactive Voice Response System or Interactive Web Response System. Treatment will start between 5 and 7 days after the onset of stroke. The patients will receive treatment with Actovegin or matching placebo for 6 months. Those randomised to Actovegin will receive 2,000 mg/day i.v. (8 mg/ml) for up to 20 infusions followed by oral Actovegin 1,200 mg/day (two 200-mg tablets three times daily) for the remainder of the 6-month treatment period. All infusion bottles will be masked to ensure that they are visually identical, with coloured infusion sets being provided to achieve blinding during administration. Actovegin and placebo tablets are identical in appearance.

The dosing regimen reflects the current label for Actovegin, except that the oral treatment period is extended. This prolonged treatment period has previously been shown to be safe and effective (at a higher daily dose of 1,800 mg/day) in a trial of patients with diabetic polyneuropathy [21].

All patients will receive the best current clinical standard of care, including treatment of vascular risk factors and rehabilitation therapy. Nootropic agents, other than glycine, are not permitted since their postulated mode of action could act to negate any between-group difference, even though there is little evidence that they improve cognitive function after stroke. Glycine is allowed as it is included in the national standards of stroke care in Russia (where the majority of study sites are located) and is typically given to the patient by the emergency services.

A 6-month treatment period (followed by a further 6-month follow-up period) was chosen since European Medicines Agency (EMA) guidelines indicate this as a minimum duration of treatment in dementia trials [27]. Given the assumed mode of action of Actovegin, the early intervention and the study objectives, treatment for 6 months with a subsequent 6-month follow-up is considered adequate. Follow-up assessment at 12 months will allow the investigation of any disease-modifying effect using a slope-analysis method.

Study Outcomes

ADAS-cog+ score change from baseline was chosen as the primary endpoint of the trial. Previous large studies on acute stroke have not focused on cognitive impairment as a primary objective, and when cognitive function has been assessed, it has primarily been with tools designed for screening rather than outcomes (e.g. MMSE, MoCA) although these may not be ideal [28, 29]. The few clinical trials assessing PSCI have mostly been explorative and used a variety of different primary cognitive outcome measurements [30, 31].

The ADAS-cog, a cognitive subscale of ADAS, has been widely used to measure change in cognitive function in clinical trials of patients with Alzheimer's disease [32] and vascular cognitive impairment [13]. The ADAS-cog measures cognitive performance by combining ratings of 11 items. The cognitive domains mainly addressed by ADAS-cog are memory (short-term), language, ability to orientate (reflects memory), construction/planning of simple designs and performance. The extended version of the ADAS-cog (ADAS-cog+) includes 3 additional items: a two-number cancellation task to test for attention, a delayed recall task to test for memory consolidation and a maze test for executive performance [33]. The ADAS-cog+ is designed to have greater sensitivity in detecting patients with milder dementia and could be particularly useful in vascular cognitive impairment-no dementia, since attentional and executive performance is particularly affected in the early phases of this condition.

Although used in studies of patients with Alzheimer's disease, the ADAS-cog+ scale has not been validated or proven in the acute period following stroke. However, we considered it to be the most appropriate tool to assess cognition in both the acute and delayed period of stroke. The Dementia Rating Scale-2 was also taken into account, but ADAS-cog+ was thought

Table 1. Study timeline and endpoints

	End of infusion	3 months	6 months	12 months
Primary endpoint				
ADAS-cog+ (6 months)[1]			✓	
Secondary endpoints: cognition-specific				
ADAS-cog+ (3 and 12 months)[1]		✓		✓
Proportion of ADAS-cog+ responders		✓	✓	✓
MoCA[1]	✓	✓	✓	✓
Diagnosis of dementia (ICD-10)			✓	✓
Secondary endpoints: stroke-specific				
NIHSS[1]	✓	✓	✓	✓
Barthel Index			✓	
Other secondary endpoints				
EQ-5D			✓	✓
BDI-II		✓	✓	✓

[1] Change from baseline (NIHSS: relative change, baseline assessment at screening).

to be preferable due to its recognition in the EMA guidelines for dementia trials [27], and the previous use of the scale or its variants in vascular dementia trials [14].

One possible limitation in the trial design is the use of ADAS-cog+ change from baseline, with baseline assessment 5–7 days after stroke. However, it may be difficult for patients to complete the baseline assessment during the acute period of stroke. Secondly, it is not known how the ADAS-cog+ scale reflects cognitive impairment and its dynamics in this period, meaning that the baseline measurement may increase variation in the primary endpoint. However, this limitation is handled in the statistical analysis by including the baseline ADAS-cog+ as a covariate.

The use of the ADAS-cog+ scale in this study will provide a useful insight into its utility for assessing cognitive impairment after stroke and so may help inform the design of further trials in the treatment of PSCI.

Secondary endpoints are listed in table 1. In addition to ADAS-cog+, cognitive impairment will also be assessed using the MoCA test (at baseline, end of infusion, and at 3, 6 and 12 months). As patients will be aged ≥60 years, the vast majority will have at least 10 years of education (completing secondary education was mandatory in the Soviet Union) so there should be no need to adjust MoCA for educational status. However, adjustment for lower educated patients will be done according to recommendations if required [34].

Neither the MMSE nor the Clinician's Interview-Based Impression of Change with Caregiver Input scale will be used. The MMSE is generally considered to be less sensitive in detecting changes in mild cognitive impairment, while the Clinician's Interview-Based Impression of Change with Caregiver Input scale is less sensitive to clinical improvement (more sensitive in detecting decline) and a valid baseline is difficult to define. The ability of Actovegin to prevent dementia will be assessed by the investigator, with dementia diagnosed according to the *ICD-10 Classification of Mental and Behavioural Disorders* [35], at 6 and 12 months.

The study is not powered to assess the effects of treatment on neurological deficits. However, some insight may be obtained through the use of the NIHSS to assess stroke severity (at screening, end of infusion, and at 3, 6 and 12 months) and the Barthel Index to assess daily

functioning (at 6 months). Quality of life will be assessed with the EQ-5D at 6 and 12 months. This was chosen rather than the SF-12 or SF-36 since it is considered to be more consistent when used across different languages and different ethnic groups. The Beck Depression Inventory, version II (BDI-II) will be used to assess symptoms of depression at 3, 6 and 12 months.

Safety will be evaluated through the recording of adverse events, laboratory parameters, physical examination, vital signs and ECG.

Statistics

The planned total number of patients was 500. Assuming an estimated drop-out rate of 20%, 200 patients in each group will have a 90% power to detect a difference in means of at least 2.6 for the ADAS-cog+ endpoint at 6 months, assuming a common standard deviation of 8.0 using a two-group t test with a 0.05 two-sided significance level. Sample size assumptions were based on several RCTs in vascular dementia and Alzheimer's disease; the precision of 8.0 of the ADAS-cog/ADA-cog+ endpoints and the relevance of the effect size of 2.6 were based on four previously reported studies [14, 36–38] and one planned trial [39]. The fairly large sample size and randomised design should also ensure that potentially confounding factors that are not controlled for during the study period (e.g. smoking status, development of comorbidities) do not affect the study endpoints.

The primary analysis will be conducted on the intention-to-treat population, including early discontinued subjects. The primary analysis of the ADAS-cog+ change from baseline to 6 months will be a two-sided test of the treatment difference in a linear effects model including treatment and centre as fixed effects and baseline as a covariate. The treatment difference will be estimated as least squares means and presented with the corresponding 95% confidence interval. For missing data at month 6, a last observation carried forward approach using month 3 ADAS-cog+ data will be used. This includes patients who experience a recurrent stroke and are withdrawn. Efficacy data after the recurrent stroke will be excluded and a last observation carried forward approach for data obtained prior to the recurrent stroke will be applied.

The analysis will be supported by a responder analysis, as indicated in the EMA dementia guidelines [26], with responder defined as an improvement on the ADAS-cog+ scale of ≥4. The analysis of the MoCA, NIHSS and BDI-II will be similar to the analysis of the primary endpoint, with the exceptions that the NIHSS will be calculated as a relative change from baseline and the BDI-II will be analysed without a baseline.

The responder analysis and the analysis of the dementia diagnoses will be conducted as a 2 × 2 Fisher's exact test to compare the treatment difference. The incidence in the two groups will be calculated using the number of subjects with non-missing data as the denominator. The corresponding exact 95% confidence intervals for the incidence will be calculated in the binomial distribution.

Conclusions

PSCI is a frequent occurrence after stroke and represents a significant burden to patients, caregivers and health care systems. There is a clear unmet medical need for novel treatments for PSCI. Currently, there are no RCTs showing effective pharmacological treatment of PSCI based on recognised scales such as the ADAS-cog+.

Actovegin has been shown to be neuroprotective in vitro, and has shown promising clinical efficacy without safety concerns in randomised, placebo-controlled trials of patients

with mixed dementia and pilot studies of stroke patients [16, 22–26]. The ongoing randomised, placebo-controlled ARTEMIDA study will provide important insights into the use of a novel drug therapy for PSCI. In addition to assessing the efficacy and tolerability of Actovegin in the treatment of PSCI, the study will also explore whether treatment has a disease-modifying effect, as shown by a sustained improvement in cognitive function or prevention of dementia in patients who have experienced an ischaemic stroke.

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