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# Predictors of response to treatment with actovegin for 6 months in patients with type 2 diabetes and symptomatic polyneuropathy

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ABSTRACT

*Aims:* To evaluate two definitions of response and the predictive value of baseline covariates for response to actovegin treatment in type 2 diabetic patients with symptomatic diabetic sensorimotor polyneuropathy (DSPN).
*Methods:* Response to 6-months treatment with actovegin or placebo was defined as a clinically meaningful decline from baseline to 6 months in (1) both Neuropathy Impairment Score of Lower Limbs (NIS-LL) ≥2 points and Total Symptom Score (TSS) >50% and (2) NIS-LL ≥2 points only. Nineteen baseline covariates were evaluated using separate logistic regression models and either both NIS-LL and TSS or NIS-LL response definitions.
*Results:* Intention-to-treat analysis included 567 patients. Actovegin treatment compared to placebo was associated with better odds of response (OR [95% CI] of 1.73 [1.21–2.48] for definition 1 and 1.94 [1.33–2.84] for definition 2). Significant interaction with actovegin treatment was noted only for baseline use of angiotensin receptor blockers (ARBs)/angiotensinogen converting enzyme inhibitors (ACEIs), resulting in a reduced treatment response ($P = 0.03$).
*Conclusions:* Actovegin treatment was associated with a clinically meaningful response in neuropathic symptoms and/or impairments in patients with symptomatic DSPN. Since only one predictor of response to actovegin treatment was identified, this drug seems an appropriate therapy for the majority of patients with DSPN.
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## 1. Introduction

Diabetic sensorimotor polyneuropathy (DSPN) is one of the most common complications of diabetes and estimated to affect approximately one third of patients.[43] Around half of patients with DSPN suffer from chronic painful and non-painful neuropathic symptoms which may significantly reduce quality of life (QoL) as well as social and psychological well-being.[3] DSPN is also the major causative factor for diabetic foot ulcers and lower-limb amputation.[7] Notably, the rate of lower-limb amputations in diabetic patients is 15 times higher than in non-diabetic individuals.[7] Early detection by screening and appropriate diagnosis/treatment are therefore essential for optimal risk management in patients with DSPN.[7]

Treatment of DSPN has generally focused on glucose control, risk factor management, and relieving painful symptoms.[29] Given the limited effectiveness and frequent side effects of current pharmacotherapy for neuropathic pain,[15] alternative strategies have been explored based on the pathogenetic concepts for diabetic neuropathy.[6] Several pathogenetic therapies for DSPN have been investigated in phase III trials with varying success including actovegin,[42] alpha-lipoic acid,[28] aldose reductase inhibitors,[10] and C-peptide.[35]

Actovegin, a deproteinized hemoderivative of ultrafiltered calf serum that contains low-molecular weight compounds of up to 5000 Da,[42] is approved as a drug in a number of countries.[8] The hemoderivative is a potent antihypoxic agent that stimulates the utilization of oxygen and glucose metabolism in brain cells. It has been hypothesized that these cellular mechanisms may underlie the observed neuroprotective benefits of actovegin in DSPN.[14] Potential mechanisms leading to nerve damage in DSPN include oxidative

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injury, activation of the polyol pathway of glucose metabolism, and deposition of advanced glycosylation end products within the nerves and vascular insufficiency.[9] Based on in vivo experiments in rat brains, indicating that actovegin exerts potent antiapoptotic and antioxidant effects, administration of this drug was proposed as a potential neuroprotective strategy for diabetic patients.[25] Indeed, favorable therapeutic effects of actovegin on neuropathic symptoms, vibration perception threshold (VPT), sensory function, and QoL were demonstrated in a randomized, double-blind placebo-controlled clinical trial including 567 type 2 diabetic patients with symptomatic DSPN.[42] In the present post-hoc analysis of that trial, the clinical significance of the actovegin treatment effect was assessed, and baseline covariates most relevant for association with DSPN development were selected for analysis. The primary objectives were: (1) to determine whether 6-months treatment with actovegin exerted a clinically meaningful effect on the main neuropathic symptoms and/or impairments compared to placebo; and (2) to assess the possible predictive value of various baseline covariates for the response to treatment (actovegin or placebo) in type 2 diabetic patients with symptomatic DSPN.

## 2. Materials and methods

This post-hoc analysis included data from a multicenter, randomized, double-blind, parallel-group efficacy trial (AV-007-IM) of type 2 diabetic patients with symptomatic DSPN who received treatment with actovegin or placebo. The trial design and results have been previously reported.[42] Briefly, subjects were randomly assigned to receive 20 once-daily intravenous infusions of either actovegin or placebo for 20–36 days, followed by three tablets (actovegin or placebo) t.i.d. for 140 days.

### 2.1. Outcome measures and definitions

Two co-primary outcome measures, average TSS (of the lower limbs) and average VPT scores over the treatment period, were computed as the area under the curve (AUC) from repeated scores divided by duration of exposure, as described previously.[42] Secondary endpoints were individual TSS symptoms, average neuropathy impairment score of the lower limbs (NIS-LL) over the treatment period, and quality of life (QoL) short form-36.[24] A clinically meaningful response to treatment was defined using two criteria, NIS-LL and TSS, proposed by consensus statements.[1,13] While an improvement of NIS-LL by ≥2 points is generally agreed to represent a clinically meaningful change in neuropathic signs,[13,30] an improvement of neuropathic pain by ≥50% is accepted to translate into a substantial ("very much improved") response to treatment.[12] Based on these recommendations, the following two response definitions were used considering either both neuropathic signs and symptoms or neuropathic signs only: (1) a decrease in NIS-LL by ≥2 points and >50% decrease in TSS from baseline to 6 months; and (2) a decrease in NIS-LL by ≥2 points from baseline to 6 months. The rationale for the first, more stringent, definition was to reflect the best possible response to treatment, i.e. concordant and clinically meaningful improvement of both symptoms and signs. However, since the progression and regression of neuropathic symptoms and signs diverge,[2] the second criterion considered only the improvement of DSPN defined by NIS-LL irrespective of neuropathic symptoms. Patients not meeting either definition of response, including those with missing response, were included as non-responders in the statistical analysis. Furthermore, patients discontinuing treatment early were included in the analysis and evaluated at their end of treatment.

### 2.2. Statistical analysis

Exploratory analyses were performed for each of the two response definitions. Firstly, a logistic regression model was performed for both response definitions to determine the overall treatment effect and included terms for treatment group (actovegin or placebo), baseline insulin treatment, country, NIS-LL, and TSS. Notably, insulin treatment (yes or no) was included in all models as this was a stratification factor in the randomization.

The effects of a series of baseline covariates were then explored using separate logistic regression models: VPT (≥16 both feet/<16 either foot); gender (male/female); age (years); smoker (yes/no); alcohol drinker (yes/no); BMI (<30/≥30 kg/m$^2$); baseline SF-36 physical health; baseline SF-36 mental health; time since diabetes diagnosis (years); time since DSPN diagnosis (years); HbA1c (%), fasting plasma glucose (mmol/L), concomitant disease: retinopathy (yes/no), hypertension (yes/no), cardiovascular disease (yes/no); and concomitant medications: statins (yes/no), angiotensin receptor blockers (ARBs)/angiotensin converting enzyme inhibitors (ACEIs) (yes/no), antihypertensive medications (yes/no), analgesics/NSAIDs (yes/no). Each baseline covariate was added to the first model separately. The separate models were used to estimate the main effects, in particular the predictive effect of each baseline covariate on response. Finally, the treatment by baseline covariate interaction was added to each of the main effect models. The interaction term was tested at both the 5% and 10% significance level, and where significant, treatment effects were estimated within levels of the covariates within the same model.

Main effects were reported using odds ratios (ORs) of response with 95% confidence intervals (CI) and p-values. For the interaction terms, the p-value is reported. ORs with 95% CI for significant treatment by baseline covariate interactions were also reported. All analyses were exploratory in nature and no multiplicity adjustment was made. The statistical analysis software used was SAS Version 9.2 by SAS Institute Inc., Cary, NC, USA.

## 3. Results

The present analysis was based on the 567 originally randomized participants which were treated with actovegin (n = 281) or placebo (n = 286), see supplement Table A. The number of patients in the two treatment groups from each of the three countries that took part in the study is shown in Table 1. The percentage of patients taking concomitant medications at baseline was high (99%). Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and statins at baseline was equally low in both treatment groups.

### 3.1. Logistic regression analysis

The initial logistic regression model included the following variables: treatment, insulin use, country, baseline NIS-LL, and baseline TSS score (for the baseline NIS-LL and TSS definition only)

**Table 1**
Demographic and baseline medication parameters of patients in the ITT population at baseline.

| Parameter | Actovegin (N = 281) | | Placebo (N = 286) | | Total (N = 567) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Country | | | | | | |
| Kazakhstan | 28 | 10.0 | 30 | 10.5 | 58 | 10.2 |
| Russia | 110 | 39.1 | 110 | 38.5 | 220 | 38.8 |
| Ukraine | 143 | 50.9 | 146 | 51.0 | 289 | 51.0 |
| Concomitant medications at baseline | | | | | | |
| All concomitant medications | 277 | 98.6 | 286 | 100 | 563 | 99.3 |
| Statins | 6 | 2.1 | 4 | 1.4 | 10 | 1.8 |
| Analgesics/NSAIDs | 2 | 0.7 | 2 | 0.7 | 4 | 0.7 |
| All antihypertensive medications | 49 | 17.4 | 39 | 13.6 | 88 | 15.5 |
| ARBs/ACEIs | 46 | 16.4 | 52 | 18.2 | 98 | 17.3 |

ARBs: angiotensin receptor blockers; ACEIs: angiotensinogen converting enzyme inhibitors; NSAIDs: nonsteroidal anti-inflammatory drugs; ITT: intent-to-treat.

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