The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

Clinical Trial Report Synopsis

Name of Company: Nycomed	**Tabular format** Referring to Part of the Dossier:	*(For National Authority Use only)*
Name of Finished Product: Actovegin®		
Name of Active Ingredient: DHC: Deproteinised haemoderivate of calf blood		

Title of Trial:

A multi-centre, double-blind, placebo-controlled, randomised, parallel group clinical trial to evaluate efficacy and safety of Actovegin® in diabetic type 2 patients with symptomatic diabetic peripheral polyneuropathy

Principal Investigators (National Co-ordinating Investigators):

[redacted]

Trial Centres:

26 sites in three countries: Kazakhstan (2), Russia (14) and Ukraine (10)

Publication (reference):

None

Studied period (years):	**Phase of development:**
28 Dec 2006 – 1 Mar 2008	Therapeutic confirmatory

Objectives:

To assess the clinical efficacy and safety of Actovegin vs. placebo in type 2 diabetic patients with symptomatic diabetic peripheral polyneuropathy after 250 ml i.v. infusions once daily for 20 days followed by 3 x 600 mg p.o. daily for 140 days

Methodology:

This was a multi-centre, double-blind, placebo-controlled, randomised and parallel group clinical trial. Patients were followed for approx. 6 months from the screening visit to the end of the oral treatment period with efficacy assessments at screening, at every 5th infusion visit and every 4 weeks during the oral treatment period. Adverse events (AEs) were assessed at all visits. The trial consisted of three periods: a screening period (max. 5 days), an i.v. infusion period (max. 36 days) and an oral treatment period (140 +/- 15 days)

Number of patients (total and for each treatment):

Planned: 550 randomised patients stratified according to intake of insulin; entered: 569 patients; treated: 567 patients (Actovegin: 281; placebo: 286); analysed: 567 patients (ITT and safety analysis set), 506 patients (PP analysis set)

Diagnosis and main criteria for inclusion:

Diagnosis: symptomatic diabetic peripheral polyneuropathy; Main criteria for inclusion: Age ≥ 18 years and ≤ 65 years; Total symptom score (TSS) ≥ 6; Neurological impairment score

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of lower limbs (NIS-LL) ≥ 2; Vibration perception threshold (VPT) ≤ 30 V; Glycosylated haemoglobin (HbA_{1c}) < 10%; a number of exclusion criteria applied

Test product, dose and mode of administration, batch number:

Infusion: Actovegin 20% (8 mg/ml) in NaCl 0.9%, dose 250 ml daily (rate 2 ml/min). Batch no.: G070090/07.2011

Tablet: Actovegin 200 mg, 3 tablets 3 times daily. Batch no. 10326783/08.2009

Duration of treatment:

Infusion period: 20 daily visits with once daily infusion within max. 36 days

Oral treatment period: max. 140 days +/- 15 days

Reference therapy, dose and mode of administration, batch number:

Infusion: Placebo: Nacl 0.9%, dose 250 ml daily (rate 2 ml/min). Batch no.: G070102/07.2011

Tablet: Placebo, 3 tablets 3 times daily. Batch no.: 10333256/09.2009

Criteria for evaluation:

Efficacy

Primary efficacy endpoints

TSS: average of TSS over the treatment period calculated by Area Under the Curve (AUC), divided by treatment period (days).

VPT: average of VPT measured with the biothesiometer over the treatment period using the same methods as for the TSS.

Secondary efficacy endpoint

NIS-LL: average of NIS-LL over the treatment period calculated as the primary endpoints.

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Statistical methods:

$TSS_{average}$ was analysed using analysis of covariance (ANCOVA) with treatment, centre and insulin treatment as fixed effect and baseline TSS as a covariate. Based on the linear model, an F-test was used to test the effect of treatment. The mean difference between treatments was estimated with a 95% confidence interval (CI) based on the model. Possible treatment by centre interaction was explored by including an interaction term in the ANCOVA model as a sensitivity analysis. To support the primary analysis, a comparison of the mean change in TSS from baseline to end of trial in the two treatment groups was calculated. An ANCOVA with treatment, centre and insulin treatment as fixed effects and baseline TSS as a covariate was used.

$VPT_{average}$ was defined as the $TSS_{average}$ but was log transformed in the analysis.

$NIS\text{-}LL_{average}$ was analysed and presented as the primary endpoint $TSS_{average}$.

SUMMARY:

The trial was completed as planned and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice; approvals from Ethics Committees and Competent Authorities were obtained and patients gave their signed informed consent according to local requirements.

Of the 567 patients that received trial treatment, 56 patients discontinued.

In all, 29% of the patients were male and 71% female; 94% were Caucasian; mean (range) age was 55.6 (29-65) years; mean Body Mass Index was 30.6 (18.7-55.8) kg/m^2.

Insulin treatment was taken by 41% of the patients; concomitant illness was reported by 97%, and 99% of the patients took concomitant medication. Mean s-glucose (range) for the population was 8.4 (3.5-17.2) mmol/L and mean HbA_{1c} was 7.8 (2.9-11.7)%. Mean (range) TSS was 8.4 (6.0-14.6), VPT was 19.9 (7.2-30.2) and NIS-LL was 8.6 (0.0-54.0).

No important baseline differences were seen between the two treatment groups.

Efficacy results

TSS. The overall $TSS_{average}$ (mean (range)) was lower for Actovegin (3.9 (0.2-9.3)) than for placebo (4.6 (0.3-11.9)). The estimated mean difference was -0.56 (p=0.0003) in favour of Actovegin after adjustment for baseline score, centre and insulin status. The difference for the PP analysis set was also significant (p=0.0006) in favour of Actovegin.

Improvement in TSS at the end-of-trial was significantly higher in the Actovegin group with a mean treatment effect of -0.86 ($p < 0.0001$).

There was evidence of a treatment by centre interaction (p=0.0008).

Analysis of the four TSS symptoms over the duration of exposure showed that differences

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between Actovegin and placebo were in favour of Actovegin for all symptoms (p=0.0005 (pain); p=0.0002 (burning); p=0.01 (prickling); p=0.03 (numbness)).

VPT. The overall $VPT_{average}$ (mean (range)) was 17.1 (5.2-29.8) for Actovegin and 17.7 (5.4-30.0) for placebo.

An estimated improvement in the Actovegin group (ITT) of 3% (p=0.084) vs. placebo was seen with a smaller estimate for the PP analysis set of 2% improvement (p=0.26).

The improvement in VPT at the end-of-trial was significantly higher in the Actovegin group with an advantage of 5% (p=0.02) over placebo after adjustment for baseline score, centre and insulin status.

There was evidence of a treatment by centre interaction (p=0.02).

NIS-LL. The overall $NIS\text{-}LL_{average}$ (mean (range)) was lower for Actovegin (5.3; 0.0-49.5) than for placebo (6.0; 0.0-43.3) with an estimated mean difference of -0.26 (p=0.25) after adjustment for baseline score, centre and insulin status.

The improvement in NIS-LL at the end-of-trial was higher in the Actovegin group with a mean treatment effect of -0.48 (p=0.08).

There was evidence of a treatment by centre interaction (p=0.03).

The treatment effect on sensory activity was statistically significant (p=0.0209) in favour of Actovegin.

SF-36: The Mental health component showed significant improvement in the Actovegin group compared to the placebo group (p=0.028).

Safety results

A total of 384 AEs were reported during the trial period: 186 events in 92 (33%) Actovegin patients and 198 events in 100 (35%) placebo patients. The most frequently reported AEs were headache, hypoglycaemia, hypertension, hyperglycaemia and respiratory tract infection, which are well known complications to the underlying disease.

A total of 21 serious AEs (SAEs) were reported with 10 events in seven Actovegin patients and 11 events in 10 placebo patients. Nine Actovegin patients (15 events) and 12 placebo patients (15 events) withdrew from the trial due to AEs. No patients died.

In general, data showed a small over-representation of events in the placebo group for the total number of AEs, SAEs, the most frequent AEs, severity as well as number of patients withdrawn from the trial due to AEs.

CONCLUSION:

Actovegin treatment was associated with a significant reduction of the positive sensory

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symptoms (TSS) and a decrease in VPT with clear tendency towards significance as compared with placebo treatment. Among the secondary endpoints, Quality of Life (Mental Health component) was significantly improved in patients treated with Actovegin as compared to those, who received placebo.

Actovegin was well tolerated and safe in diabetic type 2 patients with symptomatic diabetic peripheral polyneuropathy.

Date: 17. December 2008 Written by: [redacted]