SUPPLEMENTAL MATERIAL

ARTEMIDA: a randomized controlled trial to assess the efficacy and safety of Actovegin in post-stroke cognitive impairment

Alla Guekht,[1]* Ingmar Skoog,[2] Sally Edmundson,[3] Vladimir Zakharov,[4] Amos D Korczyn,[5]

[1]Department of Neurology, Neurosurgery and Genetics, Russian National Research Medical University, Moscow; Moscow Research and Clinical Center for Neuropsychiatry, Russia

[2]Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[3]Takeda Development Centre Europe, London, UK

[4]Department of Neurology, 1st Moscow State Medical University, Moscow, Russia

[5]Department of Neurology, Tel Aviv University, Tel Aviv, Israel

*Corresponding author:

Prof. Alla Guekht, Department of Neurology, Neurosurgery and Genetics

Russian National Research Medical University

Moscow; Moscow Research and Clinical Center for Neuropsychiatry

Donskaya Street 43, Moscow 115419, Russia

Email: guekht@mail.ru

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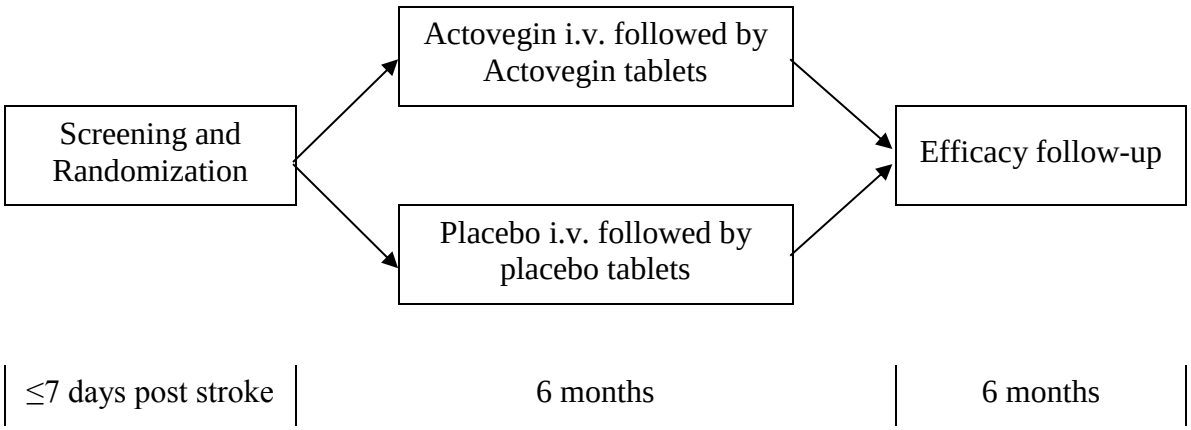

Subjects who had suffered ischemic stroke were randomized to receive either Actovegin or placebo in a 1:1 ratio within 5 to 7 days following the stroke onset. The trial consisted of a screening period (up to 6 days), followed by a randomized treatment period (up to 20 intravenous [i.v.] daily infusions, then tablets for the remainder of the 6-month treatment period), ending with a 6-month efficacy follow-up period (where subjects were allowed to undergo treatment in accordance with standard clinical practice).

Supplemental Table I: Full list of investigators and study centers

Investigator	Centre number, address	Number of patients randomized
Russia		
Dr. Larisa Voronkova	St. Petersburg State Budgeted Healthcare Institution "City Hospital#26", 2 Kostyushko str., 196247, St. Petersburg, Russia	41
Dr. Alina Agafyina	St. Petersburg State Budgeted Healthcare Institution of Resort District City Hospital #40 9 Borisova str., 191014, St. Petersburg, Russia	37
Dr. Lyudmila Roshkovskaya	St. Petersburg State Budgeted Healthcare Institution Nikolaevskaya Hospital 1 Konstantinovskaya str., Petrodvorets, 198510, Saint-Petersburg, Russia	24
Dr. Konstantin V. Golikov	Saint Petersburg State Budgetary Healthcare Institution "City Multifield Hospital #2", 5, Uchebny per., St. Petersburg, 194354, Russia	23
Prof. Eduard Z. Yakupov	Scientific research medical complex "Your Health" LLC, 7, Zinina str., Kazan, 420097, Russia Clinical base: Municipal Healthcare Institution "City Emergency Hospital #2", therapy and neurology department, 31, Lieutenant Shmidt str., Kazan, 420097, Russia	23
Prof. Irina Poverennova	State Budgetary Healthcare Institution "Samara Region Clinical Hospital named after M.I. Kalinin" 159, Tashkentskaya str, Samara, 443095, Russia	23
Dr. Elena Vostrikova	Municipal Budgetary Healthcare Institution of Novosibirsk "City Clinical Hospital#34", 18, Titova str., Novosibirsk, Novosibirsk region, 630054, Russia	22

Prof. Dina R. Khasanova	State Autonomous Healthcare Institution Interregional Clinical Diagnostic Centre 12a Karbysheva str., Kazan, 420101, Russia	19
Prof. Enver I. Bogdanov	State Budgetary Educational Institution of Higher Professional Education Kazan State Medical University of the Ministry of Healthcare and Social Development of the Russian Federation, 49 Butlerova str., Kazan, 420012, Tatarstan Republic, Russia Clinical base: State Healthcare Institution Republican Clinical Hospital of the Ministry of Healthcare of Tatarstan Republic, 138 Orenburgsky tract, Kazan, 420064, Tatarstan Republic, Russia	16
Dr. Svetlana Sayutina	State Budgetary Healthcare Institution of Irkutsk "Mark of Honour" Order Clinical Regional Hospital, 100 Yubileinii microdistrict, Irkutsk, 664079, Russia	16
Dr. Liya Lukinykh	Municipal Budgetary Healthcare Institution Vsevolozhskaya Clinical Central District Hospital 20 Koltushskoye shosse, Leningrad Region, Vsevolozhsk district, Vsevolozhsk, 188640, Russia	16
Dr. Liubov Shpagina	State Budgetary Healthcare Institution of Novosibirsk region "City Clinical Hospital#2", 21, Polsunova str., Novosibirsk, Novosibirsk Region, 630051, Russia	16
Dr. Olga A. Dinisova	State Budgetary Healthcare Institution of Novosibirsk region "City Clinical Hospital #1", 6 bld, Zalesskogo str, Novosibirsk, Novosibirsk Region, 630047, Russia	14
Dr. Alexander Malygin	State Healthcare Institution of Yaroslavl region Clinical Hospital #8; 39, Suzdalskoe shosse, Yaroslavl, 150030, Russia	14
Prof. Ludmila Stakhovskaya	State Budgetary Educational Institution of High Professional Education "Russian National Research Medical University	13

	named after N.I. Pirogov" of Ministry of Healthcare and Social Development of Russian Federation based on State Budgetary Healthcare Institution of Moscow city "City Clinical Hospital #31 of Moscow Healthcare Department" 42, Lobachevskogo str., Moscow, 119415, Russia	
Dr. Vasily Vasilyuk	Saint-Petersburg State Budgetary Institution of Healthcare "City Hospital #15" 4, Avangardnaya str., Saint-Petersburg, 198204, Russia	11
Dr. Nikolay Gaiduk	Saint Petersburg State Budgeted Healthcare Institution "City Alexandrovskaya Hospital", 4, Solidarnosti pr., St. Petersburg, 193312, Russia	10
Dr. Nadezhda Korotkevich	State Budgetary Healthcare Institution of Kemerovo Regional "Kemerovo Regional Clinical Hospital", 22, Oktyabrsky prospect str., Kemerovo, Kemerovo region, 650066, Russia	8
Dr. Natalia Vakhnina	State Budgetary Healthcare Institution of Moscow city "City Clinical Hospital #61 of Moscow Healthcare Department" 15, Dovatora str., Moscow, 119048, Russia	6
Prof. Marina Maximova	Federal State Budgetary Institution "Scientific Research Centre of Neurology of RAMS" 80, Volokolamskoye shosse, Moscow, 125367, Russia	6
Prof. Oleg Levin	State Budgetary Healthcare Institution of Moscow city "City Clinical Hospital named after S.P. Botkin" of Moscow Healthcare Department 5, bld. 2, 2nd Botkinsky proezd, Moscow, 125284, Russia	5
Prof. Larisa Volkova	State Budgetary Healthcare Institution of Sverdlovsk region "Sverdlovsk Regional Clinical Hospital #1" 185, Volgogradskaya str., Ekaterinburg, 620102, Russia	5

Prof. Alla Guekht	State Budgetary Healthcare Institution of Moscow city “City Clinical Hospital #12 of Moscow Healthcare Department” 26, Bakinskaya str, Moscow, 115516, Russia	4
Dr. Ivan Sardaryan	St. Petersburg State Budgeted Healthcare Institution City Mariinskaya Hospital 56 Liteyny pr., 191014, St. Petersburg, Russia	4
Prof. Miroslav M. Odinak	Federal State Budgetary Military Educational Institution of Higher Professional Education "Military Medical Academy n.a. S.M. Kirov" of Ministry of Defense of the Russian Federation, Legal address: 6, lit. Z, Academician Lebedev str., St. Petersburg, 194044, Russia, Actual address: 2 Lesnoy pr., St. Petersburg, 194044, Russia	3
Prof. Andrey Kovalenko	Federal State Budgetary Institution Research Institute for Complex Issues of Cardiovascular Diseases under the Siberian Branch of The Russian Academy of Medical Sciences, 6, Sosnovy blvd., Kemerovo, Kemerovo region, 650002, Russia	3
Dr. Vadim Gusev	State Budgetary Educational Institution of Higher Professional Education “Ural State Medical Academy” of Ministry of Health and Social Development of Russian Federation (3, Repin str., Ekaterinburg, 620028, Russia) based on Municipal Healthcare Institution “Central City Clinical Hospital # 23” 9, Starykh Bolshevikov str., Ekaterinburg, Russia, 620017, Russia	3
Prof. Eugene Gusev	State Budgetary Educational Institution of High Professional Education “Russian National Research Medical University named after N.I. Pirogov” of Ministry of Healthcare and Social Development of Russian Federation based on State Budgetary Healthcare Institution of Moscow city “City Clinical Hospital # 1	0

	named after N.I. Pirogov of Moscow Healthcare Department" 8, Leninsky prospect, Moscow, 119049, Russia	
Prof. Valentina M. Alifirova	State Budgetary Educational Institution of Higher Professional Education "Siberia State Medical University" Ministry of Health and Social Development of Russian Federation, 2 Moskovsky trakt, Tomsk,Tomsk Region, 634050, Russia Clinical base: Regional State Budgetary Healthcare Institution Tomsk Regional Clinical Hospital	0
Prof. Semen V. Prokopenko	State Education Institution of Higher Profession Education "Krasnoyarsk State Medical University named professor V.F.Voyno-Yasenetsky Department of Health and Social Development of Russian Federation", 1, Partizana Zheleznijaka str,, Krasnoyarsk, Krasnoyrsk Region, 660049, Russia Clinical base: 1-Federal State Budgetary Institution of Healthcare "Siberian Clinical Centre of Federal Medico-Biological Agency"; 2- Municipal Budgetary Institution of Healthcare "City Clinical Hospital #6 named Karpovicha N.S.	0
Dr. Alexander Nazarov	St. Petersburg State Budgeted Healthcare Institution City Elizavetinskaya Hospital 14 Vavilovykh str., 195257, St. Petersburg, Russia	0
Kazakhstan		
Dr. Erkyn Nurguzhayev	State public institution under economic jurisdiction "City Clinical Hospital №7" of Almaty Health Administration microdistrict «Kalkaman», Almaty, 050006, Kazakhstan	4
Belarus		

Dr. Mikalai M. Bialauski	Healthcare Institution "Vitebsk Regional Clinical Hospital" 37 Voinov Internationalistov str., 210037, Vitebsk, Belarus	38
Prof. Alena I. Mikhailava	Institution "Gomel Regional Clinical Hospital" 5 Brat'ev Lizukovyh str., 246029 Gomel, Belarus	26
Prof. Natalya P. Mitkovskaya	Healthcare institution "City Clinical Emergency Hospital" 58 Kizhevatova str., 220024 Minsk, Belarus	20
Dr. Sergey D. Kulesh	Healthcare Institution "Grodno Regional Clinical Hospital" Leninskogo komsomola bulv., 52 230017 Grodno, Belarus	16
Prof. Aliaksandr S. Fedulau	Healthcare Institution "City Clinical Hospital #9" 8 Semashko str., 220116 Minsk, Belarus	14

Supplemental Table II: Full list of inclusion criteria

On study entry	
1.	Had suffered a supra-tentorial ischemic stroke supported by computed tomography (CT) scan or magnetic resonance imaging (MRI) findings (in accordance with local practice)
2.	Had provided written informed consent
3.	Were male or female, aged 60 years or above
4.	Were conscious and considered legally competent, but had symptoms or signs indicating cognitive impairment according to the investigator's opinion
5.	Had a score on the NIHSS between 3 and 18 (inclusive)
6.	Were capable of completing the MoCA scale and had a score of ≤ 25 points with adjustment for level of education (4 to 9 school years ≤ 23 points, 10 to 12 years ≤ 24 points, 12 years ≤ 25 points)
7.	If female, was post-menopausal or had been surgically sterilized/hysterectomized and did not intend to become pregnant during the course of the trial (e.g., oocyte implantation)
8.	If male, did not intend to induce pregnancy (parenthood was not desired) during clinical trial conduct or within 3 months after the last planned dose of IMP
At randomization	
9.	Were fully conscious
10.	Were still capable of completing the MoCA scale and had a score of ≤ 25 points with adjustment for level of education (4 to 9 school years ≤ 23 points, 10 to 12 years ≤ 24 points, 12 years ≤ 25 points)
11.	Were able to perform the ADAS-cog+

Supplemental Table III: Full list of exclusion criteria

On study entry	
1.	A known medical history of dementia
2.	A known medical history of or presence of major depression or psychotic disorder
3.	A known medical history or presence of malignancies or other serious/life-threatening diseases that were likely to cause the subject's death within 12 months
4.	Concomitant acute coronary syndrome (e.g. acute myocardial infarction or unstable angina)
5.	Suspected or diagnosed endocarditis
6.	Thought to have had a cardioembolic stroke (e.g., atrial fibrillation, prosthetic valve) despite adequate treatment with anticoagulants
7.	A suspicion of cerebral vasculitis as judged by the investigator
8.	Stroke due to a complication of cerebral angiography, a revascularization procedure, or trauma
9.	Evidence from imaging or pre-enrolment investigation of any diagnosis other than ischemic stroke likely to cause the presenting symptoms and signs (e.g., malignancy, hemorrhage)
10.	Treatment with thrombolytics, carotid surgery or neurosurgery during this index stroke or was indicated for such treatment
11.	Indicated for investigation with carotid angiogram
12.	Abnormal clinically relevant screening laboratory values suggesting an undiagnosed disease requiring further clinical evaluation as assessed by the investigator
13.	Neurological deficits deemed to interfere with the ability to adhere to the protocol (e.g. pronounced dysphasia)
14.	Current known alcohol or illicit drug abuse or dependence
15.	A known medical history of Parkinson's disease, multiple sclerosis, uncontrolled epilepsy, or other neurological disorders severely affecting motor or cognitive function, in the opinion of the investigator
16.	A history of clinically significant allergies or idiosyncrasies to Actovegin
17.	In a dependency situation (e.g. kept in detention, investigator in the current trial, a first-degree relative of a clinical trial investigator, an employee at the clinical trial site, minor, or had a legal guardian), or were unable to understand and give written informed consent

18.	Participation in another clinical trial with an investigational medicinal product (IMP) or device within 30 days of signing informed consent
At randomization	
19.	A suspicion of progressive stroke
20.	Eligibility for carotid angiogram, endarterectomy, or any neurosurgical intervention
21.	A planned surgery or another procedure requiring general anesthesia
22.	A blood pressure at baseline of >220 mmHg (systolic) or 140 mmHg (diastolic)
23.	Taking any of the disallowed drugs following signing of the informed consent form (ICF)

Supplemental Table IV: Full list of medications prohibited during double-blind treatment

Peripheral vasodilators
Amantadine derivatives
Psychoanaleptics in entirety, with the exception of antidepressants, including: • Centrally-acting sympathomimetics • Bicyclic compounds • Xanthine derivatives • Tricyclic units (this does not refer to tricyclic antidepressants but to tricyclic psychostimulants and nootropic compounds) • Other psychostimulants and nootropics (glycine exempted) • Antidepressants combined with psycholeptics • Psychostimulants combined with neuroleptics • Compounds for the treatment of dementia diseases, acetylcholinesterase inhibitors • Other compounds for the treatment of dementia diseases
Parasympathomimetics, cholinesterase inhibitors
Cholinesters
Other parasympathomimetics
Other compounds with effect on the nervous system
Gangliosides and ganglioside derivatives
Remaining compounds with effect on the nervous system
Cerebrolysin

Supplemental Table V: All primary, secondary and safety endpoints

Primary
Change from baseline in ADAS-cog+ at 6 months
Secondary
Change from baseline in ADAS-cog+ at 3 and 12 months
Change from baseline in MoCA at end of infusion period, 3, 6, and 12 months
Proportion of ADAS-cog+ responders at 3, 6, and 12 months
Diagnosis of dementia evaluated after 6 and 12 months classified according to International Statistical Classification and Related Health Problems, version 10 (ICD-10)
Change from baseline in NIHSS at end of infusion period, 3, 6, and 12 months
Barthel Index at 6 months
EuroQoL EQ-5D at 6 and 12 months
BDI-II at 3, 6, and 12 months
Safety
Adverse events
Safety laboratory parameters
Standard 12-lead ECG assessments
Physical examination
Vital signs including blood pressure and heart rate

ADAS-cog+: Alzheimer's Disease Assessment Scale-cognitive subscale+; MoCA: Montreal Cognitive Assessment; NIHSS: National Institutes of Health Stroke Scale; ICD: International Classification of Diseases; BDI-II: Beck Depression Inventory version II; ECG: electrocardiogram.

Supplemental Table VI: Key protocol deviations occurring in more than one patient

Key deviation	**Actovegin N=248 n (%)**	**Placebo N=255 n (%)**
Any key deviation	36 (14.5)	35 (13.7)
ADAS-Cog+ Visit 1, Task 7 was performed incorrectly. Correct 'yes' answers only were indicated on page 1	5 (2.0)	5 (2.0)
Disallowed concomitant medication	3 (1.2)	2 (0.8)
Were taking any of the disallowed drugs following signing of the ICF	0	2 (0.8)
Visit 1 – Task 7 was performed incorrectly. Correct 'yes' answers only indicated on page 1	7 (2.8)	8 (3.2)
'Number cancellation' test of the ADAS-Cog+ test on Visit 9 was conducted incorrectly. Duration of this test wasn't limited	1 (0.4)	3 (1.2)
'Number cancellation' test of the ADAS-Cog+ test on Visit 1 was done by patients to the end, without time limitation. Investigators didn't calculate correct number that subject forgotten to strike out as 'wrong'	5 (2.0)	5 (2.0)
'Number cancellation' test of the ADAS-Cog+ test on Visit 9 was done by patients to the end, without time limitation. Investigators didn't calculate correct number that subject forgotten to strike out as 'wrong'	5 (2.0)	5 (2.0)

ADAS-cog+: Alzheimer's Disease Assessment Scale-cognitive subscale+; ICF: informed consent form.

Supplemental Table VII. Summary of primary and key secondary outcomes in the ITT population.

	Actovegin N=248	**Placebo N=255**	**Actovegin versus placebo (95% CI)**
ADAS-cog+ responders*			
Month 3 (n, %)	127/215 (59.1%)	109/223 (48.9%)	10.2 (0.9, 19.5); p=0.032
Month 6 (n, %)	130/208 (62.5%)	113/216 (52.3%)	10.2 (0.8, 19.5); p=0.034
Month 12 (n, %)	138/200 (69.0%)	122/207 (58.9%)	10.1 (0.8, 19.3); p=0.035
MoCA score			
Baseline (mean, SD)	18.8 (3.83) n=248	18.6 (4.20) n=255	-
Change from baseline at Month 3	3.4 (0.20) n=224	2.7 (0.20) n=234	0.7 (0.1, 1.2); p=0.016
Change from baseline at Month 6	3.8 (0.21) n=217	3.1 (0.21) n=228	0.7 (0.2, 1.3); p=0.013
Change from baseline at Month 12	3.9 (0.25) n=211	2.9 (0.24) n=220	1.0 (0.3, 1.7); p=0.003
NIHSS			
Baseline (mean, SD)	5.3 (2.24) n=248	5.6 (2.37) n=255	-
Change from baseline at Month 3	-2.9 (0.10) n=224	-2.7 (0.10) n=235	-0.2 (-0.5, 0.1); p=0.136
Change from baseline at Month 6	-3.2 (0.10) n=219	-3.2 (0.10) n=228	0.0 (-0.3, 0.2); p=0.890
Change from baseline at Month 12	-3.5 (0.10) n=211	-3.4 (0.10) n=220	-0.1 (-0.4, 0.2); p=0.455
Dementia diagnosis (according to ICD-10 criteria)			
Month 6 (n, %)	16/218 (7.3%)	24/228 (10.5%)	-3.2 (-8.5, 2.1); p=0.251
Month 12 (n, %)	19/218 (8.7%)	29/228 (12.7%)	-4.0 (-9.7, 1.7); p=0.221

Data are LS mean (SE) unless otherwise indicated.

*A responder was defined as an improvement of 4 points or more on the ADAS-cog+ scale using Observed Case data.

Supplemental Table VIII: Summary of EuroQol EQ-5D at 6 Months and 12 Months

EuroQol Category	Month 6		Month 12	
	Actovegin N=248	**Placebo N=255**	**Actovegin N=248**	**Placebo N=255**
Mobility, n (%)				
No problem	103 (41.5)	82 (32.2)	94 (37.9)	93 (36.5)
Slight problem	74 (29.8)	81 (31.8)	77 (31.0)	75 (29.4)
Moderate problem	31 (12.5)	42 (16.5)	31 (12.5)	30 (11.8)
Severe problem	10 (4.0)	18 (7.1)	8 (3.2)	19 (7.5)
Unable	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)
Self-care, n (%)				
No problem	145 (58.5)	124 (48.6)	137 (55.2)	123 (48.2)
Slight problem	49 (19.8)	65 (25.5)	55 (22.2)	60 (23.5)
Moderate problem	19 (7.7)	25 (9.8)	15 (6.0)	24 (9.4)
Severe problem	5 (2.0)	9 (3.5)	4 (1.6)	10 (3.9)
Unable	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)
Usual activities, n (%)				
No problem	81 (32.7)	84 (32.9)	81 (32.7)	79 (31.0)
Slight problem	101 (40.7)	88 (34.5)	97 (39.1)	86 (33.7)
Moderate problem	22 (8.9)	44 (17.3)	24 (9.7)	40 (15.7)
Severe problem	10 (4.0)	6 (2.5)	7 (2.8)	11 (4.3)
Unable	5 (2.0)	2 (0.8)	3 (1.2)	3 (1.2)
Pain or discomfort, n (%)				
No pain	124 (50.0)	118 (46.3)	116 (46.8)	119 (46.7)
Slight pain	76 (30.6)	65 (25.5)	71 (28.6)	67 (26.3)
Moderate pain	15 (6.0)	39 (15.3)	21 (8.5)	29 (11.4)

EuroQol Category	Month 6		Month 12	
	Actovegin N=248	**Placebo N=255**	**Actovegin N=248**	**Placebo N=255**
Severe pain	2 (0.8)	2 (0.8)	4 (1.6)	3 (1.2)
Extreme pain	1 (0.4)	0	0	1 (0.4)
Anxiety or depression, n (%)				
Not anxious	124 (50.0)	123 (48.2)	120 (48.4)	120 (47.1)
Slightly anxious	77 (31.0)	75 (29.4)	78 (31.5)	69 (27.1)
Moderately anxious	15 (6.0)	24 (9.4)	12 (4.8)	27 (10.6)
Severely anxious	2 (0.8)	2 (0.8)	2 (0.8)	2 (0.8)
Extremely anxious	1 (0.4)	0	0	1 (0.4)
General health (on a scale of 0–100)				
n	219	224	212	220
Mean (SD)	67.3 (16.04)	65 (16.82)	67.8 (15.87)	65.6 (17.51)
Median	70.0	65.0	70.0	70.0
Min, max	30.0, 100.0	25.0, 100.0	20.0, 100.0	20.0, 100.0

Supplemental Table IX: Summary of patients with clinically significant chemistry laboratory values by visit (safety analysis set)

Visit	Analyte	Actovegin N=250 n (%)	Placebo N=253 n (%)
Screening	Alanine aminotransferase	2 (0.8)	0 (0.0)
	Alkaline phosphatase	0 (0.0)	1 (0.4)
	Aspartate aminotransferase	1 (0.4)	0 (0.0)
	Bilirubin	0 (0.0)	1 (0.4)
	Cholesterol	17 (6.8)	17 (6.7)
	Creatine kinase	2 (0.8)	4 (1.6)
	Creatinine	2 (0.8)	1 (0.4)
	Gamma-glutamyl-transpeptidase	2 (0.8)	8 (3.2)
	HDL cholesterol	6 (2.4)	7 (2.8)
	LDL cholesterol	14 (5.6)	17 (6.7)
	Triglycerides	11 (4.4)	10 (4.0)
Month 6	Alanine aminotransferase	1 (0.4)	1 (0.4)
	Alkaline phosphatase	1 (0.4)	0 (0.0)
	Aspartate aminotransferase	0 (0.0)	1 (0.4)
	Cholesterol	12 (4.8)	14 (5.5)
	Creatine kinase	1 (0.4)	0 (0.0)
	Creatinine	0 (0.0)	1 (0.4)
	Gamma-glutamyl-transpeptidase	2 (0.8)	3 (1.2)
	HDL cholesterol	5 (2.0)	3 (1.2)
	LDL cholesterol	11 (4.4)	15 (5.9)
	Potassium	2 (0.8)	1 (0.4)
	Triglycerides	6 (2.4)	8 (3.2)

Supplemental Table X: Summary of TEAEs related to chemistry laboratory results (safety analysis set)

Preferred Term	Actovegin N=250 n (%)	Placebo N=253 n (%)	Total N=503 n (%)
Metabolism and nutrition disorders			
Dyslipidaemia	8 (3.2)	2 (0.8)	10 (2.0)
Hyperkalaemia	2 (0.8)	1 (0.4)	3 (0.6)
Hypercholesterolaemia	0 (0.0)	2 (0.8)	2 (0.4)
Type 2 diabetes mellitus	0 (0.0)	1 (0.4)	1 (0.2)
Investigations			
Gamma glutamyltransferase increased	1 (0.4)	2 (0.8)	3 (0.6)
Alanine aminotransferase increased	0 (0.0)	1 (0.4)	1 (0.2)
Aspartate aminotransferase increased	0 (0.0)	1 (0.4)	1 (0.2)
Blood creatine phosphokinase increased	1 (0.4)	0 (0.0)	1 (0.2)
Blood homocysteine increased	1 (0.4)	0 (0.0)	1 (0.2)

Supplemental Table XI: Overview of TEAEs (safety analysis set)

Number of patients with:	**Actovegin N=250 n (%)**	**Placebo N=253 n (%)**	**Total N=503 n (%)**
TEAEs	89 (35.6)	96 (37.9)	185 (36.8)
Number of TEAEs	206	215	421
Severe TEAEs	11 (4.4)	13 (5.1)	24 (4.8)
SAEs	22 (8.8)	17 (6.7)	39 (7.8)
TEAEs leading to IMP discontinuation	21 (8.4)	12 (4.7)	33 (6.6)
TEAEs considered related to IMP	9 (3.6)	9 (3.6)	18 (3.6)
SAE deaths	7 (2.8)	6 (2.4)	13 (2.6)

Supplemental Table XII: Overview of TEAEs related to recurrent cerebrovascular events (safety analysis set).

Study phase	Preferred term	Actovegin N=250	Placebo N=253	Total N=503
Treatment phase	Ischemic stroke/TIA	13 (5.2%)	7 (2.8%)	20 (4.0%)
	Intracerebral hemorrhage	1 (0.4%)	0	1 (0.2%)
	Subtotal	14 (5.6%)*	7 (2.8%)	21 (4.2%)
Follow-up phase	Ischemic stroke	2 (0.8%)	3 (1.2%)	5 (1.0%)
Total		16 (6.4%)	10 (4.0%)	26 (5.2%)

Data are n (%).

*The odds ratio (95% CI) for cerebrovascular events on Actovegin compared to placebo was 2.09 (0.83, 5.26); p=0,124 suggesting this was not statistically significant (post-hoc analysis).

Randomization and masking Full Methods

Patients were randomized to receive either Actovegin or placebo in a 1:1 ratio, without stratification and using a block size of four, by means of a computerized central randomization system, IVRS/IWRS. Before dispensing treatment, investigators reviewed all eligibility criteria and provided the IVRS/IWRS with the patient number, date of birth, and gender. Based on this information, patients were assigned to a kit number determined by the program. The infusion and tablet bottles were labelled and masked with a kit number generated by the randomization. During double-blind treatment and until end of follow-up, all investigators and patients were masked to treatment assignment.

Per protocol (PP) analyses

The demographic and baseline characteristics for the PP analysis set were similar to those for the ITT set. The results of the ANCOVA for the PP analysis set (212 and 220 patients in the Actovegin and placebo groups respectively [196 and 202 respectively at 6 months) were supportive of the results of the primary analysis on the ITT set described: the LS mean (SE) change from baseline was -4.2 (0.60) for placebo and -6.4 (0.60) for Actovegin. The LS mean difference for Actovegin – placebo was -2.2, with an associated 95% CI (-3.9, -0.5), which was statistically significant in favour of Actovegin ($p = 0.010$).

Further Safety Results

Dyslipidemia was reported more frequently with Actovegin, compared with placebo during the study. All of these events were non-serious and did not lead to discontinuation from the study. Of note, the number of clinically significant chemistry laboratory values associated with cholesterol (low density lipoproteins) and triglycerides at month 6 was higher in the placebo group compared to Actovegin. Six (2.4%) deaths occurred in the placebo group and seven (2.8%) in the Actovegin group. All of the deaths were considered not related to the study medication. An overview of TEAEs is presented in Supplemental Table XI.

The noticeable difference in AEs leading to discontinuation from the study was due to recurrent stroke. However, during double-blind treatment, 21 patients (14 in the Actovegin group and seven in the placebo group) experienced cerebrovascular events (ischemic stroke, intracerebral hemorrhage and transient ischemic attack [TIA]). The odds ratio (95% CI) for cerebrovascular events on Actovegin compared to placebo was 2.09 (0.83, 5.26), suggesting this was not statistically significant (post-hoc analysis). Of these 21 patients, seven patients (2.8%) in the placebo group and 13 patients (5.2%) in the Actovegin group experienced recurrent ischemic stroke. Two patients in the placebo group and one patient in the Actovegin group had a fatal outcome as a result of this event; one patient in the Actovegin group experienced a fatal event of cerebral hemorrhage. Of seven patients in the placebo group, one patient experienced a non-serious cerebrovascular event, which was interpreted by the investigator as a transient ischemic attack. During the 6-month follow up, three patients in the placebo group and two patients in the Actovegin group discontinued due to recurrent ischemic stroke. Overall, 10 (4.0%) of 253 patients receiving placebo and 16 (6.4%) of 250 patients in the Actovegin group experienced cerebrovascular events. All cases of recurrent strokes were not related to the study medication (reported by investigators). A summary of TEAEs related to cerebrovascular events is presented in Supplemental Table XII.

Authors' contributions

A.G., I.S., V.Z., and A.D.K were members of the steering committee that developed the concept and design of the study, approved the statistical plans, had full access to and interpreted the data, critically reviewed the report, and were responsible for the decision to submit for publication. S.E. oversaw the statistical analysis and critically reviewed the report.