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### Title

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### Permalink

<https://escholarship.org/uc/item/83c6d1rw>

### Journal

International journal of stroke : official journal of the International Stroke Society, 9(3)

### ISSN

1747-4930

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### Publication Date

2014-04-01

### DOI

10.1111/ijss.12260

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Peer reviewed

# Human choriogonadotropin and epoetin alfa in acute ischemic stroke patients (REGENESIS-LED trial)

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**Introduction** Preclinical studies suggest that growth factors in the early days after stroke improve final outcome. A prior study found three doses of human choriogonadotropin alfa followed by three doses of erythropoietin to be safe after stroke in humans. A proof of concept trial (REGENESIS) was initiated but placed on regulatory hold during review of an erythropoietin neuroprotective trial. Due to financial constraints, the trial was largely moved to India, using lower erythropoietin doses, as the REGENESIS-LED trial.

**Methods** Entry criteria included National Institutes of Health Stroke Scale 8–20, supratentorial ischemic stroke, and 24–48 h poststroke at start of therapy. Patients were randomized to three QOD doses of subcutaneous human choriogonadotropin alfa followed by three QD doses of intravenous erythropoietin (three escalating dose cohorts, 4000–20 000 IU/dose) vs. placebo. Primary outcomes were safety and neurological recovery.

**Results** The study was halted early by the sponsor after 96 enrollees. There was no significant difference across treatment groups in the proportion of patients experiencing death, serious adverse events, or any adverse event. There was no significant difference in National Institutes of Health Stroke Scale score change from baseline to Day 90 between placebo and active treatment, whether active cohorts were analyzed together or separately, and no exploratory secondary measure of neurological recovery showed a significant difference between groups.

**Discussion** Administration of human choriogonadotropin alfa followed by erythropoietin is safe after a new ischemic stroke. At the doses studied, placebo and active groups did not differ significantly in neurological recovery. Study limitations, such as the use of multiple assessors, differences in rehabilitation care, and being underpowered to show efficacy, are discussed.

**Key words:** clinical trial, growth factor, restorative, safety, stroke recovery

## Introduction

Increasing evidence suggests the potential to favorably modify outcome after stroke with restorative therapies (1–3). The goals of

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Received: 22 June 2013; Accepted: 14 October 2013; Published online 03 March 2014

Conflict of interest: Steve Cramer has served as a paid consultant to Stem Cell Therapeutics, GlaxoSmithKline, Microtransponder, and Pfizer/Cogstate.

Clinicaltrials.gov ID # NCT00938314

Funding: This study was funded by Stem Cell Therapeutics.

DOI: 10.1111/j.12260

restorative interventions are to amplify innate processes of neural repair, and so differ from reperfusion and neuroprotection strategies after stroke. Preclinical work suggests the value of growth factors (4,5), in particular, that sequential administration of growth factors results in amplified endogenous neurogenesis after experimental stroke (6–8). For example, in preclinical rodent stroke studies, sequential administration of human choriogonadotropin alfa (hCG), which stimulates endogenous neural stem cell proliferation, followed by erythropoietin (EPO), which promotes neural stem cell survival and differentiation to a neuronal fate, results in improved neurological function (8). The BETAS trial, a Phase IIa safety study, translated this approach to human subjects, using subcutaneous (SQ) hCG 10 000 IU followed by intravenous (IV) EPO 30 000 IU, and found no safety concerns when initiated an average of 40 h postonset in 15 human subjects with ischemic stroke (9).

In response to these findings, the REGENESIS trial (clinicaltrials.gov ID NCT00663416 and NCT00715364) was designed as a Phase IIb proof of concept trial aimed at testing the effect of NTx®-265 (385 µg SQ hCG on Days 1, 3, and 5 of study participation, then 30 000 IU IV EPO on Days 7, 8, and 9), in patients suffering acute stroke, at 17 North American sites. This trial randomized patients 1:1 with National Institutes of Health Stroke Scale (NIHSS) score 6–24 who were 24–48 h after acute ischemic stroke to either placebo or to NTx®-265. The trial was put on hold on September 15, 2008 by the Food and Drug Administration (FDA) (United States) and Health Canada (Canada) due to concerns related to a separate acute stroke trial (10) that examined the neuroprotective effects of multiple doses of high-dose EPO (40 000 IU) started within six-hours of onset of ischemic stroke. In that neuroprotective trial (10), EPO was associated with a significant increase in mortality relative to placebo when co-administered with tissue plasminogen activator, with 63% of enrollees in that study having received thrombolytic therapy. At the time that the REGENESIS trial was put on hold, seven patients had been randomized, two of whom received active treatment, and all of whom suffered no serious adverse events related to study drug.

Subsequently, in response to a comprehensive review of NTx-265® clinical safety data by the US FDA, the REGENESIS trial was modified to be a dose-ranging safety study to characterize the safety of lower EPO doses of 'REGENESIS-LED'. Sites were initiated in the United States, Canada, and India. The objectives of the REGENESIS-LED trial were to assess the effect of sequential hCG and EPO, relative to placebo, in patients with a new ischemic stroke, with respect to (1) safety and tolerability, and (2) neurological recovery, measured as change in NIHSS score from baseline to Day 90. The current report describes the results from the REGENESIS-LED trial.

## Methods

### Study design

The REGENESIS-LED trial was a randomized, double-blind, placebo-controlled, dose escalation, multicenter, international study. The protocol was very similar in design to the BETAS trial (9), which examined the same sequential drug regimen but which used a higher and fixed dose of EPO compared with REGENESIS-LED. Patients received study drug/placebo on Study Days 1, 3, and 5 (placebo or SQ hCG) and on Study Days 7, 8, and 9 (placebo or IV EPO), followed by 81 days of observation, for total study duration of 90 days. This study used commercially available drug products: human choriogonadotropin alfa (hCG) was Ovidrel™ in North America and Ovitrele™ in India, and EPO was EPOGEN™ in the United States and EPREX™ in Canada and India. All study procedures were approved by local human subjects committees and conducted in accordance with Good Clinical Practices guidelines. Prior to study initiation, an Investigators' Meeting was conducted to provide information and training to all site and sponsor staff, including training in the performance of each outcome measure.

Enrollment of 128 patients was planned in three cohorts (32 in Cohort 1, 32 in Cohort 2, and 64 in Cohort 3). In each cohort, patients were randomized through a central interactive web response system in a 3 : 1 ratio of active (SQ hCG followed by IV EPO) or placebo (SQ saline followed by IV saline). In the active arm, the dose of hCG was fixed at 10 000 IU (385 µg) per dose, and the dose of EPO increased by 8000 IU per cohort beginning at 4000 IU – Cohort 1: 4000 IU EPO/dose; Cohort 2: 12 000 IU EPO/dose; Cohort 3: 20 000 IU EPO/dose. Entry criteria are listed in Table 1.

### Study assessments

Patients underwent a screening visit and provided informed consent within 48 h of stroke onset. Patients were serially evaluated clinically and with laboratory testing throughout the drug-dosing period, and at Days 16, 30, and 90 (see Supporting Information Table S1), including modality-specific outcome measures such as the Action Research Arm Test (ARAT). On Day 30 all patients underwent bilateral leg venous ultrasound to screen for possible asymptomatic deep venous thrombosis.

### Outcome measures

The primary outcome was safety, which was assessed based on mortality, adverse event reporting, and serial assessment of vital signs and clinical laboratory testing. A clinical monitor was assigned to each study site. In addition, the study sponsor, Stem Cell Therapeutics (SCT), monitored clinical trial sites in North America, while Maya Clinicals, a contract research organization, monitored sites in India. Safety was monitored on an ongoing basis throughout the study by an independent data safety and monitoring board (DSMB), which consisted of a chairperson (physician), a statistician, a hematologist, and a stroke neurologist. Data were provided to the DSMB for each patient who died or experienced a serious adverse event, as the event occurred. In addition, safety data were provided to the DSMB, in aggregate, for their review. The DSMB assessed safety prior to escalating to the next dose cohort. The DSMB had the authority to halt further enrollment if there were any safety concerns that needed to be addressed, and to make recommendations to the study that would ensure the safety of patients. The primary clinical endpoint was the change in the NIHSS score from baseline to Day 90.

**Table 1** Entry and exclusion criteria

#### Entry criteria

- Age 18–85 years
- NIHSS score 8–20 when assessed 24–48 h after stroke onset
- Stroke is ischemic in origin, supratentorial, and radiologically-confirmed via CT or MRI
- Patient is 24–48 h from time of stroke onset at time of first dose of study drug administration
- Reasonable expectation to be available to receive the full 9-day course of study drug and to be available for subsequent follow-up visits
- Reasonable expectation that patient would receive standard of care poststroke physical, occupational, and speech therapy
- Female patients must be either not of childbearing potential or agree to use nonhormonal forms of contraception throughout the study

#### Exclusion criteria

- Patients presenting with lacunar, hemorrhagic, and/or brain stem stroke
- Patients receiving thrombolytic treatment with tPA following the index stroke
- Comatose or obtunded (NIHSS Q1A score must be <2)
- Pregnancy, breastfeeding, or not using a highly effective method of birth control that would be maintained for the duration of the study
- Blood hemoglobin > 16 g/dl (males) or >14 g/dl (females); or platelet count > 400 000/mm<sup>3</sup>
- Advanced liver, kidney, cardiac, or pulmonary disease
- Known and documented elevated prostate specific antigen levels
- Known history of hypercoagulability
- Expected survival < one-year
- Allergy or other contraindication to either hCG or erythropoietin
- A known diagnosis of cancer in the prior five-years (except nonmalignant skin cancer)
- Patients with a pre-stroke modified Rankin Scale score (mRS) ≥ 2
- Preexisting and active major psychiatric or other chronic neurological disease
- Concurrent participation in another investigational study

CT, computed tomography; hCG, human choriogonadotropin alfa; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

## Statistical methods

Sample size determination was based upon mortality as an outcome and modeled using the 15 patients who received EPO 30 000 IU in the BETAS study (9) [of NTx®-265], among whom entry criteria were very similar to the REGENESIS-LED study. The posterior probability distribution around the true unknown probability of death associated with NTx®-265, assuming a uniform beta prior distribution as a starting point, is a beta binomial with parameters  $\alpha = 1$  and  $\beta = 16$ . Based on 1000 simulations of this posterior distribution (beta binomial with  $\alpha = 1$  and  $\beta = 16$ ), the probability that the mortality rate is less than 10% is 0.817 and the upper one-sided 95% interval estimate of mortality is 16.6%. With a cohort size of at least 25 patients, if two or fewer deaths are observed, there is a probability of at least 80% that the mortality rate is less than 10% in each cohort.

Safety analyses were performed on all randomized patients who received any amount of study medication, with patients classified according to actual treatment received. Clinical neurological outcome analyses were conducted using a modified intention-to-treat analysis set, defined as all randomized patients who received at least one dose of study drug, with patients classified according to initial randomization group. A per-protocol (PP) analysis set was also examined in secondary analyses, defined as all randomized patients who received the full course of study treatment, did not have a recurrent stroke, and had no major protocol violations.

The primary neurological endpoint related to neurological recovery, change in NIHSS score from baseline to Day 90, was analyzed using an analysis of covariance, with treatment group as a fixed effect, and with baseline NIHSS score and age used as covariates. Primary analysis compared patients receiving placebo with all patients in the three active treatment groups combined. Outcomes for patients who did not complete the Day 90 assessment were imputed based on the last available score carried forward method; patients missing all postbaseline data had a change score of 0 imputed. A secondary analysis using the same model explored the dose response using a closed testing procedure to compare placebo with each of the individual active dose groups. Clinical operations personnel from SCT and Maya Clinicals remained blinded to data analyses until the database was locked. All analyses were conducted using SAS v9.2 (SAS Institute Inc., Cary, NC, USA), with two-sided  $\alpha = 0.05$ , and no corrections were made for multiplicity.

## Results

### Enrollees

Enrollment in the REGENESIS-LED study occurred between August 2009 and March 2010 (Fig. 1). Enrollment was terminated by the sponsor early, after 96 patients, due to slow enrollment, and implemented by halving the size of Cohort 3 to 32 patients. Of the 96 enrollees, 93 were from India and 3 were from North America. Baseline features are presented in Table 2, and were similar across treatment groups. Overall, strokes were moderate in severity at baseline (Table 3).

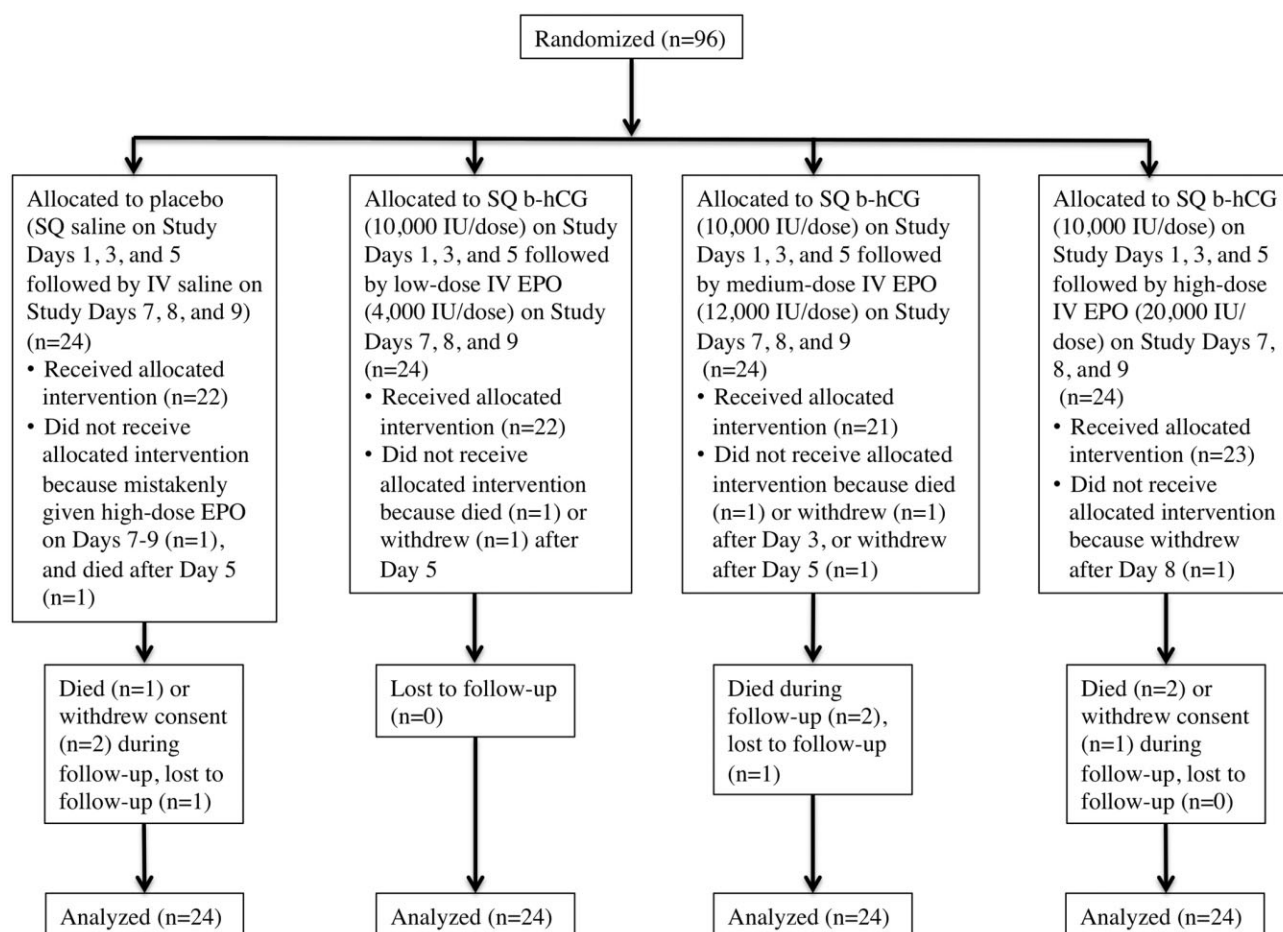
All 96 enrollees were included in the safety analyses and in the modified intention-to-treat population. The PP population was 88 patients, with 8 patients excluded (two placebo, two low-dose, three medium-dose, and one in the high-dose group), including one for incorrect dosing; this patient was randomized to the placebo group, received placebo on Days 1, 3, and 5 as planned, but mistakenly received high-dose EPO on Days 7, 8, and 9. This patient was considered to be in the high-dose NTx®-265 group for safety and PP analyses but the placebo group for the modified intention-to-treat analyses. Protocol deviations were noted in 52 patients (54.2%), were mainly related to timing of procedures and assessments, and their rate did not significantly differ between groups (45.8% placebo group, 54.2% low-dose group, 70.8% medium-dose group, and 45.8% high-dose group;  $P > 0.25$ ).

All 96 randomized patients received at least one dose of study medication. Administration of all study drug doses was completed in 88 (91.7%) enrollees, and this did not differ significantly between study groups.

Of these 96, 82% completed the study through Day 90, 19 (79%) in the placebo group and 60 (83%) in the active therapy groups. Reasons for noncompletion included death in eight (8.3%), withdrawal of consent in seven (7.3%), and loss to follow-up in two (2.1%) patients. The nine patients who specifically terminated before Day 90 due to adverse events were similarly distributed across treatment groups, eight of whom died and one of whom experienced pyrexia and withdrew from further study participation.

### Safety

There was no significant difference across treatment groups in the proportion of patients experiencing death, any serious adverse event, or any adverse event (Table 4). Patient classification for safety analyses was 23 in the placebo group, 24 in low-dose, 24 in medium-dose, and 25 in the high-dose group. A list of all serious adverse events is presented in Supporting Information Table S2. A total of 12 serious adverse events were reported across 11 of the 96 patients (two placebo, three low-dose, four medium-dose, and three high-dose group), the most common of which were cardiac arrest ( $n = 6$ ) and new stroke ( $n = 4$ ). None of these 12 were considered by the principal investigators or medical monitor to be possibly, probably, or definitely related to the study drug, and the DSMB did not identify any safety issues precluding continued enrollment into the study. This rate was not significantly different between groups ( $P > 0.5$ , two-tailed Fisher's exact test), whether active groups were analyzed together or separately. Eight of these serious adverse events were fatal, for a study mortality rate of 8.3%: one in placebo, one in the low-dose, three in the medium-dose, and three in the high-dose group. The mortality rate was not significantly different between groups ( $P > 0.5$ ) whether active groups were analyzed together or separately. In the placebo group, a 50-year-old died from ventricular fibrillation on Study Day 6. In the low-dose active group, a 78-year-old suffered respiratory distress followed by cardiac arrest on Day 6. In the medium-dose active group, a 60-year-old experienced cardiorespiratory arrest



**Fig. 1** CONSORT diagram. The number of subjects screened was not recorded in this trial. Values displayed are for the modified intention-to-treat population. EPO, erythropoietin; hCG, human choriongonadotropin alfa.

on Day 3; an 83-year-old experienced sudden cardiac death on Day 14; and a 70-year-old experienced sudden cardiac death on Day 16. In the high-dose active group, a 68-year-old experienced cardiorespiratory arrest on Day 31; a 62-year-old experienced dyspnea then died on Day 41; and a 61-year-old experienced cardiorespiratory arrest on Day 20.

A total of 84 patients (87.5%) received a venous duplex scan, with only one patient (medium-dose group) found to have a deep vein thrombosis, which was asymptomatic. No study patient experienced a pulmonary embolism or myocardial infarction.

The rate of any adverse events was similar between treatment groups, reported in 52.2% of placebo patients and 52.1% of active group patients (45.8% of low-dose, 79.2% of medium-dose, and 32.0% of high-dose patients); this rate was not significantly different between groups. A list of all adverse events appears in Supporting Information Table S3. Vital signs were similar across the four groups, including blood pressure one-hour after EPO (or after placebo) administration on Study Days 7, 8, and 9. Active treatment was not associated with a significant difference as compared with placebo in the evolution of any of the blood chemistry measures (screening to Study Day 9) or hematological tests (screening to Study Day 9, 30, or 90, including hemoglobin and reticulocyte count). There were also no significant differences between treatment groups in serum iron measures (screening to

Study Day 9 or 30, including iron, total iron binding capacity, and ferritin). Serum concentrations of hCG and EPO were tested after the third dose, and in each case drug levels corresponded to expected ranges.

### Neurological recovery

Of the 96 enrollees, serial NIHSS score assessments were performed by multiple examiners over time for 30 (31%) patients despite pretrial training to use a single examiner, with NIHSS assessments being compliant (i.e., using the same examiner over time) for 66 patients. Using the modified intention-to treat population (Fig. 1, Table 3), there was no statistically significant difference in the change in NIHSS score from baseline to Day 90 between placebo and active treatment ( $P = 0.31$ ). This remained true when each of the three active groups was separately compared with placebo (Table 3).

None of the exploratory secondary measures of neurological recovery showed a significant difference between groups, including the total NIHSS score, % modified Rankin Scale  $\leq 2$ , and the Barthel Index score, at Day 30 and at Day 90, whether active groups were analyzed together or separately, for either the modified intention-to-treat population or the PP population. Sites were inconsistent in measuring modality-specific outcome measures, for example, an ARAT score was provided in 23 (24% of



**Table 2** Baseline characteristics and demographics

	Active: combined groups	Active: separate groups			Placebo group
		Low-dose	Medium-dose	High-dose	
<i>n</i>	72	24	24	24	24
Age (years)	56.9 ± 12.3	57.4 ± 10.5	58.6 ± 13.3	54.8 ± 13.0	61.7 ± 12.4
Gender (M/F)	23/49	6/18	10/14	7/17	8/16
Race					
Asian	70	24	22	24	23
White	2	0	2	0	1
History of					
Hypertension	65.3%	66.7%	50%	79.2%	58.3%
Diabetes mellitus	36.1%	41.7%	33.3%	33.3%	37.5%
Atrial fibrillation	2.8%	4.2%	4.2%	0%	4.2%
Coronary artery disease	4.2%	4.2%	0%	8.3%	12.5%
Stroke	11.1%	12.5%	12.5%	8.3%	0%
Weight (kg)	65.4 ± 8.7	64.9 ± 5.8	66.0 ± 8.1	65.2 ± 11.4	65.1 ± 10.9
Height (cm)	164.2 ± 6.6	163.6 ± 5.7	164.6 ± 7.8	164.5 ± 6.5	161.1 ± 7.5
Tobacco use					
Current/Past use	23 (31.9%)	8 (33.3%)	7 (29.2%)	8 (33.3%)	10 (41.7%)
Never	48 (66.7%)	16 (66.7%)	16 (66.7%)	16 (66.7%)	14 (58.3%)
Unknown	1 (1.4%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)
Alcohol use					
Current/Past use	16 (22.2%)	4 (16.7%)	7 (29.2%)	5 (20.8%)	6 (25.0%)
Never	55 (76.4%)	20 (83.3%)	16 (66.7%)	19 (79.2%)	18 (75.0%)
Unknown	1 (1.4%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)
Time from stroke onset to initiation of study drug (hours)	38.4 ± 6.4	38.2 ± 6.4	40.9 ± 6.1	36.1 ± 6.1	37.9 ± 6.9
OCSF classification					
TACS	24 (33.3%)	9 (37.5%)	9 (37.5%)	6 (25.0%)	7 (29.2%)
PACS	44 (61.1%)	14 (58.3%)	13 (54.2%)	17 (70.8%)	16 (66.7%)
POCS	4 (5.6%)	1 (4.2%)	2 (8.3%)	1 (4.2%)	1 (4.2%)

Values are for the modified intention-to-treat population and are mean ± SD or percentage.

PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome.

**Table 3** NIHSS scores from baseline to day 90

	Active: combined groups	Active: separate groups			Placebo group
		Low-dose	Medium-dose	High-dose	
<i>n</i>	72	24	24	24	24
Baseline	13 [10 to 15.75]	14 [11 to 16.75]	12 [10.25 to 14]	12 [9 to 14.5]	12 [10 to 14]
Day 90	5.5 [2.25 to 9.75]	7 [4 to 11]	5.5 [2 to 9]	3 [2 to 8.75]	2.5 [2 to 8.25]
Change, Baseline to Day 90	−8 [−9 to −3.25]	−8 [−9.75 to 3.25]	−7.5 [−10 to −1.5]	−6 [−9 to −5]	−8 [−10 to −5]

Values are for the modified intention-to-treat population and are median [IQR]. Baseline scores were obtained at Visit 1, that is, the first day of study participation. The change in NIHSS score did not differ significantly between placebo and active groups, whether evaluating active groups combined or separately.

NIHSS, National Institutes of Health Stroke Scale.

enrollees) at baseline and in 56 (58% of enrollees) at Study Day 90.

At least one 15-min session of post-stroke occupational therapy (OT) was provided to 23% of patients; physical therapy, to 81%; and speech therapy, to 29%. Post hoc analysis indicated that patients who received at least one session of OT during the study (23% of enrollees, with eight in placebo, eight in low-dose, five in medium-dose, and one in high-dose group) might have had better neurological recovery with active treatment: in the low-dose group, the change in NIHSS score from baseline to Day 90 was 4.0 points greater than with placebo ( $P = 0.05$ ); and in the

medium-dose group, the change in NIHSS score was 4.9 points greater than with placebo ( $P = 0.03$ ).

## Discussion

Preclinical studies suggest the utility of sequential growth factors to improve behavioral outcome when administered subacutely after stroke (4,6–8), and a study in 15 patients with stroke 24–48 h prior found hCG followed by EPO to be safe (9). The current report describes the REGENESIS-LED study, which found that sequential administration of SQ hCG and IV EPO over nine-days

**Table 4** Safety outcomes

	Active: combined groups	Active: separate groups			Placebo group
		Low-dose	Medium-dose	High-dose	
<i>n</i>	73	24	24	25	23
Serious adverse events	10	3	4	3	2
Fatalities	7	1	3	3	1
Any adverse event	38	11	19	8	12

Safety analyses were performed on all randomized patients who received any amount of study medication, with patients classified according to actual treatment received. Any adverse event includes serious adverse events, and serious adverse events include fatalities. There were no significant differences across treatment groups in the proportion of patients experiencing a serious adverse event, fatality, or any adverse event.

beginning 24–48 h after stroke onset is safe but is not associated with improved neurological recovery at Day 90.

Administration of hCG followed by EPO is safe in patients with a new ischemic stroke, including the absence of adverse events related to EPO dose. There were no clinically significant differences between groups over time across the serum chemistry, iron, coagulation, or hematology parameters, including hemoglobin. At the doses studied, including EPO up to 20 000 IU/dose, placebo and active groups did not differ significantly in neurological recovery.

The study was, ultimately, underpowered to show efficacy. It remains possible that there is a small effect of growth factor administration on stroke outcome and we have made a type 2 error. Interestingly, post hoc subgroup analysis suggested a potential benefit of active treatment among the 23% of patients who received poststroke OT, although this was an exploratory observation. There were several observations in trial conduct that may serve as future learning points for the studies in this area. The first pertains to the potential impact of using multiple patient assessors over time. Stroke scales do not have perfect reproducibility. In the current trial, multiple raters assessed patients at the various time-points throughout the course of patient treatment. This may have substantially increased noise as compared with use of a single rater over time. Second, the choice of EPO dosing was affected by concerns about an unrelated neuroprotective study (10), and it remains possible that this reduction in dose substantially attenuated any possible biological effect. The effect of this reduction was that the dose of EPO studied in the REGENESIS-LED study was lower than the equivalent dose used in rodent models, and so we were unable to conform to the STAIR criteria and administer drug in humans at similar dose levels to that used in preclinical models. Third, the type and availability of rehabilitation care that was available in India, where most study patients were enrolled, is substantially different from what is available in North America. Abundant evidence suggests that the brain plasticity induced by a restorative therapy after stroke is experience dependent (11–13) – the favorable milieu produced by a restorative therapy has maximum impact when it is shaped by behavioral experience, just as during normal brain development (14). We would predict a priori that consistent provision of physical and occupational therapy for several weeks after stroke would interact with any therapy designed to enhance neurogenesis.

Overall, hCG followed by EPO was not effective in promoting neurological recovery after stroke, in the dosing paradigm and stroke care settings studied here. The concept of induced stimulation of neurogenesis as a treatment paradigm for stroke remains to be proven.

## Study sites

Steven C. Cramer – co-Primary Investigator.

Michael D. Hill – co-Primary Investigator.

## India

Mathew Alexander, Christian Medical College Hospital, Vellore, Tamilnadu; Subhashini Prabhakar, Apollo Hospitals, Hyderabad, Andhra Pradesh; Puneet Agarwal, Max Super Speciality Hospital, New Delhi; PN Sylaja, Ananthapuri Hospitals and Research Institute, Thiruvananthapuram, Kerala; Chandra Sekhar Reddy, Krishna Institute of Medical Sciences, Hyderabad, Andhra Pradesh; JMK Murthy, Care Hospital, Hyderabad, Andhra Pradesh; Jayaraj Pandian, Christian Medical College and Hospital, Ludhiana, Punjab; Jayanta Roy, Apollo Gleneagles Hospitals, Kolkata, West Bengal; Dr.BS Keshava, JSS Medical College & Hospital, Bangalore, Karnataka; Srinivasa Rangasetty, MS Ramaiah Memorial Hospital, Bangalore, Karnataka; Vikram Sharma, St. Theresa's General Hospital, Hyderabad, Andhra Pradesh; Vijaya Pami-dimukkala, Lalitha Super Specialities Hospital Pvt Ltd, Guntur Hyderabad, AP; Suresh Kumar, Vijaya Health Center, Chennai, Tamilnadu; E Srikantha Reddy, Kamineni Hospitals, Hyderabad, Andhra Pradesh; Bhaskar Rao, Mediciti Hospital, Hyderabad, Andhra Pradesh; Umesh Tukaram, Owaisi Hospital and Research Center, Hyderabad, Andhra Pradesh; Anthathi S Keerthi, DBR&SK Superspeciality Hospital, Tirupati, Andhra Pradesh; Chalasani Pramod, Latha Superspecialities Hospital, Vijayawada, Andhra Pradesh; Dr.VVVB Choudary, Suraksha Neuro Centre, Vijayawada, Andhra Pradesh; G Kishore Babu, Care Hospital, Vishakapatnam, Andhra Pradesh; B Vengamma, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh

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Steven C. Cramer, University of California, Irvine Medical Center.

## Acknowledgement

We thank Brian Mangal, MSc, for biostatistics support.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Table S1.** Schedule of testing.

**Table S2.** List of serious adverse events.

**Table S3.** List of all adverse events.