Infrared Laser Therapy for Ischemic Stroke: A New Treatment Strategy

Results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1)

Yair Lampl, MD; Justin A. Zivin, MD, PhD; Marc Fisher, MD; Robert Lew, PhD; Lennart Welin, MD; Bjorn Dahlof, MD; Peter Borenstein, MD; Bjorn Andersson, MD; Julio Perez, MD; Cesar Caparo, MD; Sanja Ilic, MD, MS Uri Oron, PhD

From the Wolfson Medical Center (Y.L.), Department of Neurology, Holon, Israel; the University of California San Diego (J.Z.), Department of Neurosciences, La Jolla, Calif; the University of Massachusetts Medical Center (M.F.), Worchester, Mass; the MAVERIC Massachusetts Veterans Epidemiology Research and Information Center (R.L), Boston, Mass; the Lidkoping Hospital (L.W.), Department of Medicine, Lidkoping, Sweden; the Ostra University Hospital (B.D.), Department of Medicine, University of Goteborg, Sweden; the SÁS/Skene Iasarett (B.A.), Department of Medicine, Skene, Sweden; the Sahlgrenska University Hospital (J.P.), Department of Medicine, University of Goteborg, Sweden; the Hospital National "Dos de Mayo" (C.C.), Parque de La Medicina Peruana S/N; Cercado-Barrios Altos, Lima, Peru; the Universidad Nacional San Augustin de Arequipa (S.I.), Department of Medicine, Arequipa, Peru; and the Tel Aviv University (U.O.), Department of Zoology, Tel Aviv, Israel.

Correspondence to Sanja Ilic, MD, MS, 2260 Rutherford Road suite 101 Carlsbad, CA 92008. E-mail silic@photothera.com

Background and Purpose— The NeuroThera Effectiveness and Safety Trial-1 (NEST-1) study evaluated the safety and preliminary effectiveness of the NeuroThera **Laser** System in the ability to improve 90-day outcomes in **ischemic stroke** patients treated within 24 hours from **stroke** onset. The NeuroThera **Laser** System therapeutic approach involves use of **infrared laser** technology and has shown significant and sustained beneficial effects in animal models of **ischemic stroke**.

Methods— This was a prospective, intention-to-treat, multicenter, international, double-blind, trial involving 120 **ischemic stroke** patients treated, randomized 2:1 ratio, with 79 patients in the active treatment group and 41 in the sham (placebo) control group. Only patients with baseline **stroke** severity measured by National Institutes of Health **Stroke** Scale (NIHSS) scores of 7 to 22 were included. Patients who received tissue plasminogen activator were excluded. Outcome measures were the patients' scores on the NIHSS, modified Rankin Scale (mRS), Barthel Index, and Glasgow Outcome Scale at 90 days after treatment. The primary outcome measure, prospectively identified, was successful treatment, documented by NIHSS. This was defined as a complete recovery at day 90 (NIHSS 0 to 1), or a decrease in NIHSS score of at least 9 points (day 90 versus baseline), and was tested as a binary measure (bNIH). Secondary outcome measures included mRS, Barthel Index, and Glasgow Outcome Scale. Primary statistical analyses were performed with the Cochran-Mantel-Haenszel rank test, stratified by baseline NIHSS score or by time to treatment **for** the bNIH and mRS. Logistic regression analyses were conducted to confirm the results.

Results— Mean time to treatment was >16 hours (median time to treatment 18 hours **for** active and 17 hours **for** control). Time to treatment ranged from 2 to 24 hours. More patients (70%) in the active treatment group had successful outcomes than did controls (51%), as measured prospectively on the bNIH (*P*=0.035 stratified by severity and time to treatment; *P*=0.048 stratified only by severity). Similarly, more patients (59%) had successful outcomes than did controls (44%) as measured at 90 days as a binary mRS score of 0 to 2 (*P*=0.034 stratified by severity and time to treatment; *P*=0.043 stratified only by severity). Also, more

patients in the active treatment group had successful outcomes than controls as measured by the change in mean NIHSS score from baseline to 90 days (P=0.021 stratified by time to treatment) and the full mRS ("shift in Rankin") score (P=0.020 stratified by severity and time to treatment; P=0.026 stratified only by severity). The prevalence odds ratio **for** bNIH was 1.40 (95% CI, 1.01 to 1.93) and **for** binary mRS was 1.38 (95% CI, 1.03 to 1.83), controlling **for** baseline severity. Similar results held **for** the Barthel Index and Glasgow Outcome Scale. Mortality rates and serious adverse events (SAEs) did not differ significantly (8.9% and 25.3% **for** active 9.8% and 36.6% **for** control, respectively, **for** mortality and SAEs).

Conclusion— The NEST-1 study indicates that **infrared laser therapy** has shown initial safety and effectiveness **for** the treatment of **ischemic stroke** in humans when initiated within 24 hours of **stroke** onset. A larger confirmatory trial to demonstrate safety and effectiveness is warranted.

Stroke is the leading cause of adult disability and remains the third most common cause of death in industrialized nations.[1] At the present time, the only FDA approved treatment **for ischemic stroke** is tissue plasminogen activator; it must be used within 3 hours of **stroke** onset. No treatment is currently approved beyond this time point.[2–3] Rapid intervention currently results in treatment of <5% of patients with **stroke**, leaving over 95% of the patients with no **therapy** other than rehabilitation.[4] An effective treatment **for stroke** that could be administered up to 24 hours after **stroke** onset would address a significant unmet medical need.

The NeuroThera **Laser** System (NTS) uses an **infrared laser** technology that involves photobiostimulation. A large and growing body of scientific literature is available documenting the photobiostimulation effects of **infrared laser therapy** both in vitro and in vivo.[5–9] The biological effects of **infrared laser therapy** are wavelength-specific and are not attributable to thermal effects.[10–12] Energy in this region of the electromagnetic spectrum is nonionizing and, there**for**e, poses none of the hazards associated with UV light. It has been demonstrated that irradiation of specific **infrared** wavelengths is able to penetrate deeply into the brain.[13] This **for**m of **therapy** is distinguished from photodynamic **therapy**, which involves using light energy to penetrate the body and to activate a photosensitive drug.

Photobiostimulation involves increased adenosine triphosphate (ATP) **for**mation after energy absorption inside mitochondria.[5,14] A compound that absorbs energy in the spectral region of interest is known as a chromophore. There is evidence that suggests that a primary mitochondrial chromophore **for** photobiostimulation is cytochrome c oxidase.[5,6,14] This enzyme complex contains 2 copper centers, Cu_A and Cu_B. The primary chromophore **for** the NTS wavelength is in the Cu_A center which has a broad absorption peak around 830 nm in its oxidized **for**m. The NTS delivers energy at 808 nm, which is within this absorption peak, and is able to penetrate into the brain noninvasively. Cytochrome c oxidase is a terminal enzyme in the cellular respiratory chain and is located in the inner mitochondrial membrane. It plays a central role in the bioenergetics of eukaryotic cells by delivering protons across the inner membrane, and thereby driving the **for**mation of ATP by oxidative phosphorylation. In addition to leading to increased ATP **for**mation, photobiostimulation may also initiate secondary cell-signaling pathways. The overall result is improved energy metabolism, enhanced cell viability, and may also involve prevention of apoptosis in the **ischemic** penumbra and enhancement of neurorecovery mechanisms.

In vivo studies have suggested that **infrared laser therapy** could be beneficial **for** the treatment of acute myocardial infarction, acute **ischemic stroke**, injured peripheral nerves and

spinal cord injury.[7,8,15] Lapchak et al,[16] Oron et al,[17] and DeTaboada et al[18] have shown in 2 different animal models a positive impact of **infrared laser therapy** on the experimental, **ischemic stroke** treatment outcomes in New Zealand rabbits (rabbit small clot embolic **stroke** model [RSCEM]) and Sprague-Dawley rats (permanent middle cerebral artery occlusion). Lapchak has shown that **laser** treatment at 6 hours post**stroke** onset in RSCEM improved behavioral per**for**mance and produced a durable effect that was measurable 21 days after embolization. De Taboada and Oron have also shown that **laser** treatment up to 24 hours post**stroke** onset in permanent middle cerebral artery occlusion showed significant improvement in neurological deficits which was evident at 14, 21 and 28 days post**stroke** when compared with the sham control group.

Currently, the putative mechanism **for infrared laser therapy** in **stroke** involves the stimulation of mitochondria, which then leads to preservation of tissue in the **ischemic** penumbra and enhanced neurorecovery. The exact mechanistic pathways remain to be elucidated.

Study Design
NEST-1 was a prospective, multicenter, international, double-blind, randomized, sham (placebo) controlled trial conducted at 6 medical centers in 3 countries: Israel, Peru, and Sweden. The study examined initial safety and effectiveness of **infrared** wavelength **laser therapy for** treatment of patients within 24 hours of **ischemic stroke** onset.

This study was conducted in accordance with the FDA/ICH Good Clinical Practice guidelines and applicable local regulatory requirements. Investigators were required to ensure that this study was conducted in full con**for**mity with the 1983 revision of the Declaration of Helsinki or with the laws and current regulations in biomedical research involving human patients of the country in which the study was conducted, whichever af**for**ded greater protection to the patients. The protocol and in**for**mation **for** patients and healthcare providers was approved by each center's ethics committee or Institutional Review Board. Country-specific independent data monitoring committees conducted safety reviews throughout the study.

Eligible patients were required to be between 40 to 85 years of age, have a clinical diagnosis (within 24 hours of **stroke** onset) of **ischemic stroke** causing a measurable neurological deficit (total NIHSS score ranging from 7 to 22 at admittance to the medical center), and to have NTS treatment initiated within 24 hours from **stroke** onset. The patient or parent legal representative gave written in**for**med consent be**for**e enrollment into the study.

Ineligibility Criteria
Patients were excluded if: there was evidence on a CT scan of an intracranial, subdural or subarachnoid hemorrhage, or clinical presentation suggestive of subarachnoid hemorrhage, even if the initial CT scan was normal; the patient was a candidate **for** intravenous or intra-arterial administration of tissue-type plasminogen activator or other thrombolytic **therapy for** treatment of the acute **ischemic stroke**, and tissue plasminogen activator or other thrombolytic **therapy** was administered; the patient had a seizure at **stroke** onset; serum blood glucose was >400 mg/dL (22 mmol/L) or <40 mg/dL (2.2 mmol/L); the patient had sustained hypertension (defined during the baseline period by 2 readings occurring 30 minutes apart with systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg) at time of treatment or need **for** aggressive treatment **for** blood pressure reduction; there was sustained hypotension (defined as systolic blood pressure <80 mmHg, or diastolic blood pressure <50 mmHg); there was presumed septic embolus; the patient had known hereditary or acquired hemorrhagic diathesis, eg, activated partial thromboplastin time or prothrombin time greater than normal,

unsupported coagulation factor deficiency, or oral anticoagulant **therapy** with the prothrombin time greater than normal; the patient had a skin condition (ie, hemangioma, scleroderma, psoriasis, rash, or open wound) at the site chosen **for infrared** energy application; the patient was previously enrolled in or had participated in another investigational drug or device trial within the preceding 4 weeks; if a new medication was started within 14 days be**for**e the screening visit; the participant had severe mental deficit, severe neurological deficit or disorder (dementia, multi-infarct dementia, advanced multiple sclerosis) which would interfere with the assessment of the patient's ability **for** independent functioning; there was evidence of any disorder other than **stroke** that, in the opinion of the investigator, could be considered serious or life threatening such as active serious infections, pneumonia, pulmonary emboli, or gastrointestinal bleeding; the patient had unstable cardiac arrhythmias or other cardiac illness that, in the opinion of the investigator, was life threatening; the patient was of child bearing potential; the patient was comatose or moribund level of consciousness; or the patient was otherwise determined by the investigator to be medically unsuitable **for** participation in this study.

Study Groups, Evaluation Measures, and Baseline Factors
All patients received standard medical management **therapy for** acute **ischemic stroke**. In addition, they all underwent an identical NTS procedure. A randomization code that was preprogrammed within the NeuroThera **Laser** System determined whether the treatment was active or sham (placebo). Both patients and clinicians were blinded regarding treatment arm. The National Institutes of Health **Stroke** Scale (NIHSS) was assessed at the time of screening **for** entry into the study and again immediately be**for**e randomization to treatment group. Outcome measures (NIHSS, modified Rankin Scale [mRS], Barthel Index, and Glasgow Outcome Scale) were determined at 30, 60, and 90 days. Neurological scores and clinical data were collected on standard case report **for**ms at each visit by trained investigators.

Baseline factors including patient demographics, time to treatment, medical history, vital signs, and routine laboratory values were collected. Factors also included age, sex, time from **stroke** onset to arrival at hospital, time from **stroke** onset to treatment, and a complete medical history.

After completion of the NTS procedure, patients entered the study follow-up phase until one of the following occurred: the patient decided to stop participation in the study; the sponsor or ethics committee/applicable regulatory body terminated the study; the investigator decided to discontinue the patient or site participation in the study; or the patient had participated in the study **for** 90±10 days.

The NTS Treatment Device
The NTS is an investigational device that is intended to provide noninvasive, transcranial **laser** treatment to patients diagnosed with acute **ischemic stroke**. The **laser** wavelength of 808 nm is in the near-**infrared** portion of the electromagnetic spectrum, and is invisible to the naked eye. Energy in the near-**infrared** spectrum is nonionizing and is not associated with the risks of ionizing radiation. The NTS device consists of a class IV **laser** system and delivers energy via a fiber optic cable to a handheld probe that is placed on the shaved head of the patient by a trained operator. The device is portable and is similar in size to portable ultrasound equipment.

The NTS is manufactured by PhotoThera, Inc. A complete treatment regimen consists of removing hair from the patient's scalp, followed by NTS application (active treatment or sham/control treatment) on 20 predetermined locations on the scalp **for** 2 minutes at each site.

The predetermined sites are identified by a cap which is placed on the patients head. The system is designed to deliver ≈1 Joule/cm^2 of energy over the entire surface of the cortex regardless of **stroke** location. The sham procedure is identical to the active procedure with the exception that no **laser** energy is delivered to the patient from the device.

Based on current knowledge of the technology and risk assessment analysis, the most significant known hazard with NTS treatment is potential retinal damage if the beam enters through the lens of the eye and onto the retina. Other potential hazards include skin burns and cuts to the scalp from shaving the head. Skin burns could occur if the device is not used as intended (eg, repeated treatments at the same location).

Statistical Methods
Effectiveness outcomes were reported on an intention-to-treat basis and include all 120 patients randomized to both arms. Safety outcomes were based on the same 120 patients, who also comprised all patients who received any treatment.

Patients were evaluated at baseline, 30, 60, and 90 days after baseline. Analysis focused largely on the 90-day evaluations. The NIHSS was the prospectively identified primary outcome, and the mRS, Glasgow Outcome Scale and Barthel Index scores were secondary outcomes.

Categories of baseline values of the NIHSS score and of time from **stroke** onset to treatment were entered into the analyses as strata or covariates. The three NIHSS strata were 7 to 10, 11 to 15, and 16 to 22. The categories **for** time from **stroke** onset to treatment were "less than 12 hours" and "12 to 24 hours." The NIHSS scale is not an interval scale. There**for**e, we used categories of the NIHSS score to reduce potential heterogeneity.

NIHSS outcome was collapsed into a binary outcome, bNIH, where 'success' could occur in either of 2 ways: as a 90-day NIHSS score 0 to 1 or as a decrease in score (change) of 9 or more points from baseline to 90 days.[19]

The mRS 90-day outcome took 2 **for**ms. The 7-category ordinal variable **for**m, analyzed across the whole distribution of scores on the 0 to 6 mRS scale (full mRS), and a binary mRS that makes scores of 0 to 2 as positive (success) and scores of 3 to 6 as negative (failure).

The full mRS ("shift in Rankin"), binary mRS and bNIH outcomes were tested using a stratified Cochran-Mantel-Haentzel (CMH) test: namely, the van Elteren test. The test uses the modified ridit score and thereby is a direct extension of the 2-sample Wilcoxon test. **For** the bNIH and the binary mRS outcomes, logistic regression analyses were used to explore the effects of covariates and the random effect of site: in particular, to assess how adding these factors altered the estimate of treatment effect.

The analyses were carried out in SAS version 9 using PROC FREQ to obtain the results **for** the van Elteren CMH test, and using PROC GENMOD and PROC LOGISIC to obtain results **for** logistic regression analyses with and without medical center as a random effect. Prevalence odds ratios were obtained from PROC GENMOD.

This study was an exploratory trial rather than a confirmatory trial, in the sense of FDA/ICH E8 Guidance on General Considerations **for** Clinical Trials and FDA/ICH E9 Guidance on Statistical Principles **for** Clinical Trials. Primary safety and effectiveness outcome measures and their analysis were identified prospectively. Multiple secondary and exploratory analyses

were defined in the protocol or were designed and performed after study completion and unblinding. No corrections were made **for** multiple comparisons.
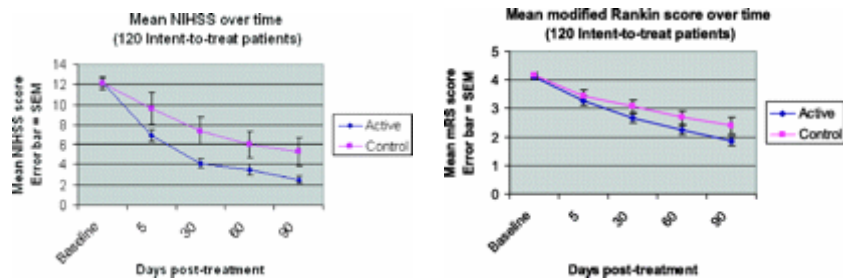
▸ Results

The study enrolled 122 eligible adult patients, between ages 40 and 85 of any ethnic background diagnosed with acute **ischemic stroke** within 24 hours of onset who provided their written in**for**med consent. Two patients withdrew be**for**e randomization and are not included in any analyses, leaving 120 patients in the effectiveness analysis. Of the 120 patients, 79 were randomized to the active treatment group and 41 were randomized to the sham control group (see Figure 1; disposition of patients in the study). There was only 1 patient lost to follow-up (0.8%). No significant differences in baseline characteristics were observed (see Table 1; baseline demographics and other baseline characteristics). Study data were reviewed by independent data monitoring committees in each country; there were no serious device-related adverse effects reported.

Effectiveness Analysis
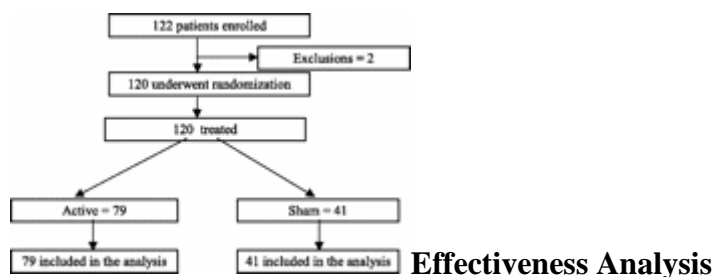
The proportion of patients who received active treatment and had a positive bNIH outcome was 70%, which is greater than the proportion who received sham control treatment with a positive bNIH outcome (51%; CMH test $P=0.035$ stratified by severity and time from **stroke** onset to treatment; $P=0.048$ stratified only by severity). The treatment effect remained significant with other choices of strata **for** the CMH analysis. Logistic regression analyses confirmed that the results held controlling **for** both fixed covariates (eg, age, sex, time-to-treatment, baseline severity, previous **stroke**) and the random effects of medical site. Controlling only **for** baseline severity the logistic regression gave a prevalence odds ratio favoring treatment of 1.40 (95% CI, 1.01 to 1.93). Among the 79 treated patients, 38% achieved both a final NIHSS score of 0 to 1 and improved by ≥9 points, 20% had only a ≥9-point improvement, 11% obtained a final score of 0 to 1 without improving by ≥9, and 30% achieved neither end point. Among the 41 control patients the corresponding proportions were 29%, 7%, 15%, and 49%.

Differences in mean NIHSS scores between the treatment groups appeared soon after treatment and were apparent throughout the 90-day study period (Figure 2). Patients in the active treatment group showed greater improvement in the change in NIHSS scores from baseline to day 90, as compared with the sham control group ($P=0.021$, CMH test stratified by time to treatment).

Mean NIHSS over time (120 Intent-to-treat patients)

Mean modified Rankin score over time (120 Intent-to-treat patients)

For the binary mRS outcome (0 to 2 versus 3 to 6), a similar pattern of significance held. The proportion of patients who received active treatment and had a positive binary mRS outcome was 60%, which is greater than the proportion who received sham control treatment with a positive binary mRS outcome (44%; CMH test P=0.034 stratified by severity and time to treatment; P=0.043 stratified only by severity). Only the CMH test without strata was not significant ($P<0.11$ x^2 test). The rate of positive results markedly varies across the baseline severity strata. Controlling only **for** baseline severity, logistic regression gave prevalence odds ratios favoring treatment of 1.38 (95% CI, 1.03 to 1.83) **for** the binary mRS outcome.

The effect of the NTS when compared with sham treatments with respect to the score on the full mRS at 90 days or the last rating, analyzed across the whole distribution of scores on the 0 to 6 mRS scale was significant, with the use of the Cochran-Mantel-Haentzel nonparametric rank test, stratified by categories of (1) baseline NIHSS score and time to treatment (P=0.020) and (2) baseline NIHSS score only (P=0.026; see Table 2).

Stratification by baseline severity gave similar results **for** the 3 outcomes (bNIH, binary mRS, and full mRS); all 3 outcomes had significance levels <0.05 (see Table 3; 2-sided significance levels **for** the van Elteren CMH test). When also controlled **for** time-to-treatment (0 to 12 hours versus 12 to 24 hours) little significance is gained. However, in a trial with a larger sample size, time-to-treatment would be expected to have a stronger association with outcome.

Results of analyses using the Glasgow Outcome Scale and Barthel Index are similar to those **for** the NIHSS and the mRS. Patients who received active treatment had better outcomes than patients who received sham control treatment as measured on the Glasgow Outcome Scale scale (CMH test P=0.056), and the Barthel Index scale (CMH test P=0.035), stratified by baseline NIHSS score and time to treatment.

The logistic regression analyses indicated the negligible effects of covariate adjustment on the logistic regression coefficient **for** treatment. The results in Table 4 indicate that treatment effect is stable across 2 binary outcomes and across 3 different nested sets of covariates. In fact, the treatment effect tends to increase as covariates are added. Furthermore, treating hospital site as a repeated measures effect virtually does not alter the logistic regression coefficient **for** treatment. The 95% CIs are not shown to focus on the consistency of the regression coefficients. In all but one model the probability value **for** treatment is <5%. In the models with the bNIH outcome, the covariate 'severity' is not significant and time-to-treatment is significant only once with P=0.0496. However with the binary mRS outcome, the covariate 'severity' is significant with $P<0.001$ in all 3 models. This indicates that the 9-point decrease in the NIHSS score captures the variation of treatment effect across the baseline severity categories. We explored many sets of additional covariates and found that after including the covariates 'gender', 'age', and 'prior **stroke**' all other covariates had negligible predictive value. Gender was significant in the binary mRS model with $P<0.01$. Otherwise, these factors did not achieve statistical significance (see Table 4).

Discussion

The NEST-1 trial provides initial evidence on the safety and effectiveness of **infrared laser therapy for** the treatment of **ischemic stroke** in humans within 24 hours of **stroke** onset.

The outcome variable scales used in the NEST-1 study had excellent correlation: $R=0.79$ to 0.92. The correlation coefficients **for** the NEST-1 trial are essentially the same as those reported in the article by Lyden and colleagues reviewing tissue plasminogen activator data.[20] That is, the outcome variables have correlation coefficients with each other of ≈ 0.8 (absolute value) or higher. This concordance with prior studies is evidence that the outcomes are being measured appropriately and consistently.

The results suggest that **infrared laser therapy** may benefit a broad spectrum of **stroke** patients without increasing the rate of adverse events. Furthermore, the relatively large magnitude of the effect implies that a phase III trial should not require a substantial number of subjects.

Patients receiving active treatment had a higher proportion of positive NIHSS outcomes than did patients receiving sham control treatment. Results were similar using the other neurological outcome scales. No significant differences between the treatment groups were observed in rates of mortality or SAEs, but the sample size (n=120) gives low power to detect small differences. Where there is a trend toward differences between the treatment groups, patients receiving active treatment appeared to have had fewer SAEs than did patients receiving sham control treatment. The safety profile of the NTS treatment as demonstrated in this study was clear. There were no adverse outcomes that can be attributed to the **laser** therapeutic procedure.

The bNIH outcome with the 9-point change incorporates variation in baseline severity (from NIHSS score 7 to 22) and suggests a global potential benefit. In contrast, the binary mRS outcome does not account **for** change from baseline. Thus, once the analysis controlled **for** baseline severity, the results based on the 2 binary outcomes closely agreed. Controlling **for** baseline severity, the analyses by the CMH test and by logistic regression gave prevalence odds ratios favoring treatment exceeding 1.40 **for** the bNIH outcome and exceeding 1.38 **for** the binary mRS outcome.

This global potential benefit is also demonstrated through the full mRS, analyzed across the entire distribution of Rankin scores, from 0 to 6. The mRS is a simple and reliable outcome measure when consistently implemented by trained clinicians. The full mRS analysis takes into consideration the entire spectrum of the patient outcomes. As a result, the full mRS is increasingly considered as a primary outcome measure **for ischemic stroke** trials involving neuroprotective technologies.

This exploratory study had a prespecified analytic plan with a primary outcome of bNIH, the binary **for**m of NIHSS that regards a final score of 0 to 1 or a 9-point decrease as a success. But our presentation of several analytic approaches raises the concern of type 1 error. We described several approaches to the same hypothesis: some having an mRS outcome, some having an NIHSS outcome, and some using logistic regression to confirm the nonparametric results. These results showed the substantial concordance among these outcomes and methods. Also, they showed that after control **for** NIHSS baseline severity, other factors had little or no effect on the magnitude of the treatment effect. Hence, we did not present a

multiple comparisons correction such as the Bonferroni correction because, in particular, the Bonferroni correction assumes that the hypotheses are independent of one another. Another reason **for** the various analyses was to associate an effect size with the results of the primary analysis by the nonparametric CMH test. We obtained simple estimates of effect size from the other tests and reported both the simple proportions of success **for** the binary outcomes and prevalence odds ratios obtained from logistic regression.

An extended treatment window of up to 24 hours after **stroke** onset will have a number of implications. Thrombolytics have a proven treatment window of 3 hours,[3] although it may be that effectiveness **for** this **for**m of **therapy** extends out somewhat further.[21,22]

The first neuroprotective trial to show efficacy was the study of NXY-059.[23] That study had a 6-hour treatment window, but a majority of patients were treated within 4 hours. It is a reasonable contention that the reason the NXY-059 study was successful, whereas all the previous neuroprotective therapies were not, was that the average time to treatment was kept so low. NEST-1 had a 24-hour treatment window and a much longer time to treatment (median 18 hours) than nearly all other clinical trials to date **for** the treatment of acute **ischemic stroke**. A major problem **for** treatment of **stroke**s has been that large numbers of patients present after 6 hours. There**for**e, an expanded treatment window of 24 hours would make it possible to treat many more **ischemic stroke** victims.

Although the mechanism of action of **infrared laser therapy for stroke** is not completely understood, a number of effects of this type of irradiation have been documented. **Infrared laser therapy** is a physical process that can produce biochemical changes at the tissue level. The putative mechanism **for** NTS treatment involves stimulation of ATP **for**mation by mitochondria and may also involve prevention of apoptosis in the **ischemic** penumbra and enhancement of neurorecovery mechanisms. An example of another physical process that reduces neurological damage is hypothermia. In animal model studies, there are few, if any, therapies, that have been shown as consistently to reduce **stroke**-related damage as hypothermia. What is clear is that **infrared** irradiation is probably delivering its effect independent of restoration of blood flow and the mechanism is probably related to an improved energy metabolism and enhanced cell viability.[5,14]

Other advantages of this **for**m of **therapy** are that treatment can be started rapidly, without any need **for** preliminary laboratory testing, invasive procedures, or extensive training of the clinicians who administer the treatment. Furthermore, it is not necessary to know the location of the vascular occlusion to administer the NTS treatment. Thus, this **for**m of **therapy** is likely to require much less infrastructure than virtually all other types of devices and medical therapies available to date **for** acute **stroke** treatment or clot removal.

Conclusion
Although the the NEST-1 study results are encouraging, and may indicate that **infrared laser therapy** has potential to become a treatment of **ischemic stroke** in humans when initiated within 24 hours of **stroke** onset, a larger confirmatory trial to demonstrate safety and effectiveness is warranted.

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