Randomized, Open-Label, Phase 1/2a Study to Determine the Maximum Tolerated Dose of Intraventricular Sustained Release Nimodipine for Subarachnoid Hemorrhage (NEWTON [Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage])

Daniel Hägggi, MD; Nima Etminan, MD; Francois Aldrich, MD; Hans Jakob Steiger, MD; Stephan A. Mayer, MD; Michael N. Diringer, MD; Brian L. Hoh, MD; J Mocco, MD; Herbert J. Faleck, DO; R. Loch Macdonald, MD; on behalf of the NEWTON Investigators

**Background and Purpose**—We conducted a randomized, open-label, phase 1/2a, dose-escalation study of intraventricular sustained-release nimodipine (EG-1962) to determine safety, tolerability, pharmacokinetics, and clinical effects in aneurysmal subarachnoid hemorrhage.

**Methods**—Subjects with aneurysmal subarachnoid hemorrhage repaired by clipping or coiling were randomized to EG-1962 or enteral nimodipine. Subjects were World Federation of Neurological Surgeons grade 2 to 4 and had an external ventricular drain. Cohorts of 12 subjects received 100 to 1200 mg EG-1962 (9 per cohort) or enteral nimodipine (3 per cohort). The primary objective was to determine the maximum tolerated dose.

**Results**—Fifty-four subjects in North America were randomized to EG-1962, and 18 subjects were randomized to enteral nimodipine. The maximum tolerated dose was 800 mg. One serious adverse event related to EG-1962 (400 mg) and 2 EG-1962 dose-limiting toxicities were without clinical sequelae. There was no EG-1962-related hypotension compared with 17% (3/18) with enteral nimodipine. Favorable outcome at 90 days on the extended Glasgow outcome scale occurred in 27/45 (60%, 95% confidence interval 46%–74%) EG-1962 subjects (5/9 with 100, 6/9 with 200, 7/9 with 400, 4/9 with 600, and 5/9 with 800 mg) and 5/18 (28%, 95% confidence interval 7%–48%, relative risk reduction of unfavorable outcome; 1.45, 95% confidence interval 1.04–2.03; \( P = 0.027 \)) enteral nimodipine subjects. EG-1962 reduced delayed cerebral ischemia (14/45 [31%] EG-1962 versus 11/18 [61%] enteral nimodipine) and rescue therapy (11/45 [24%] versus 10/18 [56%]).

**Conclusions**—EG-1962 was safe and tolerable to 800 mg, and in this, aneurysmal subarachnoid hemorrhage population was associated with reduced delayed cerebral ischemia and rescue therapy. Overall, the rate of favorable clinical outcome was greater in the EG-1962-treated group.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01893190.

(Stroke. 2017;48:145-151. DOI: 10.1161/STROKEAHA.116.014250.)

**Key Words:** brain ischemia ▪ hypotension ▪ nimodipine ▪ subarachnoid hemorrhage ▪ sustained release formulation

Nimodipine is used throughout the world to improve outcome after aneurysmal subarachnoid hemorrhage (aSAH). Its use, however, is limited by systemic hypotension that occurs in ≤56% of patients. Plasma concentrations can exceed those associated with hypotension, yet cerebrospinal fluid (CSF) concentrations remain below the optimal...
therapeutic threshold. Hypotension is deleterious to patients with aSAH because it lowers cerebral blood flow and cerebral perfusion pressure and worsens delayed cerebral ischemia (DCI). We hypothesized that EG-1962 (nimodipine in a biodegradable polymer suspended in hyaluronic acid administered as one intraventricular injection that releases nimodipine into the subarachnoid space for at least 21 days) would increase efficacy and reduce systemic side effects compared with enteral nimodipine. We performed a randomized, controlled, dose-escalation study to determine the safety, maximum tolerable dose (MTD), pharmacokinetics, and clinical effects of EG-1962 in humans (NEWTON [Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage]).

Methods

Study Design and Subjects

Subjects were randomized at 20 neurosurgical centers in the United States and Canada (online-only Data Supplement). The protocol was written by the authors, and the study was approved by institutional review boards. The protocol and written informed consent procedure are published (http://www.clinicaltrials.gov). Unique identifier: NCT01893190. Key inclusion criteria were World Federation of Neurological Surgeons (WFNS) grade 2 to 4 subjects with an external ventricular drain (EVD) inserted as standard of care and a ruptured aneurysm repaired by clipping or coiling. After the first cohort was entered, the inclusion criteria were amended to increase the time from aSAH to study drug administration from 48 to 60 hours to facilitate recruitment. The rationale was that in the first cohort, plasma pharmacokinetics showed a rapid increase in plasma nimodipine concentrations within 24 hours of administration of EG-1962. Nimodipine is approved to reduce DCI after SAH, and this occurs 3 to 14 days after SAH. The approval says to start nimodipine within 4 days of SAH. Therefore, we thought it would be safe to increase the inclusion time to 60 hours. There was no reason to think this would affect the assessment of the MTD. The second cohort was administered EG-1962, 200 mg. The study was to include a dose-escalation period followed by a treatment period (Figure I in the online-only Data Supplement). The primary objective of the dose-escalation period was to determine the MTD of EG-1962 and of the treatment period to further determine the safety and tolerability of the selected dose of EG-1962 compared with enteral nimodipine. The treatment period was not conducted based on the following. There were only 2 dose-limiting toxicities (DLT) spread among 2 different dose groups, and the number of serious adverse events (SAE) among the dose groups did not seem to have any dependence on dose. Favorable responses did not exhibit a dose–response, in that the rate was already high at the 100 mg dose. The dose–response relationship was assessed by visual inspection of the outcomes by cohort and by e-max and logistic regression models adjusting for WFNS grade and age (dichotomized). Finally, with the exception of the doses for cohort 1 (100 mg) and cohort 6 (1200 mg), the EG-1962 dose to be administered in cohorts 2, 3, 4, and 5 could be modified based on the data safety monitoring committee recommendation. Safety and DLT information was reported by the investigators up until day 90. The MTD was reached if ≥2 subjects receiving EG-1962 had a DLT or if the 1200 mg dose was reached. Management of subjects, DLT, and adverse events was outlined in the protocol and followed guidelines for management of aSAH.

Statistical Analysis

Cohort size estimates were based on the analysis of published aSAH data and supported a dose-escalation scheme with 9 EG-1962 and 3 enteral nimodipine subjects per cohort. The safety data set (all subjects randomized who received EG-1962 or enteral nimodipine and were assessed for safety at least once) included 72 subjects. Exploratory outcomes were based on a modified intent to treat (all subjects who were included in the safety analysis set and who had GOSE assessments at day 30 or 90). The modified intent to treat set included 1200 mg EG-1962 subjects because this dose was above the MTD. Only 3 subjects received the full dose, and some also received enteral nimodipine, which renders outcomes uninterpretable.

Demographics and safety data are reported as descriptive statistics (means, standard deviation). The first exploratory end point was the GOSE, analyzed as a dichotomous outcome (favorable outcome 6–8 and unfavorable outcome 1–5). This cut point was based on analysis of existing data. The GOSE was compared between subjects in all cohorts combined randomized to enteral nimodipine and those randomized to each of the EG-1962 dose groups and to the combined EG-1962 group. The prespecified analysis used Fisher exact test and the Cochran Mantel Haenszel test adjusted by WFNS grade (dichotomized as <60 or ≥60) because these are important admission prognostic factors for outcome and to adjust for differences between cohorts in WFNS grade and age. Exact 95% (2-sided) confidence intervals (CI) for proportions and approximate 95% CI were used for relative risk ratios. Missing day-90 outcome was scored as the day-30 outcome. We assessed interactions of study group with WFNS grade and age, though the power is limited by the small sample size. Analysis was in SAS (version 9.2) and STATA (version 14.0).
Results

Nine hundred and ninety-eight patients were prescreened (Figure 1 in the online-only Data Supplement). Seventy-two subjects completed the North American study between October 28, 2013, and July 31, 2015; 54 subjects were randomized to EG-1962 and 18 to enteral nimodipine (Figure 1). Demographics and baseline characteristics were consistent with patients with aSAH (Table 1).

No safety concerns limited dose escalation to 1200 mg. The maximum tolerated dose was 800 mg; 1200 mg was not tolerable because of the injection volume. Two DLT were reported, one each in cohort 3 (400 mg) and cohort 5 (800 mg). Both were elevated intracranial pressure (ICP). Elevated ICP was considered a DLT if ICP was >30 mm Hg compared with the ICP recorded just prior to the administration of EG-1962 within 24 hours after EG-1962 administration and lasting over 4 hours despite appropriate therapy. In one case, the increased ICP was not associated with neurological deterioration, and the subject had a day-90 GOSE of upper moderate disability (favorable outcome). In the second case, there was transient neurological deterioration starting 13.5 hours after administration of EG-1962. The subject had a GOSE of lower good recovery (favorable outcome) at day 90.

There were 3 deaths (6%) in the EG-1962-treated subjects (2 in the 200 mg cohort and 1 in the 800 mg cohort) and 1 death (6%) in the enteral nimodipine group (in the 1200 mg cohort). None of these deaths were considered by the investigator to be related to study drug, and all were a consequence of the initial brain injury from the aSAH, rebleeding, and withdrawal of care.

Through and including cohort 6 (1200 mg), 30 of 54 (56%) subjects treated with EG-1962 and 13 of 18 (72%) subjects treated with enteral nimodipine were reported to have treatment-emergent SAE (Table 2). Central nervous system events, including cerebral vasoconstriction, DCI, cerebral infarction, and intracranial hemorrhage, were all more frequent in the enteral nimodipine group (Table 2).

The overall incidence of study medication–related adverse events was similar between the EG-1962 (12 [22%] with 13 events) and enteral nimodipine groups (4 [22%] with 4 events). Three of the 4 adverse events related to enteral nimodipine were hypotension. Favorable outcome occurred in 1 of 4 of these subjects. In the EG-1962 treatment group, 9 of 12 study medication–related adverse events were increased ICP within 24 hours of administration of EG-1962. Two were EVD malfunctions, and 1 was a possible transient allergic reaction with no clinical sequelae. Favorable outcome occurred in 9 of 12 (75%) of these subjects. In the EG-1962-treated subjects, 1 SAE was considered by the investigator to be related to EG-1962 (possible transient allergic reaction with no clinical sequelae).

The occurrence of increased ICP was not dose related. The overall incidence of increased ICP was similar between the EG-1962 (16/54, 30%) and enteral nimodipine (7/18, 39%) groups as was the rate reported as SAE (7% and 6% for the EG-1962 and enteral nimodipine groups, respectively). In the EG-1962 group, 12/13 (92%) subjects with increased ICP had a favorable outcome on the GOSE compared with 2/7 (29%) subjects in the enteral nimodipine group. Thirteen of 54 (24%) subjects had increased ICP within 24 hours of administration of EG-1962; 10 (77%) subjects had a favorable outcome.
In the enteral nimodipine group, 3/18 (17%) subjects experienced increased ICP within 24 hours of randomization; 1 (33%) had a favorable outcome. In the EG-1962-treated group, 6/54 (11%) subjects experienced increased ICP after 24 hours; 3 (50%) had a favorable outcome. In the enteral nimodipine group, 4/18 (22%) subjects experienced late increased ICP; 1 (25%) had a favorable outcome.

There were 5 cases of CSF culture–positive ventriculitis/meningitis in subjects treated with EG-1962 (5/54, 9%) and none in those treated with enteral nimodipine. There were 3 in cohort 2 (200 mg EG-1962) and 2 in cohort 6 (1200 mg). None were considered related to EG-1962. The day-90 outcomes were favorable in 2/3 (67%) subjects who received 200 mg and in 2/2 (100%) subjects who received 1200 mg.

There was a higher incidence of hypotension reported in the enteral nimodipine group (6/18, 33%) than in the EG-1962 group (3/54, 6%). In the enteral nimodipine group, 3 of 6 events of hypotension were reported as related to treatment, whereas in the EG-1962 group, no hypotension was considered related. There were no other clinically important imbalances in adverse events in other organ systems.

The percent of subjects from cohorts 1 to 5 who achieved a favorable clinical outcome was greater in the EG-1962 group (60%, 27/45; 95% CI 46%–74%) compared with that in the enteral nimodipine group (28%, 5/18; 95% CI 7%–48%, relative risk reduction of unfavorable outcome; 1.45, 95% CI 1.04–2.03, \( P=0.027 \), not adjusted for multiplicity, Fisher exact test). In cohort 6, 67% of 3 subjects who received the full 1200

Table 1. Subject Demographics

| Variable          | Enteral Nimodipine | EG-1962 |
|-------------------|--------------------|---------|
|                   | 100 mg 200 mg 400 mg 600 mg 800 mg 1200 mg All EG-1962 |
| Age               | 56±10 (18) 64±10 (9) 54±10 (9) 49±14 (9) 56±12 (9) 52±11 (9) 54±11 (9) 55±12 (54) |
| Male              | 5 (28) 1 (11) 3 (33) 5 (56) 6 (67) 7 (78) 2 (22) 24 (44) |
| WFNS grade        |                    |         |
| Grade 2           | 5 (28) 3 (33) 4 (44) 7 (78) 2 (22) 3 (33) 6 (67) 25 (46) |
| Grade 3           | 2 (11) 2 (22) 0 1 (11) 0 2 (22) 0 5 (9) |
| Grade 4           | 11 (61) 4 (44) 5 (56) 1 (11) 7 (78) 4 (44) 3 (33) 24 (44) |
| Modified Fisher scale* |
| Grade 2           | 2 (11) 2 (22) 2 (22) 1 (11) 3 (33) 2 (22) 2 (22) 12 (24) |
| Grade 3           | 5 (28) 2 (22) 1 (11) 3 (33) 0 3 (33) 2 (22) 11 (22) |
| Grade 4           | 11 (61) 4 (44) 5 (56) 4 (44) 6 (67) 4 (44) 5 (56) 28 (55) |
| Aneurysm clipping | 12 (67) 3 (33) 7 (78) 3 (33) 5 (56) 5 (56) 4 (44) 27 (50) |

Values are means±standard error of the mean (n) or n (%). WFNS indicates World Federation of Neurological Surgeons.

*Fisher scale missing on 2 subjects (one in the 100 mg cohort and one in the 200 mg cohort); one subject in the 400 mg cohort had a score of 1.

Table 2. Adverse Events

| Event                        | Enteral Nimodipine | EG-1962 |
|------------------------------|--------------------|---------|
| Subjects with ≥1 treatment-emergent adverse event | 18 (100) 9 (100) 9 (100) 9 (100) 9 (100) 9 (100) 9 (100) 9 (100) 54 (100) |
| Number of adverse events     | 5 (28) 1 (11) 3 (33) 5 (56) 6 (67) 7 (78) 2 (22) 24 (44) |
| Suspected related to study drug | 4 (22) 0 (0) 0 (0) 3 (33) 1 (11) 5 (56) 3 (33) 12 (22) |
| Serious adverse events (including deaths) | 13 (72) 5 (56) 5 (56) 6 (67) 3 (33) 6 (67) 5 (56) 30 (56) |
| Hypotension related to study drug | 3 (17) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) |
| Ventriculitis/meningitis      | 0 (0) 0 (0) 3 (33) 0 (0) 0 (0) 0 (0) 2 (22) 5 (9) |
| Cerebral vasoconstriction/delayed cerebral ischemia | 11 (61) 5 (56) 2 (22) 4 (44) 2 (22) 2 (22) 5 (56) 20 (37) |
| Hydrocephalus                 | 3 (17) 2 (22) 2 (22) 1 (11) 2 (22) 3 (33) 3 (33) 13 (24) |
| Intracranial pressure increased at any time | 7 (40) 3 (33) 0 (0) 4 (44) 1 (11) 5 (56) 3 (33) 16 (31) |
| Any intracranial hemorrhage   | 3 (17) 0 (0) 1 (11) 1 (11) 1 (11) 0 (0) 0 (0) 3 (6) |
| Any cerebral infarction       | 3 (17) 3 (33) 1 (11) 0 (0) 0 (0) 1 (11) 0 (0) 5 (9) |

Values are n (%).
mg dose had favorable outcome. Furthermore, 29% (13/45) of subjects treated with EG-1962 had GOSE scores of upper good recovery, whereas 6% (1/18) of the subjects treated with standard-of-care enteral nimodipine achieved that result. All doses yielded higher rates of favorable outcomes compared with that of enteral nimodipine with no dose relationship apparent (Figure 2).

Favorable outcome for subjects treated with EG-1962 compared with those treated with enteral nimodipine was more likely both for subjects with WFNS 2 (89% versus 40%) and for subjects with WFNS 4 (43% versus 27%; Table 3). Exploratory analysis of the NEWTON data confirmed existing literature that the most important prognostic factors for outcome were WFNS grade and age. There were few WFNS grade 3 subjects, and the most optimal grouping for WFNS grade 2 was versus 3+4. Age was analyzed as a dichotomous variable, with the cut point selected based on prior prognostic modeling and at a point producing similar numbers of subjects in each category (<60 or ≥60 years old). The pooled relative risk reduction for favorable outcome for all EG-1962 subjects versus enteral nimodipine subjects, adjusting for WFNS grade and age, was 1.84 (95% CI 0.88–3.85; Cochran Mantel Haenszel test). For each dose cohort of EG-1962 compared with enteral nimodipine, controlling for WFNS grade and age, the relative risk reduction, adjusted for WFNS grade and age, was 1.46 (95% CI 0.97–2.20; Cochran Mantel Haenszel test). There were no interactions between treatment group and WFNS grade (2 versus 3+4) or age.

Treatment with EG-1962 at 200 mg or more was associated with less angiographic vasospasm/DCI, infarction because of DCI, and use of rescue therapy compared with enteral nimodipine (Figure 3). Subjects who did develop angiographic vasospasm or DCI were more likely to have favorable outcome if they were treated with EG-1962 (53%) compared with enteral nimodipine (18%).

**Discussion**

Nimodipine was developed to reduce angiographic vasospasm after aSAH. At tolerable doses, there was minimal effect on angiographic vasospasm. Current theory is that multiple processes contribute to DCI and delayed infarction, including angiographic vasospasm, cortical spreading ischemia, microthromboembolism, loss of autoregulation, and capillary transit time heterogeneity. Nimodipine may have improved outcome because it inhibits these deleterious processes, but at tolerable doses has only a small effect on the most widely measured process (angiographic vasospasm). Evidence consistent with this is that at some doses, nimodipine and other dihydropyridines reduce angiographic vasospasm, cortical spreading ischemia, and microthromboembolism. Nimodipine may have improved outcome because it inhibits these deleterious processes, but at tolerable doses has only a small effect on the most widely measured process (angiographic vasospasm). NEWTON tested the hypothesis that intracranial delivery of EG-1962, which achieved high and sustained CSF concentrations in preclinical studies, would increase efficacy without compromising safety.

The NEWTON study objectives were met. The MTD was determined to be 800 mg because the volume of the 1200 mg injection (12 mL) was not tolerable as a single injection. The only DLT were episodes of transient increased ICP after injection of EG-1962. One SAE, a possible allergic reaction that had no clinical sequelae, was reported as possibly related to EG-1962. EG-1962 was safe with the same or lower risk of central nervous system events such as hemorrhage compared with enteral nimodipine. As hypothesized, no EG-1962-related hypotension occurred, whereas 17% (3/18) of subjects in the enteral nimodipine group experienced dose-limiting hypotension. Meningitis and ventriculitis were the only adverse events more common in the EG-1962 group (5/54, 9%). We attribute this in part to the protocol requesting repeated sampling of CSF for nimodipine pharmacokinetics. This infection rate is comparable to analysis of 33 studies with 9667 cases from the literature that found a pooled infection incidence of 8%. This study allowed for institutional practice to be followed for EVD insertion. There was no study-mandated protocol for EVD insertion. Future studies

**Table 3. Extended Glasgow Outcome Scale by WFNS Grade**

| WFNS | Cohorts 1 to 5 | Enteral Nimodipine |
|------|----------------|-------------------|
|      | EG-1962        |                  |
|      | N   | Favorable Outcome | N   | Favorable Outcome |
| 2    | 19  | 17 (89)          | 5   | 2 (40)           |
| 3    | 5   | 1 (20)           | 2   | 0 (0)            |
| 4    | 21  | 9 (43)           | 11  | 3 (27)           |
| 3+4  | 26  | 10 (38)          | 13  | 3 (23)           |
| Total| 45  | 27 (60)          | 18  | 5 (28)           |

Values are n (%). The 30-day outcome was carried forwards for 3 subjects (200 mg cohort, WFNS grade 2, favorable outcome; 400 mg cohort, WFNS grade 2, unfavorable outcome; 600 mg cohort, WFNS grade 2, favorable outcome [this subject also had favorable outcome at 120 days]). WFNS indicates World Federation of Neurological Surgeons.
of EG-1962 will mitigate the risk of infection by requiring adherence to protocols for EVD insertion and intraventricular injection and by not obtaining CSF samples unless clinically indicated.31,32

Treatment with EG-1962 was associated with improved outcome on the GOSE, an effect that was robust over different WFNS grades (Table 3). Furthermore, EG-1962 subjects had reduction in angiographic vasospasm, DCI, and need for rescue therapy. Favorable response rates were greater than control at all doses, with no obvious dose relationship. The lack of dose–response is consistent with randomized trials of enteral nimodipine that showed similar outcomes with doses of 30 to 90 mg nimodipine every 4 hours for 21 days.3,4,23 Furthermore, studies of drugs targeting central nervous system disorders frequently do not demonstrate strong dose–responses and have wide ranges of recommended doses.

Limitations of this study include that the number of subjects treated was small, it was unblinded, and we used a modified intent–to-treat analysis for the clinical outcome. There were differences between cohorts in numbers of subjects at baseline with different WFNS grades, which was anticipated and adjusted for in the statistical analysis. Finally, subjects randomized represent a select population of SAH patients. Whether similar results could be obtained by administering EG-1962 by lumbar injection or whether an EVD could be indicated for the primary purpose of administering EG-1962 cannot be determined at this time.

**Summary**

Intraventricular EG-1962 was safe and tolerable to 800 mg and, in this aSAH population, was associated with reduced DCI and use of rescue therapy. Overall, the rate of favorable outcome was greater in the EG-1962-treated group. A pivotal phase 3, double-blind, double-dummy, randomized clinical study of EG-1962 compared with enteral nimodipine has been started.

**Figure 3.** Effect of EG-1962 and enteral nimodipine on angiographic vasospasm, delayed cerebral ischemia, delayed infarction, and rescue therapy. Numbers are number of subjects with the specified outcome for each cohort (n=9) and enteral nimodipine (n=18).

**Acknowledgments**

We thank Integrated Medical Development, LLC, for statistical and study support.

**Sources of Funding**

The study was funded by Edge Therapeutics, Inc.

**Disclosures**

Dr Macdonald receives grant support from the Physicians Services Incorporated Foundation, Brain Aneurysm Foundation, Canadian Institutes for Health Research, and the Heart and Stroke Foundation of Canada and is an employee and Chief Scientific Officer of Edge Therapeutics, Inc. Drs Hänggi, Emtnian, Aldrich, Mayer, Diringer, Hoh, and Mocco receive consulting fees from Edge Therapeutics, Inc, for serving on the steering committee for this trial and for advising Edge Therapeutics, Inc. Drs Mayer and Aldrich are consultants and receive consulting fees from Actelion Pharmaceuticals, Ltd. Dr Faleck is an employee of Edge Therapeutics, Inc. Dr Steiger reports no conflicts.

**References**

1. Dorhout Mees SM, Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev. 2007:CD000277.

2. Sandow N, Diesing D, Sarrafzadeh A, Vajkoczy P, Wolf S. Nimodipine dose reductions in the treatment of patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2016;25:29–39. doi: 10.1007/s12028-015-0230-x.

3. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, et al. Cerebral arterial spasm–a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med. 1983;308:619–624. doi: 10.1056/NEJM198303173081103.

4. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg. 1988;68:505–517. doi: 10.3171/jns.1988.68.4.0505.

5. Dankbaar JW, Slooter AJ, Rinkel GJ, Schaeff IC. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: a systematic review. Crit Care. 2010;14:R23. doi: 10.1186/cc8886.

6. Kasuya H, Onda H, Takeshita M, Okada Y, Hori T. Efficacy and safety of nicardipine prolonged-release implants for preventing vasospasm in humans. Stroke. 2002;33:1011–1015.
Hänggi et al

Intraventricular Nimodipine for SAH

7. Hänggi D, Etminan N, Macdonald RL, Steiger HJ, Mayer SA, Aldrich F, et al. NEWTON: Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage. *Neurocrit Care*. 2015;23:274–284. doi: 10.1007/s12028-015-0112-2.

8. Hänggi D, Etminan N, Steiger HJ, Johnson M, Peet MM, Tice T, et al. A site-specific, sustained-release drug delivery system for aneurysmal subarachnoid hemorrhage. *Neurotherapeutics*. 2016;13:439–449. doi: 10.1007/s13111-016-0424-8.

9. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391–2395. doi: 10.1161/STROKEAHA.110.589275.

10. Brandt J, Spencer M, Folstein M. The telephone interval for cognitive status. *Neuropsychiatr Neuropsychol Behav Neurol*. 1988;1:111–117.

11. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma*. 1998;15:573–585. doi: 10.1089/ neu.1998.15.573.

12. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J*. 1965;14:61–65.

13. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695–699. doi: 10.1111/j.1532-5415.2005.53221.x.

14. Brot T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864–870.

15. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604–607.

16. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103–115.

17. Jaja BN, Cusimano MD, Etminan N, Hanggi D, Hasan D, Hodgiewe D, et al. Clinical prediction models for aneurysmal subarachnoid hemorrhage: a systematic review. *Neurocrit Care*. 2013;18:143–153. doi: 10.1007/s12028-012-9792-z.

18. Jaja BN, Lingsma H, Schweizer TA, Thorpe KE, Steyerberg EW, Macdonald RL; SAHIT collaboration. Prognostic value of premorbidity hypertension and neurological status in aneurysmal subarachnoid hemorrhage: pooled analyses of individual patient data in the SAHIT repository. *J Neurosurg*. 2015;122:644–652. doi: 10.3171/2014.10. JNS132694.

19. Diringer MN, Bleck TP, Hemphill CJ III, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the neurocritical care society’s multi-disciplinary consensus conference. *Neurocrit Care*. 2011;15:211–240.

20. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke*. 2012;43:1711–1737. doi: 10.1161/STR.0b013e3182587839.

21. Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke*. 2007;38:2315–2321. doi: 10.1161/STROKEAHA.107.484360.

22. Sciarabine A, Schuurman T, Traber J. Pharmacological basis for the use of nimodipine in central nervous system disorders. *FASEB J*. 1989;3:1799–1806.

23. Packard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ*. 1989;298:636–642.

24. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. *Nat Rev Neurol*. 2014;10:44–58. doi: 10.1038/nrneurol.2013.246.

25. Dreier JP, Major S, Manning A, Wotizik J, Drenckhahn C, Steinbrink J, et al; COSBID study group. Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. *Brain*. 2009;132(Pt 7):1866–1881. doi: 10.1093/brain/ awp102.

26. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, et al. Impairment of cerebral autoregulation predicts delayed cerebral ischaemia after subarachnoid hemorrhage: a prospective observational study. *Stroke*. 2012;43:3230–3237. doi: 10.1161/ STROKEAHA.112.669788.

27. Østergaard L, Aamand R, Karabegovic S, Tietze A, Blicher JU, Mikkelsen IK, et al. The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. 2013;33:1825–1837. doi: 10.1038/jcbfm.2013.173.

28. Dreier JP, Windmüller O, Petzold G, Lindauer U, Einhäupl KM, Dirnagl U. Ischaemia triggered by red blood cell products in the subarachnoid space is inhibited by nimodipine administration or moderate volume expansion/hemodilution in rats. *Neurosurgery*. 2002;51:1457–1465; discussion 1465.

29. Barth M, Capelle HH, Weidauer S, Weiss C, Münch E, Thomé C, et al. Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: a prospective, randomized, double-blind phase IIa trial. *Neurosurgery*. 2010;66:186–194. doi: 10.1227/01.NEU.0000348801.74596.0f.

30. Vergouwen MD, Vermeulen M, de Haan RJ, Levi M, Roos YB. Dihydropyridine calcium antagonists increase fibrinolytic activity: a systematic review. *J Cereb Blood Flow Metab*. 2007;27:1293–1308. doi: 10.1038/sj.jcbfm.9600431.

31. Dey M, Stadnik A, Riad F, Zhang L, McBee N, Kase C, et al; CLEAR III Trial Investigators. Bleeding and infection with external ventricular drainage: a systematic review in comparison with adjudicated adverse events in the ongoing Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III (CLEAR-III IVH) trial. *Neurology*. 2015;84:291–300; discussion 301. doi: 10.1227/ NEU.0000000000000624.

32. Naff N, Williams MA, Koyal PM, Tuhrim S, Bullock MR, Mayer SA, et al. Low-dose recombinant tissue-type plasminogen activator enhances clot resolution in brain hemorrhage: the intraventricular hemorrhage thrombolysis trial. *Stroke*. 2011;42:3009–3016. doi: 10.1161/ STROKEAHA.110.610949.
Randomized, Open-Label, Phase 1/2a Study to Determine the Maximum Tolerated Dose of Intraventricular Sustained Release Nimodipine for Subarachnoid Hemorrhage (NEWTON [Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage])

Daniel Hänggi, Nima Etminan, Francois Aldrich, Hans Jakob Steiger, Stephan A. Mayer, Michael N. Diringer, Brian L. Hoh, J Mocco, Herbert J. Faleck and R. Loch Macdonald on behalf of the NEWTON Investigators

Stroke. 2017;48:145-151; originally published online December 8, 2016; doi: 10.1161/STROKEAHA.116.014250

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/48/1/145
Free via Open Access

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/12/09/STROKEAHA.116.014250.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
ONLINE SUPPLEMENT

List of sites and investigators.

| Site                                                        | Investigator                                                                 |
|-------------------------------------------------------------|------------------------------------------------------------------------------|
| University of Cincinnati, Cincinnati, Ohio, USA             | Mario Zuccarello, M.D., Todd Abruzzo, M.D., Lynn Money                       |
| Columbia University, New York, New York, USA                | Jan Claassen, M.D., Cristina Falo, Ph.D.                                     |
| University of Maryland, Baltimore, Maryland, USA            | Francois Aldrich, M.D., Charlene Aldrich                                    |
| Cleveland Clinic, Cleveland, Ohio, USA                      | Jennifer Frontera, M.D., Peter Rasmussen, M.D., Javier, Provencio, M.D., Joao Gomes, M.D., Moneen McBride, Erin Bynum |
| University of New Mexico, Albuquerque, New Mexico, USA      | Andrew Carlson, M.D., Howard Yonas, M.D., Brittany Burlbaw, Theresa Wussow   |
| Duke University, Durham, North Carolina, USA                | Carmen Graffagnino, M.D., Kristina Riemen                                   |
| Medical University of South Carolina, Charleston, South Carolina, USA | Raymond Turner, M.D., Adrian Parker, Emily Young                            |
| University of California, Los Angeles, California, USA      | Paul Vespa, M.D., Courtney Real                                              |
| Overlook Medical Center, Summit, New Jersey, USA            | Robert Felberg, M.D., Igor Ugorec, M.D., Caroline Panter, Olivia Joy Eboras  |
| St. Joseph’s Hospital, Phoenix, Arizona, USA                | Joseph Zabramski, M.D., Jean Lopez, Mary                                    |
| Institution                                           | Authors                                      |
|-------------------------------------------------------|----------------------------------------------|
| Hackensack University Medical Center, Hackensack, New Jersey, USA | Daniel Walzman, M.D., Jana Tancredi          |
| St. Michael’s Hospital, Toronto, Ontario, Canada       | Julian Spears, M.D., Marlene Santos, Ph.D.   |
| University of Calgary, Calgary, Alberta, Canada        | John Wong, M.D., Teri Steward, Karla Ryckborst |
| University of Alberta, Edmonton, Alberta, Canada       | Tim Darsaut, M.D., Brenda Poworoznik          |
| Royal University Hospital, Saskatoon, Saskatchewan, Canada | Michael Kelly, M.D., Ruth Whelan              |
| Oregon Health Sciences Center, Portland, Oregon, USA    | Wayne Clark, M.D., Hormozd Bozorgchami, M.D., Darren Larsen, Monica Dolan |
| University Health Network, Toronto, Ontario, Canada    | Michael Tymianski, M.D., Ph.D., Alex Kostynsky |
| Mount Sinai Medical Center, New York, New York, USA     | Erol Gordon, M.D., Stephen Griffiths          |
| Rush University Medical Center, Chicago, Illinois, USA  | George Lopez, M.D., Josephine Volgi           |
| North Shore Long Island Jewish Health System Lenox Hill Hospital, New York, New York, USA | John Boockvar, M.D., Michelle DeWitt          |
Supplemental Figure I: Diagram of the 2 parts, or dose-escalation and treatment parts of the study (top) and the 3 periods, or screening, treatment and follow-up, through which each patient was followed
PART 1
Dose-escalation part
Doses between 100 and 1200 mg subject to modification based on dose limiting toxicities and data monitoring committee recommendations

Dose level/ cohort:

1. EG-1962 100 mg (n=9)
   Enteral nimodipine (n=3)

2. EG-1962 200 mg (n=9)
   Enteral nimodipine (n=3)

3. EG-1962 400 mg (n=9)
   Enteral nimodipine (n=3)

4. EG-1962 600 mg (n=9)
   Enteral nimodipine (n=3)

5. EG-1962 800 mg (n=9)
   Enteral nimodipine (n=3)

6. EG-1962 1200 mg (n=9)
   Enteral nimodipine (n=3)

Maximum tolerated dose of EG-1962 established

Interim analysis of Part 1 for sample size estimation for Part 2

PART 2
Treatment part

7. Enrollment at selected dose of EG-1962 (n=[96-part 1]/2)
   Enteral nimodipine (n=[96-part 1]/2)