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ORIGINAL ARTICLE

Clinical Trial Protocol: Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study Comparing EG-1962 to Standard of Care Oral Nimodipine in Adults with Aneurysmal Subarachnoid Hemorrhage [NEWTON-2 (Nimodipine Microparticles to Enhance Recovery While Reducing TOxicity After SubarachNoid Hemorrhage)]

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Abstract

Background: Nimodipine is the only drug approved in the treatment of aneurysmal subarachnoid hemorrhage (aSAH) in many countries. EG-1962, a product developed using the Precisa™ platform, is an extended-release microparticle formulation of nimodipine that can be administered intraventricularly or intracisternally. It was developed to test the hypothesis that delivering higher concentrations of extended-release nimodipine directly to the cerebrospinal fluid would provide superior efficacy compared to systemic administration.

Results: A Phase 1/2a multicenter, controlled, randomized, open-label, dose-escalation study determined the maximum tolerated dose and supported the safety and tolerability of EG-1962 in patients with aSAH. EG-1962, 600 mg, was selected for a pivotal, Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy, and safety study comparing it to standard of care oral nimodipine in adults with aSAH. Key inclusion criteria are patients with a ruptured saccular aneurysm repaired by clipping or coiling, World Federation of Neurological Surgeons grade 2–4, and modified Fisher score of > 1. Patients must have an external ventricular drain as part of standard of

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care. Patients are randomized to receive intraventricular investigational product (EG-1962 or NaCl solution) and an oral placebo or oral nimodipine in the approved dose regimen (active control) within 48 h of aSAH. The primary objective is to determine the efficacy of EG-1962 compared to oral nimodipine.

Conclusions: The primary endpoint is the proportion of subjects with favorable outcome (6–8) on the Extended Glasgow Outcome Scale assessed 90 days after aSAH. The secondary endpoint is the proportion of subjects with favorable outcome on the Montreal Cognitive Assessment 90 days after aSAH. Data on safety, rescue therapy, delayed cerebral infarction, and health economics will be collected.

Trail registration NCT02790632.

Keywords: Cerebral aneurysm, Clinical trial, Delayed cerebral ischemia, Extended release, Nimodipine, Subarachnoid hemorrhage, aSAH

Introduction

This report follows Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [1]. The only drug approved in North America, the European Union, and many other countries to improve outcome of patients with aneurysmal subarachnoid hemorrhage (aSAH) is the L-type dihydropyridine calcium channel antagonist nimodipine. It is administered orally as capsules or a liquid solution in the United States (USA), as tablets in Canada and as an intravenous solution and tablets in Europe. Randomized clinical trials of nimodipine demonstrated efficacy, mainly based on oral nimodipine [2]. Nevertheless, there is room for improvement in outcome of patients with aSAH. Twenty-six percent of patients with aSAH still die, 55% remain dependent, and only 19% regain independence [3]. We hypothesized that higher concentrations of nimodipine in the cerebrospinal fluid could increase the efficacy of nimodipine. This cannot be achieved with systemic administration because hypotension limits nimodipine administration. Furthermore, bioavailability of oral nimodipine is variable and frequently poor, and compliance with the dose regimen is difficult to achieve [4, 5]. Edge Therapeutics developed EG-1962 (nimodipine in a biodegradable polymer suspended in sodium hyaluronate administered as one intraventricular injection which releases nimodipine into the subarachnoid space for at least 21 days) and tested the hypothesis that higher concentrations of nimodipine administered into the cerebrospinal fluid would provide superior efficacy compared to systemic administration and therefore improve the benefit/risk of nimodipine [6].

Rationale

There are ≥ 8 randomized clinical trials of nimodipine that were conducted over 25 years ago. One meta-analysis reported that the relative risk of poor outcome with oral nimodipine was 0.81 (95% confidence interval 0.72–0.92) [2]. The recommended dose of oral nimodipine can result in systemic hypotension, yet cerebrospinal fluid concentrations at this dose are low or undetectable [7]. Only 2 studies collected and reported serious adverse reactions to oral nimodipine, the most frequent event being hypotension that occurred in 2.1% of nimodipine and 1.4% of placebo patients [2]. This is inconsistent with reports of dose-limiting hypotension in up to 50% of patients given intravenous and 5–8% given oral nimodipine [8, 9]. Another study found only 44% of patients received the recommended oral dose and that it had to be discontinued in 28% [4]. This is more commensurate with recommendations that the standard of care is to begin oral nimodipine at a daily regimen of 60 milligrams (mg) every 4 h and to titrate the dose based on tolerability [8, 10–13].

On the other hand, outcome is better if more of the recommended regimen of oral nimodipine is administered [4]. Dose-limiting side effects may be reduced and effectiveness maintained or increased by local delivery of extended-release formulations of dihydropyridines, such as nicardipine, into the subarachnoid space next to cerebral arteries [14, 15]. Additional support for local delivery of dihydropyridines comes from reports of use of intrathecal and intraventricular injections of nimodipine or nicardipine to reverse angiographic vasospasm [16, 17]. Furthermore, intra-arterial infusion of nimodipine or other calcium channel antagonists reversed established angiographic vasospasm and improved clinical condition in multiple retrospective reviews of uncontrolled patient series [18]. The limitations of local intravascular or intraventricular injection of calcium channel antagonists include the need for repeated or continuous injection, which is technically difficult and invasive, as well as the risk of infection and hypotension with intraventricular and intravascular applications, respectively [19, 20].

Nimodipine was developed to reduce angiographic vasospasm; yet, at doses administered enterally, it had only minimal effect on this endpoint despite improving outcome in patients with aSAH. One theory to explain this is that the mechanism of action of nimodipine is to inhibit multiple pathophysiological processes that contribute to poor outcome. Experimental and clinical

evidence suggests that nimodipine inhibits angiographic vasospasm, cortical spreading ischemia, microthromboembolism, loss of autoregulation, increased capillary transit time heterogeneity, and that it is neuroprotective [21–25]. All of the processes inhibited by nimodipine contribute to early brain injury and delayed cerebral ischemia (DCI) that are the key contributors to poor outcome after aSAH [21, 26, 27].

EG-1962 is a novel, proprietary, Precisa™-based product with nimodipine in a bioresorbable poly-D,L-lactide-co-glycolide matrix reconstituted with a sodium hyaluronate-based buffer making a suspension that releases nimodipine over at least 21 days [28]. EG-1962 is administered as a single injection directly into a cerebral ventricle via an external ventricular drain (EVD) that is in place as standard of care.

Phase 1/2A Clinical Study

The NEWTON study (Nimodipine Microparticles to Enhance Recovery While Reducing TOxicity After SubarachNoid Hemorrhage: Phase 1/2a Multicenter, Controlled, Randomized, Open Label, Dose Escalation, Safety, Tolerability and Pharmacokinetic Study Comparing EG-1962 and Nimodipine in Subjects With Aneurysmal Subarachnoid Hemorrhage) was conducted in North America (USA and Canada) and the European Union (Finland and Czech Republic) [29, 30]. The primary objectives of the study were to determine the maximum tolerated dose and safety of a single intraventricular injection of EG-1962. The key secondary objective was to determine pharmacokinetics of EG-1962. The principal exploratory endpoint was outcome assessed on the Extended Glasgow Outcome Scale (GOSE). Favorable outcome was predefined as upper and lower good recovery and upper moderate disability (GOSE 6–8). Other outcomes included the modified Rankin Scale, Montreal Cognitive Assessment (MoCA), and Barthel index. Additional exploratory endpoints included DCI and use of rescue therapies.

Six dose cohorts of 12 patients each (9 EG-1962 and no oral nimodipine, 3 oral nimodipine standard of care) were evaluated at escalating doses of 100–1200 mg in North America. A 7th cohort of up to 12 subjects was approved for Finland and the Czech Republic where subjects were to be randomized in the same ratio but with a single dose of 600 mg EG-1962. One subject was enrolled in Finland before the sponsor elected to terminate the Phase 2 study to prepare for a Phase 3 study.

Thus, 54 patients received EG-1962 and 18 patients were administered standard of care oral nimodipine. No safety signals precluded dose escalation. The maximum tolerable/feasible dose as a single administration was 800 mg. The 1200 mg dose was not feasible as a single administration, and only 3 of 9 subjects received the entire dose. For the safety assessment, all EG-1962-treated subjects were included. The number of deaths and serious adverse events (SAEs) in the EG-1962 treatment group were comparable to those in the standard of care oral nimodipine group [29, 30].

Pharmacokinetics of plasma and cerebrospinal fluid (CSF) nimodipine following intraventricular administration of EG-1962 and oral administration of nimodipine capsules and tablets were determined using a liquid chromatographic/liquid chromatographic/mass spectrometry assay. Plasma nimodipine C_{max}, C_{ss}, and AUC_{0-14} values increased with increasing dose of EG-1962. The steady-state exposure (AUC_{0-14}) did not exceed that of oral nimodipine at any dose. Mean C_{ss} values in CSF for EG-1962 subjects were higher than mean C_{ss} values for oral nimodipine subjects for over 10 days. Mean C_{max} and exposure to nimodipine was substantially higher in the CSF than the plasma in EG-1962-treated subjects.

Clinical outcome was reported for the first 5 cohorts (EG-1962, 100–800 mg) since few subjects in the 1200 mg cohort received the full dose. The percentage of subjects from cohorts 1–5 (100–800 mg) who achieved a favorable outcome on the GOSE was greater in the EG-1962 treatment group (59%, 27/46) compared to the standard of care oral nimodipine (28%, 5/18). In addition, more favorable outcomes compared to standard of care oral nimodipine were demonstrated for subjects with a World Federation of Neurological Surgeons (WFNS) grade 2 (89%, 17/19 vs. 40%, 2/5) at randomization as well as for subjects with WFNS 4 (41%, 9/22 vs. 27%, 3/11). Of note, 28% (13/46) of subjects treated with EG-1962 had GOSE scores of 8, the best outcome possible, while only 6.0% (1/18) of subjects treated with standard of care oral nimodipine achieved that result. These results supported initiation of a pivotal Phase 3 study.

Newton 2 Study Design

Administration

The protocol was designed by Daniel Hänggi, M.D., Nima Etminan, M.D., Ph.D., Stephan A. Mayer, M.D., Francois Aldrich, M.D., Michael N. Diringer, M.D., Erich Schmutzhard, M.D., Herbert J. Faleck, D.O., R. Loch Macdonald, M.D., Ph.D., David Ng, Ph.D., and Benjamin R. Saville, Ph.D. Edge Therapeutics, Inc. is funding the study. Funding is provided not to the investigators themselves but to the sites for study-related costs. Data collection employs a contract research organization (ResearchPoint Global, Inc., Austin, Texas, USA). The steering committee (Daniel Hänggi, M.D., Nima Etminan, M.D., Ph.D., Stephan A. Mayer, M.D., Francois Aldrich, M.D., Michael N. Diringer, M.D., Erich Schmutzhard, M.D.) will have access to the final study data set and will

write a report of the study for publication, in conjunction with Edge Therapeutics, Inc. The authors will be the authors of this paper. Professional writers may assist in manuscript preparation. Disclosures of the authors accompany this paper.

Study patients who suffer complications of aSAH possibly related to the study will seek medical attention as required and according to institutional ethics boards and undergo treatment as necessary as paid for by their healthcare plans. Consent forms for the study include language indicating that Edge Therapeutics, Inc. may pay for study-related complications under certain circumstances. Patient confidentiality follows the guidelines of the jurisdictions in which the sites reside. Public and scientific inquiries can be directed to the worldwide principle investigator, Professor Daniel Hänggi, or to Edge Therapeutics, Inc. ResearchPoint Global monitors the data collection independently with input from Edge Therapeutics, Inc., who review the data entered into online case report forms. Some of the monitoring operating procedures, range checks, and such are available from Edge Therapeutics, Inc. and ResearchPoint Global, Inc. Substantive protocol modifications will be reviewed with the study steering committee and the data monitoring committee (DMC). The protocol is available (supplemental file online).

Objectives

The primary objective is to compare the efficacy of intraventricular EG-1962 to standard of care oral nimodipine in subjects with aSAH. This will be assessed by the primary efficacy endpoint which is the proportion of subjects with a favorable outcome measured on the GOSE at 90 days after study randomization (Day 90) and the secondary efficacy endpoint which is the proportion of subjects with favorable neurocognitive outcome at Day 90 measured by the MoCA [31, 32].

The secondary objective is to determine the safety of intraventricular EG-1962 compared to standard of care oral nimodipine. Safety will be assessed by the incidence and severity of adverse events based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) in EG-1962-treated subjects compared to subjects treated with standard of care oral nimodipine, and by the proportion of subjects with delayed cerebral infarctions present on computed tomography (CT) at Day 30 that were not present on CT obtained during the pre-randomization phase. A substudy will collect plasma on a total of 18 subjects randomly selected from each group for assessment of plasma nimodipine pharmacokinetics.

Health economic and outcomes assessments will include the number of days in intensive care unit, duration of hospital stay, discharge disposition (e.g., home, rehabilitation, long-term care), and use of rescue therapy for DCI. DCI will be defined by the following:

For subjects in whom the neurological scales are assessable:
A decrease of at least 2 points on the modified Glasgow Coma Scale or an increase of at least 2 points on the abbreviated National Institutes of Health stroke scale compared to the best score post-aneurysm repair, lasting for at least 2 h where other medical or surgical causes are excluded [33–35].

For subjects in whom the neurological assessment scales are not assessable:
Radiological evidence and clinical judgement.

Subjects with suspected DCI should have appropriate radiological investigations to confirm the diagnosis and exclude other causes of neurological deterioration. Rescue therapy is defined as induced hypertension (intravenous vasopressors such as dopamine, dobutamine, phenylephrine, epinephrine, norepinephrine), superselective intra-arterial infusion of vasodilator drugs (nimodipine, nicardipine, verapamil), or balloon angioplasty performed for DCI. The use of rescue therapy in the absence of documented DCI is discouraged, in keeping with current guidelines for management of aSAH and with the limited evidence that it is efficacious [36].

Synopsis

This study will be conducted according to the principles of the "Declaration of Helsinki" and with the laws and regulations of the site's country. The Investigator will follow the International Conference on Harmonization Good Clinical Practices Guidelines. The study protocol will be approved by the local institutional review board or independent ethics committee, as appropriate, before any study-related procedures are performed.

The design is a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, efficacy, and safety study in subjects with aSAH. All subjects receive both intraventricular investigational product (IP, EG-1962, or normal saline) and oral IP (nimodipine capsules [USA]/tablets [all other countries] or placebo capsules/tablets identical in appearance to oral nimodipine). The study has two phases: pre-randomization and randomization. The randomization phase includes two periods: treatment and follow-up observation (Fig. 1). The pre-randomization phase obtains informed consent and establishes protocol eligibility. The pre-randomization phase begins following repair of the ruptured saccular aneurysm and must be completed so that the intraventricular IP injection begins within 48 h

of the onset of aSAH and within 4 h after the start time of IP reconstitution in the pharmacy. Subjects may receive open-label nimodipine (oral or intravenous), according to standard of care; however, it must be discontinued upon randomization. All investigators are recommended to adhere to subject management guidelines prepared by the steering committee.

The randomization phase begins at the time of subject randomization (Day 1). Subjects are randomly assigned in a 1:1 ratio to receive treatment with an intraventricular and an oral IP in a double-blind, double-dummy design (Table 1). This phase continues until the Day 90 assessments are completed, or the subject discontinues the study prematurely. Adverse events are collected beginning at randomization and up to and including the Day 90 visit. The randomization phase is divided into a treatment period that ends 21 days after administration of intraventricular IP or upon hospital discharge, whichever occurs first. The follow-up observation period begins at the end of the treatment period and continues until Day 90 assessments are complete or the subject discontinues the study prematurely. Follow-up visits will occur at Day 30 and Day 90. A blinded assessor who is not involved in the preparation of IP or in the subject's care will assess key study endpoints.

Subject management guidelines are provided to each site and make recommendations on how to manage the EVD as well as management of other common problems associated with aSAH such as hypotension and DCI. Sites were encouraged to follow these guidelines; however, rigid and mandatory adherence could not be achieved due to lack of consensus on management of the EVD and of these problems [37].

Inclusion and Exclusion Criteria (Table 2)

The main changes to this study compared to the phase 1/2a study are the introduction of blinding, change in the randomization ratio to 1:1 and testing of one dose of EG-1962. This study will recruit adult male and female subjects with aSAH secondary to rupture of a saccular aneurysm, repaired by clipping or coiling, with a WFNS grade of 2 to 4, substantial SAH on CT scan (modified Fisher scale > 1) and requiring an EVD [38–40]. The upper age limit of 75 was set because of the low likelihood of favorable outcome above this age [41]. Neurological grading uses the WFNS score because it has lower

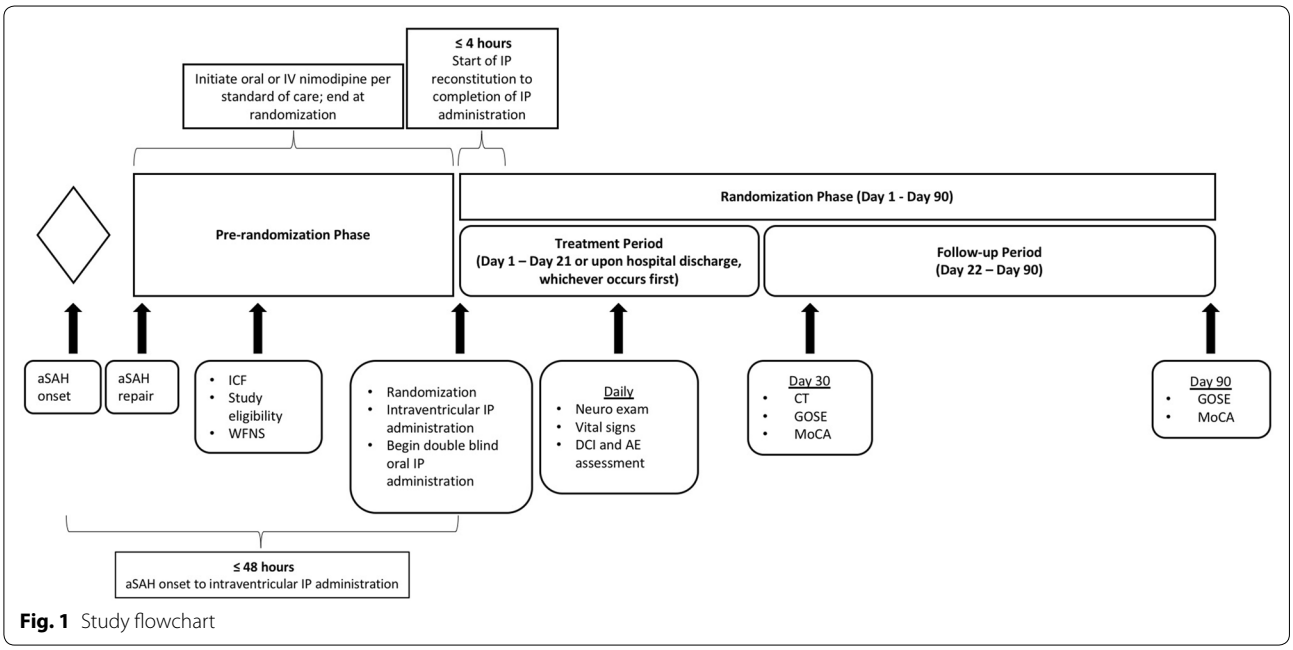

Fig. 1 Study flowchart

Table 1 Treatment groups

EG-1962 group	Oral nimodipine group
1 dose of intraventricular EG-1962 (600 mg)	1 dose of intraventricular 0.9% NaCl
Up to 21 days of placebo capsules/tablet identical in appearance to oral nimodipine (including nimodipine received during pre-randomization)	Up to 21 days of oral nimodipine capsules/tablets (including nimodipine received during pre-randomization)

inter- and intraobserver variabilities than the Hunt and Hess scale [38]. One reason for inclusion of subjects with WFNS grade 2 to 4 and substantial SAH is that these are the subjects who generally have EVDs inserted as standard of care, and an EVD is required for injection of EG-1962 [29]. Subjects with WFNS grade 1 are excluded because very few have insertion of an EVD as part of standard of care. Subjects with WFNS grade 5 are excluded as mortality in patients who are, and remain, WFNS grade 5 after resuscitation including insertion of an EVD, is high [42].

Exclusion criteria were selected to remove those subjects who may not tolerate intraventricular injections (if they have increased intracranial pressure > 30 mm Hg in sedated patients lasting > 4 h anytime since admission), patients with complications of aneurysm repair that likely would lead to infarction and poor outcome or death and cardiac, and hemodynamic criteria that would increase

Table 2 Inclusion and exclusion criteria

Inclusion criteria	
1.	Male or female between the ages of 18–75 years, inclusive
2.	Ruptured saccular aneurysm confirmed by angiography (CTA, MRA, or catheter) and repaired by neurosurgical clipping or endovascular coiling
3.	Subarachnoid hemorrhage on CT scan (pre-repair) of grade 2–4 on the modified Fisher scale (diffuse [clot present in both hemispheres] thick or thin, or local thick)
4.	External ventricular drain in place
5.	WFNS grades 2, 3, or 4 assessed during the pre-randomization phase after repair of the aneurysm but prior to randomization
6.	Able to receive intraventricular IP within 48 h after the onset of aSAH and within 4 h after the start time of intraventricular IP suspension in the pharmacy. Onset of aSAH is defined as the time the subject experiences the first symptom of aSAH (e.g., severe headache or loss of consciousness reported either by the subject or by a witness). If found unconscious, the onset of SAH is defined as the time the subject was last known normal
7.	Female subjects of child-bearing potential must have a negative pregnancy test (urine or serum) during the pre-randomization phase and must agree to use adequate birth control for at least 30 days following the end of the treatment period. Male subjects must agree to use adequate birth control for at least 30 days after the end of the treatment period
8.	Signed informed consent from the subject or the subject's legal representative after the completion of aneurysm repair but prior to any study-specific procedures being performed
9.	Able and willing to comply with follow-up visit schedule
Exclusion criteria	
1.	Major complication during aneurysm repair such as, but not limited to, massive intraoperative hemorrhage, brain swelling, arterial occlusion, or inability to secure the ruptured aneurysm
2.	Angiographic vasospasm prior to randomization
3.	Clinical or radiological evidence of a cerebral infarction with neurological deficit
4.	Increased ICP > 30 mm Hg lasting > 4 h anytime during the pre-randomization phase
5.	Substantial intraventricular hemorrhage
6.	Aneurysm repair requiring flow diverting stent or stent-assisted coiling and dual antiplatelet therapy
7.	Subject is expected to undergo repair of additional aneurysms within 90 days in cases where multiple aneurysms were identified during the pre-randomization phase
8.	Hemodynamically unstable during the pre-randomization phase (i.e., SBP < 100 mm Hg, requiring > 6 L colloid, or crystalloid fluid resuscitation)
9.	Cardiopulmonary resuscitation was required during the pre-randomization phase
10.	Symptoms or ECG signs of acute myocardial infarction or unstable angina pectoris prior to randomization
11.	Electrocardiogram evidence and/or physical findings compatible with second- or third-degree heart block or of cardiac arrhythmia associated with hemodynamic instability
12.	Echocardiogram, if performed as part of standard of care before randomization, revealing a left ventricular ejection fraction < 40%
13.	Severe or unstable concomitant condition or disease (e.g., known significant neurological deficit, cancer, hematologic or coronary disease), or chronic condition (e.g., liver disease, kidney disease, or psychiatric disorder), that, in the opinion of the investigator, may increase the risk associated with study participation or IP administration, or may interfere with the interpretation of study results
14.	Subjects who have received an investigational product or participated in another interventional clinical study within 30 days prior to randomization. Subjects participating in a non-interventional study that has no bearing on assessment of EG-1962 or oral nimodipine may be enrolled per guidelines of the local institutional review board/independent ethics committee
15.	Known hypersensitivity to nimodipine or other dihydropyridine calcium channel antagonists, poly-D, L-lactide-*co*-glycolide, or hyaluronic acid

aSAH aneurysmal subarachnoid hemorrhage, *CT* computed tomography, *CTA* computed tomography angiography, *ECG* electrocardiogram, *ICP* intracranial pressure, *IP* investigational product, *MRA* magnetic resonance angiography, *SBP* systolic blood pressure, *WFNS* World Federation of Neurological Surgeons

the risk of hypotension and confound interpretation of safety.

Patients whose aneurysms are repaired by clipping or coiling are eligible since nimodipine is used regardless of the method of aneurysm repair. Patients who require dual antiplatelet therapy after aneurysm repair are excluded to avoid extraneous intracranial hemorrhages that could confound safety assessment and adversely affect outcome independent of EG-1962.

There are approximately 72 participating sites in the USA, Canada, Germany, Austria, Israel, Finland, Czech Republic, Hong Kong, Singapore, Australia and New Zealand. The first patient was randomized on July 28, 2016.

Dose Rationale

Safety, tolerability, clinical, and ancillary outcomes and pharmacokinetic results from the NEWTON study were used to select a dose for this pivotal study. The not observed adverse effect level in a preclinical study supported the 600 mg dose, and clinical data from the Phase 2 study with this dose demonstrated a favorable benefit/risk profile.

Blinding

Great attention has been paid to maintaining blinding. The double-blind, double-dummy blinding scheme is achieved through a combination of masking the administration of EG-1962/placebo (Fig. 2), blinding of the oral nimodipine products with placebos that are identical in appearance, and assessment of key study endpoints by blinded assessors who are otherwise not involved in the preparation of IP or in the subject's care. The manifold for EG-1962/placebo is covered in opaque material so that the contents cannot be seen (Fig. 2). All subjects and/or subjects' legal representative and site, Edge Therapeutics/RPG personnel involved in the study will remain blinded to treatment assignment. The only personnel who are not blinded are the pharmacy staff that prepare and dispense IP, clinical supplies coordinators, pharmacy clinical research associates, and pharmacy project managers who are responsible for IP management. These personnel will not monitor or have access to any other subject data. Any questions that potentially unblind IP preparation or administration are discussed only with the pharmacy project managers or pharmacy clinical research associates. In addition, the Safety Unit associates, as described in the Medical and Safety Monitoring plan, and DMC and a liaison statistician, as outlined in the DMC charter, may be unblinded.

Safety Monitoring

In addition to oversight by Edge Therapeutics and its contract research organization partners, the study is monitored by an external, independent DMC. The DMC receives reports of all SAEs in an ongoing manner and makes recommendations as necessary. Safety monitoring follows those recommended by the International Conference on Harmonization Good Clinical Practices Guidelines.

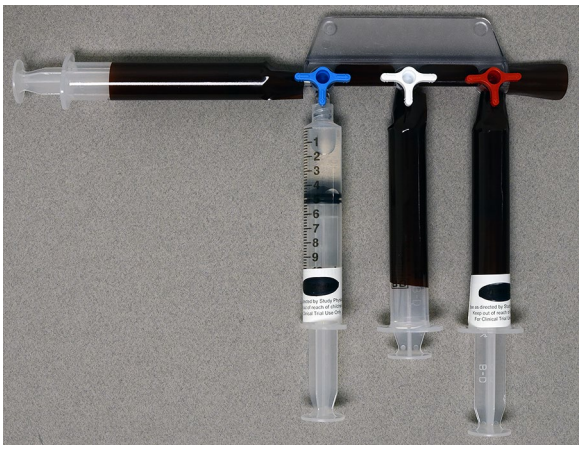

Fig. 2 The masked manifold apparatus used to accomplish blinding of the intraventricular IP injection

Follow-Up

Follow-up visits will occur at Day 30 (±7 days) and Day 90 (±10 days). Outcomes assessed will include a CT scan at 30 days and clinical assessment including GOSE and MoCA by independent assessors [31, 32]. These outcome scales and their assessment at Day 90 were selected after discussion with regulatory authorities and were based on their use in other clinical trials and their potential to detect a clinically meaningful benefit to patients.

Statistics and Analysis

Sample size considerations are based on the ability to detect a difference of 15% or more between oral nimodipine and EG-1962 in the proportion of subjects with a favorable GOSE outcome at Day 90 (responders). The NEWTON study demonstrated a difference of over 30% in Day 90 GOSE responders between the two treatment groups [30]. Based on a χ^2 test at 85% power with one-sided alpha at 0.025 and with oral nimodipine having a favorable response of 28%, the sample size needed to detect the 15% difference is 374 subjects, while a sample size of 210 subjects is sufficient to detect a >20% difference.

The randomization will be carried out separately for each of 4 strata based on post-repair WFNS and region (USA or non-USA): (a) WFNS 2 USA, (b) WFNS 2 non-USA or (c) WFNS 3 and 4 USA and (d) WFNS 3 and 4

non-USA. Analysis populations include the full analysis set defined as those randomized subjects who took at least one dose of study medication. This analysis set will be used as the primary analysis population for analysis of efficacy. Additional analyses for each efficacy parameter will also be carried out using a per protocol population consisting of all subjects with no major protocol violations. All safety data will be summarized based on the safety population consisting of all randomized subjects receiving at least one dose of study medication, but summarized based on treatment received.

Primary analysis of the Day 90 GOSE (classified as favorable or unfavorable) will be based on a logistic regression model with treatment group, randomization stratum (WFNS classification and region) as classes, and age classified into two categories (<60 vs. ≥ 60). A non-binding assessment of futility will be conducted on the first 150 randomized, treated, and completed subjects.

When 210 subjects have completed Day 90 outcomes, a pre-specified sample size analysis will be conducted to determine whether the study will stop accrual or continue until 374 subjects are completed. All randomized and treated subjects will be followed for Day 90 outcomes. The primary analysis will be conducted using a nominal significance level of 0.0223, which controls the overall Type I error of the adaptive design at 0.025. Additional statistical analyses will be defined in the statistical analysis plan prior to database lock.

Safety and health economics data will be summarized by treatment group and presented as descriptive statistics.

Pharmacokinetic Analyses

This analysis will use mixed effects population pharmacokinetic modeling using commercially available software. Pharmacokinetic evaluations will include C_{max}, time to C_{max}, C_{SS}, and AUC_{0-14}. Analysis will be done on patients in each treatment group.

Discussion

This study incorporates the basic protocol design of the first human study of EG-1962 [29, 30]. The main changes are that this phase 3 study is double-blind, double-dummy, uses a single dose of EG-1962 and the randomization ratio is 1:1. Changes from the first to the second NEWTON study protocol were kept to a minimum in view of the favorable results obtained in the first study. The rationale for key elements of the first human study of EG-1962 are published [6, 29, 30].

Multiple steps have been taken to ensure blinding by using specific procedures at each potential point where unblinding could occur, and taking measures to assess the success of the blinding procedures to ensure the credibility of any benefit from treatment. The entire injection apparatus used for the intraventricular administration of investigational product is masked so that the trained professional giving the intraventricular injection cannot see what treatment is being administered. The person giving the injection is instructed not to give any indication to the healthcare team, subject, or subjects family as to what they believe may have been injected, in keeping with ethical and good clinical practice. Other members of the health care team also are instructed not to endeavor to uncover the identity of the IP being injected or to discuss the potential treatment allocation with other members of the health care team, the subject, or their family members.

During the subsequent treatment period, to maintain blinding, subjects in both arms of the study will receive nimodipine capsules/tablets or placebo capsules/tablets that are identical in appearance to the active oral nimodipine capsules or tablets. Finally, in the follow-up period, the primary outcome assessments at Days 30 and 90 are conducted by blinded assessors not otherwise involved with the care of the subject.

It is theoretically possible that hypotension temporally related to administration of oral IP could unmask treatment allocation. This issue of pharmacologic effect is a concern common to many randomized, blinded studies comparing a new therapy to an approved therapy with a known pharmacological action. Fundamentally, however, it is not unblinding per se that matters but the actions, if any, subjects, or investigators take based on perceived knowledge of treatment assignment [43]. In this study, subjects are managed by multidisciplinary teams consisting of neurosurgeons, neurointensivists, neuroradiologists, residents, fellows, nurses, therapists and such that change during the management of the subject. Thus, it likely would be difficult for any one individual care provider to be able to discern treatment allocation and importantly, to influence subject management in a way that would affect outcome at 90 days.

The protocol and statistical analysis plan include assessment of the success of the blinding procedures by collecting and analyzing data on hypotension, DCI and use of rescue therapy and the investigator attribution of causality of adverse events. The data will be summarized by treatment groups. The frequency and severity of hypotension, DCI, and use of rescue therapy will each be tabulated and compared between treatment groups.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-0575-z) contains supplementary material, which is available to authorized users.

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Authors' Contributions

The protocol was designed by DH, NE, SAM, FA, MND, ES, HJF, RLM, DN, and BRS.

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Compliance with Ethical Standards

Conflict of interest

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