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Emelie P Fungrim

University of Copenhagen

Jesper Peter Bömers

Copenhagen University Hospital

Helene Ravnholt Jensen

Copenhagen University Hospital

Kirsten Møller

University of Copenhagen

Troels Halfeld Nielsen

Odense University Hospital

Erik Kinnman

Lund University

Diana N Krause

University of California, Irvine

Tiit Mathiesen

`tiit.illimar.mathiesen@regionh.dk`

Copenhagen University Hospital

Lars Edvinsson

Lund University

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First-in-human Phase 1b/2a trial shows safety and suggests improved clinical outcome with MEK 1/2 inhibitor EDV2209 as a novel treatment for spontaneous subarachnoid hemorrhage

Emelie P. Fungrim^{1,2#}, Jesper Peter Bömers^{2#}, Helene Ravnholt Jensen³, Kirsten Møller^{1,3}, Troels Halfeld Nielsen³, Erik Kinnman⁴, Diana N. Krause^{4,5}, Tiit Mathiesen^{1, 2, 6*}, Lars Edvinsson^{*4}

¹Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

²Department of Neurosurgery, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark

³Department of Neuroanaesthesiology, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark

³ Department of Neurosurgery, Odense University Hospital, Odense, Denmark

⁴Department of Clinical Sciences, Division of Experimental Vascular Research, Lund University, Lund, Sweden

⁵Department of Pharmaceutical Sciences, School of Pharmacy & Pharmaceutical Sciences, University of California, Irvine, CA

⁶Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

EF and JB shared first authorship

*TM and LE shared last authorship

Corresponding author: Tiit Mathiesen email: tiit.illimar.mathiesen@regionh.dk

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ABSTRACT

We report findings from a Phase 1/2a clinical trial (EUCT No. 2024-514590-22-00, STOP-DCI), an interventional, randomized, double-blind, placebo-controlled, multiple ascending-dose, first-in-human trial to determine safety and evaluate clinical outcome for the MEK 1/2 inhibitor EDV2209 in patients with severe spontaneous subarachnoid hemorrhage (SAH). In Phase 1b (N=11), three cohorts received a single intracerebral ventricular (ICV) bolus (8.55 µg, 17 µg or 28.5 µg). In Phase 2a (N=16), two cohorts were given three ICV injections of 28.5 µg EDV2209 or placebo over 18 hours, beginning within 8 hours of SAH onset.

The study found an equal distribution of adverse events between treatment and placebo with no treatment-associated safety concerns. Outcomes and mortality were as expected or better for patients with severe SAH in the patients treated with EDV2209.

Pharmacokinetics were reproducibly stable in the CSF with no detectable levels of EDV2209 in plasma.

Importantly, patients in the Phase 2a cohorts showed signs of positive clinical effects as assessed using the extended Glasgow outcome and modified Rankin scales. Treatment with EDV2209 was thus considered safe and provided potential benefit for improving patient outcome following severe SAH. These positive results provide a rationale to continue with a Phase 2b / 3 study powered to determine efficacy as well as safety.

INTRODUCTION

Subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm is a leading form of hemorrhagic stroke with severe morbidity and high mortality that typically strikes people in mid-life (40-60 years old) ¹. Treatment comprises stabilization of vital parameters and optimization of homeostatic parameters, management of acute hydrocephalus, prevention of rebleeding by surgery on interventional procedures along with the calcium channel blocker nimodipine as standard treatment ^{2,3}. Two-thirds of patients survive ictus and are at risk for DCI, a delayed phase of cerebral dysfunction which occurs typically occurs 4-10 days after ictus ⁴. DCI affects up to a third of these patients. DCI is associated with death or permanent severe neurological impairment in one third of affected patients while two-thirds recover with milder or minimal sequelae. Moreover, the remaining patients may be affected by milder neurological morbidity, cognitive dysfunction, post-traumatic stress disorder and increased risk of late post-stroke dementia. ⁴⁻⁷. Despite optimal therapy, 3-month mortality in patients that reach hospital alive after severe SAH was 23-28% in recently reported cohorts^{8,9}, the first of which reflected treatment at Rigshospitalet in Copenhagen. Moreover, morbidity is extensive with a favorable outcome only in 40% at three months¹⁰.

DCI is the result of events initiated by early brain injury (EBI) after ictus. DCI is thus potentially preventable as the treatment window between ictus and manifest DCI is several days; treatment could begin early during neurocritical care prior to DCI occurrence and the onset of irreversible neurological injury. Despite some benefit of nimodipine, DCI has remained a major cause of morbidity. So far additional, preclinically promising pharmacological approaches to prevent DCI have failed clinical efficacy¹¹⁻¹⁴.

EDV2209 represents a novel approach for prevention of DCI and delayed brain damage following SAH (Fig. 1) ¹⁵. It is based on the discovery that significant genomic changes occur throughout the brain vasculature in response to the suddenly increased intracranial pressure and subsequent decrease in cerebral blood flow following aneurysm rupture. Extensive preclinical studies have established that mechanosensors in the blood vessel wall activate intracellular MEK-ERK1/2 signaling within 6-8 hours of ictus¹⁵. This pathway activates expression of multiple vascular genes involved in vasoconstriction, inflammation and blood-brain barrier integrity that contribute to the secondary drop in blood flow and cerebral ischemia that occurs several days later. Early administration of EDV2209 in preclinical SAH models prevents this vascular response and delayed cerebral ischemia; it improves neurological outcome significantly¹⁵⁻¹⁷. In addition, preclinical safety assessment did not show any toxicity concerns.

This article reports results from the first-in-human Phase 1b/2a trial with the objective to evaluate safety and clinical outcome of the MEK 1/2 inhibitor, EDV2209, as a novel treatment for prevention of DCI in patients with severe aneurysmal subarachnoid hemorrhage.

METHODS

A Phase 1b/2a interventional, randomized, double-blind, placebo-controlled, multiple ascending-dose, first-in-human trial of EDV2209 was performed from January 2023 to January 2025 at the University Hospital of Copenhagen (Rigshospitalet), Copenhagen, Denmark and at Odense University Hospital, Odense, Denmark.

Study Design

Single Dose Escalation of EDV2209 (Phase 1b)

Cohort 1: 3 patients, open label, 8.55 µg (1 dose)

Cohort 2: 4 patients, randomized 3:1 active: placebo, 17 µg (1 dose)

Cohort 3: 4 patients, randomized 3:1 active: placebo, 28.5 µg (1 dose).

3 Doses over 18 hours (Phase 2a)

Cohort 4: 4 patients, randomized 3:1 active: placebo, 28.5 µg/dose

Cohort 5: 12 patients, randomized 3:1 active; placebo, 28.5 µg/dose

Due to an unfortunate mix-up in the administration of 2 drug kits, 2 patients in Cohort 5 were excluded from the randomization design.

Patients

A total of 27 eligible severe SAH patients were recruited and treated in the trial: 4 males (aged 47-68 years) and 23 females (aged 40-75 years). The median WFNS score (World Federation of Neurological Surgeons grading scale for subarachnoid hemorrhage) was 4 at the time of admittance. 25 patients were recruited at the department of Neurosurgery, Copenhagen University Hospital, Denmark and 2 were recruited at the department of Neurosurgery, Odense, Denmark.

Inclusion criteria: Male or female patients with moderate or severe spontaneous (non-traumatic) SAH (World Federation of Neurosurgical Societies (WFNS) grade 1-5) diagnosed with computer tomography (CT), requiring an ICV drain, and able to undergo first ICV injection of trial medication within 8 hours after symptom onset.

Exclusion criteria: Expected survival <48 hours, intraventricular or intracerebral blood in the absence of subarachnoid blood, any severe or unstable chronic or acute concomitant condition, evidence of previous major cerebral damage, pregnancy or breastfeeding.

All patients received standard neurointensive care for patients with SAH. The aneurysm rupture was repaired by clipping or coiling and nimodipine was administered to prevent vasospasm. Two-thirds of the patients also received tranexamic acid to prevent rebleeding.

EDV2209 Administration (Fig 2)

EDV2209 (1,4-diamino-2,3-dicyano-1,4-bis (2-aminophenylthio) butadiene) was formulated and supplied in vials as a sterile solution for injection as an ICV bolus. The placebo consisted of 0.9% saline formulated in identical vials as EDV2209 and given in a similar manner.

Cohorts 1-3 (phase 1b) received a single injection within 8 hours of the SAH ictus. Cohorts 4 and 5 (phase 2a) received 3 ICV bolus injections over 18 hours in the early phase after SAH. The first dose was given within 8 hours from the start of SAH symptoms. The second dose was given 6 hours after the first dose, and the third dose given 12 hours after the second dose.

Primary Objective – Safety

Safety and tolerability of EDV2209 was assessed in patients with non-traumatic SAH who received at least one dose of drug. The patients were evaluated for possible treatment emergent adverse events (TEAEs), safety laboratory parameters for clinical chemistry, hematology, arterial blood gases, ECG, body weight, vital signs (blood pressure, heart rate, respiratory rate, body temperature), and neurological function. Phase 1b studied increasing ICV doses of the test drug in three cohorts (Fig. 2). After each administration, there was a pause of one week to review safety. After each cohort, results were evaluated by the safety committee and regulatory authorities prior to proceeding to the next cohort.

Pharmacokinetic (PK) Measurements

Samples were collected via an external ventricular drain from the CSF and from plasma. CSF samples were immediately diluted by the addition of K₂-EDTA human plasma at a ratio of 1:1 to form a matrix for the subsequent analysis. Sampling was done at the following time points: before each dose, 25 and 75 min after each dose and 12 hours after the third dose.

Determination of EDV2209 in plasma and CSF was done using a specific bioanalytical method based on UPLC-MS/MS. The method was validated according to the EMA “Guideline on bioanalytical method validation” in the range of 1.00 - 1000 ng/mL for EDV2209 in CSF matrix, with a lower limit of quantification of 1.00 ng/mL. In plasma samples, the method was validated in the range of 0.500-500 ng/mL for EDV2209, with a lower limit of quantification of 0.500 ng/mL using a 100 µL plasma sample volume.

Measurements of EDV2209 in CSF included maximum (peak) concentration (C_{max}) and nominal time for the occurrence of C_{max} .

Secondary Objective - Clinical Outcome

Clinical outcomes in all patients were measured by the Extended Glasgow Outcome Scale (GOS-E)¹⁸ and the Modified Rankin Scale¹⁹ (mRS) at the time of discharge, 28 days and 84 days after ictus. With GOSE, higher scores indicate lower levels of disability. A GOSE score of 8 reflects no disability, scores in the 5-6 range indicate moderate disability whereas scores of 4 reflect severe disability; a favorable outcome was defined as GOSE>4. In the mRS scale, lower scores indicate lower levels of disability (5=severe, 4=moderately severe, 3=moderate, 2=slight, 1=no significant disability, 0=no disability at all)¹⁹; a favorable outcome was defined as mRS<3. The National Institute of Health Stroke Scale (NIHSS)²⁰ was recorded for patients alive on Day 14 or at discharge, whichever came first. The mean number of days at the Neuro-ICU from admittance until discharge was recorded for all patients in the study.

Statistical Methods and Outcome Assessment

Patients with full intended treatment were compared to placebo to explore possible benefit. Data from all patients in Cohorts 4 and 5 were combined with data from the 2 placebo patients in cohorts 2 and 3. Differences between the placebo (n=5) and EDV2209 (n=11) treatment groups in the outcome measures were evaluated with a dichotomized analysis of favorable and unfavorable outcomes for the Extended Glasgow Outcome scale (GOSE, 5- 8 scores were considered favorable) and Modified Rankin Scale (mRS, scores of 0-2 were considered favorable). In addition, GOSE values were compared to 177 historical controls from published literature¹⁰. Fisher exact tests and Wilcoxon signed rank test were used; statistical significance was set at 0.05.

RESULTS

Safety

Mortality

Four patients died within 84 days, one in cohort 2 (single dose of 17 µg active drug), one in cohort 3 (single dose of 28.5 µg active drug) and 2 in cohorts 4-5 (receiving three doses of 28.5 µg active drug). The cause of death in cohorts 2-3 was ischemic brain infarct at day 11 and day 14, respectively.

In cohorts 4-5, one patient died from rebleeding from an aneurysm that had not been fully secured at day 4 and one died from a parenchymal hemorrhage of the surgical site day 8 after ictus.

The deaths in cohorts 2-3 were considered the result of primary brain injury from the initial hemorrhage and the deaths in cohorts 4-5 were considered complications of surgical treatment.

No abnormalities with possible relation to ischemia or hemorrhage were detected in blood tests. Mortality was not significantly different in placebo (n=5) and actively treated patients (n=23); $p=1.00$, Odds Ratio = 0.3939; the difference was also not significantly different when comparing placebo and active treatment in fully treated patients (cohorts 4 and 5): $p=1.00$ and Odds Ratio = 0.5429- The deaths were considered unrelated to the test drug by the safety committee.

Serious adverse events (Table 1)

Serious adverse events were reported in 3/5 placebo-patients (60%), 8/9 in the dose-finding cohorts 1-3 (89%) and 6/13 (44%) in full-treatment cohorts 4-5. Events included cerebral infarction or transient ischemia (n=6), hydrocephalus, ventriculitis (n=4), pneumonia or COPD exacerbation (n=3), chronic subdural hematoma with aphasia and depressed level of consciousness (n=1), pleural effusion (n=1), shunt failure (n=1), pancreatitis (n=1), critical illness (n=1), rebleeding from aneurysm (n=1), intracranial parenchymal hemorrhage (n=1)

Cerebral infarction led to death in two patients, both with associated pneumonia, aneurysmal rebleed led to death in one patient and intracranial parenchymal hemorrhage led to death in one patient. The patient with epilepsy recovered from SAH with residual epilepsy. One patient with a cerebral infarction recovered with sequelae as did the patient with critical illness. The remaining ten patients recovered from SAEs.

Neither the safety committee nor the principal investigator considered the events to be related to the trial medication; rather, they were considered expected for the cohort of SAH patients.

Table 1 Serious adverse events

Cohort Active/ Placebo	Event Description	Related to IMP	Outcome
1a active	Cerebral Infarction, Anteriorly On Left Side	Not related	Recovered with Sequelae
	Pneumonia	Not related	Recovered
	Symptomatic Vasospasm Cerebral	Not related	Recovered
	Ventriculitis	Not related	Recovered
1b active	Transient Ischemic Attack	Not related	Recovered
	Vertigo	Not related	Recovered
1c active	Confusion	Not related	Recovered
	Hydrocephalus	Not related	Recovered
	Ventriculitis	Not related	Recovered
2a placebo	Ventriculitis	Not related	Recovered
2b active	Dysphagia	Not related	Recovered
	Ventriculitis	Not related	Recovered
2c active	Cerebral Ischemic Infarction	Not related	Death
	Pneumonia	Not related	Not recovered
3a placebo	Chronic Subdural Hematoma	Not related	Recovered
	Depressed Level Of Consciousness	Not related	Recovered
	Expressive Aphasia	Not related	Recovered
	Sepsis	Not related	Recovered
3b active	COPD Exacerbation	Not related	Not recovered
	Depressed Level Of Consciousness	Not related	Not recovered
	Malignant MCA Infarction	Not related	Death
3c active	Pain Thorax, Non-Cardiac	Not related	Recovered
	Pleural Effusion Right And Left Side	Not related	Recovered
3d active	Cerebral edema	Not related	Recovered
	Hydrocephalus Increased	Not related	Recovered
4a active	Epilepsy	Not related	Not recovered
	Over drainage, Ventriculoperitoneal Shunt	Not related	Recovered
	Pancreatitis	Not related	Recovered
	Shunt Failure	Not related	Recovered
4b active	Critical Illness	Not related	Recovered with Sequelae
5a placebo	Sepsis	Not related	Recovered
5b active	Infarction Intracranial Capsula Interna Right Side	Not related	Recovered
5c active	Rebleed From Aneurysm	Not related	Death
5d active	Delayed Cerebral Ischemia, Intermittent	Not related	Recovered
	Pseudoaneurysm Left Leg	Not related	Recovered
5e active	Intracranial Parenchymal Haemorrhage	Not related	Death

Adverse events (Table 2; Supplement)

Adverse events (AE) were equally distributed between treatment and placebo. The most common AE were obstipation, decrease in level of consciousness, prolonged QT-interval, headaches, electrolyte levels outside normal levels, decreased hemoglobin values, insomnia, nausea and vomiting. Ten patients with treatment were diagnosed with pulmonary infection, Transient elevation of liver enzymes were seen in 13 patients with active treatment and four with placebo.

No safety concerns arose that the safety committee judged to be related to the test drug EDV2209 in either the Phase 1b or Phase 2a parts of the trial.

Table 2 Reported AEs and SAEs

Category	Patients (27)		Events (808)	
	#	%	#	%
Reported AEs	27	100	808	100
Reported SAEs	17	63	37	4.6
Intensity = Mild	27	100	370*	45.8
Intensity = Moderate	25	93	407**	50.4
Intensity = Severe	13	48	26	3.2
Relation = Not Related	27	100	801	99.1
Relation = Possibly Related	3	11	7	0.9

* 6 mild events were assessed as possibly related to IMP, for patient number

- 2501, increasing gamma-glutamyl transferase
- 2502, hyponatremia, increased alanine transaminase, aspartate transaminase, gamma glutamyl transferase, and increased lactate dehydrogenase

** 1 moderate event was assessed as possibly related to IMP, for patient number

- 1302, hyponatremia

Table 2b. Summary of reported adverse events per treatment group; events may occur several times in one patient.							
Group	N	Not Serious			Serious		
		Not related	Possibly related	Total	Not related	Possibly related	Total
Active	22	581	6	587	31	0	31
Placebo	5	183	1	184	6	0	6
Total	27	764	7	771	37	0	37

Safety of ICV administration of drug

No adverse events occurred that were related to the procedure of administration into the cerebroventricular catheter.

Pharmacokinetics (Table 3, Figure 3)

For patients in Cohorts 4 and 5, the concentration of EDV2209 in CSF was measured in samples taken after intraventricular drug administration (Fig. 3). After administration of each of 3 doses, maximum CSF concentrations were observed at the first sampling time post-administration (25 min) in 10 patients receiving EDV2209. The resultant geometric mean C_{max} was 541 ng/mL after the first dose, 401 ng/mL after the second dose and 491 ng/mL after the last dose with an overall geometric mean of the highest C_{max} observed across all three doses of 661 ng/mL. Thereafter, EDV2209 concentrations in CSF declined steadily, and by 720 min after the last dose, the concentrations were still quantifiable in all patients but relatively low (1.36 to 26.3 ng/mL).

EDV2209 levels in plasma were analyzed at the same time points and were below the limit of quantification (0.500 ng/mL) for all subjects at all time-points.

Table 3a. Geometric mean (Geometric%CV) PK parameters of EDV2209 following ICV Single Dose administration on Day 1 (first dose for last treatment)

Matrix	CSF	CSF	CSF	CSF	CSF
Parameter (Units)	8.55 µg SD Cohort 1 (N=3)	17 µg SD Cohort 2 With outlier (N=3)	17 µg SD Cohort 2 Without outlier (N=2)	28.5 µg SD Cohort 3 (N=3)	28.5 µg MD ^c Cohort 4 and 5 (N=13)
AUC _{0-last} ^c (h*ng/mL)	970 (58.2%)	380 (779%)	1220 ^d (1100 – 1370)	1390 (29%)	586 (62.6%)
AUC ₀₋₆ ^c (h*ng/mL)	1720 ^a	1190 ^d (1050 - 1350)	1190 ^d (1050 - 1350)	1190 (35.7%)	826 (61.0%)
AUC ₀₋₁₂ ^c (h*ng/mL)	1760 ^a	1220 ^d (1100 – 1370)	1220 ^d (1100 – 1370)	1390 (29%)	NC
C ₀ (extrapolated) (ng/mL)	3860 (44.2%)	921 (1722%)	3590 ^d (2470 – 5230)	938 (50.6)	1140 (80.0%)
C _{max} (ng/mL)	699 (60.4%)	295 (555%)	861 ^d (780 – 950)	568 (44.2%)	541 (62.1%)
t _{max} ^b (h)	0.42 (0.42 – 0.42)	0.42 (0.42 – 0.42)	0.42 (0.42 – 0.42)	0.42 (0.42 – 0.42)	0.42 (0.42 – 0.42)
t _{last} ^b (h)	1.25 (1.25 – 12.00)	1.25 (1.25 – 12.00)	12.00 (12.00 – 12.00)	12.00 (12.00 – 12.00)	1.25 (1.25 – 1.25)
DAUC _{0-last} ^c (h*ng/mL/µg)	113 (58.2%)	22.3 (779%)	72.0 ^d (64.6 – 80.3)	48.9 (29%)	20.6 (62.6%)
DAUC ₀₋₁₂ ^c (h*ng/mL/µg)	206 ^a	72.0 ^d (64.6 – 80.3)	72.0 ^d (64.6 – 80.3)	48.9 (29%)	NC
DC _{max} (ng/mL/µg)	81.8 (60.4%)	17.3 (555%)	50.6 ^d (45.9 – 55.9)	19.9 (44.2)	19.0 (62.1%)

^a N = 1

^b Median (min-max) presented

^c For some subjects, only 2 quantifiable postdose concentrations available, but AUCs reported to have the most possible data available for discussion.

^d Geomean (min-max) presented

^e Parameter observed/calculated for the first administration profile

Bioanalysis was conducted for samples outside validated storage stability time for one subject in cohort 3 and for two subjects in cohort 4.

NC = not calculated

DAUC_{0-last}: AUC_{0-last} divided by the dose

DAUC₀₋₁₂: AUC₀₋₁₂ divided by the dose

DC_{max}: C_{max} divided by the dose

Table 3b Dose proportionality of EDV2209 in CSF following single dose administration (Cohorts 1 to 3)

Dose	8.55 µg	17 µg#	17 µg	28.5 µg#	28.5 µg
		With outlier	Without outlier		
Dose increment	-	2.00	2.00	1.67	1.67
Increase in mean AUC ₀₋	-	0.39	1.26	3.66	1.14
DPF AUC _{0-last}	-	0.20	0.63	2.19	0.68
Increase in mean C _{max}	-	0.42	1.23	1.93	0.66
DPF C _{max}	-	0.21	0.62	1.15	0.40

Dose proportionality based on preceding dose level

DPF = Dose Proportionality Factor – ratio of fold increase in geometric mean parameter divided by fold increase in dose

Dose proportionality for cohort 3 was reported for both with and without outlier of preceding dose level 17 µg.

#Comparison to dose level 17 µg with outlier.

Condition at admission of placebo and full treatment cohorts

Clinical condition at admission of cohorts 4 and 5 plus placebo patients from cohorts 2 and 3 was evaluated with the WFNS scale. 13 patients in cohorts 4 and 5 (mean age 57.0, median 55, range 43-77) received active drug: 9 had WFNS score 2-3 while 4 had a score of 4-5. Five patients received placebo (mean age 57.8, median 57, range 41-71): 4 had WFNS score 2-3 while 1 had a score of 4-5. The groups were similar ($p=1.0$, Fisher test)

Clinical Outcome Measures (Table 4 and 5)

Assessment of clinical outcome was the secondary objective in Phase 2a. SAH patients from Cohorts 4 and 5 (given 3 doses of EDV2209, 28.5 µg per injection, or placebo over 18 hours) were evaluated using the Extended Glasgow Outcome Scale (GOSE) at the time of discharge from neurosurgical care. The two additional placebo-patients in cohorts 2 and 3 were included in analyses to improve power.

The median and mean GOSE values were higher in the active treatment group ($n=13$; median 5, range 1-8, mean 5.1; scores of 5-8 were considered favorable)) as compared with placebo ($n=5$; median 4, range 4-8, mean 5.0). The median and mean mRS values were lower in the active treatment group ($n=13$; median 1, range 0-6, mean 1.9; scores of 0-2 were considered favorable)) as compared with placebo ($n=5$; median 3, range 0-3, mean 2.0). Dichotomized values at discharge, days 28 and 84 are shown in tables 4 and 5.

The 11 surviving SAH patients given EDV2209 were discharged from the hospital a median of 15 days after ictus (range 11-24; mean 16.3) while placebo patients ($n=5$) were discharged after a median of 18 days (range 13-21, mean 16.8).

Table 4. Dichotomized outcome according to the modified Rankin scale

Table 4		Modified Rankin Scale.		
Group		Favorable = 0, 1 or 2		
		Discharge	Day 28	Day 84
Active	Favorable	1 (8%)	1 (8%)	9 (69%)
	Unfavorable	12 (92%)	12 (92%)	4 (31%)
	Total	13 (100%)	13 (100%)	13 (100%)
Placebo	Favorable	0 (0%)	1 (20%)	2 (40%)
	Unfavorable	5 (100%)	4 (80%)	3 (60%)
	Total	5 (100%)	5 (100%)	5 (100%)
P-value	Fisher test	1.00	0.49	0.33

Table 5. Dichotomized outcome according to the Extended Glasgow Outcome Scale.

Table 5		Extended Glasgow Outcome Scale.		
Group		Favorable = 5, 6, 7, 8		
		Discharge	Day 28	Day 84
Active	Favorable	6(46%)	6 (46%)	9 (69%)
	Unfavorable	7(54%)	7 (54%)	4 (31%)
	Total	13 (100%)	13 (100%)	13 (100%)
Placebo	Favorable	1 (20%)	2 (40%)	2 (40%)
	Unfavorable	4 (80%)	3 (60%)	3(60%)
	Total	5 (100%)	5 (100%)	5 (100%)
P-value	Fisher test	0.60	1.00	0.23

Comparison to historical controls (Fig 4)

We then compared our phase 2A results with EDV2209 to a larger set of historical SAH control data, 177 patients published by Trizio et al.¹⁰. Fig. 4 shows the proportion of patients evaluated at 3 mo. post-SAH that have a favorable outcome (GOSE scores of 5-8) compared to those with an unfavorable outcome (GOSE scores of 1-4). Historically, at this time point, SAH patients are more likely to present with an unfavorable outcome (66%). In contrast, the majority of SAH patients treated with EDV2209 (70%) presented with a favorable outcome at 3 mo. after SAH.

DISCUSSION

Advancements in treatment of SAH have primarily focused on early management of the patients, i.e. better diagnosis, prevention of rebleeding by early repair of the ruptured aneurysm, hydrocephalus management, advanced intensive care support and administration of nimodipine^{1,14}. Yet, there is a need for better pharmacological alleviation of DCI.

Safety

This first clinical trial of EDV2209 in patients with acute SAH showed that treatment was feasible, and the drug was safe. This is an important result, given the promising pre-clinical findings. The trial targeted patients with severe SAH that required treatment with ventricular drainage. It was possible to place a ventricular drainage and include patients to receive the potentially neuroprotective drug into the cerebral ventricular system to bypass the blood-brain barrier (BBB) within 8 hours after ictus. Adverse events and severe adverse events were balanced between active treatment and placebo and specific treatment related adverse events were not detected.

Mortality

Three month-mortality was 15.3% in patients with full 3-dose treatment and 22.2% in the single dose escalation cohorts. Mortality was judged by the safety committee and PI to be caused by severity of initial SAH (cerebral ischemia; n=2) or complications to treatment (rebleeding of aneurysm and parenchymal hemorrhage; n=2). Importantly, mortality was comparable to or below what was expected with causes consistent with those reported previously from our department²⁵. Previous studies reported 24 - 26% mortality in SAH patients treated with EVD and 50% mortality in unconscious SAH patients who reach hospital after severe SAH²¹⁻²³. We recently found 23% mortality in SAH patients treated with ventricular drainage at our department²⁴.

The adverse and severe adverse events that were encountered in our SAH patients were similar to those typically seen in patients with severe SAH including disorders of consciousness, neurological symptoms, electrolyte aberrations, gastrointestinal symptoms, headaches and infections. They were distributed equally between treatment groups and placebo; typically, the adverse events resolved during follow-up. The safety committee, sponsor or PI could not identify any adverse events associated with treatment. Typical class-related TEAE for MEK/ERK inhibitors such as rash, alopecia, fatigue, diarrhea, peripheral edema, and nausea were not associated with active treatment. Moreover, systemic exposure to the experimental drug was not measurable, further strengthening the

assessment of systemic safety. Neither transient hepatic enzyme elevations nor pulmonary infections were statistically associated with treatment. These AEs were not severe but need to be further monitored in continued studies.

Clinical outcome

The study was not powered for efficacy and assessment of a possible drug effect was considered exploratory and a useful guide for design of a phase 2b / 3 trial. Nonetheless, groups were well balanced in terms of SAH severity and ages, and simple comparisons were compatible with, or even suggested, better outcomes in terms of GOSE and mRS scores in active treatment compared with placebo. The differences were not statistically significant but provided a favorable signal to extend efficacy assessment beyond this pilot phase. Moreover, a comparison with historical controls suggested benefit in terms of a favorable GOSE score for 70% of patients receiving active treatment compared to 33% in literature¹⁰.

Rationale for continuation

There is a clear clinical need for pharmacological therapies to ameliorate morbidity and mortality as well as prevent loss of cognitive and motor functions following SAH. Hemorrhagic stroke due to aneurysm rupture is a devastating illness with a high rate of mortality and long-term disability¹. Recent statistics show a global age adjusted incidence of 8.3 (95% UI, 7.3-9.5) and a DALY rate 125.2 (95% UI, 110.5-142.6) per 100 000 people. The latter reflects the tremendous number of years lost to premature death or disability due to SAH. Subarachnoid hemorrhage is much less common than intracerebral hemorrhages and ischemic stroke, but occurs disproportionally in younger populations, 40-70 years of age, causing a relatively larger loss of quality adjusted life years. The absolute case numbers increased from 1990 to 2021 and SAH ranked as the 36th most common cause of death in the world²⁵.

It is now recognized that the secondary brain injury that develops during the first 72 hours after SAH is the most influential clinical determinant of outcome when patients have survived ictus^{11, 13, 26}. Current research is focused on understanding the pathophysiology underlying the delayed phase of cerebral ischemia (DCI) and early brain injury following SAH. Multiple processes are involved including decreased cerebral blood flow, global brain ischemia, inflammation, mitochondrial dysfunction, cortical spreading depolarization, microcirculatory dysfunction, blood-brain-barrier breakdown, cerebral

edema, oxidative cascades, and neuronal death^{11, 13, 26}. Many potential targets have been identified, however, none of the recent trials have resulted in new treatments for SAH¹¹. For over 30 years, oral nimodipine has been the only drug specifically recommended for treating SAH^{11, 13}. Nimodipine is a vasodilator originally developed as a means to prevent the vasospasms observed angiographically after SAH². Clinical studies of nimodipine show modest efficacy in improving SAH outcome, but DCI remains an important cause of morbidity and disabilities. Better or additional treatments are needed.

It is our view that an early biological “switch”, such as the ras-raf-MEK1/2-ERK1/2 pathway that triggers multiple changes in the cerebral vasculature that evolve over time, is an important target. A key outcome in preclinical studies was preservation of global cerebral blood flow (CBF) in the delayed phase to prevent brain ischemia and its deleterious effects¹⁵. Numerous animal studies of experimental SAH have shown that inhibition of the MAP kinase pathway within 8 hours of stroke onset maintains CBF at later time points and significantly improves neurological function^{15-17, 27-30}. The overall aim of the current Phase 1/2a trial of EDV2209 was to investigate clinical feasibility and safety of a novel treatment strategy developed over 25 years of preclinical studies (Fig. 1)¹⁵. The study showed safety of intra-ventricular EDV2209 treatment, a favorable pharmacokinetic profile, and sufficiently promising observations of clinical benefit to continue development towards a trial designed to evaluate efficacy.

CONCLUSION

Intraventricular treatment with EDV2209 was found safe in a first-in-human Phase 1/2a trial. Comparisons between active treatment and placebo groups or historical controls were not powered for statistical significance but provided a rationale to continue development towards an efficacy trial. These encouraging findings may lead the way to developing effective SAH therapies that prevent the serious consequences of DCI.

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FIGURES and LEGENDS

Figure 1. Proposed mechanism of action of EDV2209 in SAH¹². In the first hours following aneurysm rupture (Acute Phase), there is subarachnoid bleeding, a sharp increase in intracranial pressure and significant decrease in global cerebral blood flow (CBF). Throughout the cerebral circulation, mechanical forces on the vascular wall are decreased, activating mechanosensors and intracellular signaling via the MEK-ERK pathway to the nucleus. During the days following, vascular genes related to vasoconstriction, inflammation and blood-brain barrier (BBB) dysfunction are switched on. This causes expression of pathophysiological changes during the Delayed Phase that result in a secondary drop in global blood flow, delayed global ischemia (DCI) and brain damage. ICV administration of EDV2209 given within 8 h of SAH onset blocks vascular MEK-ERK signaling and its consequences. This permits maintenance of proper CBF, prevention of DCI and improved outcome in the later phase.

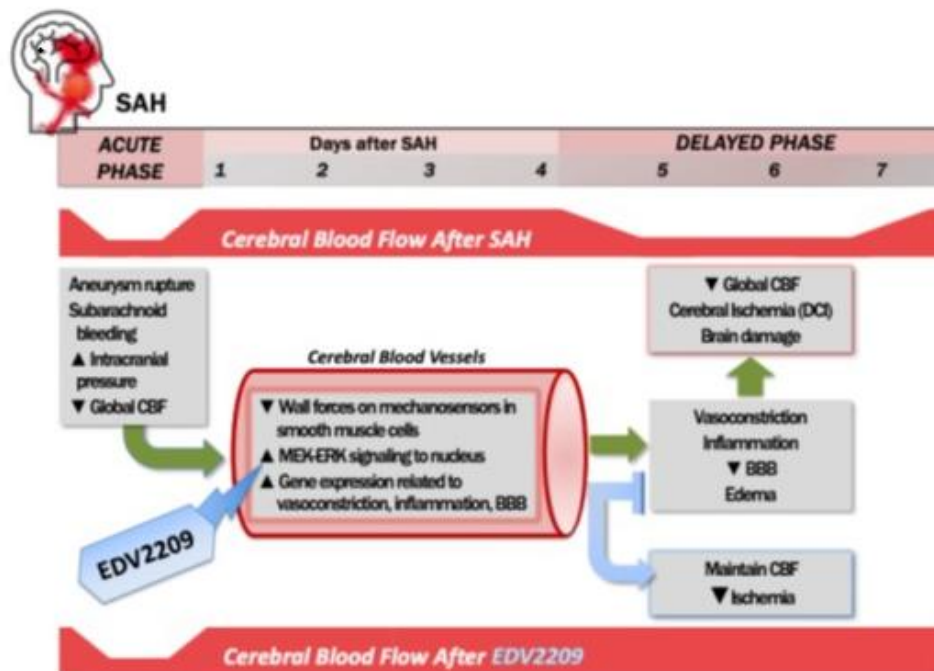


Figure 2. Study Design. Phase 1b was a Dose Escalation study to evaluate the safety of a single ICV bolus of EDV2209 in Cohort 1 (8.55 μg), Cohort 2 (17 μg drug or placebo) and Cohort 3 (28.5 μg drug or placebo). In Phase 2a, Cohorts 4 and 5 received three ICV injections of either 28.5 μg EDV2209 or placebo over a period of 18 h. Patients were assessed for any drug-related adverse events, CSF and plasma drug levels and functional outcome measures.

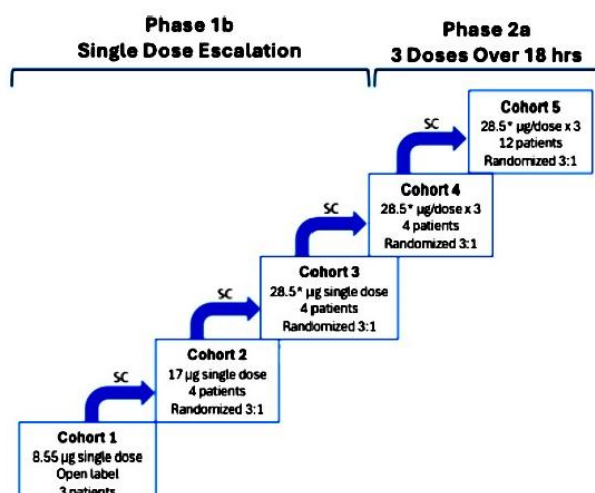


Figure 3. Individual CSF Concentrations of EDV2209 following ICV bolus injections of 28.5 μg EDV2209 at 3 time points. CSF samples were taken from SAH patients in Cohorts 4 and 5 over a 30-hour period.

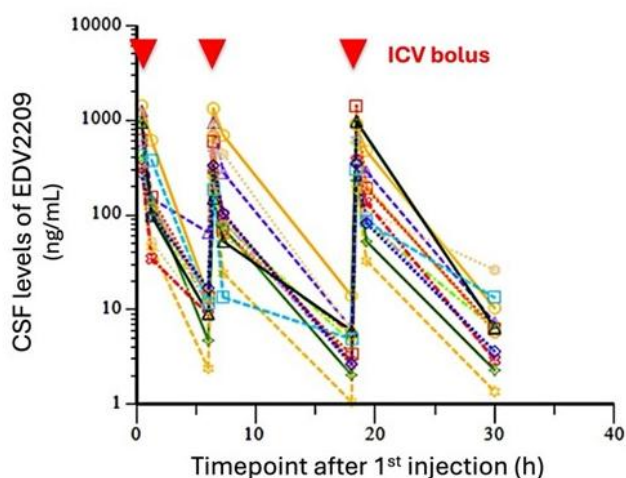
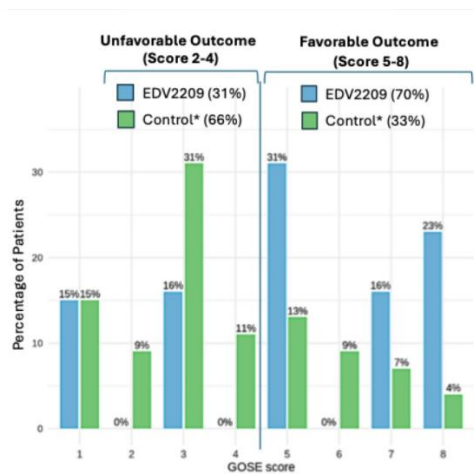


Figure 4. Comparison of GOSE scores from patients treated with EDV2209 (cohorts 4 and 5 evaluated at 3 mo. post-SAH) with historical control values published by Trizio et al.¹⁰. The proportion of patients with a favorable outcome (GOSE scores of 5-8) are compared to those with an unfavorable outcome (GOSE scores of 2-4)



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Johan Bring of Statisticon AB, Stockholm, Sweden, contributed to the analysis of the data.

Fortrea contributed to trial management

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DECLARATIONS

Conflicts of Interest

LE is a Board Member and shareholder of Edvince AB, Sweden.

EK is a Board Member of Edvince AB

DK, EF, JB, KM, TM, TN, have no relevant financial or competing interests to declare.

Author Contributions

LE, TM, JB and KM contributed to the study conception and design. TM served as principal investigator of the trial. The trial was conducted by EF, JB, HRJ, KM and THN. TM, LE, EK, JB, KM, THN, DNK and EF contributed to the analysis and interpretation of the results. Original draft preparation by TM, LE and DNK. All authors read and approved the final manuscript.

Ethical Approval

This clinical trial was authorized by the Danish Medicines Agency (Sep. 8, 2021) and approved by the Danish Scientific Ethics Committee F for Region Hovedstaden, Denmark (Dec. 7, 2021). The trial was conducted in accordance with the Declaration of Helsinki and its most recent update, the International Council for Harmonization (ICH) E6 Good Clinical Practice (GCP) guideline and the local legal and regulatory requirements in Denmark. The study received European Union Ethics Approval EUCT No. 2024-514590-22-00, STOP-DCI.

Informed Consent

Informed Consent to participate in the trial was obtained from the patient or their legal representative (trial guardian or next of kin) at the time of the first clinical intervention.

Supplementary Files

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- [Supplement.docx](#)