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ORIGINAL RESEARCH ARTICLE

Intra-arterial Injection of OTR4132, a Novel Neuroprotector in Acute Ischemic Stroke: The MaTRISS Trial

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Abstract

Background and Objectives There is an important need for the development of neuroprotective therapeutic agents that could be combined to reperfusion strategies in acute ischemic stroke to improve patient prognosis. OTR4132 is a polymer of glucose engineered to mimic heparan sulfates (HS), which demonstrated neuroprotective effects in animal models. The aim of this study was to assess the safety of OTR4132 and to identify the highest, and well-tolerated, single dose of OTR4132 in patients with anterior circulation acute ischemic stroke who underwent endovascular thrombectomy (EVT).

Methods The MaTRISS study is a multi-center, first-in-man, open-label, dose-escalation study. OTR4132 was administered intra-arterially immediately after EVT recanalization. Dose levels were determined on the basis of preclinical studies. Six doses (from 0.2 to 2.5 mg) were planned to be administered in groups of at least three patients. Each dose escalation was authorized by the data safety monitoring board (DSMB) after reviewing all clinical, biological, and radiological data from a dose group up to 7 days post-administration. Key inclusion criteria were an acute ischemic stroke in the anterior circulation territory and endovascular thrombectomy performed with recanalization (thrombolysis in cerebral infarction [TICI] score of 2b–3) confirmed by angiography. The primary endpoint was the rate of investigational treatment-related severe adverse events occurring from baseline to 7 days after injection. All other safety and efficacy endpoints were exploratory and included all serious and non-serious adverse events, stroke lesion volumes, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), Modified Barthel Index (BI), and Montreal Cognitive Assessment (MoCA) from baseline up to 3 months.

Results In total, 19 patients were recruited from three centers in France between March 2022 and March 2024 and six different doses of OTR4132 were tested (in *n* patients): 0.2 mg (3), 0.5 mg (3), 1 mg (3), 1.5 mg (6), 2 mg (3), and 2.5 mg (1). No adverse drug events and no changes in vital signs or laboratory parameters were observed up to 3 months following administration, regardless of administered doses. Four patients presented at least one serious adverse event. None was considered linked to the investigational treatment on the basis of investigator and DSMB assessment. One patient died of intracranial hemorrhagic transformation at 24 h and the causality link between OTR4132 administration and death remained unknown.

Conclusions The highest tolerated dose of OTR4132 was the highest dose administered (i.e., 2.5 mg). These safety results need to be confirmed in a larger multicenter randomized placebo-controlled clinical trial.

The trial was first registered in clinicaltrials.gov on 5 September 2019 (NCT04083001).

1 Introduction

The management of acute ischemic stroke due to proximal intracranial large vessel occlusion significantly improved over the last two decades with the development of endovascular thrombectomy (EVT) [1, 2].

However, when used under the most favorable conditions, i.e., a combination of intravenous thrombolysis performed within 4.5 h and EVT within 6–8 h after the onset of acute ischemic stroke, improved functional outcome at 90 days is observed in about half of patients, with modified Rankin scores (mRS) of 0–2 ranging from 33 to 71%, according to a set of seven randomized clinical trials [1].

Extended author information available on the last page of the article

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Key Points

There is an important need for neuroprotectors in ischemic stroke.

The heparan sulfate mimetic OTR4132 showed neuroprotective effects in animal models.

This article reports the results of a first-in-human clinical study where OTR4132 was administered intra-arterially in 19 patients with ischemic stroke, following endovascular thrombectomy.

Six escalating doses of OTR4132 were tested from 0.2 to 2.5 mg.

The results suggest that intra-arterial injection of OTR4132 has a good safety profile at all tested doses.

In addition, EVT reperfusion of the ischemic tissue itself brings secondary effects, with the most feared being hemorrhagic transformation (HT). HT occurs in up to 40% of patients treated with acute stroke therapy and is fatal in about 3% of cases [3]. In vitro and in vivo models suggested failure of endothelial integrity and loss of neurovascular homeostasis as the cellular mechanisms underlying blood extravasation and, from a structural point of view, disruption of the blood–brain barrier (BBB) as the pathophysiological step that leads to HT [3].

Thus, there is a substantial need for the development of therapeutic agents for neuroprotection in acute ischemic stroke to protect the BBB from damage prior to and during recanalization and further improve functional outcomes [4].

In line with these concerns, OTR3 has developed a new neuroprotector, OTR4132, that is intended to be administered intra-arterially after EVT to improve functional outcomes in patients with acute ischemic stroke.

OTR4132 belongs to the family of ReGeneraTing Agents or RGTA®, which are polymers of glucose (α-1,6 dextran backbone) engineered to mimic heparan sulfates (HS) in all three mechanical functions: as an extracellular matrix scaffold element, a protector of matrix proteins and communication peptides, and a storage site, but differ from HS in their resistance to glycanases [5, 6, 9]. Because the primary mode of action of OTR4132 is mechanical (and not pharmacological), it falls under medical device regulation in Europe. However, it is considered a drug in the USA, where the definition of medical devices differs. Introduced at the site of injury, RGTA® replaces destroyed HS in all their functions. This allows a restoration of the matrix architecture and cellular microenvironment, facilitating cell survival and recovery at the site of injury [7]. The RGTA® are eliminated by endocytosis and catabolized in lysosomes during the turnover of extracellular matrix remodeling, as for the other natural elements of the extracellular matrix.

The first RGTA®, OTR4120, demonstrated efficacy in wound healing and has been commercialized since 2008 under the names CACIPLIQ20® and CACICOL® for the topical treatment of chronic skin wounds and corneal ulcers, respectively, and the product is safe [8].

OTR4132 is a chemically modified dextran molecule that differs from OTR4120 by controlled addition of carboxymethyl, sulfate, and acetate groups [9–11]. It has been investigated in preclinical studies to assess its safety [11] and its neuroprotective potential in acute ischemic stroke [10 and unpublished studies performed by OTR3]. Overall, it was concluded that intra-arterial administration of OTR4132, after successful mechanical thrombectomy, was likely to have a positive benefit/risk balance to improve BBB repair, neuronal survival, and ultimately, functional recovery.

Herein, we report the results of the first-in-human dose-escalation trial "MaTRISS" to evaluate the safety and the potential efficacy of intra-arterial administration of OTR4132 in patients presenting with an acute ischemic stroke treated with endovascular thrombectomy combined (or not) with intravenous thrombolysis.

2 Methods

2.1 Study Design and Participants

The trial followed Good Clinical Practice (GCP). As this is not a randomized trial, the reporting does not follow the SPIRIT or CONSORT guidelines. The study protocol was registered in clinical trials.gov under NCT04083001 before study onset. The trial was performed according to medical device regulation (MDR) in France, since OTR4132 is considered a medical device in France (ANSM, DMCDIV/FLOW/AE/2018-A03117-48-B).

Patients were recruited from three stroke centers in France (Grenoble, Nancy, and Bordeaux). Signed informed consent was obtained from the patients, their legally authorized representative, or, by applicable national law, by an independent physician who was not otherwise participating in the trial.

Consecutive patients refereed to the above mentioned recruiting centers were included if all of the following conditions were met: (1) age between 45 and 80 years; (2) acute ischemic stroke in anterior circulation territory identified by magnetic resonance imaging (MRI); (3) occlusion of anterior circulation, i.e., internal carotid artery (ICA) or proximal middle cerebral artery (MCA) (M1 and/or M2 segment); (4) volume of the infarcted lesion estimated

below two thirds of the MCA territory (diffusion MRI sequence); (5) EVT initiated within 6 h of stroke onset with known stroke onset time or initiated within 6–16 h of symptoms onset (last known well in the case of unwitnessed onset) with perfusion core/penumbra mismatch (infarct core volume < 70 mL, critically hypo-perfused volume/infarct core volume > 1.8 and mismatch volume > 15 mL); (6) recanalization confirmed by angiography after EVT, TICI grade 2b–3; (7) NIHSS score at pre-screening, including hand testing: between 11 and 25; (8) no significant pre-stroke disability (pre-stroke mRS: 0–1); and (9) able to follow a neuro-rehabilitation program.

Main exclusion criteria were previous symptomatic stroke, evidence of intracranial hemorrhage, history of allergy or anaphylactic reactions to heparinoids, suspected cerebral vasculitis, occlusions in multiple vascular territories, pregnant or breastfeeding, or women without an adequate contraceptive method.

Subsequent groups of patients were administered increasing doses until either a non-tolerated dose was reached or the maximum dose was administered. The doses of OTR4132 tested were 0.2 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg. Following the administration of OTR4132 to a patient, an observational period of 24 h was respected before any new inclusion in the same group. A new inclusion could not occur if the investigator judged that a serious adverse device effect (SADE) or a dose-limiting toxicity event happened. A dose group had to be completed (at least three patients) before initiating another group, and the decision of dose escalation was made by an independent data safety monitoring board (DSMB). After visit 2 (V2, 7 ± 2 days) of the third patient of each group, the DSMB assessed the available safety data (including clinical data, biological tests, and MRIs) from the V1 (24 h) and V2 visits. On the basis of this evaluation the DSMB decided if dose escalation was justified. The DSMB had full authority to adapt the dose escalation scheme according to the safety data.

2.2 Procedures

OTR4132 was administered intra-arterially immediately after EVT and effective reperfusion (TICI score 2b–3) as assessed by angiography. The injection was performed using a microcatheter at the site of previous occlusion. The starting dose of OTR4132 was 0.2 mg, manufactured in a sterile saline (0.9% NaCl) solution in 10 mL volumes, as for the other tested doses. In total, 10 mL of OTR4132 (at one of the five available concentrations: 20 µg/mL, 50 µg/mL, 100 µg/mL, 150 µg/mL, and 200 µg/mL) was administrated as a slow bolus at an infusion rate of 1 mL/min using a syringe pump. For the last dose of 2.5 mg, 17 ml of OTR4132 at a concentration of 150 µg/mL was administrated at an infusion rate of 1.7 mL/min.

The respective total dose of OTR4132 received by a patient was the following: 0.2 mg, 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg. In-person clinical follow-up was obtained at 24 h (V1), 7 days (V2), 30 days (V3), and 90 days (V4) from inclusion. Where in-person follow-up was not possible, video conferencing or telephone follow-up was obtained.

2.3 Outcomes

The primary endpoint was the rate of device-related SADE occurring from baseline to 7 ± 2 days after inclusion. Secondary endpoints were exploratory, with no hierarchical order. Main safety endpoints were survival rates, all cause death, stroke-related death, the rate of device-related adverse events, the rate of device-related severe adverse events (SAE), the rate of procedure-related adverse events (AEs), the rate of procedure-related SAE, the rate of all AEs, the rate of all SAE, the rate of symptomatic intracranial hemorrhage, and the rate of intracranial hemorrhage on 24-h follow-up imaging per Heidelberg bleeding classification [12]. Potential serious adverse events that were anticipated during the study were death, puncture site complications (e.g., hematoma or hemorrhage), symptomatic intracranial hemorrhage, extracranial hemorrhage, brain edema, neurologic deterioration, orolingual angioedema, new ischemic stroke in a different vascular territory, technical complications or vascular damage, embolization into new territories outside the target downstream territory of the occluded vessel, and allergic reaction to OTR4132-MD. All these complications (except allergy to OTR4132-MD) are known to occur after thrombolysis (when performed) and thrombectomy in patients with anterior ischemic stroke.

Main secondary efficacy measures were the lesion volume, NIHSS, mRS, Modified Barthel Index (BI), and Montreal Cognitive Assessment (MoCA).

Imaging interpretation was done at a central core laboratory (Keosys, France). Infarct volumes were measured by summation of manual planimetric delineation of infarct on axial imaging. The determination of the stroke lesion volume was assessed from MRI images using DICOM viewer software image segmentation and analysis tools. Baseline and 24 h measurements were based on apparent diffusion coefficient (ADC) values, while subsequent measures (7 days and 90 days) were based on fluid-attenuated inversion recovery (FLAIR) sequences. Baseline and 24 h measurements involved capturing ADC values using the Rapid software (iSchemaView, Menlo Park, CA, USA), with manual corrections performed by the central core laboratory. The lesions visible on FLAIR were manually outlined with drawing tools, ensuring accurate demarcation of the lesion boundaries. Measurement tools were then utilized to

Table 1 Demographics and stroke characteristics at baseline

Variables		0.2 mg (*N* = 3)	0.5 mg (*N* = 3)	1 mg (*N* = 3)	1.5 mg (*N* = 6)	2 mg (*N* = 3)	2.5 mg (*N* = 1)	Total (*N* = 19)
Age (years)	Median	76.0	69.0	67.0	69.0	61.0	66.0	67.0
	Min.; max.	59; 77	53; 71	64; 71	42; 80	56; 69	66; 66	42; 80
Gender	Male	2 (66.7%)	1 (33.3%)	2 (66.7%)	5 (83.3%)	2 (66.7%)	0 (0%)	12 (63.2%)
	Female	1 (33.3%)	2 (66.7%)	1 (33.3%)	1 (16.7%)	1 (33.3%)	1 (100%)	7 (36.8%)
BMI (kg/m^2)	Median	27.20	30.50	29.00	22.95	29.70	21.30	27.00
	Min.; max.	25.2; 28	28.3; 32.4	21; 41.5	20.7; 27	26.9; 30.9	21.3; 21.3	20.7; 41.5
Site of arterial occlusion	Internal carotid artery	1 (33.3%)	0 (0%)	1 (33.3%)	3 (50%)	1 (33.3%)	0 (0%)	6 (31.6%)
	Proximal middle cerebral artery	2 (66.7%)	3 (100%)	2 (66.7%)	3 (50%)	2 (66.7%)	1 (100%)	13 (68.4%)
Intravenous thrombolysis	Yes	3 (100%)	2 (66.7%)	1 (33.3%)	6 (100%)	3 (100%)	1 (100%)	16 (84.2%)
Time between stroke onset or last know well and start of thrombolysis (h)	Median	2.9	3	8.3	3.1	2.6	14.3	3.1
	Min.; max.	2.3; 4.5	2.3; 3.7	8.3; 8.3	2.3; 4	1.6; 5.3	14.3; 14.3	1.6; 14.3
Duration of thrombectomy (min)	Median	22.0	38.0	57.0	34.5	17.0	21.0	32.0
	Min.; max.	20; 66	31; 80	33; 62	25; 75	17; 22	21; 21	17; 80
Time between stroke onset or last know well and start of thrombectomy (h)	Median	3.4	5.5	12.9	5	4.9	14.9	5.3
	Min.; max.	3.1; 5.3	2.9; 6.3	3.4; 15.3	2.8; 6.9	3.9; 5.7	14.9; 14.9	2.8; 15.3
TICI score	Grade 2b (complete filling of all of the expected vascular territory—but filling is slower than normal)	2 (66.7%)	1 (33.3%)	2 (66.7%)	4 (66.7%)	1 (33.3%)	0 (0%)	10 (52.6%)
	Grade 3 (complete perfusion)	1 (33.3%)	2 (66.7%)	1 (33.3%)	2 (33.3%)	2 (66.7%)	1 (100%)	9 (47.4%)
Total infarct volume at baseline (mL)	Median	12	20.2	8.84	41.69	21.64	11	21.64
	Min.; max.	7.7; 54.1	0; 63.7	5; 28	20.1; 50	18.4; 29.5	11; 11	0; 63.7
NIHSS at screening	Median	19.0	15.0	17.0	14.5	14.0	11.0	15.0
	Min.; max.	11; 22	15; 19	5; 19	11; 17	11; 18	11; 11	5; 22

BMI body mass index, *NIHSS* National Institutes of Health Stroke Scale, *TICI* thrombolysis in cerebral infarction scale

calculate the total volume of these outlined regions. Regions of hemorrhagic transformation, if present, were included in the total volume assessment. The assessment of hemorrhagic transformations per Heidelberg classification was performed by an independent radiologist from the central core laboratory on the basis of MRI FLAIR and T2* sequences. The independent neuroradiologist was unaware of the dose administered.

2.4 Statistical Analysis

No formal power calculations have been performed. The sample size was based on the objective to obtain adequate safety, tolerability data to achieve the objectives of the study while exposing as few subjects as possible to OTR4132 and procedure safety. Initially, 15–18 patients were planned, with 3 patients to be included in each dose group (five dose groups from 0.2 to 2 mg). Additional patients could be included in conformity with the decision of the DSMB. An amendment to the protocol was made to include three additional patients including a higher dose of 2.5 mg. Descriptive statistics were used for all the endpoints and at all timepoints. Circular visualization was made using R-package RCircos.

All statistical analyses were done on the safety protocol population. A sensitivity analysis for the efficacy endpoints was also performed on the per protocol population.

3 Results

Between March 2022 and March 2024, 19 patients with anterior circulation acute ischemic stroke successfully treated by EVT with or without thrombolysis (final TICI score 2b–3)

Table 2 Pre-planned safety endpoints

Variables	0.2 mg (*N* = 3)	0.5 mg (*N* = 3)	1.0 mg (*N* = 3)	1.5 mg (*N* = 6)	2.0 mg (*N* = 3)	2.5 mg (*N* = 1)	Total (*N* = 19)
SADE attributed to OTR4132 from baseline to 7 days after inclusion (primary endpoint)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
All-causes of death from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (5.6%)
Stroke-related death from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (5.6%)
Rate of device-related adverse events from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rate of device-related SADE from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rate of procedure-related adverse events from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rate of procedure-related severe adverse events from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rate of all adverse events from baseline to 90 days	3 (100%)	3 (100%)	3 (100%)	6 (100%)	3 (100%)	1 (100%)	18 (100%)
Rate of all serious adverse events from baseline to 90 days	1 (33.3%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	1 (100%)	4 (22.2%)
Rate of symptomatic intracranial hemorrhage from baseline to 90 days	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	1 (5.3%)
Rate of intracranial hemorrhage on 24-h follow-up imaging*	3 (100%)	3 (100%)	2 (66.7%)	5 (83.3%)	2 (66.7%)	0 (0%)	15 (78.9%)
Rate of brain edema on 24-h follow-up imaging	0 (0%)	0 (0%)	0 (0%)	2 (33.3%)	0 (0%)	0 (0%)	2 (10.5%)
Rate and volume of ischemic lesions in new territories on 24-h follow-up imaging	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.3%)
Rate of confirmed recanalization (TICI score 2b or 3) on 24-h follow-up	1 (33.3%)	3 (100%)	2 (66.7%)	4 (66.7%)	3 (100%)	1 (100%)	14 (73.7%)
Imaging							
Length of ICU stay (mean ± SD)	23.0 ± 12.3	4.3 ± 1.2	15.3 ± 3.5	6.8 ± 1.5	5.3 ± 2.1	10.0	10.4 ± 8.2
Length of full hospital stay (mean ± SD)	47.0 ± 53.7	7.0 ± 5.3	15.3 ± 3.5	10.8 ± 4.7	6.3 ± 3.5	10.0	14.4 ± 18.8

ICU intensive care unit, *SADE* serious adverse device effect, *SD* standard deviation, *TICI* thrombolysis in cerebral infarction scale

were included in the study and received one of the six following doses: 0.2 mg (3 patients), 0.5 mg (3 patients), 1 mg (3 patients), 1.5 mg (6 patients), 2 mg (3 patients), and 2.5 mg (1 patient). These 19 patients composed the safety protocol set.

Median age was 67 years and 63% were men, with a median NIHSS score of 15. Patients' characteristics at baseline were quite similar between dose groups in terms of type of artery occlusion, delay between stroke onset and thrombolysis (if performed), delay between stroke onset and EVT, EVT duration, and NIHSS scores at screening (Table 1).

All pre-planned safety endpoints are presented in Table 2.

No SADE occurred from baseline to 90 days after inclusion, regardless of the administered doses. No patient suffered from any adverse device effect (ADE), regardless of the administered doses. No patient suffered from any procedure-related serious adverse event, regardless of the administered doses. Four patients presented at least one serious adverse event (one patient in the 0.2 mg dose group, two patients from the 1.5 mg dose group, and one patient in the 2.5 mg group). More precisely, one patient from the 0.2 mg dose group presented a new ischemic stroke 90 days after initial stroke onset due to middle cerebral artery re-occlusion in the context of COVID-19 infection, dehydration, and acute kidney injury. The relationship between cerebral ischemia and device was established as unknown (possible) by the investigator. One patient from the 1.5 mg dose group suffered from re-occlusion of their middle cerebral artery after thrombectomy (without neurological worsening) that necessitated additional thrombo-aspiration, and another patient from this dose group presented fatal hemorrhagic transformation at 24 h. The latter patient benefited from intravenous thrombolysis and from a stenting procedure after thrombectomy, for which he received anti-aggregants (aspirin), which could have played a role in the bleeding. The relationship between the fatal hemorrhagic transformation and device administration was considered unknown (possible) by the investigator. A patient from the 2.5 mg dose group presented pulmonary embolism that was considered not related to the device or procedure. Adverse events were reported in all patients, and in the vast majority corresponded to minor (not clinically meaningful) abnormal biological values. No consistent abnormalities were observed.

No changes in vital signs (heart rate, blood pressure, body temperature, laboratory assessments, and device-related adverse events) were observed regardless of administered

Table 3 Biological parameters collected at visit 1 (24 h)

Variables		0.2 mg (*N* = 3)	0.5 /mg (*N* = 3)	1.0 mg (*N* = 3)	1.5 mg (*N* = 6)	2.0 mg (*N* = 3)	2.5 mg (*N* = 1)	Total (*N* = 19)
WBC (10^9/L)	*N*	3	3	2	6	3	1	18
	Mean	8.4	8.5	10.5	8.6	8.7	5.8	8.6
	Min.; max.	5.5; 11.1	6.6; 10.3	7.7; 13.2	5.6; 13.5	5.6; 10.5	5.8; 5.8	5.5; 13.5
Platelets (10^9/L)	*N*	3	3	1	6	3	1	17
	Mean	227	185	287	210	262	176	220
	Min.; max.	191; 279	163; 200	287; 287	145; 335	238; 285	176; 176	145; 335
Creatinine (µmol/L)	*N*	3	3	2	6	3	1	18
	Mean	82	76	71	74	78	57	75
	Min.; max.	67; 108	55; 96	60; 82	64; 93	49; 102	57; 57	49; 108
AST (IU/L)	*N*	3	3	2	5	3	0	16
	Mean	20	28	31	21	19	–	23
	Min.; max.	12; 31	24; 36	27; 35	17; 29	16; 25	–	12; 36
ALT (IU/L)	*N*	3	3	2	5	3	0	16
	Mean	14	21	16	17.0	20.3	–	17.9
	Min.; max.	7; 19	12; 26	16; 17	9; 30	15; 27	–	7; 30
Total bilirubin (µmol/L)	*N*	3	3	2	5	3	0	16
	Mean ± SD	16.0	17.3	13.0	14.4	13.0	–	14.8
	Min.; max.	11; 26	8; 28	11; 15	10; 21	10; 18	–	8; 28
Glucose (mmol/L)	*N*	3	3	2	6	3	0	17
	Mean	6.5	5.2	5.50	5	6	–	5.5
	Min.; max.	5.3; 8.5	4.1; 6.2	4.8; 6.2	4.2; 5.8	3.8; 8.5	–	3.8; 8.5
Na (mmol/L)	*N*	3	3	2	6	3	1	18
	Mean ± SD	141	141	140	140	141	141	140.8 ± 1.9
	Min.; max.	140; 143	139; 143	137; 144	138; 142	141; 143	141; 141	137; 144
K (mmol/L)	*N*	3	3	2	6	3	1	18
	Mean	3.7	4	3.3	3.7	3.8	4.2	3.8
	Min.; max.	3.7; 3.8	3.5; 4.7	3.3; 3.4	3.53; 4.03	3.5; 4.3	4.2; 4.2	3.3; 4.7
INR	Missing	0	1	1	1	0	0	3
	Normal	3 (100%)	2 (100%)	2 (100%)	5 (100%)	3 (100%)	1 (100%)	16 (100%)
Activated PTT (s)	*N*	3	2	2	5	3	1	16
	Mean	32	27.5	24.5	28.2	29.3	28.0	28.6
	Min.; max.	29; 35	27; 28	24; 25	25; 35	28; 31	28; 28	24; 35

ALT alanine transaminase, *AST* aspartate aminotransferase, *INR* international normalized ratio, *PTT* partial thromboplastin time test

doses of OTR4132. Biological parameters collected 24 h (V1) after OTR4132 administration are shown in Table 3.

Only one patient presented a symptomatic hemorrhagic transformation at 24 h. In contrast, asymptomatic hemorrhagic transformations, evaluated by an independent neuroradiologist on the basis of MRI sequences (FLAIR and T2*), were noticed in 79% of cases. The grading of intracranial hemorrhages using the Heidelberg classification are shown in Fig. 1. The highest doses (2 mg and 2.5 mg) were not associated with more severe hemorrhagic transformations.

Pre-planned efficacy endpoints are shown in Table 4 and Fig. 2 (see also Supplementary Table S1 for all individual scores).

Of note, all patients who received 2 mg or 2.5 mg had a NIHSS of 0 at/or before day 7.

Volumetric analyses of stroke volumes assessed from brain MRIs by an independent core laboratory are shown in Table 5 and Fig. 2. Of note (Fig. 2), the median change (min.; max.) in lesion volume at 90 days versus baseline was − 43.46% (− 100%; 57.25%) for the 0.2 mg dose group compared with − 81.80% (− 90.99%; − 74.63%) for the 2 mg dose group and − 58.18% for the 2.5 mg dose patient. Similarly, the median change in lesion volume at 90 days versus 24 h was − 37.38% (− 100%; − 16.28%) for the 0.2 mg dose group compared with − 83.42% (− 85.62%; − 59.86%) for the 2 mg dose group and − 63.78% for the 2.5 mg dose patient.

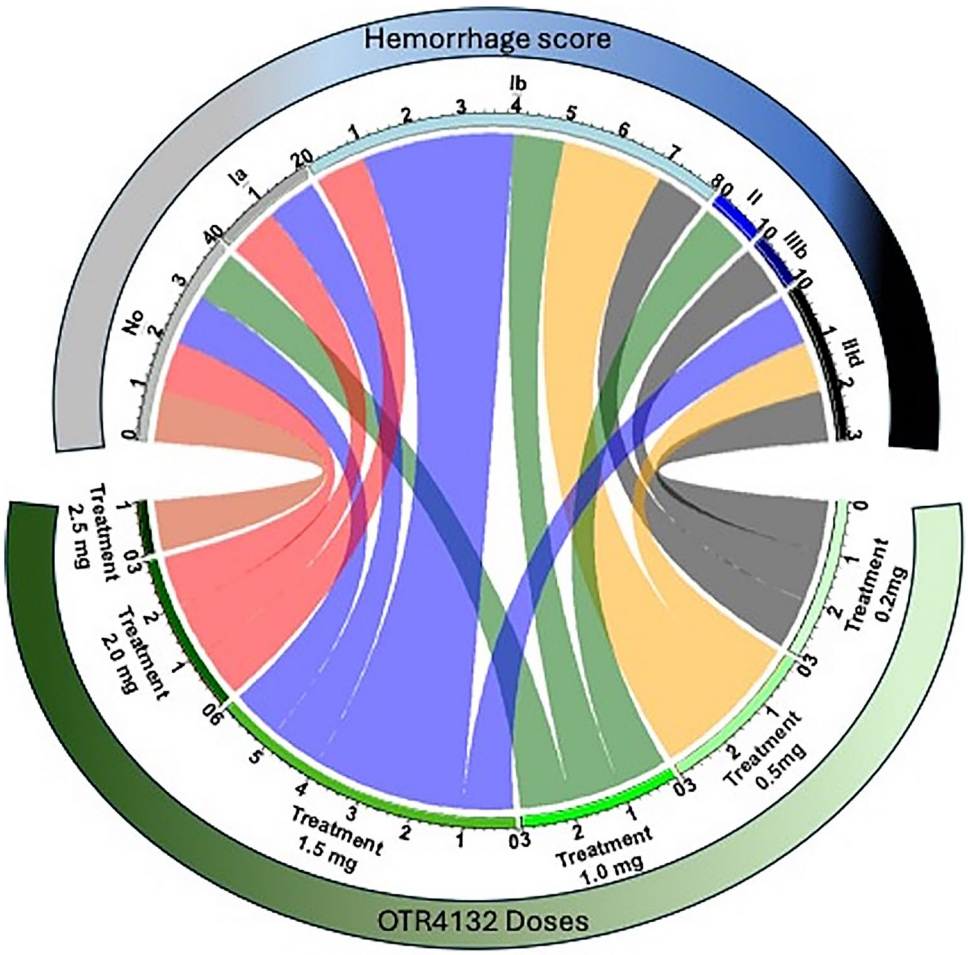

Fig. 1 Intracranial hemorrhage classification at 24 h. The figure is a circular visualization of contingency data that correlates the doses of OTR4132 in individual patients from 0.2 to 2.5 mg: 0.2 (grey), 0.5 (yellow), 1 (green), 1.5 (blue), 2 (red), or 2.5 (orange), with the degrees of hemorrhagic transformation according to the Heidelberg Bleeding Classification (from 0 to IIId). Heidelberg Bleeding Classification: No, absence of intracranial hemorrhage; 1a, scattered small petechiae, no mass effect; 1b, confluent petechiae, no mass effect; 2, intracerebral hemorrhage within and beyond infarcted brain tissue; 3b, intraventricular hemorrhage; 3d, subdural hemorrhage. Only categories found in the study cohort are shown

4 Discussion

The primary objective of this open, first-in-man, dose escalation study was to assess the safety and tolerability of OTR4132 and to identify the highest, well-tolerated, and safest single dose of OTR4132 in patients presenting with an acute ischemic stroke successfully treated with EVT. The results showed a good feasibility of intra-arterial injection of OTR4132 whatever the tested dose. Eventually, four SAEs were reported during the trial and none of them were considered a SADE. The subjects were post-stroke patients receiving thrombolytic therapy (when performed) and catheter treatments, making it very difficult to distinguish complications arising from the underlying condition or OTR4132 administration. All SAEs were expected in the protocol as part of the natural evolution of ischemic stroke following thrombolysis and thrombectomy. One patient died from hemorrhagic transformation at 24 h. Although it is impossible to rule out a possible link between treatment administration and this event, the rate of symptomatic intra-cranial hemorrhages observed in our trial (1 in 19, i.e., around 5%) is consistent with larger clinical trials that assessed medical treatments versus EVT (about 4% in the meta-analysis performed by Lin et al., 2019 [13]). Asymptomatic hemorrhagic transformation at 24 h was noticed in 79% of cases on the basis of MRI assessment (including T2* sequences), which seems high but still consistent with previous studies. Indeed, hemorrhagic transformation, whether symptomatic or asymptomatic, assessed by non-contrast computed tomography can be detected in 50% of patients with large vessel occlusion treated with mechanical thrombectomy, and this percentage increases when assessment is performed using MRI T2* sequences [13, 14]. Noticeably, the grading of hemorrhagic transformations assessed on MRI by an independent radiologist, based on the Heidelberg classification, was not higher when treatment doses were increased. Available efficacy data suggested better functional recovery (NIHSS score improvement at 24 h) at higher doses compared with lower doses. Although these trends are based on small numbers, are not statistically significant, and preclude any robust conclusion, they suggest that there is no direct toxicity of OTR4132 even when doses were increased. These results are therefore encouraging and suggest a good

Table 4 Pre-planned efficacy endpoints (functional scores)

Variables	0.2 mg (*N* = 3)	0.5 mg (*N* = 3)	1.0 mg (*N* = 3)	1.5 mg (*N* = 6)	2.0 mg (*N* = 3)	2.5 mg (*N* = 1)	Total (*N* = 19)
Changes in NIHSS in percentage (24 h versus baseline), mean ± SD	− 54.1 ± 4	− 62.6 ± 36	3.6 ± 49	− 49.3 ± 41	− 98.1 ± 3	− 54.6	− 51.8 ± 42.1
Changes in NIHSS in percentage (7 days versus baseline), mean ± SD	− 85.6 ± 13.7	− 71.5 ± 43.8	− 23 ± 57.8	− 66.8 ± 44	− 100 ± 0	− 100	− 70.8 ± 41.8
Changes in NIHSS in percentage (30 days versus baseline), mean ± SD	− 86.4 ± 19.3	− 86.7	− 35.3	− 46.4 ± 75.8	− 100 ± 0	− 100	− 76.4 ± 38
Changes in NIHSS in percentage (90 days versus baseline), mean ± SD	− 74.6 ± 29.6	− 96.7 ± 4.7	− 51.2 ± 29.1	− 71.5 ± 52.6	− 100 ± 0	− 100	− 78.6 ± 33.4
Changes in mRS in percentage (24 h versus baseline), mean ± SD	− 6.7 ± 11.5	− 20 ± 0	26.7 ± 43.7	− 20 ± 23.1	− 40 ± 56.6	− 40	− 12 ± 34
Changes in mRS in percentage (7 days versus baseline), mean ± SD	− 46.7 ± 25.7	− 58.3 ± 33.3	6.7 ± 76.9	− 35 ± 58.6	− 71.7 ± 30.1	− 60	− 41.1 ± 50.3
Changes in mRS in percentage (30 days versus baseline), mean ± SD	− 55 ± 39.7	− 58.3 ± 33.3	2.2 ± 63.4	− 51.7 ± 28.4	− 58.3 ± 17.6	− 100	− 47.7 ± 42.2
Changes in mRS in percentage (90 days versus baseline), mean ± SD	− 45 ± 63.9	− 77.5 ± 3.5	− 31.1 ± 6	− 65 ± 34.2	− 78.3 ± 2.9	− 100	− 61.1 ± 40.3
Barthel index at 24 h, mean ± SD	12.5 ± 17.7	Missing	0.0	13.3 ± 10.4	67.5 ± 10.6	50.0	25.0 ± 27.6
Barthel index at 7 days, mean ± SD	97.5 ± 3.5	95 ± 0	70	68.3 ± 46.5	92.5 ± 10.6	100	85.9 ± 25.2
Barthel index at 30 days, mean ± SD	98.3 ± 2.9	60.0 ± 56.6	61.7 ± 44.8	70.0 ± 52.0	100 ± 0	100	80.7 ± 35.2
Barthel index at 90 days, mean ± SD	73.3 ± 46.2	100 ± 0	65 ± 42.4	80 ± 40	100 ± 0	100	84.7 ± 31.1
Montreal Cognitive Assessment at 90 days, mean ± SD	25.5 ± 6.4	17.0 ± 1.4	23.7 ± 1.2	24.5 ± 5.4	25.7 ± 2.5	Missing	23.6 ± 4.4
Rapid neurological improvements (with improvement of NIHSS ≥ 8)	2 (66.7%)	2 (66.7%)	0 (0%)	4 (66.7%)	3 (100%)	0 (0%)	11 (57.9%)
Rapid neurological improvements (with NIHSS equal to 0 or 1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	3 (15.8%)
Rapid neurological improvements (combined)	2 (66.7%)	2 (66.7%)	0 (0%)	4 (66.7%)	3 (100%)	0 (0%)	11 (57.9%)

mRS modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *SD* standard deviation

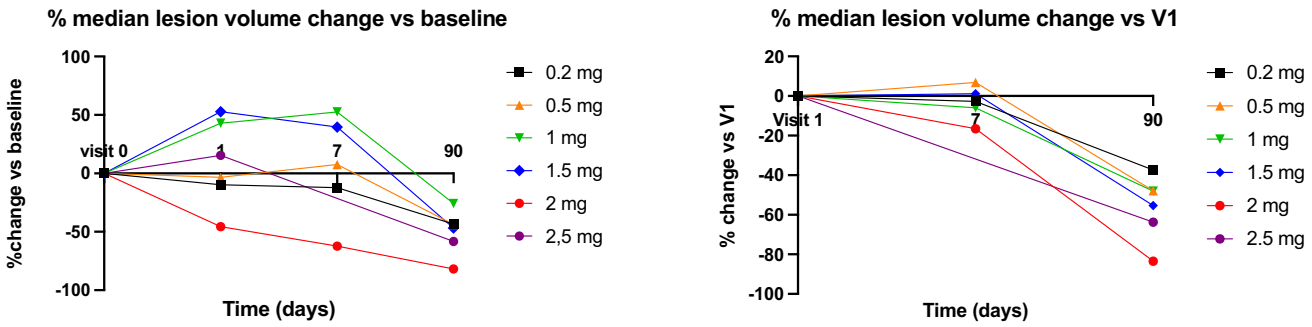

Fig. 2 Volumetric analyses of stroke lesions expressed as percentage change compared with baseline and V1 (24 h post-stroke)

safety profile of OTR4132. Efficacy and more robust safety evaluation could only be assessed by performing a larger randomized placebo-controlled trial.

The search for neuroprotective agents that would reduce the vulnerability of the brain to ischemia, to ultimately reduce permanent disability, has been an intense area of research with many failures. Indeed, despite huge efforts

Table 5 Results of volumetric analyses (absolute numbers)

Variables		0.2 mg (*N* = 3)	0.5 mg (*N* = 3)	1.0 mg (*N* = 3)	1.5 mg (*N* = 6)	2.0 mg (*N* = 3)	2.5 mg (*N* = 1)	Total (*N* = 19)
Lesion volume at baseline (mL)	*N*	3	3	3	6	3	1	19
	Mean ± SD	24.6 ± 25.6	27.9 ± 32.5	13.9 ± 12.3	38.2 ± 12.5	23.1 ± 5.7	11	26.8 ± 18.5
	Median	12	20	8.8	41.6	21.6	11	21.6
Lesion volume at 24 ± 6 h (mL)	*N*	3	3	3	6	3	1	19
	Mean ± SD	25.6 ± 21.7	41.2 ± 55.1	57.1 ± 66.3	104.3 ± 98.6	24 ± 24.2	12.7	57 ± 69.9
	Median	22.5	13.1	25.4	53.5	11.7	12.7	26.3
Lesion volume at 7 ± 2 days (mL)	*N*	3	3	3	5	3	0	17
	Mean ± SD	23.7 ± 23.5	44.4 ± 63.3	49.2 ± 66.1	85.9 ± 112.6	21 ± 24.1		49.7 ± 71.1
	Median	23	9.5	13.4	40	7.3		23
Lesion volume at 90 ± 14 days (mL)	*N*	3	3	3	4	3	1	17
	Mean ± SD	16.4 ± 15.4	21.9 ± 28	30.6 ± 44.8	58.5 ± 81.2	4.2 ± 2.8	4.6	26.9 ± 45
	Median	18.8	5.9	6.5	22.2	3.3	4.6	7.4

(more than a thousand neuroprotective drugs tested so far), no neuroprotective drug is currently approved in patients with ischemic stroke [15]. It has been advocated that, in previous clinical work, the lack of reperfusion may have prevented effective delivery of neuroprotectants to cells in the ischemic penumbra, which would be the most susceptible responsive zone to therapeutic intervention. Considering this hypothesis, Shi et al. (2018) recommended that combinations of neuroprotectants with thrombolytic drugs or EVT should be studied as new therapeutic strategies for acute ischemic stroke [1]. Although the neuroprotectant nerinetide in combination to EVT failed to demonstrate clinical efficacy, butylphthalide showed promising effects [16, 17].

Heparan sulfate mimetics have been proposed as therapeutics for brain repair [18–20]. Although this approach is conceptually attractive, most of the evidence has been theoretical or based on pre-clinical in vitro models with few supportive clinical data in the field of nervous system disorders [10, 11]. Development of heparin mimetics has been limited by anticoagulation effects. One advantage of RGTA® is their resistance to glycanases, which enables the effectiveness of very low doses, far below doses with any anticoagulation effects [21].

There are several ways through which OTR4132 could exert its neuroprotective effects. The extracellular matrix constitutes a complex environment that surrounds and supports various cells. It contains numerous signaling and structural proteins that regulate tissue homeostasis. Among these components, the glycosaminoglycans, in particular HS, play a pivotal role in the cell microenvironment and in the regulation of tissue homeostasis. HS are key components of the extracellular matrix scaffold as they bind, protect, and bridge structural proteins (collagen, fibronectin, laminin, etc.). In addition, HS store and protect numerous cellular communication peptides (e.g., the vast majority of growth factors, cytokines, chemokines, and interleukins). After ischemic stroke, spontaneous tissue repair is generally limited [22]. Both endogenous and exogenous neuroprotective/neurotrophic substances may prevent neurons from degeneration and/or enable regeneration [23, 24]. However, enzymatic degradation of these neuroprotective/neurotrophic substances, which occur rapidly after their release, may limit their effects [24]. HS are destroyed by enzymes called heparanases, and hence can no longer protect extracellular matrix proteins, leading to local communication peptides being rapidly degraded. OTR4132 is expected [1] to protect endogenously released neurotrophic factors and slow down their degradation [2] as well as reconnect structural laminin and collagen scaffolds. With local administration (i.e., intra-arterial), OTR4132 might become of high therapeutic interest as it would contribute to increasing the local availability of endogenous trophic factors exactly in the region where they are required, leading to better BBB and nervous system repair, which would be associated with less hemorrhagic transformation and better clinical recovery.

This study has several limitations inherent to a first-in-human study: there was no control group, the number of patients was limited, and there was some imbalances in baseline variables between groups. Such limitations can only be solved in a larger placebo-controlled randomized trial.

5 Conclusions

This trial demonstrates a good feasibility of OTR4132 intra-arterial injection for patients suffering from severe acute ischemic stroke treated with EVT. The efficacy and safety of

OTR4132 should be further assessed in a larger randomized controlled trial.

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Declarations

Conflicts of Interest Denis Barritault is co-inventor and co-owner in the patents describing RGTA® technology and applications. He is the founder, president, and shareholder of the company OTR3, which manufactures and commercializes CACIPLIQ20®. Frederic Sedel, Martin Inizan, Franck Chiappini, and Agnes Choppin are employees and shareholders of OTR3 and are co-inventors of patents describing OTR4132-MD technology and applications. Charlotte Rosso, Catherine Oppenheim, and Francisco Moniche received fees for their work as members of the independent data safety monitoring board. Other authors declare no conflicts of interest in relation with this work.

Ethics Approval The study was approved by the ethics committee (Comité de protection des personnes Ile de France 5) under the reference 21.01365.000016 and by the French regulatory authority (Agence nationale de sécurité du médicament et des produits de santé) under the reference DMCDIV/FLOW/AE/2018-A03117-48-B/MS2. The study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

Consent to Participate Written informed consent followed an emergency procedure with three different possibilities: (1) direct patient informed consent when the patient was conscious and able to provide its consent, (2) legal representative if the patient was not able to provide their consent, and (3) an independent physician (not investigator in the study) when the patient was not able to provide their consent and when there was no legal representative available. In cases (2) and (3), patient's written informed consent was obtained afterwards, once the patient recovered sufficiently, in order to continue the study follow-up and to authorize the use of study data.

Consent for Publication Not applicable.

Code Availability Not applicable.

Availability of Data and Materials Study data are available on request to the sponsor OTR3.

Authors Contributions All authors contributed to this work and provided feedback on the drafting of the manuscript. Olivier Detante, Frederic Sedel, Martin Inizan, and Denis Barritault were involved in the design of the clinical trial. Olivier Detante, Xavier Barreau, René Anxionnat, Olivier Heck, and Igor Sibon were investigators in the study and participated in the collection and analysis of the data. Charlotte Rosso, Catherine Oppenheim, and Francisco Moniche were members of the data safety monitoring board and were involved in data interpretation, dose escalation, methodological aspects, revising the manuscript for important intellectual content, and final approval of the version to be published. Franck Chiappini and Agnès Choppin were involved in the preclinical phases, data analysis and representation, funding, and submission to regulatory authorities. All authors read and approved the final version.

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