## 2 SYNOPSIS

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| **Name of the Sponsor/Company:**<br>Ruprecht-Karls-University Heidelberg | **INDIVIDUAL SUMMARY TABLE**<br>Volume:<br>Page:<br><br>**No. EudraCT:** 2012-003609-80 | **(For National Authority Use only)** |
| **Name of Finished Product:**<br>Actilyse® (alteplase) | | |
| **Name of Active Ingredient:**<br>Recombinant Tissue Plasminogen Activator (rt-PA) | | |

**STUDY CODE:**
ECASS-4: ExTEND

**TITLE OF STUDY:**
ECASS-4: ExTEND: **E**uropean **C**ooperative **A**cute **S**troke **S**tudy-4 **Ex**tending the time for **T**hrombolysis in **E**mergency **N**eurological **D**eficits

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Amiri, H., Bluhmki, E., Bendszus, M., Eschenfelder, C.C., Donnan, G.A., Leys, D., Molina, C., Ringleb, P.A., Schellinger, P.D., Schwab, S., et al. (2016). European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis in emergency neurological deficits ECASS-4: ExTEND. Int. J. Stroke Off. J. Int. Stroke Soc. *11*, 260–267.

Bendszus, M., Donnan, G.A., Hacke, W., Molina, C., Leys, D., Ringleb, P.A., Schellinger, P.D., Schwab, S., Toni, D., Wahlgren, N., et al. (2016). ECASS-4:EXTEND: EUROPEAN COOPERATIVE ACUTE STROKE STUDY-4 - EXTENDING THE TIME FOR THROMBOLYSIS IN EMERGENCY NEUROLOGICAL DEFICITS. Eur. Stroke Organ. Conf. 2016 *Abstract number: AS02-007*.

*Detailed addresses of study centres added as Appendix16.1.4a to this report

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**STUDY PERIOD (YEARS):**

Date of first enrolment/first patient first visit: 02nd January 2014

Date of last completed/last patient last visit: 18th December 2017

**PHASE OF DEVELOPMENT: Phase III**

**OBJECTIVES:**

The primary objective was to test the hypothesis that ischemic stroke patients with significant penumbral mismatch at 4.5 - 9 hours post onset of stroke or after waking with symptoms of stroke ("wake up stroke") will have improved clinical outcomes when given intravenous recombinant tissue plasminogen activator (rt-PA) (alteplase) compared to patients treated with placebo.

The secondary objectives were the collection of explorative data of functional outcome, including depression and cognitive impairment and the effect of thrombolysis.

**METHODOLOGY:**

The study was a randomised, multicentre, double-blind, placebo controlled phase 3 study (two arms with 1:1 randomisation). Randomisation was stratified for time of randomisation after stroke (<6 hours, 6-9 hours, wake up stroke) and for the National institute of health stroke scale (NIHSS) score prior to randomisation (≤8, 9-13, and ≥14). Inclusion and exclusion criteria were the same as that of the START-EXTEND trial, in order to allow pooled analysis.

The prospective follow-up of each patient was 90 days, with a total of 4 visits scheduled according to the protocol, at screening (Visit -1)/baseline (Visit 0), Day 1 (12-24 post treatment administration, Visit 1), Day 3 (Visit 2), Day 7±1 (Visit 3) and Day 90±7 (Visit 4).

**NUMBER OF PATIENTS (planned and analysed):**

Planned/Adapted during Interim Analyses:

The initially estimated sample size was 132 patients in each treatment group (total of 264 patients).

According to the last version of the Clinical Study Protocol (CSP)(Version 1.6, including Amendment 2, 18 April 2017), an Interim Analysis was performed when 3 month follow up data from the first 110 randomized patients were available, to provide substantiate data for an updated sample-size calculation or early stopping for futility.

According to the DSMB recommendation after the interim analysis, the study was stopped due to low recruitment rate and new treatment options (endovascular therapy), despite the futility criteria were not met and no safety endpoints were met, either. This meant an immediate stop of recruitment, but follow-up continued as planned according to the protocol (90 days) for patients that had not yet completed the study.

No sample size adaptation was finally performed during the Interim Analysis.

Analysed in the Final Analysis:

The final analysis was performed on a total of 119 evaluable patients in Safety set population:

| | rt-PA (alteplase) | Placebo | Total |
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| **No. screened:** | | | 232 |
| **Patients included in study** | | | 120 |
| **No. randomised and treated:** | 61 | 58 | 119 |
| **Males, n (%):** | 36 (59.0) | 31 (53.4) | 67 (56.3) |
| **Mean age (SD), years:** | 73.6 (12.3) | 75.3 (10.7) | 74.4 (11.5) |
| **No. analysed for efficacy and safety (Safety Set population):** | 61 | 58 | 119 |
| **No. completed the study:** | 51 | 51 | 102 |

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:**

Inclusion criteria

1. Patients presenting with acute ischemic Middle Cerebral Artery (MCA) stroke
2. Patient, or legally acceptable representative who gave written informed consent. An independent witness could sign the consent form if the patient was able to give verbal consent, but unable to sign
3. Patient's age was ≥18 years
4. Treatment onset within ≥ 4.5 – 9 hours after stroke onset*

*Patients with 'wake up' strokes could be included. 'Wake up' strokes are defined as having no stroke symptoms at sleep onset, but on waking. The time of stroke onset is to be taken as the mid-point between sleep onset (or last known to be normal) and time of waking.

5. NIHSS score of 4 to 26 with clinical signs of hemispheric infarction
6. Penumbral mismatch imaging[C] via local assessment using a computer based analysis system (e.g. Rapid processing of perfusIon and diffusion [RAPID]) if available, using a perfusion volume (on perfusion-weighted imaging [PWI]) to infarct core (on diffusion-weighted imaging [DWI]) ratio of ≥ 1.2, and a minimum perfusion lesion volume of 20 ml.

Exclusion criteria

1. Intracranial hemorrhage (ICH) identified by computer tomography (CT) or magnetic resonance imaging (MRI)
2. Rapidly improving symptoms, particularly if, in the opinion of the investigator, the improvement was likely to result in the patient having an NIHSS score of <4 at randomisation
3. Pre-stroke modified ranking score (mRS) score of >1 (indicating previous disability)
4. Contra indication to imaging with MRI
5. Infarct core >1/3 MCA territory qualitatively or >100 ml quantitatively (determined by DWI lesion on MRI).
6. Any MRI findings indicative of a high risk of ICH related to potential intavenous (IV)-rtPA treatment in the judgment of the investigator
7. Participation in any investigational study in the previous 30 days
8. A life expectancy of <3 months
9. Any condition that, in the opinion of the investigator, could impose hazards to the patient if

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study therapy is initiated or affect the participation of the patient in the study (this applies to patients with severe microangiopathy such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura).

10. Pregnant (clinically evident) or breastfeeding women
11. Previous stroke within the three months prior to randomisation
12. Recent history (in the opinion of the investigator) or clinical presentation of ICH, subarachnoid hemorrhage (SAH), arterio-venous (AV) malformation, aneurysm, or cerebral neoplasm.
13. Use of oral anticoagulants within 48 hours prior to randomisation (including, but not limited to Rivaroxaban, Apixaban, or Edoxaban) and a prolonged prothrombin time (INR > 1.6) or any activated partial thromboplastin (aPTT) time exceeding 1.5 times the normal range or prolonged Thrombin-Time (TT), indicating the potential use of Dabigatran-Etexilate.
14. Use of heparin, except for low dose subcutaneous heparin, within 48 hours prior to randomisation
15. Use of glycoprotein IIb-IIIa inhibitors within 72 hours prior to randomisation.
16. Platelet count <100.000/µl (<100G/l)
17. Blood glucose <50mg/dl (2.8 mmol/l) or >400mg/dl (22.2mmol/l)
18. Uncontrolled hypertension defined by a blood pressure > 185 mmHg systolic or >110 mmHg diastolic on at least two separate occasions at least 10 minutes apart, or requiring aggressive treatment to reduce the blood pressure to within these limits. The definition of “aggressive treatment” is left to the discretion of the investigator.
19. Hereditary or acquired hemorrhagic diathesis
20. Gastrointestinal or urinary bleeding within 21 days prior to randomisation
21. Manifest or recent acute pancreatitis
22. Manifest severe liver disease including hepatic failure, cirrhosis, portal hypertension and active hepatitis
23. Major surgery within 14 days prior to randomisation which poses a risk in the opinion of the investigator.
24. Recent (within 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a non-compressible blood-vessel
25. Exposure to a thrombolytic agent within 72 hours prior to randomisation
26. Hypersensitivity to alteplase or any of the excipients

**TEST PRODUCTS AND REFERNCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:**

**Test product:** Alteplase 50 mg and matching placebo

**Dose and mode of administration:** The investigational medicinal product (IMP) was reconstiuted with 50ml of sterile water (supplied with the vials) and immediatelly administered through a dedicated IV cannula. The dose of IMP administered was 0.9 mg/kg (maximum 90mg), 10% given

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as a bolus injection over 1 minute and the remaining 90% as an infusion over 60 minutes.

**Lot/Batch number:** 13900040/ 13900041/ 15900013/ 16900034/ 17900033/ 14900065 / 14900066/ 15900014/ 16900035/17900034 (for Alteplase 50 mg or matching placebo) and 13800493 / 13800494/ 15800187/ 16800351/ 17800625 / 14800252/ 14800253 /15800188/ 16800352/ 17800626 (for solvent)

**DURATION OF TREATMENT:** Total study duration was 3 years. Each patient participated in the trial for 3 months (90±7 days).

**CRITERIA FOR EVALUATION:**

**EFFICACY:**

**Primary endpoint**

- Categorical shift in the mRS at Day 90

**Secondary endpoints**

- Disability at Day 90, dichotomised as a favorable outcome (mRS) 0–1 vs. 2 - 6[A]
- Change in ≥ 11 NIHSS points or reaching ≤ 1 on this scale at day 1 and Day 90
- Reperfusion at 12-24 hours after treatment
- Recanalisation at 12-24 hours after treatment
- Infarct growth on DWI within 12-24 hours after treatment
- NIHSS score at Day 7
- Barthel Index (BI) at Day 90
- Montreal Cognitive Assessment (MoCA) score at Day 90

**Tertiary endpoints (in some centres)**

- Montgomery-Asberg Depression Rating Scale (MADRS) score at Day 90

**SAFETY:**

- Death due to any cause
- Neurological death
- Symptomatic intracranial hemorrhage (ICH) as defined by ECASS-3 definition[B]

[A] This is the key secondary endpoint to ensure the combined analysis with the EXTEND trial

[B] Any apparently extravascular blood within the cranium that was associated with clinical deterioration, as defined by an increase of at least 4 points on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration

**STATISTICAL METHODS:**

The primary outcome analysis of the categorical shift in mRS was undertaken on the full range (0-6) of the mRS using Cochran-Mantel-Haenszel (CMH) shift test and proportional odds logistic regression patient to the validity of shift analysis model assumptions. Initially, the stratification factors "time since stroke onset" and "stroke severity" as measured using NIHSS had to be considered for this analysis. However, since this study was stopped early due to slow recruitment, the only formal statistical analysis that was undertaken was the primary efficacy analysis but without stratification.

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For the analysis of the secondary endpoints the proportions of mRS 0-1 outcomes had to be initially compared between the treatment and placebo arm using logistic regression with time between stroke onset and treatment (<6, 6-9 hours, wake up), initial stroke severity (NIHSS), and age as covariates. However, since the study was stopped early due to slow recruitment, this secondary analysis was finally performed without covariates. Analyses of the other secondary endpoints were carried out according to standard statistical principles for comparison of parametric or non-parametric distributions as appropriate.

In the main efficacy analysis, patients who died during the follow-up were assigned a mRS score of "6" at Visit 4. Also, a sensitivity, worst-case scenario efficacy analysis was performed, in which patients with missing data at Visit 4 were assigned the score of 5 on the mRS (under the assumption that they were alive at that time point). For the NIHSS, both the observed case and Last Observation Carried Forward imputation methods were applied.

An interim analysis was performed as planned upon obtaining 3 month follow up data from the first 110 randomised patients. For this interim analysis a descriptive analysis of the primary endpoint (categorical shift in mRS) was used (no statistical testing was performed). The results were presented to the members of the Date Safety Monitoring Board (DSMB) only. Rationale for this interim-analysis was to provide substantiate data for an updated sample-size calculation or early stopping for futility, which was necessary after unexpected prolongation of the trial due to slow recruitment.

According to the DSMB recommendation after the interim analysis, the study was stopped due to low recruitment rate and new treatment options (endovascular therapy), despite the futility criteria were not met and no safety endpoints were met, either.

Despite the early stopping, data and final results will be pooled with those from the START-EXTEND trial, as initially planned in the CSP.However this will be presented in a different document.

**SUMMARY AND CONCLUSION(S):**

**DEMOGRAPHIC, BASELINE AND TREATMENT CHARACTERISTICS:**

A total of 119 patients were included in the safety set population and randomized after stratification for time after stroke onset and NIHSS score prior to randomisation into two groups: 58 patients in the rt-PA group and 61 in the placebo group. Baseline characteristics were well balanced between study groups. The total median (range) age was of 78.0 (40, 95) years and most patients were male (56.3%). The mean (SD) stroke severity at baseline, according to the NIHSS score, was 10.6 (5.8). The median (range) time to treatment was of 7.4 (5, 9) hours. A total of 42 (68.9%) patients and 40 (69.0%) patients in the rt-PA (alteplase) group and the placebo group were wake-up patients.

**EFFICACY RESULTS:**

The primary objective of this study was not met, as differences in the shift in the 90 day of mRS distribution at Day 90 were observed in the rt-PA (alteplase) over the placebo group (OR $_{\text{rt-PA vs placebo}}$ [95% CI]=1.200 [0.633, 2.273], p=0.5766) (main efficacy analysis). In the sensitivity analysis, with worst-case scenario imputation for mRS values, the shift of 90 day mRS distributions remained very similar to the ones observed in the main analysis. A slightly higher OR for rt-PA over the placebo group was observed that did not reach statistical significance either (OR $_{\text{rt-PA vs placebo}}$ [95% CI] = 1.233 [0.656, 2.317], p=0.5151).

The treatment effects were similar when the mRS values were analysed as a dichotomised

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outcome (favourable mRS score: 0-1; unfavourable mRS score: 2-6). A total of 35.0% (95% CI: 23.1, 48.4) of the patients in the rt-PA (alteplase) group had a favourable outcome compared with 28.6% (95% CI: 17.3, 42.2) of the patients in the placebo group, representing an absolute improvement of 6.4 percentage points. The OR $_{\text{rt-PA vs placebo}}$ (95% CI) was 1.346 (0.613, 2.954) in the main efficacy analysis, and did not reach statistical significance (p=0.4585). In the sensitivity analysis, with worst-case scenario imputation for mRS values, results remained very similar to those observed in the main analysis (no significant differences), although the OR for rt-PA over placebo was slightly higher (OR $_{\text{rt-PA vs placebo}}$ [95% CI] = 1.378 [0.631, 3.010], p=0.4211).

The NIHSS score decreased with time in a similar manner between groups showing a patient improvement over time that seemed independent of the treatment administered, as suggested by the overlapping 95% CIs both at baseline and at Visit 4. However, in the observed case analysis, the rt-PA (alteplase) group showed a numerically lower mean (95% CI) NIHSS score at Visit 4 (Day 90) than the one achieved in the placebo group. In the rt-PA group a decrease from 10.9 (9.4, 12.4) at baseline to 3.6 (2.3, 4.9) at Visit 4 (Day 90) was observed compared to a decrease from 10.3 (8.8, 11.8) to 5.0 (3.4, 6.7) in the placebo group (range from 0 to 42, with higher values reflecting more severe cerebral infarcts). Similar proportions (95% CI) of patients with reperfusion (rt-PA [alteplase]/placebo 50.0% [34.9, 65.1]/ 52.4% [36.4, 68.0]) and recanalisation (rt-PA [alteplase]/placebo 47.7% [32.5, 63.3]/ 43.2% [27.1, 60.5]) at 12-24h after treatment were observed. The mean lesion size (SD) on DWI MRI decreased in both groups after 12-24 hours post treatment (Visit 1), reaching very similar volumes between the rt-PA (alteplase) and the placebo groups: 11.53 (15.68) and 9.44 (13.36) ml, respectively. The mean (95%CI) decrease in stroke lesion (i.e. “infarct growth”) between screening and Visit 1 (12-24 hours) was higher in the placebo group: -2.97 (0.59, -6.53) ml in the rt-PA (alteplase) and -11.23 (-2.40, -20.06) ml in the placebo group.

The MoCA and BI scores at Visit 4 (Day 90) were also comparable between groups, showing a mild cognitive impairment and a moderate patient dependency, respectively. The mean (95%CI) MoCA score was 21.0 (18.4, 23.6) and 20.2 (18.1, 22.3) in the rt-PA (alteplase) group and the placebo group respectively (range from 0 to 30, with a score of 26 and higher generally considered normal). Similarly, a mean (95%CI) BI score of 79.2 (70.1, 88.3) and 70.4 (59.9, 80.9) in the rt-PA (alteplase) group and the placebo group respectively was observed at Day 90 (range 0 to 100 with the highest score reflecting complete independence in everyday activities).

The initial severity of depressive symptoms, as measured by the MADRS Score, was similar between groups with a score of 8.8 (4.5, 13.1) and 7.9 (2.3, 13.4) in the rt-PA (alteplase) group and the placebo group respectively indicative of mild depression (range 0 to 60, with higher values reflecting more severe depression). At Visit 4 (Day 90) a decrease in the MADRS score was observed in the rt-PA (alteplase) group (mean [95%CI] = 5.6 [3.0, 8.2]) indicative of a normal/symptom absent depression. However, in the placebo group an increase in the MADRS score was observed (mean [95%CI] = 13.7 [7.5, 19.8]) still indicative of mild depression.

**SAFETY RESULTS:**
Nearly all patients reported at least one adverse event (AE) in both groups (95.1% in the rt-PA [alteplase] group and 94.8% in placebo group). The most frequently reported AEs (>10% in any group) per preferred term were: constipation (rt-PA [alteplase]/placebo = 26.2%/15.5%), atrial fibrillation (21.3%/ 12.1%), pyrexia (23.0%/13.8%), urinary tract infection (18.0%/25.9%), headache

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(14.8%/10.3%), hypokalaemia (11.5%/15.5%), haemorrhagic transformation stroke (11.5%/5.2%) and nausea (8.2%/12.1%).

More patients presented an AE related to the study treatment in the rt-PA (alteplase) group (24.6% [n=15]) than in the placebo group (6.9% [n=4]). The most frequently reported treatment related AEs (>2%) by preferred term in the rt-PA (alteplase) group were: haemorrhage transformation stroke (9.8%), haematoma (8.2%), cerebral haemorrhage (4.9%) and haematuria (3.3%); in the placebo group: two (3.4%) patients had a haemorrhagic transformation stroke, one (1.7%) patient had a haemorrhagic cerebral infarction and one (1.7%) patient had haemorrhage urinary tract.

In total, seven (11.5%) and four (6.8%) patients in the rt-PA (alteplase) and placebo groups, respectively, had a fatal outcome; only one (1.6%) death in the rt-PA group was considered related to the study treatment (cerebral haemorrhage [which fulfilled the ECASS-III criteria for symptomatic ICH]). In the rt-PA (alteplase), two (3.3%) patients had a neurological death (one patient died due to the previously indicated cerebral haemorrhage and one patient died due to neurological decompensation) versus none in the placebo group. The other reasons for death in the rt-PA group were: road traffic accident, acute renal failure, aspiration pneumonia (in a patient with ongoing pulmonary oedema and cardiac failure) and unknown (two cases). The reasons for death in the placebo group were: aspiration pneumonia, bacterial pneumonia (two cases) and unspecified pneumonia.

Including the aforementioned deaths, a total of 34.4% of patients and 31.0% of patients presented at least one serious AE (SAE) in the rt-PA (alteplase) and placebo groups, respectively. The most common SAEs (≥2% in any group) by preferred term were: aspiration pneumonia (rt-PA [alteplase]/placebo = 3.3%/1.7%), haematuria (3.3%/0%), carotid artery stenosis (3.3%/3.4%), pneumonia (1.6%/3.4%), pneumonia embolism (1.6%/3.4%), pneumonia bacterial (0%/3.4%) and deep vein thrombosis (0%/3.4%). Of these patients, 5 patients in the rt-PA (alteplase) group (8.2% of total group) presented one treatment related SAE: brain oedema (1.6%), cerebral haemorrhage (1.6%), pleural effusion (1.6%), haematuria (1.6%), and haemorrhagic transformation stroke (1.6%); no patients from the placebo group presented a treatment related SAE (0%).

Adverse events of special interest (AESI) were defined for this study as follows: intracranial hemorrhage. Only one patient (patient #1103) in the rt-PA group (1.6%) and none in the placebo group suffered a symptomatic ICH throughout the study; this AE of special interest (AESI) was considered serious and related to study treatment, and had a fatal outcome. In total, five (8.2%) patients in the rt-PA (alteplase) and one (1.7%) in the placebo group had an AE that was considered an AESI (intracranial haemorrhage) by the investigator. In the rt-PA group, besides the symptomatic ICH in the aforementioned patient #1103, four (6.6%) patients had a haemorrhagic transformation stroke (all of them related to the study treatment). The AESI in the placebo group was: haemorrhagic transformation stroke (related to study treatment).

No patients discontinued due to an AE in the rt-PA (alteplase) group. However, two patients in the placebo group discontinued the study prematurely due to a serious, non-related AE (aspiration pneumonia and bacterial pneumonia); these two patients had a fatal outcome.

**CONCLUSION(S):**
Similar clinical outcomes and safety results were observed between ischemic stroke patients with significant penumbral mismatch treated with rt-PA (alteplase) or placebo at 4.5 - 9 hours after stroke onset (or, in “wake up” strokes, after mid-point between sleep onset and waking). After early stopping of the trial, with only 44% of initially targeted sample size due to slow recruitment, the primary objective of the study was not met. There was no significant shift in the 90 day mRS

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| distribution favouring rt-PA (alteplase) over the placebo group. Therefore, although the safety profile was good, the clinical benefit of rt-PA (alteplase) treatment 4.5 to 9 hours after the onset of stroke could not be tested do the small number of patients included in the trial. | | |