Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Alteplase

Proprietary Product Name: Actilyse

Submission No: PM-2009-02549-3-3

Sponsor: Boehringer Ingelheim Pty Ltd

January 2011

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	22 September 2010
Active ingredient(s):	Alteplase
Product Name(s):	Actilyse
Sponsor's Name and Address:	Boehringer Ingelheim Pty Ltd PO Box 1969, Macquarie Centre, North Ryde, NSW 2113
Dose form(s):	Powder for reconstitution for injection
Strength(s):	10mg, 20mg and 50mg.
Container(s):	Glass vial
Pack size(s):	One vial of diluent (10 mL) and one vial of powder (10 mg) One vial of diluent (20 mL) and one vial of powder (20 mg) One vial of diluent (50 mL) and one vial of powder (50 mg)
Approved Therapeutic use:	Actilyse is indicated for thrombolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (for example, cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.
Route(s) of administration:	Intravenous (IV)
Dosage	0.9 mg/kg body weight (maximum 90mg) IV over 60 minutes with 10% of total dose as a bolus.
ARTG number(s):	64240 (10 mg), 43375 (20 mg), 17905 (50 mg)

Product Background

Alteplase is a recombinant tissue plasminogen activator that binds to fibrin in a thrombus and converts plasminogen to plasmin which leads to local fibrinolysis. Actilyse (alteplase) is currently registered for use as a thrombolytic in patients with myocardial infarction, pulmonary embolism and acute ischemic stroke. This submission only relates to the acute ischemic stroke indication: the sponsor proposes to increase the patient group for whom Actilyse is approved for by increasing the treatment window from 0-3 h after the onset of symptoms of acute ischaemic stroke to 0-4.5 h. The sponsor is also applying to make a number of changes to the PI, notably removing the contraindication for use in patients >80 years of age and updating the clinical trials section for all three indications.

Alteplase has been considered by the Australian Drug Evaluation Committee (ADEC; now called Advisory Committee for Prescription Medicines (ACPM)) previously at the following meetings:

-February 1988: Recommended for approval for myocardial infarction.

-April 1995: Recommended for approval for pulmonary embolism.

-June 1996: Recommended for approval for a modified use in myocardial infarction.

-October 1998: Recommended for rejection in acute ischemic stroke due to the benefit risk ratio being unconvincing (efficacy demonstrated in one of two pivotal studies and increased risk of intracranial haemorrhage). This used data from the NINDS 1 and 2 and ECASS I studies.

-June 2003: Recommended for approval for acute ischemic stroke within 0-3 hours. This used data from ECASS II and Atlantis studies.

Actilyse alteplase 10, 20, 50 mg powder for injection vial (AUST R 64240, 43375 & 17905) is currently approved by the TGA as a thrombolytic treatment of myocardial infarction associated with suspected occlusive artery thrombi, acute massive pulmonary embolism and acute ischaemic stroke for the following indications:

> ***Myocardial infarction.*** Actilyse is indicated for intravenous use in adults for the lysis of suspected occlusive coronary artery thrombi associated with evolving transmural myocardial infarction. Treatment should be initiated as soon as possible after the onset of symptoms. The treatment can be initiated within 12 hours of symptom onset.
>
> ***Pulmonary embolism.*** Actilyse is also indicated in patients with acute massive pulmonary embolism in whom thrombolytic therapy is considered appropriate.
>
> ***Acute ischaemic stroke:*** Actilyse is indicated for thrombolytic treatment of acute ischaemic stroke. Treatment should only be initiated within 3 hours after the onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques such as cranial computerised tomography (CT).

Alteplase for the treatment of acute stroke in the 0-3 hour time window was approved by the European Medicines Evaluation Agency (EMEA) in 2002. The ECASS III, randomized, placebo-controlled, "confirmatory" efficacy and safety study, and the observational Safe Implementation of Thrombolysis for Stroke- MOnitoring STudy (SITS-MOST) safety monitoring study were both initiated by the sponsor as part of a post-approval commitment to the EMEA. The intention of ECASS III was to replicate the positive findings of the NINDS study in a European setting and to investigate whether the approved time window of 0-3 hours could be extended.

The current guidelines of the European Stroke Organisation (ESO) recommend the use of alteplase within 4.5 hours of onset of ischaemic stroke. These guidelines were updated to include the 0-4.5 hour treatment window recommendation in January 2009. In addition, the American Heart Association/American Stroke Association (AHA/ASA) issued a Science Advisory in 2009 recommending that recombinant tissue plasminogen activator (rtPA) should be administered to eligible patients within 3 hours of onset of stroke and to eligible patients who can be treated within 3 to 4.5 hours after stroke [Zoppo *et al*., 2009[1]]. Both the recommendations of the ESO and the AHA/ASA appear to have been based primarily on the results of ECASS III [Hacke *et al*., 2008][2], supported by the findings in SITS- International Stroke Thrombolysis Register (SITS-ISTR)

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[1] Zoppo del *et al*., (2009). Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke* 40:2495-2948.

[2] Hacke *et al*., (2008). Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. *N Engl J Med.* 359:1317-1329.

[Wahlgren *et al*., 2008][3]. The ESO and AHA/ASA recommend the same dose for the extended time interval of 0-4.5 hour time window as that for the 0-3 hour time window.

Regulatory Status

Alteplase has been submitted for this extension of indications in Europe (June 2009) and New Zealand (July 2009) and is under evaluation in both places. The new indication has not been approved by any major regulatory agency. In the USA and Canada, the sponsor does not hold marketing authorisation which is held by Genentech in the USA and Hoffman-La Roche in Canada.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

No new quality data were submitted.

III. Nonclinical Findings

No new nonclinical data were submitted with this application.

IV. Clinical Findings

Introduction

In support of its application to extend the time window from 0-3 hours to 0-4.5 hours the sponsor has submitted the following key data:

- the pivotal European Cooperative Acute Stroke Study III (ECASS III);
- the supporting observational Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) study;
- pooled efficacy and safety analyses from ECASS III and five previously evaluated placebo-controlled trials of alteplase (0.9 mg/kg body weight) for the treatment of acute ischaemic stroke. The five placebo-controlled clinical trials previously evaluated by the Therapeutic Goods Administration (TGA) were ECASS II, ATLANTIS A and B, and NINDS 1 and 2; and
- integrated summaries of clinical efficacy and safety for alteplase for acute ischaemic stroke in the 3-4.5 hour time window.

The sponsor has also submitted: two, post-marketing safety reports relating to alteplase, a clinical overview supporting the use of alteplase in the 0-4.5 hour time window for the treatment of acute ischaemic stroke; an addendum to the clinical overview to support the removal of the absolute contraindication in the PI for patients aged ≥ 80 years age; the SITS-MOST study to support additional statements in the PI relating to the use of alteplase in the 0-3 hour time window; and an overview of seven additional published alteplase efficacy and safety studies relating to treatment onset in various time windows. The sponsor has also submitted a Risk Managements Plan (RMP) relating to the use of alteplase for the treatment of acute ischaemic stroke.

Good Clinical Practice Aspects

The sponsor has provided an assurance that it is in possession of documentation to demonstrate that the clinical studies conducted outside of Australia are in line with the International Conference on

[3] Wahlgren *et al*. (2008). Thrombolysis with alteplase for acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 372:1303-1309.

Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and conform to the declaration of Helsinki. The sponsor understands that the documentation includes Ethics Review Committee approvals and patient consent forms. The sponsor also stated that the assurance does not apply to the published (non-Boehringer Ingelheim) studies.

Pharmacokinetics

No new data were submitted under this heading.

Drug Interactions

No new data were submitted under this heading.

Pharmacodynamics

No new data were submitted under this heading.

Efficacy

Introduction

The key efficacy data supporting the application to extend the treatment time window from 0-3 hours to 0-4.5 hours are:

- the pivotal European Cooperative Acute Stroke Study III (ECASS III);
- the supporting observational Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) study;
- the pooled efficacy and safety analyses from ECASS III and five previously evaluated placebo-controlled trials of alteplase (0.9 mg/kg body weight) for the treatment of acute ischaemic stroke. The five previously evaluated placebo-controlled clinical trials included in the pooled data analysis with ECASS III were ECASS II, ATLANTIS A and B, and NINDS 1 and 2; and
- an integrated summary of clinical efficacy.

The efficacy data also included pooled data in very elderly patients (aged ≥ 80) aimed at removing the current absolute contraindication in the Actilyse PI relating to the use of the drug for the treatment of acute stroke in this age group.

Dose Response Studies and Main Clinical Studies

The pivotal study in the application was ECASS III. The two main supportive studies were SITS-ISTR, and a pooled data analysis of six randomized, placebo-controlled studies (including ECASS III). There were no dose response studies. The alteplase dose being proposed for approval is the same as that currently approved for the 0-3 hour time window: that is, 0.9 mg/kg body weight, maximum of 90 mg, infused intravenously over 60 minutes with 10% of the dose administered as an initial intravenous bolus.

ECASS III (pivotal study) included 821 patients aged 18 to > 80 years with acute ischaemic stroke of whom 418 were randomized to alteplase and 403 to placebo. The study was approved by the independent ethics committees (IECS) of the participating clinical centres and relevant competent authorities according to relevant ICH guidelines. Informed consent was obtained from individual patients (written or according to relevant national guidelines or legislation for those patients unable to write), or their legal representatives in exceptional circumstances where patients were unable to give informed consent due to the severity of the stroke. The study included one randomized patient without valid informed consent. ECASS III has been published (Hacke *et al*., 2008).

SITS-ISTR (a main supportive study) is a large, ongoing, observational study involving information submitted to a central registry by participating centres on patients in the general community treated with alteplase for acute ischaemic stroke. In the SITS-ISTR published paper, data were provided on 664 patients treated in the 3-4.5 hour time window and 11,865 patients treated in the 0-3 hour time window (Wahlgren *et al*., 2008). The integrated clinical summary included updated SITS-ISTR information collected between 16 November 2007 and December 2008 on an additional 283 patient treated in the 3-4.5 hour time window giving an updated total of 757 patients, and 1,310 patients treated in the 3-4.5 hour time window giving an updated total of 13,175. The need for ethics approval or patient consent for participation in SITS-ISTR varied between participating countries. In general, approvals were obtained in those countries in which it was a requirement while in other countries approval was obtained as part of the register for conduct of the audit.

The randomized, controlled trial (RCT) pooled analysis (a main supportive study) included information on 1,355 patients treated with alteplase within the 3-4.5 hour time window (681 alteplase; 674 placebo) and 2,958 treated within the 0-6 hour time window (1,490 alteplase; 1,468 placebo).

Dose Response Studies

No new dose response studies.

Main (pivotal) study

European Cooperative Acute Stroke Study III (ECASS III)

Methods

a. Objectives

The objective of this pivotal study was to establish the efficacy and safety of alteplase compared with placebo for treatment of acute ischaemic stroke in patients presenting between 3.0 and 4.5 hours after onset of symptoms. The *primary null hypothesis* was that the magnitude of response with regard to the primary endpoint of the modified Rankin Scale score [mRS (0-1)] was inferior (presumably meaning to placebo) in both of the two treatment groups or not different between the two treatment groups, and the *alternative hypothesis* was that alteplase was superior to placebo. Hypothesis testing used two-sided methods.

Comment: The original objective was to compare the efficacy and safety of alteplase and placebo in patients presenting between 3.0 and 4.0 hours after onset of acute ischaemic stroke. However, following a protocol modification in May 2005 the time window was increased from 3.0 to 4.0 hours to 3.0 to 4.5 hours. The reasons given for extension of the time window were, firstly, publication of a pooled analysis in 2004 suggesting patients may benefit from thrombolytic treatment administered up to 4.5 hours after the onset of symptoms and, secondly, slow recruitment of patients to the study [Hacke *et al*., 2008]. The trial protocol and the amendments were accepted by the European Medicines Agency (EMA) and were approved by the institutional review boards of the participating centres [Hacke *et al*., 2008].

b. Design

ECASS III was a Phase III, multinational, multicentred, randomized, placebo-controlled, double-blind, parallel-group, efficacy and safety study of alteplase initiated within 3.0 to 4.5 hours of the onset of symptoms of acute ischaemic stroke. The study recruited patients from 130 study sites from 19 European countries. It was conducted at neurology clinics or hospitals with stroke units or

intensive care units and 24 hour access to CT. The study was carried out from 29 July 2003 to 11 February 2008, and the report was dated 15 December 2008 and revised on 15 April 2009.

Comment: The study was well designed and included multiple centres from multiple European countries.

c. Study Participants

The study included patients of either sex aged 18 to 80 years with a clinical diagnosis of acute ischemic stroke who were able to be treated with the study drug within 3.0 to 4.5 hours of the onset of symptoms. A cerebral CT scan was required before randomization to exclude patients who had an intracranial haemorrhage or major ischaemic infarction. In some patients cerebral magnetic resonance imaging (MRI) scan was performed instead of CT.

Comment: The most clinically significant exclusion criteria are considered to be patients aged > 80 years, patients taking oral anticoagulants, patients presenting with severe stroke assessed clinically (for example, a National Institutes of Health Stroke Scale (NIHSS) score > 25) or by appropriate brain imaging techniques, significant hypertension (systolic blood pressure (SBP) > 185 mmHg or diastolic blood pressure (DBP) > 110 mmHg), symptoms rapidly improving or only minor before the start of the infusion, and patients with a combined history of stroke and diabetes mellitus.

d. Treatment

Of the 821 randomized subjects, 418 were treated with alteplase (0.9 mg/kg body weight, maximum 90 mg) administered intravenously and 403 with placebo. Alteplase and matched placebo were reconstituted from a lyophilized powder in sterile water for injection. Of the total dose, 10% was administered as a bolus, and the remainder was given by continuous intravenous infusion over 60 minutes. Except for the extended time window, alteplase was used in accordance with current EU prescribing information. Treatment with intravenous heparin, oral anticoagulants, aspirin, or volume expanders during the first 24 hours after administration of the study drug was prohibited. However, the use of subcutaneous (SC) heparin (≤ 10,000 IU), or equivalent doses of low molecular weight heparin (LMWH), was permitted for deep vein thrombosis (DVT) prophylaxis.

Comment: The dose of alteplase used in the study matches that being proposed and is identical to that currently approved for treatment in the 0-3 hour time window. The haematologically active medicines permitted or prohibited within the first 24 hours of the study appear reasonable and are unlikely to have confounded the results.

e. Outcomes/endpoints

The *primary efficacy endpoint* was disability at Day 90 (3 month visit) as assessed by the modified Rankin Scale (mRS) score dichotomized as a favourable outcome (a score of 0 or 1) or an unfavourable outcome (a score of 2 to 6). The mRS measures disability with scores ranging from 0 (no symptoms at all) to 6 (death), with a score of 5 indicating severe disability (patient is bedridden, incontinent and requires constant nursing care and attention).

The *secondary efficacy endpoint* was a global outcome measure that combined the dichotomized outcomes at Day 90 of a score of 0 or 1 on the mRS, a score of 95 or higher on the Barthel Index (BI), a score of 0 or 1 on the National Institute of Health Stroke Scale (NIHSS), and a score of 1 on the Glasgow Outcome Scale (GOS). The NIHSS is a 15-item scale that provides a quantitative measure of the level of neurologic impairment. The scale assesses the effect of acute cerebral infarction on consciousness, language, neglect, visual field-loss, extra-ocular movement, motor strength, ataxia, dysarthria and sensory loss. Ratings for each item are scored with 3 to 5 grades

with 0 as normal. Total scores range from 0 to 42, with higher scores reflecting more severe strokes (<5 mild impairment, ≥ 25 very severe neurologic impairment). The BI assesses the ability to perform the "activities of daily living" on a scale ranging from 0 (complete dependence) to 100 (independence). Patients who died were given an mRS score of 0. The GOS assesses the effect of disability on function on a 5-point scale with a score of 1 indicating independence, 3 severe disability, and 5 death. The *tertiary efficacy outcomes* included functional assessments at Days 0, 1, 7, 30, and 90 using the mRS, NIHSS and/or the BI, assessments of infarct volume, stratified NIHSS and mRS analyses, and length of stay in hospital. Pre-specified exploratory *subgroup analyses* were also undertaken.

Patients were assessed by examiners trained in the use of the assessment scales and unaware of the assigned treatment. Assessments were made at the time of enrolment and then at 1 hour, 2 hours, 24 hours, 7 days, 30 days, and 90 days after administration of the study drug. In addition, clinical condition (for example, blood pressure, oxygenation, and heart rate) was closely monitored for the first 24 hours. Initial assessments included a physical examination, brain imaging with CT or MRI, and measurement of neurologic deficit with the NIHSS. Brain imaging was undertaken at baseline and 1, 7, and 30 days after the study drug with days 7 and 30 being optional.

Comment: The pre-specified primary, secondary, and tertiary efficacy endpoints are considered to be satisfactory and assess a range of relevant functional and neurological outcomes. The pre-specified primary and secondary efficacy endpoints have been commonly used in other studies of alteplase for the treatment of acute ischaemic stroke. The efficacy outcomes are considered to be consistent with the relevant Committee for Proprietary Medicinal Products (CPMP) Points to Consider document (CPMP/EWP/560/98).

f. Randomization and blinding (masking)

Patients were randomized (1:1) double-blinded to either alteplase or placebo using an interactive voice response system (IVRS). Randomization within treatment centres was undertaken in blocks of 4 to ensure balanced distribution of treatment. All members of the Boehringer Ingelheim Clinical Trial Support team were blinded to treatment allocation apart from the group responsible for the randomisation schedule. All investigators and patients were also blinded to treatment allocation.

g. Sample Size

The sample size was based on a two-sample, chi-square test of proportions with a two-sided alpha level of 5% and a power of about 90%. To detect or disprove a difference of about 10% (odds ratio [OR] of about 1.5) between treatment groups with regard to the percentage of patients with a favourable outcome (mRS of 0-1), a sample size of about 400 patients was required with an expected placebo response rate of about 30% for the 3.0 to 4.5 hours time-interval (as observed in ECASS II).

Comment: The study was adequately powered. The pre-specified absolute difference of at least 10% between treatment groups for favourable outcome and an OR of at least 1.5 are considered to be clinically meaningful. However, mean effect sizes below the pre-specified absolute difference and OR values are considered to be of modest size and of doubtful clinical significance

h. Statistical Methods

Pre-specified (Protocol Specified) Analyses

The *primary efficacy endpoint* of disability at Day 90 as defined by the mRS was assessed in the ITT population. The ITT population included 821 patients and was defined as patients who were enrolled and randomized to a study group, regardless of whether or not they received the assigned

treatment. The *primary null hypothesis* was that the magnitude of response with regard to the primary endpoint mRS (0-1) was inferior (presumably meaning to placebo) for both treatment groups or not different between the two treatment groups, and the *alternative hypothesis* was that alteplase was superior to placebo. The number of mRS 0-1 responders (favourable outcome) and mRS 2-6 non-responders (unfavourable outcome) at Day 90 were compared by a Pearson's chi-square test between treatment groups (alpha level 5%, two-sided). In addition, 95% confidence intervals (CIs) were calculated for the odds ratio (OR) and for the relative risk (RR). The same statistical tests were also applied in the Per-Protocol (PP) population. The PP population included 730 patients and was defined as all randomized patients who had received alteplase or placebo and were not excluded because of major protocol violations. All pre-specified analyses were performed without adjustment for baseline covariates. The rules for handling missing data were pre-specified. Missing data not due to death were replaced by the last observation carried forward (LOCF). If missing data were due to death at Day 90 an mRS score of 6 (dead) was imputed, and if information on vital status (that is, alive/dead) was missing an MRS score of 5 (that is, severe disability) was imputed.

The *secondary efficacy endpoint* of global outcome at Day 90 was analysed by the global OR based on a linear logistic regression model, a method that uses generalized estimating equations to perform a Wald-type test. In addition, 95% CIs for the global OR were calculated. No alpha adjustments for multiple testing were undertaken on the primary or secondary endpoints. However, alpha adjustment of the secondary efficacy endpoint for multiple testing was to be applied if the primary endpoint was statistically non-significant. The analyses of *tertiary efficacy endpoint*s were analysed by Pearson's chi-square test and/or logistic regression depending on the endpoint. No alpha adjustments were made for multiple testing of tertiary efficacy endpoints because the analyses of these endpoints were considered to be exploratory.

Post Hoc Analyses

The study included a *post-hoc* adjusted analysis (logistic regression) of the primary and secondary efficacy endpoints due to numerical imbalances being found between treatment groups for some baseline covariates of potential clinical significance (for example, mean/median NIHSS scores; prior history of stroke). The initial adjusted model included all baseline covariates and a stepwise backwards selection procedure was undertaken with those baseline covariates having a significance level of > 0.1 being included in the final model. The baseline covariates included in the final model were treatment group, baseline NIHSS score, smoking status, time from onset of stroke, and presence or absence of hypertension.

The study also included a *post hoc* stratified analysis of mRS scores at 90 days adjusted for the two strongest prognostic variables (that is, NIHSS baseline score and time between onset of symptoms and initiation of treatment). The study also included a *post hoc* analysis of the effect of stroke severity at baseline (that is, NIHSS score) on the primary endpoint (mRS 0-1) and NIHSS scores (0-1) at Day 90.

Comment: The statistical methods are considered appropriate for analysis of the pre-specified endpoints. The post-hoc analyses are exploratory and for the purposes of this application should be considered to be neither pivotal nor supportive.

Results

a. Participants

The study enrolled and randomized 821 patients (ITT population) between 29 July, 2003, and 13 November 13, 2007. Of the 821 patients, 418 were randomized to alteplase and 403 to placebo. The

PP population consisted of 375 patients randomized to alteplase and 355 randomized to placebo. The patient disposition including vital and mRS status in the ITT population is summarised below in Table 1.

Table 1: ECASS III – Patient disposition at end of trial (ITT population).

	Alteplase n (%)	Placebo n (%)	Total n (%)
Randomized	418 (100%)	403 (100%)	821 (100%)
Not Treated	12 (2.9%)	13 (3.2%)	25 (3.1%)
Treated	406 (97.1%)	390 (96.8%)	796 (97.0%)
Completed Study [1]	417 (99.8%)	402 (99.8%)	819 (99.8%)
Alive status available	12 (2.9%)	9 (2.2%)	21 (2.6%)
Death within 90 days	28 (6.7%)	31 (7.7%)	59 (7.2%)
Death [2]	32 (7.7%)	34 (8.4%)	66 (8.0%)
mRS Day 90 assessed	379 (90.7%)	365 (90.6%)	744 (90.6%)
mRS Day 90 imputed (LOCF)	13 (3.1%)	10 (2.5%)	23 (2.8%)
mRS Day 90 imputed (dead patients)	26 (6.2%)	28 (7.0%)	54 (6.6%)
Not completed	1 (0.24%)	1 (0.25%)	2 (0.24%)
Consent withdrawn	1 (0.24%)	1 (0.25%)	2 (0.24%)
Invalid consent	0	1 (0.25%)	1 (0.12%)

[1] Completed study is according to termination in CRF or with visit 5 (day 90) information of patient alive status at Day 90 available. As vital status was one of the criteria for imputation of main criteria, patients who died during the study were counted in the same category as completers.

[2] Including 7 patients who died after Day 90 (4 alteplase, 3 placebo).

A CT scan was required before randomization for all patients to exclude intracranial haemorrhage or major ischaemic infarction. Of the 821 randomized patients, 771 were evaluated by CT at baseline and 50 by MRI. A second CT scan at 24 hours after administration of the study drug (between 22 and 36 hours was mandatory). Further CT scans at Day 7 and 30 were optional in the case of clinical deterioration. MRI instead of CT was performed on 50 patients at baseline, 17 patients at 24 hours after study drug administration, 12 patients at Day 7 and 1 patient at Day 30. The use of MRI instead of CT was considered to be a minor protocol deviation due to literature confirming the validity of MRI to exclude cerebral haemorrhage. All MRI and CT scans performed by investigators were reviewed and interpreted by a Safety and Outcome Adjudication Committee (SOAC). This committee consisted of three neuroradiologists with experience in major stroke trials blinded to treatment allocation. The CT/MRI scans evaluated by the SOAC and the investigators are summarised below in Table 2.

Table 2: ECASS III - Number of CT/MRI scans evaluated by investigators and SOAC in the ITT population.

Randomized (n)	Alteplase (n=418)		Placebo (n=403)		Total (n=821)	
	Investigator	SOAC	Investigator	SOAC	Investigator	SOAC
Baseline (mandatory)	418	406	402 [1]	390	820 [1]	796
24 hours (mandatory)	407	397	391	382	798	779
Day 7 (optional)	53	41	64	53	117	94
Day 30 (optional)	10	3	8	7	18	10
Total	888	847	865	832	1753	1679

[1] CT scan was considered missing for 1 patient as consent was considered to be invalid.

The treatment blind was broken for 7 patients during the study (3 alteplase, 4 placebo). The reasons were: medical emergency in the first 48 hours following administration of the study drug in 4 patients (myocardial infarction or subdural haematoma); irregular use of study medication for a patient not enrolled in the study (n=1); blind broken at 4 months after treatment (n=1); patient request at 7 months after treatment (n=1); and clinical deterioration during treatment administration (n=1).

At least one major protocol variation occurred in 91 (11.1%) of the 821 randomized patients with similar percentages for both alteplase (10.2%, n=43) and placebo (11.9%, n=48). The most common major protocol deviation in the 821 randomized patients was no treatment received (3.1%).

Comment: The percentage of the 821 randomized patients who received study drug (about 97.0%) was high and similar for both alteplase (97.1%) and placebo (96.8%). Of the 25 patients not treated with the study drug, the main reason was the presence of exclusion criteria after randomization (n=17), with other reasons being consent withdrawn (n=2), allocated treatment kit not available (n=2), suspicion of basilar artery thrombosis (n=1), coagulopathy (n=1), infusion not accurately connected (n=1), and unexpected worsening of disease (n=1). Complete follow-up was undertaken for 13 of the 25 patients not treated and information on vital status at Day 90 was available for 11 of the remaining 12 patients. All 25 patients were included in the ITT population and analysed according to the randomized treatment group using LOCF or imputed worse case for missing data.

The percentage of the 821 randomized patients who completed the study (about 99.8%) was high and similar for both alteplase (99.8%) and placebo (99.8%). The percentage of patients with assessed mRS data at Day 90 was high (about 90.6%) and similar for both alteplase (90.7%) and placebo (90.6%). There were only a small number of patients (n=7) in whom the treatment blind was broken. Major protocol variations occurred in 11.1% (n=91) of the 821 randomized patients and were similar for both treatment groups. Overall, the patient disposition data have been well described. The high percentage of patients who received the study drug and completed the study indicate that the outcome data are likely to be reliable and unbiased.

b. Baseline Data

The mean±standard deviation (sd) age of the alteplase group was 64.9±12.2 years and 65.6±11.0 years for the placebo group. The majority of patients in both treatment groups were aged from 61-80 years with only a small number of patients in both groups being older than 80 years. Nearly all patients in the study were Caucasian. The "average" and "excessive" alcohol consumption was not defined in the study, but percentages for these two groups were similar for both treatment groups. Mean systolic and diastolic blood pressure were similar for both treatment groups. Treatment was

initiated within the 3.0 to 4.5 hour time window in 96.9% of the 418 randomized patients in the alteplase group and 95.0% of the 403 randomized patients in the placebo group. The median time to initiation of treatment was 3 hours 59 minutes in the alteplase group and 3 hours 58 minutes in the placebo group. The mean±sd and median [range] NIHSS scores were lower in the alteplase group (10.7±5.6; 9.0 [1-27]) than in the placebo group (11.6±6.0; 10.0 [0-25]). This imbalance was primarily due to the greater percentage of patients with severe stroke (NIHSS > 20) in the placebo group (9.9%, 40/403) compared with the alteplase group (5.0%, 21/418). In addition, a history of prior stroke in the 3 months before study entry occurred more frequently in the placebo group (14.1%, 57/403) compared with the alteplase group (7.7%, 32/418). The incidence of concomitant diabetes (overall 15.7%), hypertension (overall 62.6%), and atrial fibrillation (overall 13.2%) was similar in both treatment groups. In the ITT population, prior chronic aspirin or antiplatelet treatment was similar in the alteplase (31.1%) and placebo groups (32.5%) as was prior heparin/anticoagulant treatment (2.9% alteplase and 3.2% placebo).

Comment: The main differences in baseline variables between the two treatment groups were increased mean/median NIHSS scores and higher incidence of previous stroke in the placebo group compared with the alteplase group. These imbalances appear to have arisen by chance as the randomization method was satisfactory. The imbalances might be a source of bias as both (particularly high baseline NIHSS scores) might be associated with a higher risk of less favourable outcomes. The sponsor undertook a *post hoc* analysis of the OR by adjusting for baseline differences in covariates. It would have been preferable to have pre-specified an adjusted analysis in the protocol, nominating and justifying those baseline covariates to be adjusted. The decision to undertake the adjusted *post hoc* analysis appears to have been made when potentially important differences between treatment groups were observed in baseline variables following randomization. The median time to onset of treatment was similar for both treatment groups as was the percentage of patients in whom treatment was initiated within the 3.0 to 4.5 hour time window. The study included predominantly patients classified as Caucasian (87.1%, n=715), and included a small number of patients aged greater than 80 years (1.8%, n=15).

c. Primary Efficacy Endpoint Outcome

The primary endpoint was defined as disability status at Day 90 as assessed by the mRS dichotomized into favourable (mRS 0-1) and unfavourable (mRS 2-6) outcomes. The protocol specified analysis was unadjusted for baseline covariates. The results for the ITT population are summarised below in Table 3. The results for the PP analysis were consistent with those for the ITT analysis.

Table 3: ECASS III – Primary efficacy endpoint (favourable outcome mRS) in the ITT population.

	Alteplase (n=418)	Placebo (n=403)	OR [95%CI] [1]	RR [95%CI] [1]	p value
Favourable Outcome (mRS 0-1)	219 (52.39%)	182 (45.16%)	1.34 [1.02 – 1.76]	1.16 [1.01 – 1.34]	p = 0.0383 (Pearson chi-square)
Unfavourable Outcome (mRS 2-6)	199 (47.61%)	221 (54.84%)			
Risk Difference (mRS 0-1)	7.23% [95%CI: 0.39-13.97] [2]				

[1] Unadjusted for baseline covariates
[2] 95% confidence intervals for the absolute difference between favourable outcomes calculated by the clinical evaluator.

Comment: The pre-specified RR and OR analyses (unadjusted for baseline covariates) both showed statistically significantly favourable outcomes (mRS 0-1) with alteplase relative to placebo. The likelihood (that is, RR) of a favourable outcome (mRS 0-1) was 16% higher [95%CI: 1-34%] with alteplase compared with placebo. The odds (that is, OR) of a favourable outcome were 34% higher [95%CI: 2-76%] with alteplase compared with placebo. The wide 95% confidence intervals for the OR and the RR suggest marked inter-subject response to alteplase. The risk difference between treatments for favourable outcome (mRS 0-1) was 7.23% [95%CI: 0.39-13.97%]. Based on the observed risk difference it can be estimated that the number of patients needed to be treated with alteplase to observe 1 favourable outcome compared with placebo is about 14 (that is, the number needed to treat (NNT)).

It is considered that a risk difference of 7.23% and an OR of 1.34 are of doubtful clinical significance. The study was powered on a significant difference between the two treatments of 10% (OR of about 1.5). Consequently, it can be reasonably inferred that a risk difference of 10% or an OR of 1.5 are likely to be the effect sizes considered by the study designers to be of minimum clinical significance.

The placebo response for favourable outcome (mRS 0-1) was about 45% which was higher than the placebo response rate of about 30% observed in ECASS II in the 3-4.5 hour cohort. This suggests that patients in ECASS III might have had less severe acute ischaemic strokes at baseline than those in ECASS II.

d. Secondary Efficacy Endpoint

The secondary efficacy endpoint was a global outcome measure that combined the outcomes at Day 90 of mRS score of 0 or 1, BI score of ≥ 95, NIHSS score of 0 or 1, and GOS score of 1. The results for the ITT population are summarised below in Table 4. The odds of a favourable global outcome in the PP population favoured alteplase over placebo and the results were statistically significant.

Table 4: ECASS III – Secondary efficacy endpoint (and components) in the ITT population.

	Alteplase (n=418)	Placebo (n=403)	OR [95%CI] *	p value
Global Outcome [1]	N/A	N/A	1.28 [1.00-1.65]	0.0481
mRS score 0-1	219 (52.39%)	182 (45.16%)	1.34 [1.02-1.76]	0.0383 [2]
BI score ≥ 95	265 (63.40%)	236 (58.56%)	1.23 [0.93-1.62]	0.1555 [2]
NIHSS score 0 or 1	210 (50.24%)	174 (43.18%)	1.33 [1.01-1.75]	0.0462 [2]
GOS score of 1	213 (50.96%)	183 (45.41%)	1.25 [0.95-1.64]	0.1182 [2]

* Unadjusted for baseline variables.
[1] Estimates from the GEE analysis.
[2] P values refer to the Pearson chi-square test.

Comment: The odds of a favourable global outcome were 28% higher [95%CI: 0-65%] with alteplase compared with placebo in the pre-specified unadjusted OR analysis (OR = 1.28 [95%CI 1.00-1.65]). However, this outcome is not statistically significant as the 95% confidence interval of the OR includes the value of 1. Of the four components of the global outcome, two were statistically significant (mRS and NIHSS scores) and two were not statistically significant (BI and GOS scores). It is considered that the statistically non-significant secondary efficacy outcome in the ITT populations does not support the clinical superiority of alteplase over placebo. The *post-hoc* adjusted OR analysis showed that the odds of a favourable global outcome were 38% higher [95%CI: 4-83%] with alteplase compared with placebo. The 95% CIs of both the unadjusted and adjusted 95% confidence intervals for the global OR were wide suggesting marked inter-subject variability to alteplase as assessed by the global outcome.

e. Tertiary Endpoints and Subgroup Analyses

The main results for the pre-defined tertiary endpoints in the ITT and PP populations consistently favoured alteplase over placebo, but the observed differences were mostly not statistically significant and no alpha adjustment was made for multiple testing as the endpoints were pre-specified as exploratory. The study also included a number of individual sub-group analyses of the mRS score 0-1 at Day 90 in the ITT and PP populations. These subgroup analyses also included interaction analyses between subgroup and outcome.

f. Post-Hoc Analyses

The *post-hoc* analysis of the primary efficacy endpoint adjusted for baseline variables (treatment group, baseline NIHSS, smoking history, stroke onset to treatment time, hypertension) in the ITT population showed that the alteplase was associated with a statistically significantly increased favourable outcome compared with placebo: mRS score 219/418 [52.4%] for alteplase versus 182/403 [45.2%] for placebo; OR = 1.42 [95%CI: 1.02-1.98]; p=0.0373. Similar results were seen in the PP population.

The *post-hoc* analysis of the secondary efficacy endpoint adjusted for baseline variables (treatment group, baseline NIHSS, smoking history, stroke onset to treatment time, hypertension) in the ITT population showed that the alteplase was associated with a statistically significant favourable outcome compared with placebo: global outcome OR = 1.38 [95%CI: 1.04-1.83]; p=0.0270. Similar results were seen in the PP population.

The *post hoc* analysis of stroke outcomes at Day 90, as assessed by both mRS (0-1) and NIHSS (0-1) by baseline stroke severity showed favourable outcomes in the alteplase group compared with placebo. In the subgroup with severe baseline stroke (NIHSS ≥ 20), the absolute benefit as assessed by mRS (0-1) at Day 90 was greater than both subgroups with less severe baseline stroke (0-9 and 10-19). The absolute benefit as assessed by NIHSS (0-1) at Day 90 did not differ markedly between alteplase and placebo when stratified according to baseline stroke severity (0-9, 10-19, ≥ 20). None of the absolute benefits for any of the pair-wise comparisons were > 10% and none of the ORs were statistically significant.

The *post-hoc* stratified analysis of mRS scores (0-6) at Day 90 adjusted for baseline NIHSS (5 groups) and time from onset of symptoms to treatment (5 subgroups of 15 minute intervals) showed a favourable outcome with alteplase compared with placebo by the Cochrane-Mantel-Haenszel test in both the ITT (p=0.0244) and the PP (p=0.0115) populations.

Comment: The *post-hoc* analyses are considered to be exploratory and are neither pivotal nor supportive as regards to the current application.

Clinical Studies in Special Populations

Integrated Summary of Efficacy in the Very Elderly

a. Overview

The application included an addendum to the Clinical Overview relating to efficacy and safety of alteplase treatment for acute ischaemic stroke in the "very elderly". This addendum was provided to support removal of the absolute PI contraindication on the use of alteplase in patients aged > 80 years and the addition of a new statement to the "Special warnings and precautions" section of the PI. The proposed additional statement is "patients over 80 years may have an increased risk for intracerebral haemorrhage compared to younger patients. Therefore, the use of Actilyse should be weighed carefully against anticipated risks on an individual patient basis".

Six randomized, placebo-controlled studies (ECASS II, ECASS III, ATLANTIS A and B, NINDS 1 and 2), included a total of 164 very elderly patients (≥ 80 years). Of these 164 very elderly patients, 73 had been treated with placebo and 91 with alteplase. NINDS 1 and 2 contributed 78 patients (47.5%), ECASS III 34 patients (20.7%), ECASS II 31 patients (18.9%), and ATLANTIS A and B 21 patients (12.8%). There were 137 patients (61 placebo, 76 alteplase) in the 0-4.5 hour time interval treated with alteplase at a dose of 0.9 mg/kg bodyweight. The baseline demographics in the very elderly cohort were generally well balanced. The mean baseline NIHSS score was 15.1 in the placebo group and 16.5 in the alteplase group, and the respective mean±sd times from onset of symptoms to initiation of treatment were 165.6±63.6 minutes and 168.0±61.7 minutes.

The document also reported on meta-analyses of uncontrolled studies on the use of alteplase in very elderly patients from two published studies, *Engelter et al., 2005*[4] and *Ringleb et al., 2007*[5]. In *Engelter et al., 2005*, a favourable outcome at 90 days (mRS 0-1) was observed in 101/391 (25.8%) of patients aged ≥ 80 years compared with 604/1481 (40.8%) of patients aged < 80 years: OR = 0.53 [95%CI: 0.42-0.66]. In *Ringleb et al., 2007*, a favourable outcome at 90 days (mRS 0-1) was observed in 130/501 (25.9%) of patients aged ≥ 80 years compared with 784/1904 (41.1%) of patients aged < 80 years: OR = 0.52 [95%CI: 0.42-0.64]. Both meta-analyses showed that favourable 90 day outcomes (mRS 0-1) were observed significantly more frequently in the patient group aged < 80 than in the patient group aged ≥ 80 years.

b. Total very elderly cohort (n=137) – Pooled Analysis

The main efficacy outcome measures in the pooled analysis in the total cohort (n=137) were favourable outcome (mRS 0-1) and independence (mRS 0-2) at Day 90 in the 0-4.5 hour treatment cohorts. The results are summarised below in Table 5.

[4] Engelter *et al*. (2005) Thrombolysis in stroke patients aged 80 years and older: Swiss survey of iv thrombolysis. *Neurology* 65 (11);1795-1798.

[5] Ringleb *et al*. (2007). Thrombolytic therapy for acute ischaemic stroke in octogenarians: selection by magnetic resonance imaging improves safety but does no improve outcome. J *Neurol Neurosurg Psychiatry* 78(7): 690-693.

Table 5: Very-Elderly Pooled data analysis - Efficacy outcomes in the 0-4.5 hour treatment cohort.

Cohort	Treatment	n (%)	Difference (%)	OR [95%CI] *	OR [95%CI] **
mRS 0-1 at Day 90 in 0-4.5 h cohort	Placebo (n=61)	16 (26.2)	1.4%	1.07 [0.50-2.30]	1.72 [0.67-4.41]
	Alteplase (n=76)	21 (27.6)			
mRS 0-2 at Day 90 in 0-4.5 h cohort	Placebo (n=61)	22 (36.1)	2.1%	1.09 [0.54-2.20]	1.77 [0.73-4.25]
	Alteplase (n=76)	29 (38.2)			

* OR = Odds Ration unadjusted.
** OR = Odds Ratio adjusted for baseline NIHSS

Comment: The risk difference between alteplase and placebo for both efficacy endpoints in the 0-4.5 hour cohorts was small and unlikely to be clinically significance. The odds ratios for both outcomes (unadjusted and adjusted for baseline NIHSS) were not statistically significant.

c. Very elderly cohort excluding those with severe stroke NIHSS (≥ 20) (n=89) – Pooled Analysis

The main efficacy outcome measures in the pooled analysis in the total cohort (n=89) of elderly patients excluding those with severe stroke (NIHSS ≥ 20) were favourable outcome (mRS 0-1) and independence (mRS 0-2) at Day 90 in the 0-4.5 hour treatment cohorts. The results are summarised below in Table 6.

Table 6: Efficacy outcome in the 0-4.5 hour cohort treatment cohort excluding those with severe stroke (NIHSS ≥ 20).

Cohort	Treatment	n (%)	Difference (%)	OR [95%CI] *	OR [95%CI] **
mRS 0-1 at Day 90 in 0-4.5 h cohort	Placebo (n=44)	16 (36.4)	8.0%	1.40 [0.60-3.28]	1.63 [0.63-4.21]
	Alteplase (n=45)	20 (44.4)			
mRS 0-2 at Day 90 in 0-4.5 h cohort	Placebo (n=44)	21 (47.7)	10.1%	1.50 [0.65-3.46]	1.87 [0.71-4.91]
	Alteplase (n=45)	26 (57.8)			

* OR (odds ratio) unadjusted.
** OR (odds ratio) adjusted for baseline NIHSS.

Comment: The treatment effect (odds ratios) for both endpoints in the unadjusted and adjusted for baseline NIHSS score were not statistically significant.

d. Very elderly cohort with severe stroke (NIHSS > 20) (n=48) – Pooled Analysis

There were 48 very elderly patients in the pooled analysis with severe stroke (NIHSS > 20) treated in the 0-4.5 time window. The functional outcome at Day 90 in these patients was very poor. In the placebo group (n=17) no patient achieved a favourable outcome (mRS 0-1) and 1 patient achieved independence (mRS 0-2) compared with 1 and 3 patients, respectively, in the alteplase group (n=31). In these patients mortality was very high in both treatment groups (54.8% with alteplase and 52.9% for placebo).

e. Overall Comment

The pooled data from the randomized, placebo-controlled studies failed to show a statistically significant difference in efficacy outcomes between alteplase (initiated in the 0-4.5 hour treatment window) and placebo in the total very elderly cohort (n=137), and the very elderly cohort excluding severe stroke (NIHSS ≥ 20). The data in the very elderly patients with severe stroke showed that functional outcome at Day 90 was very poor and mortality high in both treatment groups. It is considered that the available efficacy data do not support the removal of the absolute PI contraindication on the use of alteplase in patients > 80 years.

Analysis Performed Across Trials

Pooled Analysis Study

Data Set

The submission included a pooled analysis of data from ECASS III and five previously evaluated randomized, controlled studies of alteplase administered at a dose of 0.9 mg/kg bodyweight to a maximum of 90 mg for the treatment of acute ischaemic stroke. The pooled analyses were based on data from six studies: ECASS III; ECASS II; ATLANTIS A and B; and NINDS Parts 1 and 2. Data from ECASS I were excluded as this study used a dose of alteplase of 1.1 mg/kg bodyweight.

The pooled data analysis focused on treatment initiated in either the 3.0-4.5 hour time widow or the 0-6 hour time widow. The 3.0-4.5 hour time window analysis included two different populations: (a) all patients in the 3.0-4.5 hour cohort (n=1355); and (b) patients who satisfied the current Actilyse treatment European “labelled” treatment criteria, apart from time from onset of stroke to treatment (n=1251). The 0-6 hour time window analysis combined all patients from the six studies (n=2958). The number of patients included in the pooled analysis and each of the original studies shown by study, inclusion and exclusion criteria, and time window is summarised below in Table 7.

Table 7: Number of patients included in pooled data analysis by study and inclusion/exclusion criteria.

	ECASS III	ECASS II	ATLANTIS A +B	NINDS Part 1 + 2	Pooled
Randomized (total)	821	800	755	624	3000
Randomized within 6h and treatment onset time available.	794	791	749	624	2958
Randomized within 3.0-4.5h and treatment onset time available.	788	265	302	0	1355
Randomized within 3.0-4.5h and treatment onset time available excluding patients with major CIs	743	242	266	0	1251
3-4.5 h cohort *					
Alteplase	405	131	145	0	681
Placebo	383	134	157	0	674
3-4.5h cohort excluding major CIs †	382	118	121	0	621
Alteplase	361	124	145	0	630
Placebo					
0-6h cohort					
Alteplase	406	406	366	312	1490
Placebo	388	385	383	312	1468

† CIs = Contraindications.
* Fulfilling the inclusion and exclusion criteria shared by the original randomized controlled studies.
† Fulfilling all the main inclusion and according to the current approved Actilyse "label", except for the time from onset to treatment.

b. Baseline Parameters

The following baseline parameters were collected and deemed comparable for all six studies: NIHSS on admission; time from stroke onset to treatment; age (years); weight (kg); baseline systolic and diastolic blood pressure (mmHg); sex; race; history of stroke; history of diabetes; previous or current atrial fibrillation; history of hypertension; smoking history; and prior aspirin/anti-platelet treatment. Overall, the demographic characteristics were similar for ECASS III and the pooled data set. However, baseline NIHSS scores were marginally lower in ECASS III compared with the pooled data set as was the incidence of atrial fibrillation.

The main exclusion criteria shared by the six RCTs were: stroke/trauma within the last 14 days to 3 months; SBP > 185 mmHg and/or DBP >110 mmHg; oral anticoagulants; heparin within the last 48 hours; prolonged activated partial thromboplastin time (aPTT) or partial thromboplastin time (PT); platelet count <100,000/mm^3; seizure at stroke onset; blood glucose < 50 or > 400 mg/dL; rapid improvement of symptoms before start of treatment; and time to onset of treatment unknown.

c. Efficacy Outcome and Analytical Methods

The efficacy outcome in the pooled analysis was the mRS score (0-1) at Day 90. While the primary and secondary efficacy endpoints differed among the six studies all had an efficacy endpoint of mRS (0-1) at Day 90. The LOCF method and worst-case rule for imputation of missing data were used in the pooled analyses of the randomized controlled studies. If missing patients were known to be dead at Day 90 an mRS score of 6 was imputed, and if missing patients were known to be alive at Day 90 an mRS score of 5 was imputed.

d. Main efficacy results in the 3.0-4.5 hour time window cohort

Four studies contributed patients to the 3.0-4.5 hour cohort: ECASS II; ECASS III; and ATLANTIS (A and B). The frequencies of the major contraindications for the four studies are summarised below in Table 8.

Table 8: Major contraindications by study.

Parameter	ECASS II n (%)	ECASS III n (%)	ATLANTIS (A and B)	Total
Total treated	265 (100.0)	788 (100.0)	302 (100.0)	1355 (100.0)
Treated without major contraindication.	242 (91.3)	743 (94.3)	266 (88.1)	1251 (92.3)
Excluded with major contraindication	23 (8.7)	45 (5.7)	36 (11.9)	104 (7.7)
Prior stroke and prior diabetes	9 (3.4)	4 (0.5)	17 (5.6)	30 (2.2)
Severe stroke clinically NIHSS > 25	8 (3.0)	2 (0.3)	12 (4.0)	22 (1.6)
Severe stroke on imaging *	0 (0)	14 (1.8)	0 (0)	14 (1.0)
Age > 80 years	2 (0.8)	15 (1.9)	0 (0)	17 (1.3)
SBP > 185 or DBP > 110 mmHg	2 (0.8)	10 (1.3)	7 (2.3)	19 (1.4)
Blood glucose < 50 or > 400 mg/dL	2 (0.8)	0 (0)	0 (0)	2 (0.2)

* Exclusion criteria available only for ECASS III.

The results for the mRS (0-1) at Day 90 in the 3.0-4.5 hour time window are summarised below in Table 9 for all patients in the cohort (n=1355), and for patients in the 3.0-4.5 hour time window cohort who satisfied all the current Actilyse "labelled" treatment criteria apart from time from onset of stroke to treatment (n=1251).

Table 9: Response as assessed by mRS 0 or 1 at Day 90 in the 3.0-4.5 hour pooled cohort.

Population	Treatment	n (%)	Δ % [95%CI]	OR [95%CI]	p value *
Pooled 3-4.5h cohort	Alteplase (n=681) Placebo (n=674)	316 (46.4%) 268 (39.76%)	6.64 [1.37-11.86]	1.31 [1.06-1.63]	0.0137
Pooled 3-4.5 h cohort excluding patients with major contraindications	Alteplase (n=621) Placebo (n=630)	304 (48.95%) 254 (40.32%)	8.63 [3.13-14.07]	1.42 [1.13-1.78]	0.0022

Δ [95%CI] = Risk difference with 95% CI (95% CI calculated by the evaluator).
OR [95%CI] = Odds Ratio with 95% confidence interval.
* p value obtained by the Wald chi-square test.

Comment: The OR for mRS (0-1) at Day 90 was statistically significantly in favour of alteplase relative to placebo in both the 3.0-4.5 hour cohorts. However, the risk difference between treatments in both cohorts was < 10% which raises doubts about the clinical significance of the observed results. Of the 1,355 patients in the 3.0-4.5 hour total cohort, the majority came from ECASS III (58.2%, n=788). Similarly, of the 1251 patients in the 3.0-4.5 hour cohort of patients excluding major contraindications the majority also came from ECASS III (59.4%, n=743). Other efficacy outcomes included stratified analyses of the outcome distribution of the mRS scores 0-6 at Day 90 in the 3-4.5 hour cohort who fulfilled all the inclusion and exclusion criteria (n=1251). This showed a general statistically significant (p=0.0017) shift towards improved outcome in patients treated with alteplase compared with placebo for each mRS score from 1-6.

e. Main efficacy results in the 0-6 hour time window cohort

The main efficacy outcome of mRS (0-1) at Day 90 in the 0-6 hour cohort in the alteplase and placebo groups according to the time windows to treatment is summarised below in Table 10.

Table 10: Pooled analysis of efficacy assessed by mRS 0-1 at Day 90 with alteplase versus placebo by 90 minute time groups from symptom onset to treatment in the 0-6 hour time window cohort.

Time from onset to treatment	Patients (n)	Odds Ratio [95%CI]	p value
0 -90 minutes	285	2.31 [1.28-4.17]	0.0055
91-180 minutes	498	1.74 [1.14-2.66]	0.0100
181-270 minutes	1296	1.32 [1.03-1.71]	0.0298
271-360 minutes	669	1.04 [0.74-1.46]	0.8234

Odds Ratio of treatment (alteplase versus placebo) adjusted for baseline NIHSS scores; age; SBP ≤ 160, > 160 mmHg; DBP (<70, 70-90, >90 mmHg); weight (≤ 70, 71-90, >90 kg); prior hypertension; smoking history; and interaction of age and NIHSS.

Comment: The results showed decreasing efficacy with increasing time from onset of symptoms to initiation of treatment. In the time window of interest (181-270 minutes), the OR for the mRS (0-1) at Day 90 was statistically significant and favoured alteplase over placebo with the odds being 32% higher [95%CI: 3-71%]. The data showed that efficacy decreases with increasing time from onset of symptoms to initiation of treatment. The OR for mRS (0-1) at Day 90 was not statistically

significant for alteplase compared with placebo when treatment was initiated from 4.5 to 6.0 hours after stroke onset.

Supportive Studies

SITS-ISTR Observational Study

Methods

a. Objectives

SITS-ISTR was a supportive study submitted in the form of a published paper [Wahlgren *et al*., 2008] supplemented by recent unpublished updated data. The study compared patients treated with alteplase in the 3.0-4.5 hour and 0-3.0 hour time windows. The published study included a total of 664 patients in the 3.0-4.5 hour time window and 11,865 patients in the 0-3.0 hour time window. The study was sponsored by Boehringer Ingelheim and the European Union Public Executive Authority. However, the sponsors "had no role in study design, data analysis, data interpretation, or writing of the report" [Wahlgren *et al*., 2008]. The study hypothesised that outcomes would be similar for patients treated with alteplase between 3.0-4.5 hours and 0-3.0 hours after symptom onset.

b. Design

SITS-ISTR is a monitored, observational, post-marketing, clinical efficacy and safety study based on data from patients treated for stroke held in an international stroke treatment registry. SITS is a collaboration of more than 700 clinical centres in 35 countries that have documented treatments for stroke and collected them in a prospective, multinational, internet based register (that is, the ISTR).

c. Study Participants and Treatment

The published paper (Wahlgren *et al*., 2008) included efficacy data on 664 patients in the 3.0-4.5 hour cohort and 11,865 patients in the 0-3.0 hour cohort) entered in the ISTR between 25 December 2002 and 15 November 2007. The sponsor's integrated summary included updated information collected between 16 November 2007 and December 2008 on an additional 283 patients treated in the 3-4.5 hour time window giving an updated total of 757 patients, and 1,310 patients treated in the 3-4.5 hour time window giving an updated total of 13,175 patients. The recent additional efficacy data have not been published but have been made available to Boehringer Ingelheim by the Stroke research unit, Department of Neurology, Karolinska University Hospital, the owner and originator of the SITS-ISTR registry. The registry includes data on patients treated for acute stroke in accordance with "broadly accepted guidelines" and includes a sub-group of patients from European centres treated according to SITS-MOST criteria (that is, European marketing criteria for alteplase treatment of acute ischaemic stroke). Centres participating in SITS undertake to register all treated patients irrespective of whether they meet SITS-MOST criteria.

In the SITS-ISTR study it was hypothesised that efficacy and safety outcomes for patients treated in routine clinical practice with alteplase between 3.0 and 4.5 hours of symptom onset would be similar to those for patients treated within 0 and 3 hours of symptom onset. The 3.0-4.5 hour cohort included 947 patients (updated number) and the within 3.0 hour cohort included 13,175 patients (updated number). The alteplase dose for all patients was 0.9 mg/kg, with an upper limit of 90 mg, given as a continuous infusion over 60 min with 10% of the total dose administered as a bolus. All patients satisfied the requirements of the European Summary of Product Characteristics (SPC) for alteplase for the treatment of acute ischaemic stroke, apart from variations in the time to initiation of treatment.

Local investigators documented baseline and demographic characteristics, stroke severity measured by score on the NIHSS, onset to treatment time, risk factors, medication history, admission to hospital, and follow-up brain imaging scan. Imaging scans were not interpreted centrally but at individual treatment sites consistent with normal clinical practice. The SITS International Coordination Office (ICO) regularly monitored the SITS-ISTR data online and checked individual patient data every month to deal with errors or inconsistencies. Source data for a sample of patients who were also included in the SITS-MOST study were verified on-site under the supervision of a national coordinator

Comment: This was an observational epidemiological study using registry data. Consequently, the evidence from this study carries less weight than that from a randomised controlled trial. The study included a large number of patients treated with alteplase according to the clinical routine of individual contributing centres. Patients treated in the 3.0 to 4.5 window after acute ischaemic stroke were treated "off-label" as the European approved time window is within the first 3 hours.

d. Efficacy Outcomes

The study included two efficacy outcomes: independence for activities of daily living at 3 months after treatment (that is, functional independence defined as mRS ≤ 2); and excellent recovery at 3 months after treatment (mRS 0-1). The mRS defines a score of 0 as no symptoms at all, a score of 1 as no significant disability despite symptoms (able to carry out all usual duties and activities), and a score of 2 as slight disability (unable to carry out all previous activities but able to look after own affairs without assistance).

Comment: The two efficacy outcomes are considered to be clinically relevant. The study did not define whether the efficacy outcomes were primary or secondary objectives. In SITS-MOST, the same functional independence efficacy outcome (mRS ≤ 2) as assessed in SITS-ISTR was defined as a secondary objective with symptomatic intracerebral haemorrhage (sICH) within 22-36 after alteplase and mortality at 3 months being the primary objectives.

e. Sample Size

The sample size was stated by the investigators to be able to identify absolute changes of 5% in the functional independence rate at 3 months between patients treated between 3.0 and 4.5 hours and patients treated within the first 3.0 hours.

f. Statistical methods

Descriptive statistics were reported for baseline and demographic data. Percentage proportions (number of events divided by total number of patients, excluding missing or unknown cases) were used to summarise categorical variables. The chi-square test was used to analyse the differences between proportions, and the Mann-Whitney U test was used to analyse the differences between medians. The 95% confidence intervals (CIs) were calculated for the proportions of symptomatic intracranial haemorrhage, mortality, and functional independence. The statistical methods also included a multivariate analysis of difference between patient treatment groups after adjustment for the covariates of age, sex, history of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, congestive heart failure, previous stroke, independence before present stroke (mRS 0–1), smoking, aspirin treatment at stroke onset, baseline NIHSS, baseline blood glucose, baseline blood pressure, bodyweight, alteplase (mg/kg bodyweight), baseline antihypertensive therapy, and signs of present infarction in the baseline imaging study. The analyses were done by logistic regression. No confirmatory hypotheses (null or alternate) were pre-specified.

Comment: The statistical methods were acceptable for a non-randomized, non-controlled, non-blinded, observational cohort study.

Results

a. Participants and Baseline Characteristics

SITS-ISTR [Wahlgren *et al.,* 2008] included 644 patients given alteplase between 3.0 and 4.5 hours after onset of acute ischaemic stroke symptom and 11,865 patients given alteplase within the first 3 hours after onset. Of the 478 clinical centres in 31 countries that were actively documenting thrombolysis data, 203 centres from 25 countries registered treatments during 3-4.5 hour time interval. In general, the baseline characteristics of both cohorts were similar. In the 3-4.5 hour cohort versus the 0-3 hour cohort: median time to treatment after stroke onset was started 55 minutes later (195 versus 140 minutes); median age was 3 years younger (65 versus 68 years); and median baseline NIHSS stroke severity was 1 point lower (11 versus 12). Reported histories of hypertension and hyperlipidaemia were less frequent in the 3-4.5 hour cohort compared with the 0-3 hour cohort, but histories of diabetes mellitus were similar. The incidence of cerebral infarct at baseline imaging was higher in the 3-4.5 hour cohort (30%) than the 0-3 hour cohort (20%). There were no baseline data on the recently included patients added to the registry.

Comment: The differences in baseline characteristics between the two treatment groups are unlikely to have significantly biased the results.

b. Efficacy Outcomes

The results for the two efficacy outcomes of excellent recovery at 3 months (mRS 0-1) and independence at 3 months (mRS 0-2) are summarised below in Table 11.

Table 11: SITS-ISTR: Efficacy endpoints data entered into database on or before 15 December 2008.

	Unadjusted Analysis			Adjusted Analysis
Efficacy Outcome	Between 3.0 and 4.5 hours	Within 3 hours	OR [95%CI]	OR [95%CI]
Excellent recovery at 3 months (mRS 0-1)	310/757 40.95% [95%CI: 37.44-44.56]	5303/13175 40.25% [95%CI: 39.41-41.09]	1.01 [0.94-1.09]	-
Independence at 3 months (mRS 0-2)	438/757 57.86% [95%CI: 54.2-61.39]	7471/13175 56.71% [95% CI: 55.86-57.56	1.02 [0.95-1.10]	0.92 [0.85-1.01]

OR = Odds Ratios were calculated by comparing.
OR adjusted for age, sex, history of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, congestive heart failure, previous stroke, independence before present stroke, smoking, aspirin treatment at stroke onset, baseline NIHSS score, baseline blood pressure, baseline blood glucose, bodyweight, alteplase, baseline antihypertensive therapy, and signs of current infarction on baseline imaging.

Comment: The unadjusted ORs for independence at 3 months and excellent recovery at 3 months were not statistically significant for the 3.0-4.5 hour cohort relative to the 0-3.0 hour cohort. The adjusted OR was not statistically significant for the outcome of independence at 3 months for the two time cohorts. Overall, the outcomes for both excellent recovery at 3 months and independence at 3 months were similar for both the 3-4.5 hour and 0-3.0 hour cohorts.

Evaluator's Overall Conclusions on Clinical Efficacy

The pivotal, randomized, placebo-controlled study (ECASS III) was well designed and methodological sound. It compared alteplase and placebo for the treatment of acute stroke when administered from 3.0-4.5 hours after the onset of symptoms. It included a total of 821 patients (418 alteplase; 403 placebo) from 130 centres located in 19 European countries. The study population is considered to reasonably represent the acute ischaemic stroke patient population who might be treated with alteplase in the general community. However, the study included only a small number of patients aged > 80 years (15, 1.8%). Consequently, the study is considered not to support treatment in patients aged > 80 years. The study also excluded patients taking anti-coagulants and patients with a history of diabetes combined with a history of stroke.

In the ITT population, the pre-specified unadjusted RR and OR for the primary efficacy endpoint of favourable outcome (mRS 0-1 at Day 90) both statistically significantly favoured alteplase relative to placebo. The odds of a favourable outcome were 34% higher [95%CI: 2-76%] for alteplase compared with placebo. The likelihood of a favourable outcome was 16% higher [95%CI: 1-34%] for alteplase compared with placebo. However, the risk difference between alteplase (52.39%, 219/418) and placebo (45.16%, 182/403) was only 7.23% [95%CI: 0.39-13.97%]. This is a modest difference of doubtful clinical significance. The sample size estimate was based on a between treatment difference of 10%. Therefore, it can be reasonably inferred that for this study the minimum clinically significant treatment difference between alteplase and placebo is 10%. The risk difference of about 7% translates into a NNT of about 14. In the ITT population, the pre-specified OR (unadjusted) of the secondary efficacy endpoint of composite functional global outcome favoured alteplase over placebo and was 1.28 [95%: 1.00, 1.65]; p=0.0481. However, although the OR (unadjusted) favoured alteplase over placebo, the result is not statistically significant as the 95% confidence interval included a value of 1. Of the four individual components contributing to the global outcome, two were statistically significant (mRS score 0-1 and NIHSS score of 0 or 1) and two were not statistically significant (BI score ≥ 95 and GOS score of 1). ECASS III included multiple pre-specified tertiary efficacy endpoints which were defined in the study as exploratory. These endpoints consistently favoured alteplase over placebo, but the differences between individual endpoints were generally not statistically significant and the alpha value had not been adjusted for multiple testing which means that the observed statistically significant results might have arisen by chance. The tertiary endpoints are considered to provide no evidentiary weight as regards approval of the application. The ORs of the primary and secondary efficacy endpoints adjusted for baseline covariates both statistically significantly favoured alteplase over placebo. However, the adjusted analyses were not pre-specified and appear to have been undertaken after imbalances in baseline variables were observed in the two randomized treatment groups. Overall, the pre-specified primary and secondary efficacy endpoints are considered to show a modest clinical benefit in patients treated with alteplase in the 3.0-4.5 time window compared with placebo. However, this modest benefit is considered to be of doubtful clinically significance.

The unpublished updated data from the supportive observational study (SITS-ISTR) showed that the ORs (unadjusted) of the efficacy outcomes of independence at 3 months (mRS 0-2) and excellent recovery at 3 months (mRS 0-1) in alteplase treated patients were not statistically significant for the 3.0-4.5 hour time cohort (n=757) relative to the 0-3.0 hour time cohort (n=13,175). The OR (adjusted) for independence at 3 months (mRS 0-1) was also not statistically significant for the two time cohorts. The outcome rates for both the excellent recovery and independence at 3 months were similar for the two time cohorts. SITS-ISTR provides supportive evidence for similar efficacy for alteplase in the two time window cohorts of 3.0-4.5 hours and 0-3.0 hours. However, there are limitations associated with large observational cohort studies using registry data (for example, non-randomized, uncontrolled, and non-blinded). The limitations include differences in routine clinical practice between centres which might have affect collection,

interpretation and reporting of data, differences in clinical characteristics between patients selected for treatment within the two time windows, and unaccounted for confounders.

In the RCT pooled analysis, the OR for both 3.0-4.5 hour time window cohorts statistically significantly favoured alteplase over placebo: OR (total cohort) = 1.31 [95%CI: 1.06-1.63]; OR (cohort excluding major protocol contraindications) = 1.42 [95%CI: 1.13-1.78]. However, the risk difference between alteplase and placebo was < 10% in both 3.0-4.5 hour time cohorts suggesting that, while the observed differences are statistically significant, the differences are of modest benefit and of doubtful clinical significance. The risk difference was 6.6% [95%: 1.4-11.9%] in favour of alteplase for the 3.0-4.5 hour total cohort, and 8.6% [95%CI: 3.1-14.1%] in favour of alteplase for the 3.0-4.5 hour cohort excluding patients with major contraindications. In the 0-6 hour time cohort, the OR for the mRS (0-1) at Day 90 for the 181-270 minutes interval (the interval of interest) statistically significantly favoured alteplase over placebo: OR 1.32 [95%CI: 1.03-1.71]. The data showed that efficacy decreased with increasing time from onset of symptoms to initiation of treatment with the OR for the 271-360 minute time window being not statistically significant.

Safety

Introduction

The submitted safety data included an integrated summary of the clinical safety of alteplase for the treatment of acute ischaemic stroke in the 3.0 to 4.5 hour time window. This summary included safety data from the pivotal Study ECASS III, the observational Study SITS-ISTR, the RCT pooled data, and safety data from seven additional published studies identified by the sponsor from the literature in which alteplase was used according to the current European "label" apart from the time from stroke onset to initiation of treatment.

In *ECASS III*, the key safety endpoints were death and the incidence of symptomatic intracranial haemorrhage (sICH). Further safety endpoints were the incidence of stroke related and neurological deaths, incidence of cerebral haemorrhage and symptomatic oedema, adverse events and vital signs. In this study, a Data Safety and Monitoring Board (DSMB) regularly reviewed the patients independently of the sponsor. In *SITS-ISTR*, recording of safety data was limited to cases of (sICH) and death. In RCT pooled data and the data from the *published literature studies*, safety data were limited to death and to adverse events relating to intracranial bleeding.

The seven additional studies were identified by the sponsor from the literature using the following criteria: (a) treatment with the approved dose of alteplase (0.9 mg/kg); (b) time from onset of stroke symptoms > 3 hours; and (c) recorded outcomes for safety (mortality and sICH). The seven studies were: DEFUSE [2006][6], a prospective, open-labelled, uncontrolled, multinational, multicentred study of 74 patients with ischemic stroke aimed at determining whether baseline MRI can identify patients who have a robust clinical response when treated with alteplase 3-6 hour after stroke; EPITHET [2008], a prospective, placebo-controlled, Phase II study in 52 patients randomized to alteplase and 49 to placebo treated 3-6 hours after onset of stroke; Kohrmann [2006][7], a single-centre, prospective, open-labelled, uncontrolled study, comparing MRI and CT based alteplase

[6] DEFUSE (2006). Albers *et al*. Magnetic Resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation study for understanding stroke evolution (DEFUSE) study. *Ann Neurol* 60:508-517.

[7] Kohrmann *et al*. (2006). MRI versus CT-based thrombolysis treatment within and beyond the 3 h time window after stroke onset: a cohort study. *Lancet Neurol*5:661-67.

treatment in 382 patients treated within or beyond 3 hours; Ribo [2005][8], a single-centre, prospective, open-labelled, uncontrolled study, in 56 patients treated with alteplase in a 3-6 hour treatment window; Schellinger [2007][9], a retrospective, observational, database analysis of 1,210 patients treated with CT and MRI alteplase in European stroke centres; Thomalla [2006][10], a retrospective study of pooled MRI data from ATLANTIS, ECASS II, and NINDS in 174 alteplase treated patients; and Uyttenboogaart [2008][11], a single-centre, prospective, observational cohort study comparing outcomes in 89 patients who received anti-platelet drugs before alteplase with 212 patients who had not received anti-platelet drugs before alteplase.

The integrated clinical safety data included a summary of adverse events focusing primarily on mortality, intracranial haemorrhage (ICH) and symptomatic intracranial haemorrhage (sICH). As the definition of sICH used in the major randomized clinical trials has changed over the years the integrated safety summary applied, where possible, the SITS-MOST definition of sICH (see below in Table 17).

Patient Exposure

The RCT pooled data (including ECASS III) included a total of 2958 patients treated within the 0-6 hour time window (1490 in the alteplase group and 1468 in the placebo group). Of these 2958 patients, 1355 were treated within the 3-4.5 hour time window (681 in the alteplase group and 674 in the placebo group). The SITS-ISTR and seven additional study data included 1545 patients treated with alteplase in the time window beyond 3 hours and 48 with placebo. Overall, data were available on 3035 patients exposed to alteplase and 1516 exposed to placebo. The number of patients in *ECASS III and RCT pooled data* exposed to alteplase (0.9 mg/kg) or placebo later than 3 hours after onset of acute ischaemic stroke is summarised below in Table 12.

[8] Ribo *et al*. (2005). Safety and efficacy of intravenous tissue plasminogen activator stroke treatment in the 3- to 60hour window using multimodal transcranial Doppler/MRI section protocol. *Stroke* 36:602-606.

[9] Schellinger *et al*.(2007). MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time interval: an analysis of 1210 patients. *Stroke* 38:2640-2645.

[10] Thomalla *et al*. (2006). Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI selected stroke patients. Comparison of a German multicenter study with pooled data of ATLANTIS, ECASS, and NINDS tPA trials. *Stroke* 37:852-858.

[11] Uyttenboogaart *et al*. (2008). Safety of antiplatelet therapy prior to intravenous thrombolysis in acute ischemic stroke. *Arch Neurol* 65:607-611.

Table 12: Number of patients in ECASS III and RCTs exposed to alteplase (0.9 mg/kg) or placebo later than 3 hours after onset of symptoms.

	Patients exposed to alteplase (n) *	Patients exposed to placebo (n) **
ECASS III	406	390
RCTs – pooled analysis 3-4.5 h window	681	674
RCTs – pooled analysis 0-6 h window	1492	1470

* In the six RCTs, the number of patients randomized but not exposed to the standard dose of alteplase (0.9 mg/kg) was: 12 in ECASS III; 2 in ECASS II; 3 in ATLANTIS B; and 2 in NINDS.
** In the RCTs, the number of patients randomised but not exposed to placebo was: 13 in ECASS III; 5 in ECASS II; and 1 in NINDS.

In *ECASS III*, of the 418 patients randomised to alteplase, 405 were exposed in the 3.0 to 4.5 hour time window, 1 outside this window, and 12 were not exposed (not treated). The mean±sd infusion times (bolus + infusion) were 62.8±6.0 minutes for alteplase (n=406) and 63.0±5.2 minutes for placebo (n=387). Total duration of infusion was not available in 12 patients in the alteplase group (all received no alteplase) and 16 patients in the placebo group (13 of whom received no placebo).

In the *RCT pooled analysis* (including ECASS III), the 3.0 to 4.5 hour time window cohort included 694 patients randomized to alteplase and safety data were available from 681 of these patients. The 0 to 6 hour time window cohort included 1511 patients randomized to alteplase and safety data were available from 1490 of these patients. There were 674 patients exposed to placebo in the 3.0 to 4.5 hour time window and 1470 exposed in the 0 to 6 hour time window.

The individual numbers of patients in *SITS-ISTR and in the additional seven studies* exposed to alteplase later than 3 hours after onset of acute stroke are summarised below in Table 13. It was not possible to completely rule out multiple reporting of the same patient in calculation of overall exposure to alteplase in the seven studies and SITS-ISTR.

Table 13: Number of patients in SITS-ISTR and seven additional literature studies exposed to alteplase (0.9 mg/kg) or placebo later than 3 hours after onset of symptoms.

	Exposed to alteplase (n)	Exposed to placebo (n)
SITS-ISTR [Wahlgren *et al*., 2008]	664	N/A
SITS-ISTR updated additional patients (unpublished) [2009]	283	N/A
DEFUSE [2006]	74	N/A
EPITHET [2008]	52	48
Ribo *et al* [2005]	43	N/A
Schellinger *et al* [2007]	180	N/A
Uyttenboogart *et al* [2008]	113	N/A
Kohrmann *et al* [2006]	70 *	N/A
Thomalla *et al* [2006]	66 *	N/A
Total excluding possible multiple reporting and unpublished data †	1126	48
Overall total of data sets ††	1545	48

* Patients reported are also included in Schellinger [2007] and are therefore not included in the total of exposed patients.
† Includes SITS-ISTR published registry data, DEFUSE [2006], EPITHET [2008], Ribo [2005], Schellinger [2077], Uyttenboogart [2008].
†† Includes SITS-ISTR updated (unpublished) data and possible multiple reporting of patients.

Adverse Events

The safety profile of alteplase is well known and is comprehensively described in the current Australian Actilyse PI. In the current application, the main safety issue is whether the safety profiles of alteplase administered within the 3-4.5 hour and the 0-3 hour time windows are similar. ECASS III was the primary source of data on non-serious adverse advents (AEs) reported with alteplase and placebo. The study provided comprehensive information on AEs occurring from baseline to day 90. The other sources of safety data limited reporting of serious adverse events to death and intracranial haemorrhage.

In ECASS III, AEs were defined as any untoward medical occurrence whether or not related to the study drug. Non-serious AEs were reported from baseline to hospital discharge in the appropriate case report form (CRF). New non-serious AEs occurring between hospital discharge and day 90 were not documented in the CRF. However, all AEs occurring in this period were presented in the study report. All AEs were followed up until either complete recovery or the event had been adequately characterised. In the ITT population, at least one AE was experienced by 78.2% (327/418) patients in the alteplase group and 79.2% (319/403) of patients in the placebo group (see Table 14, below). The overall AE distribution was similar in both treatment groups, apart from investigator defined drug related AEs which occurred more frequently in alteplase treated patients (23.9%) compared with placebo (6.9%). The AEs leading to discontinuation were: 1x haematemesis immediately after bolus injection (placebo); 1x unexpected worsening of stroke (alteplase); 2x gingival haemorrhage (alteplase).

Table 14: ECASS III – adverse event overall summary in ITT population

	Alteplase n=418	Placebo (n=403)
Patients with and AE	327 (78.2%)	319 (79.2%)
Patients with investigator defined drug related AEs	100 (23.9%)	28 (6.9%)
Patients with AEs leading to discontinuation	3 (0.7%)	1 (0.2%)
Patients with serious adverse events [1]	105 (25.1%)	99 (24.6%)
Fatal	32 (7.7%)	34 (8.4%)
Immediately life threatening	21 (5.0%)	21 (5.2%)
Disabling	10 (2.4%)	11 (2.7%)
Requiring prolonged hospitalization	69 (16.5%)	68 (16.9%)
Other	10 (2.4%)	6 (1.5%)

[1] A patient may have more than one serious adverse event.

The SOCs in which the most frequent AEs occurred in the alteplase group (versus placebo) were: nervous system disorders 38.5%, n=161 (versus 39.5%, n=159); gastrointestinal disorders 27.8%, n=116 (versus 30.8%, n=124); psychiatric disorders 26.8%, n=112 (versus 26.6%, n=107); infections and infestations 20.3%, n=85 (versus 23.1%, n=93); and vascular disorders 21.5%, n=90 (versus 21.8%, n=88). The most frequently reported AEs by preferred term occurring in the alteplase group (versus placebo) were: headache 14.6%, n=61 (versus 17.6%, n=71); constipation 12.9%, n=54 (versus 14.4%, n=58); pyrexia 11.2%, n=47 (versus 13.6%, n=55); and depression 10.3%, n=43 (versus 9.9%, n=40). Intracranial haemorrhage occurred more frequently in the alteplase group compared with placebo (7.2%, n=30 versus 3.2%, n=13), as did haematoma (4.3%, n=18 versus 0.5%, n=2), cerebral haemorrhage (3.8%, n=16 versus 1.2%, n=5), brain oedema (3.3%, n=14 versus 2.7%, n=11), and gingival bleeding (2.9%, 12 versus 0.2%, n=1).

Comment: As expected, intra and extracranial haemorrhage occurred more frequently in the alteplase group than in the placebo group. Other types of AEs were similar in both treatment groups. There were no unexpected AEs occurring with alteplase.

Serious Adverse Events and Death

Overview

In ECASS III, in the ITT population serious adverse events (SAEs) were reported in 25.1% (105/418) of patients in the alteplase group and 24.6% (99/403) in the placebo group. SAEs in the alteplase group (versus placebo) occurred most frequently in the SOC of nervous system disorders (14.4%, n=60 versus 11.9%, n=48). The most common SAEs occurring in nervous system disorders (SOC) with alteplase (versus placebo) by preferred term were: brain oedema 2.2%, n=8 (versus 1.0%, n=4); cerebrovascular accident 1.9%, n=8 (versus 3.7%, n=14); coma 1.4%, n=6 (versus 1.5%, n=6); carotid artery stenosis 1.4%, n=6 (versus .0.5%, n=2); cerebral haemorrhage 1.4%, n=6 (versus 0.7%, n=3); intracranial haemorrhage 1.2%, n=5 (versus 0.2%, n=1); haemorrhagic transformation 1.2% (versus 0.7%, n=3); and ischaemic stroke 1.0%, n=4 (versus 1.5%, n=6). Other SAEs occurring with an incidence of $\geq$ 1% with alteplase (versus placebo) were: pneumonia 1.4%, n=6 (versus 2.2%, n=9); pulmonary embolism 1.4%, n=6 (versus 1.5%, n=6); deep vein thrombosis

1.2%, n=5 (versus 0.5%, n=2); cardiac failure 1.0%, n=4 (versus 1.2%, n=5); and myocardial infarction 1.0%, n=4 (versus 0.5%, n=2).

Intracranial Haemorrhage (Any)

ECASS III

In ECASS III, intracranial haemorrhage (ICH) was assessed blinded by investigators and also by a central independent safety and outcome committee (SOAC). Overall, 74 (4.22%) of the 1753 images performed in the study could not be assessed by the SOAC due to technical difficulties (alteplase n=41, 4.6%; placebo n=33, 3.8%). In the ITT population, significantly more patients in the alteplase group (27.0%) experienced an ICH diagnosed by CT or MRI imaging than in the placebo group (17.6%) (see Table 15 below).

Table 15: ECASS III – results for any ICH experienced in the ITT population.

	Alteplase n=418	Placebo n=403	p- value [1]
ICH: yes - n (%)	113 (27.03%)	71 (17.62%)	0.0012
ICH: no - n (%) [2]	305 (72.97%)	332 (82.38%)	
Odds Ratio [95%CI]	1.73 [1.24-2.42]		
Relative Risk [95%CI]	1.53 [1.18-2.00]		
Fatal ICH	3 (0.72%)	0 (0%)	

1 Pearson chi-square test (no continuity correction).

2 Includes patients assessed as having no ICH as well as patients for whom SOAC adjudication was missing or technically not possible.

Most of the ICHs occurred within the first 24 hours of treatment: 88.5% (100/113) in the alteplase group and 76.1% (54/71) in the placebo group. The remaining ICHs occurred from day 1 to day 7 (9.7%, 11/113 alteplase versus 5.1%, 14/71 placebo), or from day 7 to day 30 (0.8%, 1/113 alteplase versus 4.2%, 3/71 placebo).

Haemorrhagic transformations H1 and H2[12] occurred in 16.0% of patients in the alteplase group (versus 13.9% placebo) and 6.2% (versus 2.2% placebo), respectively. Parenchymal haemorrhages PH1 and PH2[13] occurred in 2.2% of alteplase treated patients (versus 0.5% placebo) and 2.6% (versus 1.0% placebo), respectively. A *post-hoc analysis* of the ECASS II study showed that only PH2 haemorrhages were associated with an increased risk of deterioration at 24 hours after stroke compared with no ICH (adjusted OR = 18 [95%CI: 6-56]), and for death at 3 months (adjusted OR = 11 [95%CI: 3.7-36]). All other types of haemorrhage transformation did not independently increase the risk of late deterioration [Berger *et al*., 2001][14].

SITS-ISTR

In SITS-ISTR [Wahlgren *et al*., 2008], 16.6% (107/643) of patients treated with alteplase in the 3-4.5 hour time window and scanned at any time after treatment experienced an ICH of any type compared with 19.1% (2202/11552-4) of patients treated with alteplase within the 0-3 hour time

[12] H1 transformations are defined as small petechiae along the margins of the infarct. H2 transformations include more confluent petechiae within the infarct but without space occupying effect.

[13] PH1 consist of blood clot(s) not exceeding 30% of the infarct area with some mild space occupying effect. PH2 consist of dense blood clots exceeding 30% of the infarct area with substantial space occupying effect.

[14] Berger C *et al*. (2001). Hemorrhagic transformation of ischemic brain tissue asymptomatic of symptomatic. *Stroke* 32:1330-1335.

window. ICH was recorded as a primary cause of death in 1.2% (8/664) of patients treated in the 3-4.5 hour time window and 1.1% (131/11865) of patients treated within the 0-3 hour time window (p=0.92). On average, patients in the 3-4.5 hour time window cohort were a median of 3 years younger than the 0-3 hour cohort (65 versus 68 years) and baseline NIHSS was a median of 1 point lower (11 versus 12). The differences in age and baseline stroke severity might have accounted for the lower frequency of ICH in the 3-4.5 hour time window cohort.

RCT Pooled Analysis

In the RCT pooled analysis, the incidence of any ICH in the 3-4.5 hour total cohort was 28.6% (195/681) for alteplase and 18.6% (125/674) for placebo: OR unadjusted = 1.76 [95%CI: 1.36-2.28]; p< 0.0001. The ICH rates in the 0-6 hour cohort were 31.0% (464/1511) for alteplase and 22.3% (327/1468) for placebo: OR unadjusted = 1.57 [95%CI 1.33-1.8]; p < 0.001. The pooled analysis (0-6 h cohort), showed that the adjusted odds of experiencing any ICH with alteplase were significantly increased in the 181-270 minute and 271-360 treatment windows (see Table 16, below).

Table 16: RCT (0-6 h cohort) - ICH (any) adjusted ORs for 90 minute treatment onset time intervals.

Treatment Onset Time intervals	n	Odds Ratio [95%C] Alteplase versus Placebo – adjusted *	p value
0-90 minutes	284	1.39 [0.81-2.38]	0.2357
91-181 minutes	494	1.13 [0.74-1.71]	0.5759
181-279 minutes	1296	1.87 [1.42-2.47]	< 0.001
271-360 minutes	669	2.35 [1.61-3.43]	< 0.001

* OR adjusted at baseline for NIHSS (0-7, 8-14, 15-18, > 18); age; DBP (<70, 70-90, >90 mmHg); weight (≤70, 71-90, >90 kg); prior stroke; hypertension; smoking history; and interaction of age and NIHSS.

Seven Additional Studies (Literature)

Ribo (2005, was the only one of the seven studies to include incidence data on all ICH. In this study, all ICH was reported in 22.5% of 79 patients treated with alteplase in the 0-3 hour time window compared with 29.0% of 43 patients treated in the 3-6 hour time window.

Symptomatic Intracranial Haemorrhage (sICH)

Overview

The sponsor considered symptomatic intracranial haemorrhage (sICH) to be the most clinically relevant AE because of its detrimental effect on patient outcome. There have been four sICH definitions used in the main randomized controlled studies and these are provided below in Table 17. In the RCT pooled analysis, it was stated that the SITS-MOST definition of sICH was used because of its clinical relevance. The SITS-MOST definition has been included below in Table 17.

Table 17: Definitions of symptomatic intracranial haemorrhage (sICH).

ECASS III	Symptomatic intracerebral haemorrhage was defined as any blood in the brain or intracranially associated with a clinical deterioration of ≥ 4 points on the NIHSS for which the haemorrhage has been identified as the dominating cause of the neurological deterioration.
SITS-MOST	Local or remote PH2 on the 22-36 hour post-treatment imaging scan, combined with neurologic deterioration of ≥ 4 points on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.
ECASS II	Any intracranial bleed and ≥ 4 point worsening on the NIHSS score from baseline or the lowest value in the first 7 days, or any haemorrhage leading to death.
NINDS	A haemorrhage was considered symptomatic if it was not seen on a previous CT scan and there had been either a suspicion of haemorrhage or any decline in neurologic status. To detect intracranial haemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical findings suggested haemorrhage.

ECASS III

In ECASS III, sICH was assessed by the SOAC using a protocol definition (ECASS III) and ECASS II, SITS-MOST, and NINDS definitions. All sICHs occurred within the first 22 to 36 hours of treatment. The results for the ITT populations are summarised below in Table 18.

Table 18: ECASS III – sICH following treatment in the 3-4.5 hour time window in the ITT population

Definition	Alteplase (n=418)	Placebo (n=403)	Odds Ratio [95%CI]	Relative Risk [95%CI]	RD% [95%CI] *	P value
ECASS III	10 (2.4%)	1 (0.2%)	9.85 [1.26-77.32]	9.64 [1.24-74.90] **	2.2 [0.6-4.1]	0.008
ECASS II	22 (5.3%)	9 (2.2%)	2.43 [1.11-5.35]	2.36 [1.10-5.06]	3.1 [0.4-5.8]	0.02
SITS-MOST	8 (1.9%)	1 (0.2%)	7.84 [0.98-63.00]	7.71 [0.97-61.39] **	1.7 [0.2-3.5]	0.02
NINDS	33 (7.9%)	14 (3.5%)	2.38 [1.25-4.52]	2.27 [1.23-4.18]	4.4 [1.3-7.7]	0.006

* RD [95%CI] = Risk Difference [95% confidence interval] – calculated by the clinical evaluator.
** Relative Risk [95%CI] calculated by the clinical evaluator.

SITS-ISTR

The results for the odds ratios (unadjusted) from the SITS-ISTR published study for sICH following alteplase initiated in the 3-4.5 hour and 0-3 hour cohorts are provided below in Table 19. The updated unpublished incidence rates are similar to the published figures.

Table 19: SITS-ISTR - sICH results (unadjusted) in the 3-4.5 hour within 3 hours time windows.

Definition	Alteplase 3-4.5 hours	Alteplase within 3 hours	Odds Ratio [95%CI]	P value
SITS-MOST	14/649 (2.2%)	183/11861 (1.6%)	1.18 [0.89-1.55]	0.24
ECASS II	34/636 (5.3%)	553/11505 (4.8%)	1.06 [0.89-1.26]	0.54
NINDS	52/647 (8.0%)	846/11646 (7.3%)	1.06 [0.91-1.27]	0.46

Source: Wahlgren *et al*., 2008.

RCT Pooled Analysis

The results for the odds ratios (unadjusted) from the RCT pooled analysis for alteplase and placebo in the 3-4.5 hour total cohort and the 0-6 hour cohort for sICH using the SITS-MOST definition are provided below in Table 20.

Table 20: Pooled RCT data: sICH using SITS-MOST definition.

Cohort	Alteplase	Placebo	Odds Ratio [95%CI]	P value
3-4.5 h total cohort	17/681 (2.5%)	2/672 (0.3%)	8.60 [1.98-37.36]	0.0041
0-6 h cohort	51/1511 (3.4%)	6/1468 (0.4%)	8.46 [3.61-19.79]	< 0.0001

Published Studies

The sICH results for the seven published studies have been examined and the results summarised below in Table 21. These studies used sICH criteria from NINDS, ECASS II or SITS-MOST and alteplase was initiated in differing time windows. The sICH rates varied among the studies. In those studies which included data from earlier and later time windows sICH rates were generally similar for both windows.

Table 21: Summary of sICH incidence from the 7 submitted published studies.

Study		Treatment window	Alteplase	Placebo
DEFUSE [2006]	NINDS	3-6 hours	9.5% [95%CI:5-18] of 74 patients	N/A
Schellinger [2007]	NINDS	< 3 hours (CT group)	5.3% of 714 patients	N/A
	NINDS	< 3 hours (MRI group)	2.8% of 322 patients	N/A
	NINDS	> 3 hours (MRI group)	4.4% of 174 patients	N/A
Kohrmann [2006[	NINDS	≤ 3 hours (CT group)	1% of 209 patients	N/A
	NINDS	≤ 3 hours (MRI group)	6% of 103 patients	N/A
	NINDS	> 3 hour (MRI group)	9% of 70 patients	N/A
EPITHET [2008]	SITS-MOST	3-6 hours	7.7% (4/52; 95%CI:2.1-18.5)	0%
Uyttenboogaart [2008]	SITS MOST	0-4.5 hours	6.0% (18/301; 95% 3.8-9.3]	N/A
	SITS MOST	< 3 hours	6.4% (12/188)	N/A
	SITS MOST	3-4.5 hours	5.3% (6/113)	N/A
Ribo [2005]	ECASS II	0-3 hours	3.8% of 79 patients	N/A
	ECASS II	3-6 hours	2.4% of 43 patients	N/A
Thomalla [2006]	ECASS II	0-6 hours	8.2% (89/1085; 95%CI:6.5-9.8)	1.9% (21/1081; 95%1.1-2.8)
	ECASS II	0-3 hours	7.9% (33/416; 95%CI: 5.3-10.4)	1.6% (7/427; 95%CI: 0.4-2.8)
	ECASS II	3-6 hours	8.4% (56/669; 95%CI: 6.2-10.4)	2.1% (14/654; 95%CI: 1.0-3.2)

Source: Data extracted directly from published studies.

Mortality

ECASS III

The total all cause mortality was similar in the alteplase group 7.7% (32/418) and the placebo group 8.4% (34/403) in the ITT populations: OR = 0.90 [95%CI: 0.54-1.49]; p=0.6807. Survival at Day 90 was not significantly different between the two groups: 93.3% (390/418) for alteplase and 92.3% (372/403) for placebo; p=0.5928. Of the total number of deaths (n=66): 25/66 (37.9%) occurred between day 1 and 7 (12/32, 37.5% alteplase; 13/34, 38.2% placebo); 18/66 (27.3%) between day 8

and 30 (10/32, 31.3% alteplase; 8/34, 23.5% placebo); and 16/66 (24.2%) between day 30 and 90 (6/32, 18.8% alteplase; 10/34, 29.4% placebo). There were 7/66 (10.6%) deaths after day 90 (4/32, 12.5% alteplase; 3/34, 8.8% placebo).

Deaths in the ITT population as adjudicated by the SOAC are summarised below in Table 22. The major causes of mortality were similar for alteplase and placebo, although vascular causes (cerebral and non cerebral) were marginally more common with alteplase than with placebo.

Table 22: ECASS III – Deaths in the ITT population as adjudicated by the SOAC.

	Alteplase n=418	Placebo n=403
Deaths (all cause)	32 (7.7%)	34 (8.4%)
Cerebral Reason (neurological deaths)	13 (3.1%)	12 (3.0%)
Haemorrhage	3 (0.7%)	0 (0%)
Oedema	10 (2.4%)	12 (3.0%)
Non-cerebral Reason	18 (4.3%)	20 (5.0%)
Vascular Reason	8 (1.9%)	5 (1.2%)
Non-vascular Reason	10 (2.4%)	15 (3.7%)
Unknown	1 (0.2%)	1 (0.3%)
Adjudication not possible	0 (0%)	1 (0.3%)

SITS-ISTR

The 3 month and 7 day mortality data from the SITS-ISTR published data are summarised below in Table 23. The 3 month mortality figures based on the updated unpublished data were 12.3% (1263/13357) for the 0-3 hour time window and 12.4% (97/768) for the 3-4.5 hour time window (that is, similar values to the earlier published figures).

Table 23: SITS-ISTR – Mortality OR (unadjusted) in the 3-4.5 and 0-3 hour time windows.

Definition	Alteplase 3-4.5 h	Alteplase within 3 h	Odds Ratio [95%CI]	P value
Mortality at 3 months	70/551 (12.7%)	1263/10368 (12.2%)	1.02 [0.90-1.17]	0.72
Mortality at 7 days	49/650 (7.5%)	751/11621 (6.5%)	1.19 [0.88-1.60]	0.31

Source: Wahlgren *et al*., 2008.

RCT Pooled Analysis

The RCT pooled all cause mortality results are summarised below in Table 24. The mortality rates were similar for both alteplase and placebo in both the 3-4.5 hour and 0-6 hour cohorts.

Table 24: Pooled RCTs - Mortality OR (unadjusted) in the 3-4.5 and 0-6 hour time windows.

Definition	Alteplase	Placebo	Odds Ratio [95%CI]	P value
3-4.5 h total cohort	62/674 (9.2%)	57/681 (8.4%)	0.90 [0.62-1.31]	0.5901
0-6 h cohort	175/1490 (11.7%)	63/1468 (11.1%)	1.07 [0.85-1.34]	0.5836

Seven Published Studies

The mortality rates associated with alteplase varied from 4.1% to 25.5% in the seven additional published studies. The results from the two studies which included a placebo comparison are briefly discussed. In *EPITHET [2008]*[15], the all cause mortality rate at Day 90 reported with alteplase (treatment onset 0-6 hours) was 25.5% (13/51) compared with 14.3% (7/49) with placebo. No discussion was provided in the study about the imbalance in mortality between the two treatments. However, the two treatment groups were unbalanced at baseline for stroke severity (NIHSS median 14 [range 4-26] for alteplase and 10 [5-25] for placebo). It is possible that this imbalance might have contributed to the greater incidence of mortality reported with alteplase compared with placebo. In *Thomalla [2006]*, in the 0-3 hour treatment window the all cause mortality rates were 16.9% (72/427) for placebo and 16.6% (69/416) for alteplase, and in the 3-6 hour treatment window the rates were 9.0% (59/654) for placebo and 11.4% (76/669) for alteplase.

Laboratory Findings and Vital Signs

Laboratory Findings

No clinical laboratory findings were reported in ECASS III. No systematic analyses of laboratory data were presented in the other studies.

Vital Signs

Only ECASS III included a specific description of vital signs. Blood pressure and heart rate were measured throughout the study at various time points, especially during the first 24 hours. The SBP, DBP and pulse rate results were similar for alteplase and placebo. Hypertension was recorded as an AE in 7.4% (n=31) of alteplase treated patients and 8.7% (n=35) of placebo treated patients. Hypotension was reported as an AE in 3.6% (n=15) of alteplase treated patients and 5.7% (n=23) of placebo treated patients. There was no systematic reporting of ECG findings.

Safety in Special Populations

ECASS III

ECASS III included a number of subgroup analyses of sICH and mortality. There were no significant subgroup-by-treatment interactions in this analysis ($p<0.05$), apart from age. The analysis for age showed a significant sub-group-by-treatment interaction ($p=0.035$). The sICH (NINDS criteria) incidence in patients aged < 65 years was 4.3% (8/184) for alteplase and 5.8% (9/155) for placebo, with the respective figures in patients aged ≥ 65 years being 13.6% (25/184) and 3.2% (5/155). This interaction was also seen in the PP population of sICH (NINDS criteria).

[15] EPITHET [2008]: Davis *et al*. (2008). Effects of alteplase beyond 3 h after stroke in the Echoplanar imaging thrombolytic evaluation trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol* 7:299-309.

In the subgroup analysis of mortality in the ITT population significant subgroup-by-treatment interactions were seen for smoking status (p=0.0196) with current smokers being (paradoxically) at a greater risk than non current smokers, and gender (p=0.0495) with males being at a greater risk than females. The 3 month mortality rate in current smokers in the ITT population was 3.9% (5/128) for alteplase compared with 12.9% (15/116) for placebo: OR = 0.27 [95%CI: 0.1-0.78]. The sponsor comments "that it has been postulated that the pathogenesis of vascular occlusion in smokers may be more thrombogenic than atherogenic due to the fact smoking is associated with increased platelet activation and aggregation and increased level of circulating fibrinogen and thrombin. All of this may result in a better susceptibility of cerebral thrombi to fibrinolysis in smokers versus non-smokers."

Comment: There was no adjustment of alpha for multiple subgroup testing. Consequently, the observed statistically significant subgroup results might have arisen by chance.

RCT Pooled Analysis

In the subgroup analysis of all mortality in the pooled RCT data (3-4.5 hour total cohort), the only subgroup to show a significant subgroup-by-treatment interaction was gender (p=0.0451). In the gender subgroup, the incidence of mortality in males treated with alteplase was greater than with placebo (10.3%, 43/419 versus 8.8%, 35/400; OR [95%CI] = 1.20 [0.75-1.92]), and the incidence of mortality in females was lower with alteplase compared with placebo (5.3%, 14/262 versus 9.9%, 27/274; OR [95%CI] = 0.52 [0.27-1.01]). The significant interaction for gender seen in the 3-4.5 hour total cohort was not seen in the 3-4.5 hour cohort which excluded patients with major protocol violations (p=0.201).

In the subgroup analysis of any ICH in the pooled RCT data, the only two subgroups which showed a significant sub-group-by treatment interaction were prior aspirin treatment (p=0.0283) and hypertension (p=0.0483). Prior aspirin treatment increased the relative risk of any ICH by about 2 fold and the odds of any ICH by about 3 fold: alteplase 32.0%, 57/178 versus placebo 16.9%, 32/189; OR [95%CI] = 3.09 [1.80-5.30]. Hypertension increased the relative risk of any ICH by about 2 fold and the odds of any ICH by about 2.3 fold: alteplase 29.8%, 122/409 versus 16.2%, 64/394 placebo; OR [95%CI] = 2.29 [1.61-3.26].

Comment: There was no adjustment of alpha for multiple subgroup testing. Consequently, the observed statistically significant subgroup results might have arisen by chance.

Very Elderly (≥80 years)

RCT Pooled Data Analysis

In the pooled data from the RCTs (0-4.5 hour cohort), the main safety endpoints were incidence of any ICH, incidence of sICH (SITS-MOST definition), and 90 day mortality. The incidence of mortality in alteplase treated patients (versus placebo) was 27.6%, 21/76 (versus 23.0%, 14/61) in the very elderly cohort (aged ≥ 80 years), and 10.2%, 104/1021 (versus 11.5%, 120/1041) in the younger cohort (aged < 80 years). The risk difference (alteplase – placebo) was 4.6% in the very elderly cohort and -1.3% in the younger cohort. The unadjusted ORs (alteplase versus placebo) were 0.87 [95%CI: 0.66-1.15] for the younger cohort and 1.28 [95%CI: 0.59-2.80] for the very elderly. The ORs (alteplase versus placebo) adjusted for baseline NIHSS score were 0.92 [95%CI: 0.69-1.23] for the younger cohort and 0.96 [95%CI: 0-36-2.49] for the very elderly.

The incidence of any ICH in alteplase treated patients (versus placebo) in the very elderly cohort was 51.3%, n=39 (versus 21.3%, n=13) and in the younger cohort was 28.9%, n=295 (versus 23.5%, n=245). The risk difference (alteplase – placebo) was 30% in the very elderly and 5.4% in

the younger cohort. The OR (adjusted for baseline NIHSS) was 4.01 [95%CI: 1.76-9.13] for the very elderly cohort and 1.44 [95%CI: 1.17-1.77] for the younger cohort.

The incidence of sICH in alteplase treated patients (versus placebo) in the very elderly cohort was 6.6%, 5/76 (versus 0%, 0/61) and 2.5%, 25/1021 (versus 0.5%, 5/1041) in the younger cohort. The risk difference (alteplase - placebo) was 6.6% in the very elderly cohort and 2.0% in the younger cohort. The OR (adjusted for baseline NIHSS) was 6.17 [95%CI: 2.38-15.96] for the very elderly cohort and 5.24 [95%CI: 2.00-13.75] for the younger cohort.

In the subgroup of very elderly patients with less severe stroke (NIHSS < 20) the overall mortality in the alteplase and placebo groups was, respectively: 8.9%, 4/45 and 11.4%, 5/44; OR (adjusted for baseline NIHSS) = 0.61 [95%CI: 0.13-2.88]. The risk difference (alteplase - placebo) was -2.5%. In this subgroup, the incidence of any ICH in the alteplase and placebo groups was, respectively: 40.0%, 18/27 versus 13.6%, 6/44; OR (adjusted) = 4.82 [95%CI: 1.44-14.94]. The risk difference (alteplase – placebo) was 26.4%. In this subgroup, the incidence of sICH in the alteplase and placebo groups was, respectively: 6.7%, 3/42 (versus 0%, 0/44; OR (unadjusted with imputation of 0.5 for no events) = 6.21 [95%CI: 0.30-127.81]. The risk difference (alteplase – placebo) was 6.7%.

In the subgroup of very elderly patients with severe stroke (NIHSS ≥ 20) the overall mortality in the alteplase and placebo groups was, respectively: 54.8%, 17/31 and 52.9%, 9/17; OR (adjusted for baseline NIHSS) = 1.36 [95%: 0.37-4.98]. In this subgroup, the incidence of any ICH in the alteplase and placebo groups was, respectively: 67.7%, 21/31 and 41.2%, 7/17; OR (adjusted for baseline NIHSS) = 3.03 [95%CI: 0.88-10.47]. The risk difference (alteplase – placebo) was 26.5%. In this subgroup, the incidence of sICH in the alteplase and placebo treated groups was, respectively: 6.5%, 2/17 and 0%, 0/17; OR (unadjusted with imputation of incidence 0.5 for 0 events) = 2.28 [95%CI: 0.10-53.50]. The risk difference (alteplase – placebo) was 6.5%.

Systematic Reviews by Engelter et al., 2006 and Ringleb et al., 2007

The integrated safety summary included results from two meta-analyses in alteplase treated patients comparing very elderly patients (≥ 80 years) with younger patients (< 80 years). The results for the two studies were similar. In summary, the odds of all cause mortality were statistically significantly higher in very elderly patients compared with younger patients, while the odds of sICH were similar in the two age cohorts.

In the Engelter [2006] meta-analysis, the incidence of 3 month all cause mortality in patients aged ≥ 80 years and < 80 years treated with alteplase was, respectively: 31.5%, 150/477 and 15.8%, 279/1767; OR [95%CI] = 3.09 [2.37-4.03]; p<0.0001. The incidence of sICH (definition varied among included studies) in patients aged ≥ 80 years and < 80 years treated with alteplase was, respectively: 5.9%, 28/477 and 5.2%, 91/1767: OR [95%CI] = 1.22 [0.77-1.94]; p=0.34. *In the Ringleb [2007] meta-analysis*, the incidence of all cause mortality in patients aged ≥ 80 years and < 80 years treated with alteplase was, respectively: 32.3%, 172/532 and 13.3% 283/1969; OR [95%CI] = 3.18 [2.48-4.09]. The incidence of sICH (definition varied among studies) in patients aged ≥ 80 years and < 80 years treated with alteplase was, respectively: 6.1%, 38/621 and 5.1%, 116/2259; OR [95%CI] = 1.27 [0.85-1.91].

Overall Comment on safety in the very elderly

The most relevant results for safety in the elderly are considered to be those from the RCTs. These results showed that mortality, any ICH, and sICH in alteplase treated patients all occurred more frequently in very elderly patients (aged ≥ 80 years) treated with alteplase in the 0-4.5 hour time window than in younger patients (< 80 years). Mortality occurred more frequently in the very elderly treated with alteplase compared with placebo, as did both all ICHs and sICHs. However, in

a subgroup analysis of patients aged ≥ 80 years excluding those with severe stroke (NIHSS ≥ 20) showed that mortality was not increased with alteplase compared with placebo. These results suggest that the increased mortality in patients aged ≥ 80 years treated with alteplase compared with placebo is being driven primarily by patients with severe baseline stroke (NIHSS ≥ 20). However, the odds of any ICH and of sICH were greater in alteplase treated very elderly patients with baseline stroke severity NIHSS < 20 compared with placebo.

The data from the *Engelter [2005]* and *Ringleb [2007]* meta-analyses showed that the odds of mortality at 3 months were about 3 fold higher (statistically significant) in very elderly patients (≥ 80 years) treated with alteplase compared with younger patients, while the odds of sICH were 22-27% (not statistically significant) higher. In *Engelter [2006]*, the authors concluded that there is "scope for benefit from thrombolysis for stroke patients aged ≥ 80 years", but note that data from ongoing RCTs will "hopefully yield more conclusive answers to the question whether (and which) stroke patients aged ≥ 80 years have a net benefit from rtPA[16]". The sponsor argues that the relative increase in mortality with alteplase in patients aged ≥ 80 years compared with < 80 years observed in these two meta-analyses should be regarded as part of the natural history of stroke in the very elderly as the increased mortality rate was similar to a very elderly non treated comparator group.

Immunological Events

In ECASS III, a test dose of study drug was initially administered as a bolus (10% of total) over 1-2 minutes to check for any allergic reactions prior to administration of the remaining dose. Perusal of the SOC and preferred term AE data for "immune system disorders" showed that 1 placebo treated patient was reported as having a hypersensitivity reaction compared with 1 alteplase treated patient, and 1 alteplase treated patient was reported as having amyloidosis. In the SOC of "skin and subcutaneous tissue disorders" 1 alteplase treated patient was reported as experiencing angioedema, 1 alteplase treated patient with allergic dermatitis (versus 4 with placebo), 2 alteplase treated patients with eczema, 1 placebo treated patient with drug eruption. There were no data in the submission on antibodies to alteplase. None of the other studies provided immunological AE data. Overall, there were no significant immunological AEs in the submitted safety data.

Safety Related Drug-Drug Interactions and Other Interactions

There were no new data on pharmacokinetic or pharmacodynamic drug-drug interactions. The subgroup analysis referring to the effect of prior aspirin on ICH following alteplase treatment has been referred to above.

Discontinuations Due to Adverse Events

Discontinuations due to AEs in ECASS III have been discussed above in section 4.3 of the evaluation, and included in Table 14.

Post-Marketing Experience

The application included a recent Periodic Safety Update Report (PSUR) for alteplase (Actilyse) dated 22 July 2009 and covering the period 02 May 2008 to 31 May 2009, and a Summary Bridging Report (SBR) dated 06 August 2008 covering the period from 16 November 2003 to 1 May 2008. The international birth date of alteplase is 06 June 1987.

The PSUR indicates that the total number of vials of alteplase sold worldwide from 01 July 1992 to 31 May 2009 was 4,399,319. This PSUR included a review of PSURS numbers 7-11 (16 November 2003 to 1 May 2008). During this 4 year period, a total of 3164 cases of alteplase associated adverse

[16] recombinant tissue plasminogen activator (rtPA).

reactions have been reported with a total of 4809 events. Of the 3164 cases, 2891 (91.4%) reported at least one serious reaction and 968 (30.6%) had a fatal outcome. The largest number of events for PSURs numbers 7-11 has been reported in the SOC of "nervous system disorders" ranging from 23.8% (PSUR 7) to 68.3% (PSUR 11) of all events. The next largest number of events for PSURS numbers 7-11 have been reported in the SOC of "general disorders and administration site conditions" ranging from 15.0% (PSUR 10) to 34.0% (PSUR 7) of all events. In the PSURs numbers 7-11, intracranial haemorrhage was the most common event in almost all PSURS ranging from 17.7% (PSUR 7) to 40.5% (PSUR 8) of all events. Intracranial haemorrhage occurred most frequently in patients treated for ischaemic stroke, followed by pulmonary embolism, and myocardial infarction. Reports of mortality were highly variable across the five PSURs for the indications ischaemic stroke, myocardial infarction, and pulmonary embolism.

In summary, the post-marketing data are extensive and the post-marketing adverse drug reactions reported for alteplase are well known. The drug has been marketed worldwide (and in Australia) for more than 20 years.

Evaluator's Overall Conclusions on Clinical Safety

The main safety issues relate to sICH, mortality and all ICH in patients treated with alteplase in the 3-4.5 hour time window compared with the 0-3 hour time window. In ECASS III, the odds of sICH were greater with alteplase compared with placebo as assessed by the ECASS definition III (OR statistically significant), the ECASS II definition (OR statistically significant), the SITS-MOST definition (OR not statistically significant), and the NINDS definition (OR statistically significant) (see Table 18, above). The incidence of sICH varied from 2.4% to 7.9% with alteplase and from 0.2% to 3.5% with placebo (that is, risk difference varied from 2.2% to 4.4%). All sICHs in ECASS III occurred within the first 22-36 hours of treatment. In the RCT pooled analysis, the odds and risks of sICH (SITS-MOST criteria) were statistically significantly greater with alteplase than with placebo in the 3-4.5 hour time window (total cohort) and the 0-6 hour cohort (see Table 20, above). The incidence of sICH (SITS-MOST definition) in the RCT pooled analysis in the 3-4.5 hour cohort was greater for both alteplase and placebo compared with the corresponding results in ECASS III. The observational data from SITS-ISTR showed similar incidences of sICH in the 3-4.5 hour time window as ECASS III for the same definitions (SITS-MOST, ECASS II, and NINDS) (see Table 19, above). The incidence of sICH in the SITS-ISTR study was marginally, but not statistically significantly greater, for patients in the 3-4.5 hour window compared with the 0-3 hour window for each of the three sICH definitions. The results for sICH in alteplase treated patients in the seven additional published studies generally showed increased incidences for patients treated with alteplase for more than 3 hours compared with patients treated for less than 3 hours (see Table 21, above). In *Uyttenboogaart [2008]*, the incidence of sICH (SITS-MOST) was similar in alteplase treated patients in the 0-4.5 hour, < 3 hour, and 3-4.5 hour time windows (see Table 21, above).

In ECASS III, the all cause mortality rate in the ITT population was similar in the alteplase (7.7%, 32/418) and placebo groups (8.4%, 32/402) in the 3-4.5 hour time window. There were 3 (0.7%) deaths due to ICH in the alteplase group compared with no (0%) deaths in the placebo group, and there were 10 (2.4%) deaths due to cerebral oedema in the alteplase group compared with 12 (3.0%) in the placebo group. In the RCT pooled analysis, the mortality rates for alteplase and placebo were similar in the 3-4.5 hour cohort (total) and 0-6 hour cohorts. The all cause mortality rates in the 3-4.5 hour cohort (total) were about 2-3% lower for both alteplase and placebo than the rates in the 0-6 hour cohort.

In ECASS III, the relative risk of all ICH was 53% statistically greater for alteplase compared with placebo and the risk difference was 9.4% (27.0% versus 17.6%) (see Table 15 above). The risk of haemorrhagic transformation PH2 (a transformation that has been associated with worse outcome compared with no ICH) was 2.6% in the alteplase group compared with 1.0% in the placebo group.

In the RCT pooled data analysis, the incidences of all IHC for both alteplase and placebo were similar to those in ECASS III, and the odds of an ICH with alteplase compared with placebo increased with increasing time from treatment onset. In SITS-ISTR [Wahlgren *et al*., 2008], the incidences of all ICH and death due to all ICH in the 3-4.5 hour cohort were both similar to that in the 0-6 hour cohort. However, patients in the 3-4.5 hour cohort might have had less baseline risk for all ICH than patients in the 0-6 hour cohort.

In the very elderly (aged ≥ 80 years), the risks of sICH, all ICH, and all cause mortality with alteplase were all greater than in younger patients (aged < 80 years). In the very elderly, the odds of sICH and ICH were statistically significantly greater with alteplase compared with placebo, while for patients with baseline stroke severity NIHSS < 20 the odds for all cause mortality were not statistically significantly different between alteplase and placebo.

Clinical Summary and Conclusions

Benefits

It is considered that the submitted efficacy data (ECASS III, RCT pooled analysis) demonstrated a statistically significant modest benefit in patients treated with alteplase for acute ischaemic stroke compared with placebo when treatment was initiated in the 3-4.5 hour time window. However, this statistically significant modest benefit is considered to be of doubtful clinical significance.

ECASS III was the pivotal, multi-centred (130 centres), multi-national (19 European countries), randomized, placebo-controlled efficacy and safety study. It compared alteplase at a dose of 0.9 mg/kg (n=418) and placebo (n=403) for the treatment of acute stroke when administered between 3.0 and 4.5 hours after the onset of symptoms. The study was well designed and methodologically satisfactory. The study participants are considered to be a reasonable representative sample of patients in the general population presenting to hospital with acute ischaemic stroke and likely to be considered for alteplase treatment. However, in ECASS III, patients receiving oral anticoagulants (for example, warfarin) were absolutely excluded from the study while the current Actilyse PI for patients treated within 0-3 hours conditionally excludes patients receiving oral coagulants (for example, warfarin INR > 1.3). The study included only a small number of patients aged > 80 years (n=15, 1.8%) and, consequently, it is considered not to support treatment in patients in this age group.

In the ECASS III (ITT population), the pre-specified unadjusted RR and OR analyses of the primary efficacy endpoint of favourable outcome (mRS 0-1 at Day 90) both statistically significantly favoured alteplase over placebo (see Table 25 below).

Table 25: ECASS III – Primary efficacy endpoint (favourable outcome mRS 0-1) in the ITT population.

	Alteplase (n=418)	Placebo (n=403)	OR [95%CI] [1]	RR [95%CI]	p value
Favourable Outcome (mRS 0-1)	219 (52.4%)	182 (45.2%)	1.34 [1.02 – 1.76]	1.16 [1.01 – 1.34]	p = 0.0383 (Pearson chi-square)
Unfavourable Outcome (mRS 2-6)	199 (47.6%)	221 (54.8%)			
Risk Difference (mRS 0-1)	7.23 % [95%CI: 0.39-13.97] [2]				

[1] OR = Odds ratio unadjusted for baseline variables.
[2] 95% confidence intervals for the absolute difference between favourable outcomes calculated by the clinical evaluator.

In ECASS III, both the likelihood (16 % [95%CI: 1-34%]) and odds (34% [95%CI: 2-76%]) of a favourable outcome (mRS 0-1) statistically significantly favoured patients treated with alteplase

compared with placebo. However, the 95% confidence intervals were relatively large suggesting significant variability in beneficial outcome in alteplase treated patients. The absolute risk difference was 7.23% [95%CI: 0.39-13.97%] between alteplase (52.4%, 219/418) and placebo (45.2%, 182/403). This absolute risk difference translates into an NNT of 14. The sample size calculation was based on the assumption that the risk difference between treatments on the primary efficacy endpoint would be 10% (OR of about 1.5). Therefore, it is reasonable to infer that the minimal clinically effect sizes as regards the primary endpoint in this study were a risk difference of at least 10% and an OR of at least 1.5. Consequently, the observed risk difference of 7.23% and the observed OR (unadjusted) of 1.34 are considered to be of doubtful clinical significance. Furthermore, the current Actilyse PI states that a meta-analysis of NINDS (1 and 2), ECASS I, ECASS II, and ATLANTIS (A and B) demonstrated that the likelihood of a~~n~~ mRS (0-1) ("favourable outcome") was 14% higher [95%CI: 7, 20] in alteplase patients treated within the 0-3 hour time window compared with placebo. Based on the cross-study comparison, the NNT in alteplase treated patients was 7 in the 0-3 hour time window and 14 in the 3-4.5 hour time window. Consequently, the cross-study comparison between the meta-analysis referred to in the Actilyse PI and ECASS III shows that the likelihood of a favourable outcome (mRS 0-1) in patients treated with alteplase in the 0-3 hour time window is twice that of patients treated in the 3-4.5 hour time window.

In ECASS III (ITT population), the pre-specified OR (unadjusted) analysis of the secondary efficacy endpoint of composite functional global outcome was 1.28 [95%: 1.00, 1.65]; p=0.0481 (see Table 26, below).

Table 26: ECASS III – Secondary efficacy endpoint (and components) in the ITT population.

	Alteplase (n=418)	Placebo (n=403)	OR [95%CI] *	p value
Global Outcome [1]	N/A	N/A	1.28 [1.00-1.65]	0.0481
mRS score 0-1	219 (52.39%)	182 (45.16%)	1.34 [1.02-1.76]	0.0383 [2]
BI score ≥ 95	265 (63.40%)	236 (58.56%)	1.23 [0.93-1.62]	0.1555 [2]
NIHSS score 0 or 1	210 (50.24%)	174 (43.18%)	1.33 [1.01-1.75]	0.0462 [2]
GOS score of 1	213 (50.96%)	183 (45.41%)	1.25 [0.95-1.64]	0.1182 [2]

* Unadjusted for baseline variables
[1] Estimates from the GEE analysis.
[2] P values refer to the Pearson chi-square test.

It is considered that, although the OR (unadjusted) of the global outcome favoured alteplase over placebo the result is not significant as the 95% confidence interval includes a value of 1. Of the four individual components contributing to the global outcome, two were statistically significant (mRS score 0-1 and NIHSS score of 0-1) and two were statistically non-significant (BI score ≥ 95 and GOS score of 1). The risk difference between alteplase and placebo for the statistically significant NIHSS of 0-1 (functional independency) was 7.1 %, which was half that seen for this outcome in the meta-analysis reported in the Actilyse PI in patients treated in the 0-3 hour time window (that is, risk difference in meta-analysis = 14% [95%: 8-20]). In ECASS III, the OR for a tertiary efficacy "independent outcome" (mRS 0-2) was not statistically significant (OR = 1.24 [95%CI: 0.93-1.65]) while the risk difference and RR for this outcome in the meta-analysis reported in the Actilyse PI were both statistically significant. Overall, the ECASS III pre-specified primary outcome (statistically significant) is considered to show a modest clinical benefit for alteplase compared with placebo for the treatment of acute ischaemic stroke when initiated within 3-4.5 hours of symptom onset. However, this benefit is considered to be of doubtful clinical significance and about two-fold lower than that observed in patients treated with alteplase in the 0-3 hour time window.

SITS-ITRS (supportive study) was a large observational study based on international registry data collected on patients with acute ischaemic stroke routinely treated with alteplase. The study analysed data collected for two cohorts treated with alteplase (0.9 mg/kg) in 3-4.5 hour and 0-3 hour time windows. The two efficacy outcomes were excellent recovery at 3 months (mRS 0-1) and independence at 3 months (mRS 0-2). The outcomes based on the recent SITS-ITRS updated data are summarised below in Table 27. The results showed that there were no statistically significant differences in outcomes between the 3-4.5 hour and 0-3.0 hour cohorts.

Table 27: SITS-ISTR: Efficacy endpoints data entered into database on or before 15 December 2008.

	Unadjusted Analysis			Adjusted Analysis
Efficacy Outcome	Between 3.0 and 4.5 hours	Within 3 hours	OR [95%CI]	OR [95%CI]
Excellent recovery at 3 months (mRS 0-1)	310/757 40.95% [95%CI: 37.44-44.56]	5303/13175 40.25% [95%CI: 39.41-41.09]	1.01 [0.94-1.09]	-
Independence at 3 months (mRS 0-2)	438/757 57.86% [95%CI: 54.2-61.39]	7471/13175 56.71% [95% CI: 55.86-57.56	1.02 [0.95-1.10]	0.92 [0.85-1.01]

OR = Odds Ratios were calculated by comparing 3.0-4.5 hour data versus within 3 hours cohort.
OR adjusted for age, sex, history of hypertension, diabetes mellitus, hyperlipidaemia, atrial fibrillation, congestive heart failure, previous stroke, independence before present stroke, smoking, aspirin treatment at stroke onset, baseline NIHSS score, baseline blood pressure, baseline blood glucose, bodyweight, alteplase, baseline antihypertensive therapy, and signs of current infarction on baseline imaging.

It is considered that SITS-ISTR provides satisfactory supportive evidence for similar efficacy of alteplase 0.9 mg/kg administered between 3.0 and 4.5 hours and within 0 to 3.0 hours of onset of acute ischaemic stroke. The sample size was large and sufficient to demonstrate a 5% difference in functional independence rate at 3 months. However, observational studies are subject to a number of potential biases as they are not randomized, not placebo-controlled, not blinded to patients or investigators, and treatments are not standardized. Overall, the data from this supportive observational study (SITS-ISTR) is considered not to outweigh the data from the pivotal study (ECASS III) suggesting that the benefit of alteplase in the 3.0 to 4.5 hour time window is modest and of doubtful clinical significance.

The submission included pooled efficacy data from RCTs investigating the use of alteplase (0.9 mg/kg) for the treatment of acute stroke in the 3.0 to 4.5 hour time window (two cohorts) and the 0 to 6 hour time window (one cohort) [ECASS II, ECASS III, ATLANTIS A and B, NINDS 1 and 2]. In the RCT pooled analysis of four of the studies with 3.0 to 4.5 hour data [ECASS III, ECASS III, ATLANTIS A and B], the odds for mRS 0-1 at Day 90 for both the 3.0 to 4.5 hour total cohort and the 3.0 to 4.5 hour cohort excluding patients with major contraindications were statistically significant and favoured alteplase over placebo: OR 1.31 = [95%CI: 1.06-1.63]; and OR = 1.42 [95%CI: 1.13-1.78], respectively (see Table 28, below). However, the risk difference for the mRS (0-1) at Day 90 between alteplase and placebo was < 10% and the OR was < 1.5 in both cohorts suggesting that while the observed differences were statistically significant they are modest and of doubtful clinical significance. The risk difference was 6.64% [95%: 1.37-11.86%] in favour of alteplase in the 3-4.5 hour total cohort, and 8.63% [95%CI: 3.13-14.07%] in favour of alteplase for the 3-4.5 hour cohort excluding patients with major contraindications. The results for the pooled analyses in both of the 3-4.5 hour cohorts were consistent with the results from ECASS III in the ITT population. However, this is not surprising as the majority of the patients in the 3.0-4.5 hour

total cohort came from ECASS III (58.2%, 785/1355), as did the majority of patients in the 3-4.5 hour cohort excluding the major contraindications (59.5%, 743/1251).

Table 28: Pooled Data: Response as assessed by mRS 0 or 1 at Day 90 in the 3.0-4.5 hour cohorts.

Population	Treatment	n (%)	Δ % [95%CI]	OR [95%CI]	p value *
Pooled 3-4.5h cohort	Alteplase (n=681)	316 (46.40)	6.64 [1.37-11.86]	1.31 [1.06-1.63]	0.0137
	Placebo (n=674)	268 (39.76)			
Pooled 3-4.5h cohort excluding patients with major contraindications	Alteplase (n=621)	304 (48.95)	8.63 [3.13-14.07]	1.42 [1.13-1.78]	0.0022
	Placebo (n=630)	254 (40.32)			

Δ [95%CI] = Risk difference with 95% CI (95% CI calculated by the evaluator).
OR [95%CI] = Odds Ratio with 95% confidence interval.
* p value obtained by the Wald chi-square test.

The RCT pooled analysis of the 0-6 hour cohort showed that the OR for the mRS (0-1) at Day 90 (adjusted for baseline covariates) statistically significantly favoured alteplase in the cohort of interest (181-270 minutes) (see Table 29, below). The 0-6 hour pooled analysis showed that the efficacy of alteplase decreased with increasing time from onset of symptoms to initiation of treatment. The OR for mRS (0-1) at Day 90 was not statistically significant for alteplase compared with placebo when treatment was initiated in the 4.5 to 6 hour window.

Table 29: Pooled analysis of efficacy assessed by OR (alteplase versus placebo) mRS 0-1 at Day 90 by 90 minute time group from symptom onset to treatment in the 0-6 hour window cohort.

Time from onset to treatment	Patients (n)	Odds Ratio [95%CI]	p value
0 -90 minutes	285	2.31 [1.28-4.17]	0.0055
91-180 minutes	498	1.74 [1.14-2.66]	0.0100
181-270 minutes	1296	1.32 [1.03-1.71]	0.0298
271-360 minutes	669	1.04 [0.74-1.46]	0.8234

Odds Ratio of treatment (alteplase versus placebo) adjusted for baseline NIHSS scores; age; SBP ≤ 160, > 160 mmHg; DBP (<70, 70-90, >90 mmHg); weight (≤ 70, 71-90, >90 kg); prior hypertension; smoking history; and interaction of age and NIHSS.

The RCT pooled efficacy data suggest that alteplase initiated in the 3-4.5 hour time window has a modest statistically significant effect of doubtful clinical significance when compared with placebo. The RCT results are consistent with those from ECASS III (which was the major contributor to the 3-4.5 hour pooled data).

Risks

The major risks of alteplase for the treatment of acute ischaemic stroke are sICH, death and all ICH. In ECASS III, the incidence of AEs and SAEs, other than the three of primary interest, was similar for both alteplase and placebo when treatment was initiated in the 3-4.5 hour time window. There were no systematic comparisons of laboratory or electrocardiogram (ECG) data between alteplase and placebo in ECASS III or in the application generally. The vital sign data (heart rate, blood

pressure) in ECASS III were similar for alteplase and placebo. The post-marketing data did not reveal any significant new safety concerns with alteplase.

In ECASS III, the risk of sICH in the first 22-36 hours following initiation of treatment varied from 1.9% to 7.9% with alteplase and 0.2% to 3.5% with placebo, and the risk difference varied from 2.4% to 4.4% (see Table 30, below).

Table 30: ECASS III – sICH results in for alteplase and placebo following treatment onset in the 3-4.5 hour time window in the ITT population.

Definition	Alteplase (n=418)	Placebo (n=403)	Odds Ratio [95%CI]	Relative Risk [95%CI]	RD% [95%CI] *	P value
ECASS III	10 (2.4%)	1 (0.2%)	9.85 [1.26-77.32]	9.64 [1.24-74.90] **	2.2 [0.6-4.1]	0.008
ECASS II	22 (5.3%)	9 (2.2%)	2.43 [1.11-5.35]	2.36 [1.10-5.06]	3.1 [0.4-5.8]	0.02
SITS-MOST	8 (1.9%)	1 (0.2%)	7.84 [0.98-63.00]	7.71 [0.97-61.39] **	1.7 [0.2-3.5]	0.02
NINDS	33 (7.9%)	14 (3.5%)	2.38 [1.25-4.52]	2.27 [1.23-4.18]	4.4 [1.3-7.7]	0.006

* RD [95%CI] = Risk Difference [95% confidence interval] calculated by the clinical evaluator.
** Relative Risk [95%CI] calculated by the clinical evaluator.

The results of the meta-analysis reported in the Actilyse PI showed that the incidence of sICH (criteria not stated) in the 0-3 hour time window was 7.9% (33/416) in alteplase treated patients and 1.6% (7/427) in placebo treated patients giving a risk difference 6% [95%CI: 3, 9]. These rates are within the ranges observed in ECASS III. The cross-study comparison suggests that the risk of sICH in patients treated with alteplase in the 0-3 hour time window is similar to that of patients treated in the 3-4.5 hour time window. The sICH (SITS-MOST definition) results for alteplase and placebo in the 3-4.5 hour time window in the RCT pooled analysis were similar to those in ECASS III. In the RCT pooled analysis, the incidence of sICH was statistically significantly higher for alteplase compared with placebo in both the 3-4.5 hour total cohort and the 0-6 hour cohort (see Table 31, below). The incidence of sICH for alteplase was 0.9% higher in the 3-4.5 hour total cohort compared with the 0-6 hour cohort, with the respective value for placebo being 0.1%.

Table 31: Pooled RCT data: sICH using SITS-MOST criteria.

Definition	Alteplase	Placebo	Odds Ratio [95%CI]	P value
3-4.5 h total cohort	17/681 (2.5%)	2/672 (0.3%)	8.60 [1.98-37.36]	0.0041
0-6 h cohort	51/1511 (3.4%)	6/1468 (0.4%)	8.46 [3.61-19.79]	< 0.0001

The data from the SITS-ISTR observational study showed that the odds of sICH (SITS-MOST, ECASS II, and NINDS definitions) did not differ significantly between patients treated with alteplase in the 3-4.5 hour and 0-3 hour cohorts (see Table 32, below). The RCT pooled analysis and the observational data from SITS-ISTR support similar outcomes for sICH in patients treated with alteplase in the 0-3 hour and the 3-4.5 hour time windows.

Table 32: SITS-ISTR - sICH results (unadjusted) for alteplase following treatment onset in the 3-4.5 hour and within 3 hours time windows.

Definition	Alteplase 3-4.5 hours	Alteplase within 3 hours	Odds Ratio [95%CI]	P value
SITS-MOST	14/649 (2.2%)	183/11861 (1.6%)	1.18 [0.89-1.55]	0.24
ECASS II	34/636 (5.3%)	553/11505 (4.8%)	1.06 [0.89-1.26]	0.54
NINDS	52/647 (8.0%)	846/11646 (7.3%)	1.06 [0.91-1.27]	0.46

Source: Wahlgren *et al*., 2008.

In ECASS III (3-4.5 hour), total mortality did not significantly differ between alteplase (6.7%, 32/418) and placebo (7.7%, 34/403). The causes of death were similar in the two treatment groups. Death due to ICH occurred in 3 (0.7%) alteplase treated patients and 0 (0%) placebo treated patients. In NINDS (0-3 hour), all cause mortality at 90 days was 20.5% (64/312) in placebo treated patients and 17.3% (54/312) in alteplase treated patients (p=0.36) (see Actilyse PI). The 90 day mortality rates in ECASS III were 6.7% (28/418) in alteplase treated patients and 7.6% (31/403) in placebo treated patients (p=0.68). The median baseline NIHSS score in the relevant NINDS alteplase and placebo treated patients was 14 and 15 points, respectively, compared with 9 and 10 in ECASS III (ITT population). The greater severity of baseline stroke in NINDS compared with ECASS III in both the alteplase and placebo groups might account for the marked observed differences between the studies in 90 day mortality rates. In the RCT pooled analysis, the all cause mortality rate for alteplase was not significantly higher than for placebo in both the 3-4.5 hour total cohorts (9.2%, 62/674 versus 8.4%, 57/681; p=0.5901) and the 0-6 hour cohorts (11.7%, 175/1490 versus 11.1%, 63/1468; p=0.5836). In SITS-ISTR [Wahlgren *et al*., 2008], the observational mortality rate at 3 months with alteplase was 12.7% (70/551) in the 3-4.5 hour cohort and 12.2% (1263/10368) in the 0-3 hour cohort; p=0.72. Overall, the submitted data showed that mortality was similar for alteplase and placebo in the 3-4.5 hour treatment window, and not significantly different from mortality in the 0-3 hour treatment window.

In ECASS III (3-4.5 hour), the incidence of any ICH for alteplase (27%, 113/418) was statistically significantly higher than for placebo (17.6%, 71/403); p=0.0012. In NINDS (0-3 hour), total ICH stroke was also significantly higher for alteplase (15.4%, 48/312) than for placebo (6.4%, 20/312); p<0.01 (see Actilyse PI). The reason for the increased all ICH rates in ECASS III compared with NINDS is unknown. It is possible that the criteria for all ICH were different for the two studies. Nevertheless, the risk difference (alteplase – placebo) for all ICH in ECASS III (9.4%) was similar to that in NINDS (9.0%). In ECASS III, the incidence of haemorrhagic transformations (PH2) was 2.6% in alteplase treated patients and 1.0% in placebo treated patients. There is evidence that deterioration at 24 hours and mortality at 3 months is greater in patients experiencing a PH2 transformation than patients experiencing no ICH.

In the RCT pooled analysis, the incidence of any ICH in the 3-4.5 hour total cohort was 28.6% (195/681) for alteplase and 18.6% (125/674) for placebo (OR = 1.76 [95%CI:1.36-2.28; p< 0.0001), and the respective rates in the 0-6 hour cohort were 31.0% (464/1511) and 22.3% (327/1468) (unadjusted OR = 1.57 [95%CI 1.33-1.85; p < 0.001). The risk difference (alteplase – placebo) for any ICH was 10% in the 3-4.5 hour total cohort and 8.7% in the 0-6 hour cohort. These risk difference rates for any ICH are consistent with that of 9.4% observed in ECASS III. In the RCT pooled analysis (0-6 h cohort), the adjusted odds of experiencing any ICH with alteplase compared with placebo were significantly increased in the 181-270 and 271-360 minute treatment windows, but not significantly increased in the 0-90 and 91-181 minute treatment windows (see Table 33, below). In SITS-ISTR [Wahlgren *et al*., 2008], the observational data showed that the incidence of any ICH (local plus remote) in the 3-4.5 hour cohort was 16.6% (107/643) and 19.1% (2202/11552-4) in the 0-3 hour cohort. Overall, the submitted data showed that all ICH occurred more frequently

in alteplase treated patients than in placebo treated patients irrespective of the database or time interval.

Table 33: RCT (0-6 h cohort) - ICH (any) adjusted ORs for 90 minute treatment groups for treatment onset.

Treatment Onset Time intervals	n	Odds Ratio [95%C] Alteplase versus Placebo – adjusted *	p value
0-90 minutes	284	1.39 [0.81-2.38]	0.2357
91-181 minutes	494	1.13 [0.74-1.71]	0.5759
181-270 minutes	1296	1.87 [1.42-2.47]	< 0.001
271-360 minutes	669	2.35 [1.61-3.43]	< 0.001

* OR adjusted at baseline for NIHSS (0-7, 8-14, 15-18, > 18); age; DBP (<70, 70-90, >90 mmHg); weight (≤70, 71-90, >90 kg); prior stroke; hypertension; smoking history; and interaction of age and NIHSS.

Safety Specification

The submitted data included a Risk Management Plan (RMP). No additional safety specifications are required other than those already applying to alteplase for the treatment of acute stroke in the 0-3 hour time window.

Balance

In ECASS III, the benefits of alteplase when initiated in a 3-4.5 hour time window for the treatment of acute stroke are considered to be modest and of doubtful clinical significance. Based on the ECASS III primary endpoint of mRS (0-1) it can be estimated that the NNT is 14 (risk difference 7.23% [95%CI: 0.39-13.97]). This compares with a NNT of 7 in the meta-analysis of RCT studies reported in the Actilyse PI in which alteplase was initiated within a 0-3 hour time window (risk difference 14% [95%CI: 7-20]). Consequently, the available data suggest that the benefits of alteplase initiated within the 0-3 hour time window is two-fold greater than when initiated within the 3-4.5 hour time window. Furthermore, although the odds of the secondary efficacy global outcome endpoint in ECASS III were 28% greater with alteplase compared with placebo this was not statistically significant as the 95% confidence interval (0-65%) of the OR included 0%. The risk in ESCASS III of sICH assessed by each of the four definitions was greater with alteplase (1.9% to 7.9%) than with placebo (0.2% to 3%), and the ORs for sICH were statistically significant for three of the four sICH definitions. The risk difference between alteplase and placebo for sICH showed that the number needed to harm (NNH) is 23-45 calculated from the risk difference of 2.4% to 4.4%. In ECASS III, the risk of any ICH was statistically significantly greater for alteplase (27%) than for placebo (17.6%); p=0.0012. The NNH for any ICH is 11 (based on a risk difference of 9.4%). There was no significant difference in mortality between alteplase and placebo in ECASS III. On balance, it is considered that the modest benefit of doubtful clinical significance observed in ECASS III is outweighed by the increased risk of sICH and ICH. Overall, it is considered that the totality of the submitted data demonstrate that the risks of sICH, mortality, and possibly all ICH are similar for alteplase when initiated within the 0-3 hour and 3-4.5 time window. However, the benefits of alteplase are two-fold greater when initiated within the 0-3 hour window compared with the 3-4.5 hour window. In summary, it is considered that the benefit/risk balance is superior for alteplase when initiated within the 0-3 hour time window compared with the 3-4.5 hour time window, and that the benefit/risk balance for alteplase is unfavourable when initiated within the 3-4.5 hour time window.

Conclusions

It is recommended that the application to extend the alteplase treatment window from 0-3 hours to 0-4.5 hours should be rejected on the grounds that the application has failed to demonstrate

meaningful clinical benefit of alteplase for acute ischaemic stroke when treatment is initiated within the 3-4.5 hour time window. The benefit/risk balance for alteplase when initiated within the 3-4.5 hour time window is considered to be unfavourable.

Recommended Conditions for Registration

No additional conditions to those for alteplase for the treatment of acute ischaemic stroke in the 0-3 hour treatment window.

V. Pharmacovigilance Findings

Risk Management Plan (RMP)

The sponsor has stated that the single on-going safety concern in the sense of an important identified risk remains that of sICH being an inherent risk of the treatment of AIS with thrombolytic agents in general and alteplase in particular being the only thrombolytic to have gained acceptance and approval in this indication. Hypersensitivity reactions are also considered an important identified risk.

Consequently the sponsor has proposed that the RMP for Actilyse in the treatment of AIS in the 0 – 4.5 hour treatment window will consist of routine pharmacovigilance and continuing emphasis by on the importance of adhering to the product labelling for alteplase. Risk minimisation will be achieved by adherence to the guidance to prescribers contained in the labelling for alteplase and by observing the various treatment guidelines for the management of AIS including the improved understanding of brain imaging that helps substantially the selection of patients eligible for treatment. Such risk minimisation is consistent for the 0-3 hours and the 3-4.5 hours time windows and therefore applies to the proposed window of 0 – 4.5 hours.

The sponsor summarises these activities as follows (Table 34):

Table 34.

Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed Risk minimisation activities (routine and additional)
Identified risk: sICH	Routine Pharmacovigilance with adherence to labelling	None additional
Identified risk: Non-sICH bleeding	Routine Pharmacovigilance with adherence to labelling	None additional
Identified risk: Hypertensitivity reactions	Routine Pharmacovigilance with adherence to labelling	None additional

Recommendations:

It would appear that the proposed changes do not adversely affect the risk-benefit or safety profile of these products and the proposed application of routine pharmacovigilance activities for all the important safety concerns is acceptable. The proposed application of routine risk minimisation activities to the safety concerns, as specified by the sponsor, is also acceptable.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new data were submitted under this heading.

Nonclinical

No new data were submitted under this heading.

Clinical

The current clinical submission comprises the following main data:

1. ECASS III (European Cooperative Acute Stroke Study III) trial.
2. Pooled Analysis of ECASS III and five previously evaluated clinical trials by the TGA.
3. SITS-ISTR (Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry) study.
4. Two post-marketing safety studies and SITS-MOST study.

The ECASS III and SITS-MOST studies were initiated by the sponsor as post-approval commitments in Europe. The intention of the ECASS III study was to confirm the findings from the NINDS study in a European setting and to see if the time period could be extended beyond 3 hours.

The clinical evaluator recommended rejection of the extension of indications to 4.5hours. The issues noted by the evaluator in this submission included:

a. The efficacy benefit in the 3-4.5hr period is modest and of doubtful clinical significance (benefit is halved in the 3-4.5hr period compared to 0-3hr period with NNT of 14 versus. 7).
b. The risk of symptomatic intracranial haemorrhage (sICH) was greater on alteplase than placebo with 3 of the 4 definitions being significantly greater for alteplase. The NNH was 23-45.
c. The risk of any ICH was significantly greater on alteplase (27 versus. 17.6%) with a NNH of 11.
d. No significant difference in mortality between alteplase and placebo.
e. The risks of sICH, mortality and possibly any ICH are similar for alteplase when initiated within the 0-3hr and 3-4.5hr periods.

Pharmacology

No new data submitted.

Efficacy:

ECASS III: This was a pivotal, multicentre, multinational, randomised, double blind, placebo controlled trial of 821 patients aged 18-80 years with acute ischaemic stroke who were able to be treated within the 3-4.5hr period. Patients had a CT/MRI to exclude intracranial haemorrhage and the study was conducted in neurology clinics or hospitals with stroke or ICU units. Patients >80 years, on oral anticoagulants, with severe stroke (NIHSS>25) or severe hypertension were excluded. The study was considered internally and externally valid. Patients were dosed as per the currently approved dose for the 0-3hr period (0.9mg/kg body weight to a maximum of 90mg IV, 10% bolus, with the remainder within 60 minutes). The study was adequately powered to detect a 10% difference between groups for a favourable outcome and had a high completion rate (91% at Day 90). Baseline data were similar between groups except a slightly higher NIHSS score in the placebo group (mean 11.6 versus. 10.7) which was driven by an increase in severe stroke on placebo (9.9 versus. 5%). History of stroke was also higher on placebo (14.1 versus. 7.7%). The primary efficacy endpoint of disability at Day 90 as assessed by the modified Rankin scale (dichotomised at 0-1 favourable and 2-6 unfavourable with 0 being no symptoms at all and 6 being death) was statistically significantly in favour of alteplase with a 16% higher likelihood of a favourable outcome and an absolute risk difference of 7.23% (NNT = 14) (see Table 35).

Table 35. ECASS III – Primary efficacy endpoint (favourable outcome mRS) in the ITT population.

	Alteplase (n=418)	Placebo (n=403)	OR [95%CI] [1]	RR [95%CI] [1]	p value
Favourable Outcome (mRS 0-1)	219 (52.39%)	182 (45.16%)	1.34 [1.02 – 1.76]	1.16 [1.01 – 1.34]	p = 0.0383
Unfavourable Outcome (mRS 2-6)	199 (47.61%)	221 (54.84%)			(Pearson chi-square)
Risk Difference (mRS 0-1)	7.23% [95%CI: 0.39-13.97] [2]				

[1] Unadjusted for baseline covariates

[2] 95% CI for the absolute difference between favourable outcomes calculated by the clinical evaluator

The secondary efficacy endpoint using a global outcome measure at Day 90 (mRS of 0-1, BI score of ≥95, NIHSS score of 0-1 and GOS of 1) was an OR of 1.28 [1.00, 1.65] using an ITT analysis and OR of 1.39 [1.07, 1.80] using a PP analysis. A post-hoc analysis of the primary endpoint adjusted for baseline variables was statistically significantly in favour of alteplase over placebo (52.4% versus. 45.2%, OR 1.42 [1.02, 1.98]). Other post-hoc analyses using the secondary efficacy endpoint and stroke severity also favoured alteplase but these are all considered exploratory findings.

The ECASS III data have demonstrated a statistically significant benefit for alteplase versus placebo with an absolute risk difference in the primary endpoint of 7.23% (NNT = 14). This is below the pre-specified difference of 10% that was used to power the study and therefore was concluded by the clinical evaluator that the difference is modest and of doubtful clinical significance. The wide confidence intervals in the primary endpoint also suggest significant variability in favourable outcomes for patients.

Pooled Analysis: The current PI notes from a meta-analysis of trials NINDS 1 and 2, ECASS I and II and ATLANTIS A and B that the absolute risk difference for the 0-3hr period was 14% for alteplase versus placebo (NNT=7), thus indicating a halving of benefit for patients if treated in the 3-4.5hr period compared to the 0-3hr period. The pooled analysis of ECASS III and five previously evaluated trials (ECASS II, ATLANTIS A and B, NINDS 1 and 2) using the same dose and comparable baseline parameters with an efficacy outcome of mRS score (0-1) at Day 90 looking at the 3-4.5hr period (ECASS II and III and ATLANTIS A and B) was statistically significantly in favour of alteplase compared to placebo with an absolute risk difference of 6.64% (8.63% if patients with major contraindications excluded) (see Table 36).

Table 36. Response as assessed by mRS 0 or 1 at Day 90 in the 3.0-4.5 hour pooled cohort.

Population	Treatment	n (%)	Δ % [95%CI]	OR [95%CI]	p value *
Pooled 3-4.5h cohort	Alteplase (n=681) Placebo (n=674)	316 (46.4%) 268 (39.76%)	6.64 [1.37-11.86]	1.31 [1.06-1.63]	0.0137
Pooled 3-4.5h cohort excluding patients with major contraindications	Alteplase (n=621) Placebo (n=630)	304 (48.95%) 254 (40.32%)	8.63 [3.13-14.07]	1.42 [1.13-1.78]	0.0022

Δ [95%CI] = Risk difference with 95% CI (95% CI calculated by the evaluator). OR [95%CI] = Odds Ratio with 95% confidence interval. * p value obtained by the Wald chi-square test.

The sponsor notes that the primary endpoint of modified Rankin Scale for disability takes into consideration to some extent the harm to a patient, therefore it does not only reflect benefit but also some harm. There is merit in this approach. An NNT of 14 does still appear to be of net clinical benefit when considered in this manner but for comparison with the 0-3hr period. However, it is the same endpoint being used in both time periods and therefore it is appropriate to compare them in this way. The secondary efficacy endpoint of global outcome was borderline for the ITT analysis and supportive for the PP analysis. The pooled analysis provided similar results to that of the ECASS III trial which is reassuring. The SITS-ISTR provided supportive evidence for similar efficacy outcomes using the same dose in the two time periods which is also reassuring. However, an observational study of this type has inherent bias and confounding.

SITS-ISTR: This study is a large observational post-marketing study submitted as a published paper but with updated unpublished data using international registry data that are prospectively collected on stroke patients treated with alteplase. The study compared 757 patients in the 3-4.5hr period with 13,175 in the 0-3hr period using the same dose and showed no significant difference between the groups for excellent recovery at Day 90 (mRS of 0-1) and independence at Day 90 (mRS of 0-2).

Patients ≥80 years: An integrated analysis of six trials with 164 patients ≥80 years of age was conducted comparing alteplase with placebo (137 of whom were within the 0-4.5hr period). The pooled analysis showed the absolute risk difference between alteplase and placebo for a favourable outcome using mRS (0-1) at Day 90 was 1.4% and for independence using mRS (0-2) at Day 90 was 2.1% which are not statistically significant. If patients with severe stroke were excluded then the results were more favourable for alteplase (8% difference for favourable outcome and 10.1% difference for independence) but not statistically significant. The functional outcome for patients with a severe stroke was very poor. Two published meta-analyses in this age group showed that efficacy was reduced in this group compared to younger patients (for example, a favourable outcome in mRS(0-1) at Day 90 was seen in 25.8% of the patients aged ≥80 years compared to 40.8% of patients aged <80years; OR 0.53 [0.42, 0.66]).

Safety:

The sponsor included an integrated safety summary from ECASS III, SITS-ISTR, the pooled data and seven published studies. Exposure from the pooled analysis was 681 patients on alteplase in the 3-4.5hr period; of these 406 were from ECASS III. Total exposure from all data sources was estimated at 1126 patients for this time period. In ECASS III, adverse events and serious adverse events had a similar frequency between alteplase and placebo, except for haemorrhagic events but adverse drug reactions were greater on alteplase (23.9% versus. 6.9%). Adverse events were

mainly neurological, then gastrointestinal, infections and vascular disorders. Headache, constipation, pyrexia and depression were most common. Intracranial haemorrhage (7.2 versus. 3.2%), haematoma (4.3 versus. 0.5%), cerebral haemorrhage (3.8 versus. 1.2%) and gingival bleeding (2.9 versus. 0.2%) were higher on alteplase. Of the serious adverse events, the most common were: brain oedema (2.2 versus. 1%), CVA (1.9 versus. 3.7%), coma (1.4 versus. 1.5%), carotid artery stenosis (1.4 versus. 0.5%), cerebral haemorrhage (1.4 versus. 0.7%), intracranial haemorrhage (1.2 versus. 0.2%), haemorrhagic transformation (1.2 versus. 0.7%) and ischaemic stroke (1 versus. 1.5%). Vital signs were similar between the groups.

Any intracranial haemorrhage findings were as follows:

ECASS III showed any ICH was significantly higher on alteplase than placebo (27 versus. 17.6%, p=0.0012, RR 1.53 [95%CI 1.18, 2.00]) with most in the first 24 hrs and 3 fatal ICH on alteplase compared to none on placebo. Haemorrhagic transformation H1 (16 versus. 13.9%) and H2 (6.2 versus. 2.2%) were higher on alteplase as too were parenchymal haemorrhage (PH1 was 2.2 versus. 0.5% and PH2 was 2.6 versus. 1%).

Pooled analysis showed 28.6% had an ICH in 3-4.5hr period on alteplase compared to 18.6% on placebo (OR 1.76 [1.36, 2.28]).

SITS-ISTR showed 16.6% had an ICH in 3-4.5hr period compared to 19.1% in the 0-3hr period.

Symptomatic Intracranial haemorrhage findings had different definitions.

ECASS III using four of these definitions showed sICH was significantly higher on alteplase than placebo (see Table 37 below).

Pooled analysis showed 2.5% had an sICH in 3-4.5hr period on alteplase compared to 0.3% on placebo (OR 8.6 [1.98, 37.36]). sICH was higher in the elderly (>65 years) given alteplase than those younger (13.6% versus. 3.2%).

SITS-ISTR showed a non-significantly slightly higher risk for patients given alteplase in the 3-4.5hr period than the 0-3hr period (see Table 38 below).

Table 37. ECASS III – sICH following treatment in the 3-4.5 hour time window in the ITT population

Definition	Alteplase (n=418)	Placebo (n=403)	Odds Ratio [95%CI]	Relative Risk [95%CI]	RD% [95%CI] *	P value
ECASS III	10 (2.4%)	1 (0.2%)	9.85 [1.26-77.32]	9.64 [1.24-74.90] **	2.2 [0.6-4.1]	0.008
ECASS II	22 (5.3%)	9 (2.2%)	2.43 [1.11-5.35]	2.36 [1.10-5.06]	3.1 [0.4-5.8]	0.02
SITS-MOST	8 (1.9%)	1 (0.2%)	7.84 [0.98-63.00]	7.71 [0.97-61.39] **	1.7 [0.2-3.5]	0.02
NINDS	33 (7.9%)	14 (3.5%)	2.38 [1.25-4.52]	2.27 [1.23-4.18]	4.4 [1.3-7.7]	0.006

* RD [95%CI] = Risk Difference [95% confidence interval] – calculated by the evaluator.

** Relative Risk [95%CI] calculated by the clinical evaluator.

Table 38. SITS-ISTR - sICH results (unadjusted) for alteplase in the 3-4.5 hour and within 3 hours time windows.

Definition	Alteplase 3-4.5 hours	Alteplase within 3 hours	Odds Ratio [95%CI]	P value
SITS-MOST	14/649 (2.2%)	183/11861 (1.6%)	1.18 [0.89-1.55]	0.24
ECASS II	34/636 (5.3%)	553/11505 (4.8%)	1.06 [0.89-1.26]	0.54
NINDS	52/647 (8.0%)	846/11646 (7.3%)	1.06 [0.91-1.27]	0.46

Source: Wahlgren *et al*., 2008.

Mortality findings were as follows:

ECASS III was similar between alteplase and placebo (7.7 versus. 8.4%).

Pooled analysis was 9.2% on alteplase versus. 8.4% on placebo for the 3-4.5hr period. An interaction was seen for smoking status and gender, with males given alteplase at higher risk of mortality.

SITS-ISTR on alteplase at 3 months was 12.7% for the 3-4.5hr period versus. 12.2% for the 0-3hr period.

Patients ≥80 years: In the pooled data the following were noted:

a. Mortality was 27.6% on alteplase versus. 23% on placebo compared to younger patients (10.2 versus. 11.5%).

b. Any ICH was significantly higher on alteplase versus placebo in this age group at 51.3% versus. 21.3% (OR 4.01 [1.76, 9.13]) compared to the younger group (28.9% versus. 23.5%).

c. sICH was significantly higher on alteplase versus placebo at 6.6% versus. 0% (OR 6.17 [2.38, 15.96]) compared to the younger group (2.5 versus. 0.5%).

d. Two meta-analyses comparing this age group with the younger age group given alteplase noted mortality was significantly higher whilst sICH rates were similar.

Safety and RMP: Mortality, any ICH and sICH are the main safety concerns from alteplase treatment. Mortality was slightly less for patient treated with alteplase compared to placebo in the 3-4.5hr period from the ECASS III study but slightly higher from the pooled analysis, whereas the SITS-ISTR showed mortality to be similar between the two time periods.

Any ICH (NNH=11) was significantly higher for patients treated with alteplase compared to placebo in the 3-4.5hr time period from the ECASS III study and the pooled analysis. The SITS-ISTR, however, showed it was slightly less than in the 0-3hr period. The sponsor objected to the clinical evaluator's assessment of harm using the NNH for any ICH as it is too broad a measure given it includes varying degrees of severity regardless of symptoms or not. Whilst this claim may have some merit, it is an accepted measure in stroke trials that is supported by the European Union (EU) guideline on stroke and was used in the previously submitted trials. The types of ICH were mostly of the haemorrhagic transformation (H1 and H2) type which is claimed by the sponsor and their clinical experts to carry no long term clinical consequences. H1 (small petechiae along the margins of the infarct) and H2 (more confluent petechiae within the infarct but without space occupying effect) were the main type of ICH and would therefore sway the NNH to being less favourable. The sponsor has provided a summary table of any ICH with NNHs below (Table 39). The risk of any ICH in the NINDS trial (0-3hr period) in the PI was 15.4% on alteplase versus. 6.4% placebo compared to the ECASS III trial which was 27% versus. 17.6%. It is unclear why the risks were higher on both alteplase and placebo in the ECASS III trial compared to NINDS trial but the risk difference is about 9% for both trials suggesting the same risk difference for the 0-3hr

period as the 3-4.5hr period. Therefore the risk of any ICH is greater in the 3-4.5hr period compared to the 0-3hr period regardless of treatment but the difference in rates within the time periods for alteplase versus placebo remains similar.

Table 39. NNH at varying levels of ICH severity.

ICH		Alteplase (n=418)	Placebo (n=403)	Risk Difference	NNH
ITT	Any ICH (sICH and asymptomatic ICH)	27.03%	17.62%	9.41%	11
	Haemorrhagic transformations HI1	16.03%	13.90%	2.13%	47
	Haemorrhagic transformations HI2	6.22%	2.23%	3.99%	25
	Parenchymal haemorrhages PH1	2.15%	0.50%	1.65%	61
	Parenchymal haemorrhages PH2	2.63%	0.99%	1.64%	61

Haemorrhagic infarct type 1 = small petechiae along the margins of the infarct.
Haemorrhagic infarct type 2 = more confluent petechiae within the infarct area but without space-occupying effect.
Parenchymal haemorrhage type 1 = blood clot(s) not exceeding 30% of the infarct area with some mild space-occupying effect.
Parenchymal haemorrhage type 2 = dense blood clots exceeding 30% of the infarct area with substantial space occupying effect.

sICH (NNH=23-45) was significantly higher on alteplase compared to placebo in the 3-4.5 hr time period from the ECASS III study and the pooled analysis and the SITS-ISTR showed it was similar but slightly higher than in the 0-3 hr period. For the 0-3 hr period, the incidence of sICH is 7.9% which is within the range observed in the ECASS III trial suggesting a similar risk of sICH in the 0-3hr and 3-4.5hr periods, although this is a cross-study comparison (see Australian PI).

Overall the safety data indicate that the risks of mortality, any ICH and sICH are higher on alteplase than placebo in the 3-4.5hr period, but that these risks are similar (mortality and sICH) and possibly similar (any ICH) to the 0-3 hr period. No additional concerns were raised from the RMP assessment.

Patients ≥80 years: The Australian PI for Actilyse currently includes a contraindication for the use of alteplase in patients ≥80 years of age with an acute ischaemic stroke. Only the NINDS trial included patients >80 years of age. All other randomised trials, including ECASS III, excluded this group. The sponsor has proposed deletion of this contraindication and to have it replaced with a precaution noting the increased risk of intracerebral haemorrhage in this group. The efficacy data did not demonstrate a significant difference in favourable outcome or independence between alteplase and placebo in this age group. If patients with severe stroke were excluded then the efficacy data were more favourable for alteplase but still not significantly different to placebo. Safety findings were concerned with an increased risk of mortality and significantly increased risks of any ICH and sICH for patients treated with alteplase versus placebo in this age group in the 0-4.5hr period. This was in addition to the increased risks of these outcomes compared to the younger cohort. However if patients with severe stroke were excluded, then mortality was not increased. The meta-analyses also noted the increased mortality (3-fold) and sICH in this age group treated with alteplase compared to younger patients. Given the increased risks, especially mortality, and lack of significant difference in efficacy, the Delegate is inclined to retain the contraindication in patients ≥80 years of age.

Guidelines, Clinical Expert Statements and Publications

International guidelines on the treatment of actor ischaemic stroke note the following:

European Stroke Organisation (Jan 2009): within 4.5 hours of stroke onset using same dose for 0-3 hours as 0-4.5 hours. They note that treatment is time dependent with the NNT to get one more favourable outcome being 2 in the first 90 minutes, 7 within 3 hours and 14 within 3-4.5 hours.

American Heart Association/American Stroke Association (2009): within 3 hours of stroke onset and to eligible patients within 3-4.5 hours after stroke using the same dose for 0-3 hours as 0-4.5 hours. However for the 3-4.5 hour period, they recommended that patients >80 years and those on oral anticoagulants be excluded.

National Stroke Foundation of Australia's clinical guidelines for stroke management (draft 2010) is, according the clinical experts below, updating their guidelines on stroke management and the draft version is recommending treatment up to 4.5 hours.

A clinical expert statement from the sponsor recommended the use of alteplase up to 4.5 hours and to remove the contraindication for patients >80 years.

Recent publications noted the following:

Saver *et al*, 2009[17] preformed an analysis of the ECASS III trial using benefits and harms for all levels of post-stroke disability using the modified Rankin scale. Treatment with alteplase in the 3-4.5 hour period confers a benefit to approximately half the number of patients as in the 0-3 hour period without an increase in harm. It says that 1 in 6 patients has a better and 1 in 35 has a worse disability outcome from treatment.

Lees *et al*, 2010[18] conducted a pooled analysis of the three ECASS trial, the two NINDS trials, the two ATLANTIS trials and the EPITHET trial. The study assessed the relation of stroke onset to start of treatment. Patients benefited from treatment up to 4.5 hours but beyond risks might outweigh benefit.

Data deficiencies: No dose response studies have been conducted for the 3-4.5hr period and no direct comparative trial has been conducted of both time periods. Data in the elderly are also limited.

Risk Management Plan (RMP)

The Office of Medicines Safety Monitoring has found the RMP submitted by the sponsor dated 16 June 2009 acceptable and has noted that routine pharmacovigilance with adherence to labelling for all important safety concerns and routine risk minimisation activities (adherence to PI, observing treatment guidelines for acute ischaemic stroke including brain imaging) for the safety concerns as specified by the sponsor are acceptable. No changes have been recommended to the PI, CMI or RMP. The following risks were noted for alteplase:

Identified Risks: sICH, non-sICH bleeding, and hypersensitivity reactions.

Potential Risks: None identified.

Risk-Benefit Analysis

Summary: The efficacy of alteplase in the 3-4.5hr period was significantly greater than for placebo but the magnitude of the benefit appears to be half that observed for patients in the 0-3hr period. However the primary endpoint of mRS does take into consideration some harm as well as benefits so that a NNT of 14 does still appear to be meaningful for the primary endpoint. The use of alteplase within the 3-4.5hr period is associated with an increase risk of any ICH (NNH=11) and sICH (NNH = 23-45) compared to placebo but a similar mortality rate. The findings for mortality and sICH are similar to the data for the 0-3hr period, and any ICH demonstrated a similar risk difference to placebo for the two periods. Therefore, although the benefit as measured by the mRS is reduced by half (NNT from 7 to 14) for patients being treated in the 3-4.5hr period compared to the 0-3 hr period, this benefit was still significantly better than placebo and therefore may still be

[17] Saver *et al*. (2009). Number Needed to Treat to Benefit and to Harm for Intravenous Tissue Plasminogen Activator Therapy in the 3- to 4.5-Hour Window. Joint Outcome Table Analysis of the ECASS 3 Trial. *Stroke*. 40:2433.

[18] Lees *et al.* (2010). Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *The Lancet* 375:1695 - 1703

meaningful. When balanced against the risks for the two time periods, the Delegate is inclined to view the submission as approvable.

The Delegate proposed to **approve** this submission by Boehringer Ingelheim Pty Ltd to extend the indications for Actilyse (alteplase), based on the safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Discussion, providing adequate information is conveyed in the PI on the reduced benefit/risk ratio in the 3-4.5 hour treatment period compared to the 0–3hour period:

Actilyse is indicated for thrombolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (for example, cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

The sponsor should advice in their Pre-ACPM response if any further trials are being conducted in the elderly, especially those >80 years of age.

The Advisory Committee on Prescription Medicines (ACPM) advice is requested regarding following issues:

Is the risk/benefit balance acceptable to extend the time period to 4.5 hours?

Should the contraindication for use in patients ≥80 years be replaced with a precaution?

The ACPM (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal. The ACPM recommends approval of the submission from Boehringer Ingelheim Pty Ltd to register the extension of indication for alteplase (Actilyse) powder for reconstitution for injection. 10 mg, 20 mg and 50 mg for the indication:

> *For thrombolytic treatment of acute ischaemic stroke.*
>
> *Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (for example, cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.*

In making this recommendation, the ACPM considered that an overall positive risk benefit profile for the amended indication was adequately demonstrated for the increased target population.
It is recommended that the Australian Product Information (PI) and Consumer Medicine Information (CMI) includes a stronger reference to the imperative of timely imaging evidence to exclude haemorrhage (in the Precautions section) and a reference in the Precautions section and not the Contraindications section of the PI to the increased risk of haemorrhage in older patients and specifically in patients aged over 80 years.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actilyse containing alteplase 10 mg, 20 mg and 50 mg powder for injection, indicated for:

> *Thrombolytic treatment of acute ischaemic stroke.*
>
> *Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (for example, cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

ACTILYSE®
(Alteplase)

NAME OF THE DRUG

ACTILYSE® (alteplase, recombinant tissue plasminogen activator, rt-PA)

DESCRIPTION

ACTILYSE is a tissue plasminogen activator produced by recombinant DNA technology. It is a purified fibrinolytic glycoprotein of 527 amino acids, synthesised using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator. The manufacturing process involves the secretion of the serine protease t-PA into the culture medium by an established mammalian cell line into which the cDNA for tissue plasminogen activator has been genetically inserted.

ACTILYSE is presented as a sterile, white to off-white, lyophilised powder, intended for intravenous administration after reconstitution with sterilised Water for Injections.

PHARMACOLOGY

ACTILYSE is a serine protease which has the property of fibrin-enhanced conversion of plasminogen to plasmin. ACTILYSE produces minimal conversion of plasminogen in the absence of fibrin; and when introduced into the systemic circulation, ACTILYSE binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with minimal systemic effects.

ACTILYSE at a dose of 100 mg leads to a modest decrease of the circulating fibrinogen levels to 54%-60% at 4 hours, which generally reverts to about 80% after 24 hours. Plasminogen and alpha-2-antiplasmin decrease to 52%-70% and 25%-35% respectively after 4 hours and increase again to about 80% at 24 hours. A marked and prolonged decrease of the circulating fibrinogen level is only seen in a few patients.

In patients evaluated within four hours of onset of symptoms an occlusive thrombus is present in the infarct-related coronary artery in approximately 80% of patients experiencing a transmural myocardial infarction. In patients studied with coronary angiography prior to and following infusion of ACTILYSE, the use of ACTILYSE resulted in reperfusion of documented obstructed vessels within 90 minutes after the commencement of thrombolytic therapy in approximately 70% of the patients.

Treatment of myocardial infarction with ACTILYSE is intended to restore coronary artery patency, reduce infarct size, preserve ventricular function and reduce mortality.

Effect on Coagulation

ACTILYSE differs from other plasminogen activators in that it is fibrin-dependent. Relatively selective fibrinolysis with ACTILYSE, i.e. localised activation of the fibrinolytic system, is possible due to several factors such as the high affinity of tissue plasminogen activator for fibrin, the fibrin-dependent activation of tissue plasminogen activator, and the coprecipitation of plasminogen within the fibrin clot. As a result, ACTILYSE produces clot dissolution in vivo with minimal systemic effects.

Pharmacokinetics

ACTILYSE is cleared rapidly from circulating plasma primarily by the liver, at a rate of approximately 500 mL/min in patients with vascular disease, and approximately 700 mL/min in normal subjects. More than 50% of ACTILYSE present in plasma is cleared within 5 minutes after the infusion has been terminated, and approximately 80% is cleared within 10 minutes. For the residual amount remaining in a deep compartment, a beta half-life of about 40 minutes was measured.

CLINICAL TRIALS

Acute Myocardial Infarction (AMI)

Two ACTILYSE dose regimens have been studied in patients experiencing acute myocardial infarction. The comparative efficacy of these two regimens has not been evaluated.

Accelerated Infusion in AMI patients

Accelerated infusion of ACTILYSE was studied in an international, multi-centre trial (GUSTO) that randomised 41,021 patients with acute myocardial infarction to four thrombolytic regimens. Entry criteria included onset of chest pain within 6 hours of treatment and ST elevation of the ECG. The four regimens were:

- Streptokinase + subcutaneous heparin (n = 9841)
- Streptokinase + intravenous heparin (n = 10410)
- Accelerated alteplase + intravenous heparin (n = 10396), and
- Alteplase + streptokinase + intravenous heparin (n = 10374).

The accelerated alteplase dose was ≤ 100 mg over 90 minutes (see DOSAGE AND ADMINISTRATION).

The streptokinase (Kabikinase®) dose was 1.5 million units over 60 minutes.

Aspirin and heparin use were directed by the GUSTO protocol as follows:

- Aspirin: 160 mg (chewable) as soon as possible, followed by 160-325 mg daily.
- Heparin intravenous (IV): 5,000 units IV bolus as soon as possible, followed by 1,000 units per hour continuous IV infusion for at least 48 hours; subsequent heparin therapy was at the discretion of the attending physician.
- Heparin subcutaneous (SQ): 12,500 units four hours after initiation of streptokinase therapy, followed by 12,500 units twice daily for 7 days or until discharge, whichever came first. Many patients randomised to SQ heparin received some IV heparin, usually in response to recurrent chest pain and or the need for a medical procedure. Some received IV heparin on arrival in the emergency room prior to enrolment and randomisation.

Results are given in the Table 1. The primary endpoint was 30-day mortality.

Table 1 GUSTO study results

Event	*Accelerated Alteplase + IV Heparin*	*Streptokinase + IV Heparin*	*p-value1*	*Streptokinase + SQ Heparin*	*p-value1*
30-Day Mortality	6.3%	7.3%	0.003	7.3%	0.007
30-Day Mortality or Non-Fatal Stroke	7.2%	8.2%	0.006	8.0%	0.036
24-Hour Mortality	2.4%	2.9%	0.009	2.8%	0.029
Any Stroke	1.6%	1.4%	0.32	1.2%	0.03
Intracerebral Haemorrhage	0.7%	0.6%	0.22	0.5%	0.02

[1] *Two-tailed p-value for comparison of accelerated alteplase with each streptokinase control arm.*

Administration of 100 mg alteplase over 90 minutes, with concomitant IV heparin infusion, led to a lower mortality after 30 days (6.3%) as compared to the administration of streptokinase, 1.5 million IU over 60 minutes, with SQ or IV heparin (7.3%). The 1% absolute decrease in 30-day mortality for alteplase compared to streptokinase was statistically significant (p = 0.001).

There was a definite further reduction in mortality in the accelerated alteplase treated patients as compared to the patients treated with any of the three regimens using streptokinase. This improvement was independent of age, site of infarction, or area of infarction. This difference may be due to the higher patency rate achieved with accelerated alteplase in the acute patient with ST-segment elevation.

Alteplase-treated patients showed higher infarct related vessel patency rates at 90 minutes after thrombolysis than the streptokinase-treated patients. No differences in patency rates were noted at 180 minutes or longer.

ACTILYSE has been shown to reduce 30-day mortality in patients with acute myocardial infarction treated up to 12 hours after symptom onset.

A large scale mortality trial (ASSENT-2) in approximately 17,000 patients showed that alteplase and tenecteplase are therapeutically equivalent in reducing mortality (6.2% for both treatments, at 30 days). The use of tenecteplase was associated with a significantly lower incidence of non-intracranial bleedings compared to alteplase (26.4% versus 28.9%, p = 0.0003).

3-hour infusion in AMI patients

In patients studied in a controlled trial with coronary angiography at 90 and 120 minutes, following infusion of alteplase, infarct artery patency was observed in 71% and 85% of patients (n = 85), respectively. In a second study, where patients received coronary angiography prior to and following infusion of alteplase within 6 hours of the onset of symptoms, reperfusion of the obstructed vessel occurred within 90 minutes after the commencement of therapy in 71% of 83 patients.

In a double-blind, randomised trial (n = 138) comparing alteplase to placebo, patients infused with alteplase within 4 hours of onset of symptoms experienced improved left ventricular function at day 10 compared with placebo, when ejection fraction was measured by gated blood pool scan (53.2% versus 46.4%, P = 0.018). Relative to baseline values, the net changes in ejection fraction were +3.6% and -4.7% for the treated and placebo groups, respectively (P = 0.0001). Also documented was a reduced incidence of clinical congestive heart failure in the treated group (14%) compared to the placebo group (33%) (P = 0.009).

In a double-blind, randomised trial (n = 145) comparing alteplase to placebo, patients infused with alteplase within 2.5 hours of onset of symptoms experienced improved left ventricular function at a mean of 21 days compared to the placebo group, when ejection fraction was measured by gated blood pool scan (52% versus 48%, P = 0.08) and by contrast ventriculogram (61% versus 54%, P = 0.006). Although the contribution of alteplase alone is unclear, the incidence of nonischaemic cardiac complications when taken as a group (ie, congestive heart failure, pericarditis, atrial fibrillation, and conduction disturbance) was reduced when compared to those patients treated with placebo (P < 0.01).

In a double-blind, randomised trial (ASSET) (n = 5,013) comparing alteplase to placebo, patients infused with alteplase within 5 hours of the onset of symptoms of AMI experienced improved 30-day survival compared to those treated with placebo. At 1 month, the overall mortality rates were 7.2% for the alteplase group and 9.8% for the placebo group (P = 0.001). This benefit was maintained at 6 months for alteplase treated patients (10.4%) compared to those treated with placebo (13.1%, P = 0.008).

In a double-blind, randomised trial (n = 721) comparing alteplase to placebo, patients infused with alteplase within 5 hours of the onset of symptoms experienced improved ventricular function 10-22 days after treatment compared to the placebo group, when global ejection fraction was measured by contrast ventriculography (50.7% versus 48.5%, P = 0.01). Patients treated with alteplase had a 19% reduction in infarct size, as measured by cumulative release of HBDH (α-hydroxybutyrate dehydrogenase) activity compared to placebo-treated patients (P = 0.001). Patients treated with alteplase had significantly fewer episodes of cardiogenic shock (P = 0.02), ventricular fibrillation (P < 0.04) and pericarditis (P = 0.01) compared to patients treated with placebo. Mortality at 21 days in alteplase treated patients was reduced to 3.7% compared to 6.3% in placebo-treated patients

(P = 0.05). Although these data do not demonstrate unequivocally a significant reduction in mortality for this study, they do indicate a trend that is supported by the results of the ASSET study.

In a randomised, double-blind study (LATE), 5,711 patients with symptoms of AMI received intravenous alteplase (100 mg over 3 hours) or matching placebo, between 6 and 24 hours from symptom onset. Both groups received immediate oral aspirin and for later recruits intravenous heparin for 48 hours. All patients were followed up for at least 6 months and 73% were followed up for 1 year. Intention-to-treat analysis of survival revealed a non-significant reduction in the alteplase group compared with placebo. 35-day mortality was 8.86% and 10.31% respectively, a relative reduction of 14.1% (95% CI: 0-28.1%, P = 0.07). Pre-specified survival analysis according to treatment within 12 hours of symptom onset, showed a significant reduction in mortality in favour of alteplase, 35-day mortality was 8.90% versus 11.97% for placebo, a relative reduction of 25.6% (95% CI: 6.3-45.0%, P = 0.0229). For patients admitted between 12 and 24 hours, the mortality after alteplase was 8.7% versus 9.2% (relative reduction of 5.4%, P = 0.14). This benefit was not significant overall but varied across subgroups.

Pulmonary Embolism

In a comparative randomised trial of alteplase versus urokinase in 63 patients with angiographically documented acute massive pulmonary embolism, patients were randomly assigned to treatment with either alteplase (10 mg as an intravenous bolus infusion, then 90 mg over 2 hours followed by heparin; n= 34) or urokinase (4,400 U/kg as an intravenous bolus infusion, then 4,400 U/kg per hour over 12 hours; n=29). Both treatment groups experienced a significant reduction in pulmonary embolism-induced pulmonary hypertension. Pulmonary haemodynamics improved significantly faster with alteplase than with urokinase. At 2 hours, total pulmonary resistance decreased by 36% in the alteplase group compared with 18% in the urokinase group (p = 0.0009). After 12 hours, the decrease in total pulmonary resistance was not statistically different between the treatment groups, 48% in the alteplase group versus 53% in the urokinase group.

There are no data available on survival following use of ACTILYSE in massive pulmonary embolism.

Acute Ischaemic Stroke

Several studies have been carried out in the field of acute ischaemic stroke. The NINDS study is the only study without an upper age limit, i.e. which also included patients over 80 years. All other randomised trials have excluded patients over 80 years of age. Therefore, treatment decisions in this patient group require particular care on an individual patient basis.

Meta-analysis of Stroke Studies

A meta-analysis of data from six placebo-controlled, double-blind trials was performed. The analysis was based on individual patient data from the ITT-population (n = 2,799) by means of a logistic regression model. The six trials included the NINDS (parts 1 & 2), ECASS (I & II) and ATLANTIS (parts A & B) studies.

The objective of the meta-analysis was to study the comparability as well as to combine the data of the various trials of alteplase in acute ischaemic stroke and thereby to put the results of the NINDS Part 2 study into perspective (see '*NINDS Stroke Trials'* below).

An overview of these trials is presented in Table 2. With the exception of ECASS-I, the dose of alteplase used in the other studies was 0.9 mg/kg; a higher dose of alteplase of 1.1 mg/kg was used in the ECASS-I study. While the pivotal NINDS Part 1 & Part 2 studies examined the treatment window of 0-3 hours after onset of stroke symptoms, the other studies investigated an extended treatment window of up to 6 hours (after onset of stroke symptoms). With respect to patient selection, the inclusion and exclusion criteria were similar across the studies. The most relevant difference was that in ECASS (I & II) and ATLANTIS (Part B) studies, patients with major infarctions based on their CT scan (>1/3 of the middle cerebral artery territory) were excluded while this criterion was not applied in the NINDS studies.

Table 2 Meta-analysis: Alteplase trials

STUDY	NINDS		ECASS-I	ECASS-II	ATLANTIS	
	Part 1	Part 2			Part A	Part B
Dosage	0.9 mg/kg (max. 90 mg)		1.1 mg/kg (max. 100 mg)	0.9 mg/kg (max. 90 mg)	0.9 mg/kg (max. 90 mg)	
Treatment Time Window	0-3 hrs		0-6 hrs	0-6 hrs	0-6 hrs	0-5 hrs
*Number of subjects treated within **0-3** hrs of onset (total number of subjects in each treatment group)*						
Alteplase	144	168	49 (313)	81 (409)	23 (372)	
Placebo	147	165	38 (307)	77 (391)	38 (383)	

The efficacy and safety results of the meta-analysis are summarised in Table 3. The results are presented as risk differences (RD) and as relative risks (RR) divided into subjects treated within 0-3 hrs of onset of stroke symptoms ('0-3 hrs') versus those treated between 3-6 hrs after onset of stroke symptoms ('3-6 hrs') and include the following endpoints (at day 90):

For efficacy:

- Functional independency, i.e. NIHSS 0-1
- Favourable outcome, i.e. modified Rankin Scale (mRS) 0-1
- Independent outcome, i.e. mRS 0-2

For safety:

- Disability or death, i.e. mRS 5-6
- Death (of all causes), i.e. mRS 6
- Intracerebral haemorrhage (ICH)
- Symptomatic ICH

Table 3 Meta-analysis: Summary of Efficacy and Safety results

Outcome at day 90	0-3 hrs				3-6 hrs			
	Placebo	Actilyse	RD^ (95% CI)	RR^^ (95% CI)	Placebo	Actilyse	RD^ (95% CI)	RR^^ (95% CI)
EFFICACY								
NIHSS 0-1 Functional independency	108/465 23.2%	172/465 37.0%	14% (8, 20)	1.59 (1.30, 1.94)	275/921 29.9%	324/932 34.8%	5% (1, 9)	1.15 (1.01, 1.31)
mRS# 0-1 Favourable outcome	136/465 29.2%	197/465 42.4%	14% (7, 20)	1.47 (1.23, 1.76)	314/921 34.1%	346/932 37.1%	2% (-2, 6)	1.09 (0.97, 1.23)
mRS# 0-2 Independent outcome	185/465 39.8%	233/465 50.1%	11% (5, 17)	1.29 (1.12, 1.48)	424/921 46.0%	457/932 49.0%	2% (-2, 7)	1.07 (0.97, 1.17)
SAFETY								
mRS# 5-6 Disability or death	117/465 25.2%	112/465 24.1%	-1% (-7, 4)	0.96 (0.77, 1.19)	189/921 20.5%	226/932 24.2%	3% (-0, 7)	1.18 (1.03, 1.36)
mRS# 6 Death (of all causes)	80/465 17.2%	82/465 17.6%	1% (-4, 5)	0.97 (0.73, 1.29)	99/921 10.7%	132/932 14.2%	3% (0, 6)	1.32 (1.03, 1.68)
ICH Intracerebral haemorrhage	147/465 31.6%	158/465 34.0%	2% (-4, 8)	1.01 (0.85, 1.22)	220/921 23.9%	317/932 34.0%	11% (7, 14)	1.31 (1.14, 1.50)
Symptomatic ICH	7/427 1.6%	33/416 7.9%	6% (3, 9)	4.03 (1.85, 8.79)	14/654 2.1%	56/671 8.3%	6% (4, 8)	3.58 (2.02, 6.34)

#mRS: 0 = no symptoms; 1 = no significant disability; 5 = severe disability; 6 = death

^RD = Risk Difference. ^^RR = Relative Risk.

The meta-analysis of all patients treated within 3 hours after stroke onset confirmed the beneficial effect of alteplase as observed in the NINDS Part 2 study. In this analysis, the probability of a favourable outcome at day 90 increased as the time to treatment with alteplase decreased. The risk difference versus placebo for a good recovery (favourable outcome) was approximately 14% despite an increased risk of symptomatic intracranial haemorrhage (see Table 3). A symptomatic intracranial haemorrhage rate (parenchymal haematoma, type II) was seen in 5.9% of patients treated with alteplase versus 1.1% with placebo ($p<0.0001$). The data do not allow drawing a definite conclusion on the treatment effect on death. The point estimate for the relative risk of death suggests that it is similar between the alteplase and placebo groups (RR=0.97, 95% CI = [0.73-1.29]). The meta-analysis also showed that alteplase is less effective in patients treated after 3 hours of onset (3 to 6 hours) compared with those treated within 3 hours of onset of symptoms, while the risks were higher.

In conclusion, the benefit/risk of alteplase, when given within 3 hours of stroke onset and taking into account the precautions stated, is considered favourable. This analysis confirms that rapid treatment with alteplase is associated with better outcomes at day 90. It also provides evidence that the therapeutic window may extend as far out as 4.5 hours (which was later confirmed by the results of the ECASS III trial – see below).

NINDS Stroke Trials

The pivotal NINDS Part 1 and Part 2 trials enrolled acute ischaemic stroke patients with measurable neurological deficit who could complete screening and begin study treatment within 3 hours from symptom onset. A cranial computerised tomography (CT) scan was performed prior to treatment to rule out the presence of intracranial haemorrhage. Patients were also excluded for the presence of conditions related to risks of bleeding, for minor neurological deficit, for rapidly improving symptoms prior to initiating study treatment, or for blood glucose of < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L) (see CONTRAINDICATIONS). Patients were randomised to receive either 0.9 mg/kg alteplase (maximum of 90 mg), or placebo. Alteplase was administered as a 10% initial bolus over 1 minute followed by continuous intravenous infusion of the remainder over 60 minutes.

The initial study NINDS Part 1 (n = 291, ITT-analysis) evaluated neurological improvement at 24 hours after stroke onset. The primary endpoint, the proportion of patients with a 4 or more point improvement in the National Institutes of Health Stroke Scale (NIHSS) score or complete recovery (NIHSS score = 0), was not significantly different between treatment groups. A secondary analysis demonstrated a significantly superior 3-month outcome associated with alteplase treatment using the following stroke assessment scales: Barthel Index (score $\geq$ 95), Modified Rankin Scale (score $\leq$ 1), Glasgow Outcome Scale (score = 1), and the NIHSS (score $\leq$ 1).

A second study NINDS Part 2 (n = 333, ITT-analysis) assessed clinical outcome at 3 months as the primary outcome. A favourable outcome was a priori defined as minimal or no disability using the four stroke assessment scales: Barthel Index (score $\geq$ 95), Modified Rankin Scale (score $\leq$ 1), Glasgow Outcome Scale (score = 1), and NIHSS (score $\leq$ 1). The results comparing alteplase and placebo-treated patients for the four outcome scales together (Generalised Estimating Equations) and individually are presented in Table 4. In this study, depending upon the scale, the favourable outcome of minimal or no disability occurred in at least 11 per 100 more patients treated with alteplase than those receiving placebo. The odds ratio for favourable outcome in the alteplase group was 1.7 (95% CI = 1.2 - 2.6). Compared to placebo there was 13% absolute increase in the number of patients with minimal or no disability (mRS 0-1) (OR =1.7; 95% CI = 1.1 - 2.6). There was also a consistent benefit seen with alteplase on other neurologic and disability scales (see Table 4). Secondary analyses demonstrated consistent functional and neurological improvement within all four stroke scales as indicated by median scores. These results were highly consistent with the 3-month outcome treatment effects as observed in the Part 1 study.

Table 4 The NINDS rt-PA Stroke Trial, Part 2: *3-Month Efficacy Outcomes*

Analysis	*Frequency of Favourable Outcome*[a]				
	Placebo (n = 165)	*Alteplase (n = 168)*	*Absolute Difference (95% CI)*	*Relative Frequency*[b] *(95% CI)*	*p-Value*[c]
Generalised Estimating Equations (Multivariate)	-	-	-	1.34 (1.05, 1.72)	0.02
Barthel Index	37.6%	50.0%	12.4% (3.0, 21.9)	1.33 (1.04, 1.71)	0.02
Modified Rankin Scale	26.1%	38.7%	12.6% (3.7, 21.6)	1.48 (1.08, 2.04)	0.02
Glasgow Outcome Scale	31.5%	44.0%	12.5% (3.3, 21.8)	1.40 (1.05, 1.85)	0.02
NIHSS	20.0%	31.0%	11.0% (2.6, 19.3)	1.55 (1.06, 2.26)	0.02

[a] *Favourable Outcome is defined as recovery with minimal or no disability.*

[b] *Value > 1 indicates frequency of recovery in favour of alteplase treatment.*

[c] *p-Value for Relative Frequency is from Generalised Estimating Equations with log link.*

The incidences of all-cause 90-day mortality, ICH, and new ischaemic stroke following alteplase treatment compared to placebo are presented in Table 5 as a combined safety analysis (n = 624) for Parts 1 and 2. These data indicated a significant increase in ICH following alteplase treatment, particularly symptomatic ICH within 36 hours. However, in alteplase-treated patients, there were no increases compared to placebo in the incidences of 90-day mortality or severe disability.

Table 5 The NINDS rt-PA Stroke Trial: *3-Month Safety Outcome*

	Part 1 and Part 2 Combined		
	Placebo (n = 312)	*Alteplase (n = 312)*	*p-Value***
All-Cause 90-day Mortality	64 (20.5%)	54 (17.3%)	0.36
Total ICH*	20 (6.4%)	48 (15.4%)	<0.01
Symptomatic	4 (1.3%)	25 (8.0%)	< 0.01
Asymptomatic	16 (5.1%)	23 (7.4%)	0.32
Symptomatic ICH within 36 hours	2 (0.6%)	20 (6.4%)	< 0.01
New Ischaemic Stroke (3-months)	17 (5.4%)	18 (5.8%)	1.00

* *Within trial follow-up period. Symptomatic ICH was defined as the occurrence of sudden clinical worsening followed by subsequent verification of ICH on CT scan. Asymptomatic ICH was defined as ICH detected on a routine repeat CT scan without preceding clinical worsening.*

** *Fisher's Exact Test*

In a pre-specified subgroup analysis in patients receiving aspirin prior to onset of stroke symptoms, there was preserved favourable outcome for alteplase-treated patients.

Exploratory, multivariate analyses of both studies combined (n = 624) to investigate potential predictors of ICH and treatment effect modifiers were performed. In alteplase-treated patients presenting with severe neurological deficit (e.g., NIHSS > 25) or of advanced age (e.g., > 80 years of age), the trends toward increased risk for symptomatic ICH within the first 36 hours were more prominent. Similar trends were also seen for total ICH and for all-cause 90-day mortality in these patients. When risk was assessed by the combination of death and severe disability in these patients, there was no difference between placebo and alteplase groups. Analyses for efficacy suggested a reduced but still favourable clinical outcome for alteplase-treated patients with severe neurological deficit or advanced age at presentation.

SITS-MOST Study

In a large observational study (SITS-MOST: The Safe Implementation of Thrombolysis in Stroke – Monitoring Study), the safety and efficacy of alteplase for acute stroke treatment within 3 hours in a routine clinical setting was assessed and compared with results from randomised clinical trials. All patients had to be compliant with the Product Information of ACTILYSE. Treatment and outcome data of 6,483 patients from 285 centres in 14 European countries were collected. Primary outcomes were symptomatic intracranial haemorrhage within 24 hours and mortality at 3 months. The rate of symptomatic intracranial haemorrhage (as per NINDS definition) found in SITS-MOST was comparable with the symptomatic intracranial haemorrhage rate as reported in randomised trials, 7.3% (468/6437; 95% CI = 6.7 - 7.9) in SITS-MOST versus 8.6% (40/465; 95% CI = 6.3 - 11.6) in randomised clinical trials. Mortality was 11.3% (701/6218; 95% CI = 10.5 - 12.1) in SITS-MOST versus 17.3% (83/479; 95% CI = 14.1 - 21.1) in randomised clinical trials. The results of SITS-MOST indicate that, the routine clinical use of alteplase within 3 hours of stroke onset is as safe as reported in randomised clinical trials.

ECASS III Trial

The ECASS III trial was a placebo-controlled, double-blind trial conducted in patients with acute stroke in a time-window of 3 to 4.5 hours. The study enrolled patients with measurable neurological deficit compliant with the Product Information of ACTILYSE except the time-window. After exclusion of brain haemorrhage or major infarction by computed tomography and/or as assessed clinically (e.g. NIHSS > 25), patients with acute ischemic stroke were randomised in a 1:1 double-blind fashion to intravenous alteplase (0.9 mg/kg bodyweight) or placebo. The primary endpoint was disability at 90 days, dichotomised for favourable (modified Rankin scale [mRS] 0 to 1) or unfavourable (mRS 2 to 6) outcome. The principal secondary endpoint was a global outcome analysis of four neurologic and disability scores combined. Safety endpoints included mortality, any intracranial haemorrhage, symptomatic intracranial haemorrhage, and serious adverse events.

A total of 821 patients (418 alteplase/403 placebo) were randomised. Of the 730 patients (375 alteplase/355 placebo) treated, the age ranged between 20 to 80 years of age, 68.8% aged between 61 and 80 years. More patients achieved favourable outcome with alteplase (52.4%) versus placebo (45.2%; odds ratio [OR] = 1.3; 95% CI = 1.02 - 1.76; relative risk [RR] = 1.16; 95% CI = 1.01 - 1.34; p = 0.038). On the global analysis, outcome was also improved (OR = 1.28; 95% CI = 1.00 - 1.65; p = 0.048). The incidence of intracranial haemorrhage was higher with alteplase versus placebo (any ICH 27.0% versus 17.6%, p = 0.0012; symptomatic ICH by NINDS definition 7.9% versus 3.5%, p = 0.006). Haemorrhagic transformations were seen in 22.24% of patients in the alteplase group versus 16.13% in the placebo group. Parenchymatous haemorrhages occurred in 4.78% with alteplase versus 1.49% with placebo. Mortality was low and not significantly different between alteplase (7.7%) and placebo (8.4%; p = 0.681). There were 3 cases of fatal intracranial haemorrhages in the alteplase group, none with placebo. The results of ECASS III show that alteplase between 3 and 4.5 hours after symptom onset significantly improves clinical outcomes in patients with acute ischemic stroke. See Table 6.

Since generally, the net clinical benefit for alteplase decreases over time, the benefits and risks need to be carefully weighed and earlier treatment increases the probability of a favourable outcome. Pooled data demonstrate that the net-clinical benefit is no longer favourable for alteplase in the time window beyond 4.5 hours.

Table 6 ECASS III Trial: Summary of main Efficacy and Safety outcomes

Outcomes at day 90	**Placebo**	**Actilyse**	**Odds Ratio** (95% CI)	**Relative Risk** (95% CI)	**p-value**
EFFICACY					
mRS 0-1 Favourable outcome	182/403 (45.2%)	219/418 (52.4%)	1.34 (1.02, 1.76)	1.16 (1.01, 1.34)	0.038
SAFETY					
All cause mortality	34/403 (8.4%)	32/418 (7.7%)	0.90 (0.54, 1.76)	0.91 (0.57, 1.44)	0.681
Any ICH	71/403 (17.6%)	113/418 (27.0%)	1.72 (1.24, 2.42)	1.53 (1.18, 2.00)	0.001

Symptomatic ICH by definition[a]	ECASS III	1/403 (0.2%)	10/418 (2.4%)	9.85 (1.26, 77.32)	9.64 (1.24, 74.97)	0.008
	ECASS II	9/403 (2.2%)	22/418 (5.3%)	2.43 (11.1, 5.35)	2.36 (1.10, 5.06)	0.023
	NINDS	14/403 (3.5%)	33/418 (7.9%)	2.38 (1.25, 4.52)	2.27 (1.23, 4.18)	0.006
	SITS-MOST	1/403 (0.2%)	8/418 (1.9%)	7.84 (0.98, 63.00)	7.71 (0.97, 61.39)	0.022

[a] *Definitions of symptomatic ICH:*

ECASS III definition – Symptomatic cerebral haemorrhage was defined as any blood in the brain or intracranially associated with a clinical deterioration of ≥ 4 points of the NIHSS for which the haemorrhage has been identified as the dominating cause of the neurologic deterioration.

ECASS II definition – Any intracranial bleed and 4 points or more worsening on the NIHSS score from baseline or the lowest value in the first 7 days, or any haemorrhage leading to death.

NINDS definition – A haemorrhage was considered symptomatic if it was not seen on a previous CT scan and there had subsequently been either a suspicion of haemorrhage or any decline in neurologic status. To detect intracranial haemorrhage, CT scans were required at 24 hours and 7 to 10 days after the onset of stroke and when clinical finding suggested haemorrhage.

SITS-MOST definition – Local or remote parenchymal haematoma type 2 on the 22- to 36-hour post-treatment imaging scan, combined with a neurologic deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.

Use in the Elderly

Data of patients over 80 years of age are very limited. A pooled analysis was performed on the available data from six randomised controlled clinical trials (NINDS parts 1 & 2, ATLANTIS parts A & B, ECASS II & III) involving 137 patients aged ≥ 80 years treated within the 0-4.5 hour period.

The pooled analysis showed that the absolute risk difference between alteplase and placebo for a favourable outcome (mRS 0-1) at day 90 was 1.4% and for independence (mRS 0-2) at day 90 was 2.1%, which was not statistically significant. A greater absolute difference of 8.1% for favourable outcome (mRS 0-1) and 10.1% for independence (mRS 0-2) was observed in favour of alteplase compared to placebo in the subgroup excluding patients with severe stroke at baseline (NIHSS ≥ 20), however the treatment difference was not statistically significant. In the small subgroup of patients with severe stroke (n=48), the functional outcome was very poor.

Efficacy was reduced in patients over 80 years of age compared to younger patients. A favourable outcome (mRS 0-1) at day 90 was seen in 27.63% (n=21/76) of the patients aged ≥ 80 years treated with alteplase compared to 46.03% (n=470/1021) of patients aged < 80 years (OR alteplase over placebo combined for both age groups and adjusted for NIHSS at baseline = 1.43; 95% CI = 1.18 - 1.74). Excluding those patients with severe stroke, a favourable outcome (mRS 0-1) at day 90 was seen in 44.4% (n=20/45) of the patients aged ≥ 80 years treated with alteplase compared to 52.2% (n=443/849) of patients aged < 80 years (OR alteplase over placebo combined for both age groups and adjusted for NIHSS at baseline = 1.39; 95% CI = 1.13 - 1.70).

All-cause mortality was 27.6% (n=21/76) on alteplase versus 23% (n=14/61) on placebo in the group of patients aged ≥ 80 years (OR adjusted for NIHSS at baseline = 0.96; 95% CI = 0.36 - 2.59); compared to 10.2% (n=104/1021) on alteplase versus 11.5% (n=120/1041) on placebo in the group of younger patients aged < 80 years.

Any ICH was significantly higher on alteplase (51.3%; n=39/76) versus placebo (21.3%; n=13/61) in patients aged ≥ 80 years (OR adjusted for NIHSS at baseline = 4.01; 95% CI = 1.76 - 9.13) compared to those < 80 years of age (28.9%; n=295/1021 on alteplase versus 23.5%; n=245/1041 on placebo).

Symptomatic ICH (as per SITS-MOST definition) was significantly higher on alteplase (6.6%; n=5/76) versus placebo (0%; n=0/0) in patients aged ≥ 80 years (unadjusted OR = 8.51; 95% CI = 0.45 - 159.02) compared to those < 80 years of age (2.5%; n=25/1021 on alteplase versus 0.5%; n=5/1041 on placebo).

INDICATIONS

Myocardial Infarction

ACTILYSE is indicated for intravenous use in adults for the lysis of suspected occlusive coronary artery thrombi associated with evolving transmural myocardial infarction. Treatment should be initiated as soon as possible after the onset of symptoms. The treatment can be initiated within 12 hours of symptom onset.

Pulmonary Embolism

ACTILYSE is also indicated in patients with acute massive pulmonary embolism in whom thrombolytic therapy is considered appropriate.

Acute Ischaemic Stroke

ACTILYSE is indicated for thrombolytic treatment of acute ischaemic stroke. Treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms and after exclusion of intracranial haemorrhage by appropriate imaging techniques (e.g. cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage). The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

CONTRAINDICATIONS

ACTILYSE should not be administered to patients with known hypersensitivity to alteplase, gentamicin (a trace residue from the manufacturing process) or any of the excipients (listed under PRESENTATION).

ACTILYSE should not be used in cases where there is a high risk of haemorrhage such as:

- Significant bleeding disorder at present or within the past 6 months, known haemorrhagic diathesis
- History or evidence of or suspected intracranial haemorrhage, including subarachnoid haemorrhage
- History of central nervous system damage (e.g. neoplasm, aneurysm, intracranial or spinal surgery)
- Severe uncontrolled hypertension
- Recent (within 10 days) prolonged or traumatic cardiopulmonary resuscitation (> 2 minutes), obstetrical delivery, organ biopsy, puncture of noncompressible blood vessel (e.g. subclavian or jugular vein puncture)
- Major surgery (e.g. coronary artery bypass graft) or significant trauma (including any trauma associated with acute myocardial infarction) within the past 3 months, recent trauma to the head or cranium
- Documented ulcerative gastrointestinal disease during the last 3 months
- Arterial aneurysms, arterial/venous malformations
- Neoplasm with increased bleeding risk
- Bacterial endocarditis, pericarditis
- Acute pancreatitis
- Haemostatic defects including those secondary to severe hepatic or renal disease; special attention should be paid to coagulation parameters in patients with significant liver dysfunction
- Severe hepatic disease/dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis

- Patients receiving other intravenous thrombolytic agents
- Patients currently receiving oral anticoagulants, e.g. warfarin sodium (INR> 1.3)

Additional Contraindications for patients with Acute Myocardial Infarction / Pulmonary Embolism:

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke or transient ischaemic attack (TIA) in the preceding 6 months, except current acute ischaemic stroke within 4.5 hours

Additional Contraindications for patients with Acute Ischaemic Stroke:

- Symptoms of ischaemic attack began more than 4.5 hours prior to infusion start or when time of symptom onset is unknown
- Minor neurological deficit or symptoms rapidly improving before start of infusion
- Severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques
- Seizure at onset of stroke
- Evidence of intracranial haemorrhage (ICH) on the CT-scan
- Symptoms suggestive of subarachnoid haemorrhage, even if CT-scan is normal
- Administration of heparin within 48 hours preceding the onset of stroke and with an elevated activated partial thromboplastin time (aPTT) at presentation
- History of prior stroke and concomitant diabetes
- History of previous stroke or serious head-trauma within the last 3 months
- Platelet count of below 100,000/mm^3
- Systolic blood pressure (BP) > 185 mm Hg or diastolic BP > 110 mm Hg, or aggressive management (IV medication) necessary to reduce BP to these limits
- Blood glucose < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L)
- Patients < 18 years

For use in patients over 80 years of age, see PRECAUTIONS – Additional Warnings in Acute Ischaemic Stroke.

PRECAUTIONS

The appropriate presentation of alteplase should be chosen carefully and in accordance with the intended use. The 2 mg presentation of alteplase (ACTILYSE CATHFLO) is not suitable for use in acute myocardial infarction, acute pulmonary embolism or acute ischaemic stroke (due to risk of massive under dosing). Only the 10 mg, 20 mg and 50 mg presentations of alteplase (ACTILYSE) are indicated for use in these indications.

ACTILYSE should be used by physicians experienced in the use of thrombolytic treatment and with the facilities to monitor its use. As with other thrombolytics, it is recommended that when ACTILYSE is administered standard resuscitation equipment and medication be available in all circumstances.

Bleeding

The most common complication encountered during therapy with ACTILYSE is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding at any site or body cavity;
- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g. venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation undoubtedly contributes to the bleeding.

Fibrin will be lysed during the infusion of ACTILYSE and bleeding from recent puncture sites may occur. Therefore, therapy with ACTILYSE, as with other thrombolytic agents, requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

The use of rigid catheters, intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTILYSE. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTILYSE, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, in particular cerebral haemorrhage, the infusion of ACTILYSE and any concomitant heparin should be terminated immediately and treatment instituted as described under OVERDOSAGE.

As with all thrombolytics, the use of ACTILYSE therapy has to be carefully evaluated in order to balance the potential risks of bleeding with expected benefits under the following conditions:

- Diabetic haemorrhagic retinopathy or other haemorrhagic ophthalmic conditions (vision disturbances may indicate haemorrhagic retinopathy);
- Recent minor traumas (within 10 days), such as biopsies, puncture of major vessels, intramuscular injections, cardiopulmonary resuscitation;
- Any other conditions not mentioned under CONTRAINDICATIONS in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Cholesterol Embolisation

Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g. cardiac catherisation, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Additional Warnings in Acute Myocardial Infarction / Pulmonary Embolism:

Additionally, the potential risks of ACTILYSE therapy should be carefully evaluated against the expected benefits in patients treated for acute Myocardial Infarction / Pulmonary Embolism with the following conditions:

- Systolic blood pressure > 160 mm Hg
- Advanced age, which may increase the risk of intracerebral haemorrhage. As there is also a therapeutic benefit to these patients, the risk-benefit evaluation should be carried out carefully.
- The use of thrombolytics can increase the risk of thrombo-embolic events in patients with left heart thrombus, e.g. mitral stenosis or atrial fibrillation
- Clinical evidence or history of ischaemic stroke or transient ischaemic attacks more than 6 months previously (see CONTRAINDICATIONS)
- A history or clinical evidence of hypertensive disease in a patient over 70 years old
- Septic thrombophlebitis or occluded AV cannula at seriously infected site.

Arrhythmias

Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarisations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction. Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTILYSE are administered.

Use of Anticoagulants

In the management of acute myocardial infarction or pulmonary embolism, antithrombotic adjunctive therapy such as heparin may be administered concomitantly with and following infusion of ACTILYSE to reduce the possibility of reocclusion (see DOSAGE AND ADMINISTRATION). The usual doses of heparin used may increase the risk of bleeding, independent of ACTILYSE. Because either heparin or ACTILYSE alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

The concomitant use of GP IIb/IIIa antagonists increases the risk of bleeding.

Additional Warnings in Acute Ischaemic Stroke:

Treatment must be performed only by a physician trained and experienced in neurological care.

Before ACTILYSE treatment is initiated, timely imaging evidence must be obtained to exclude intracranial haemorrhage, e.g. by cranial computerised tomography or other diagnostic imaging method sensitive for the presence of haemorrhage.

Compared to other indications, patients with acute ischaemic stroke treated with ACTILYSE have a markedly increased risk of intracranial haemorrhage as the bleeding occurs predominantly into the infarcted area. This applies in particular in the following cases:

- Any situations involving a high risk of haemorrhage (see CONTRAINDICATIONS)
- Small asymptomatic aneurysms of the cerebral vessels
- Late time-to-treatment onset
- Patients pre-treated with aspirin may have a greater risk of intracerebral haemorrhage, particularly if ACTILYSE treatment is delayed. Not more than 0.9 mg alteplase/kg bodyweight (max. of 90 mg) should be administered in view of the increased risk of cerebral haemorrhage.
- Patients over 80 years of age have an increased risk of haemorrhage (both ICH and symptomatic ICH), mortality and decreased efficacy compared to younger patients (see CLINICAL TRIALS), reducing the net benefit from treatment compared to young patients. Therefore, the use of ACTILYSE should be weighed carefully against anticipated risks on an individual patient basis.

ACTILYSE treatment should not be initiated later than 4.5 hours after the onset of stroke symptoms (see CONTRAINDICATIONS) because of an unfavourable benefit/risk ratio mainly based on the following:

- Positive treatment effects decrease over time
- Particularly in patients with prior aspirin treatment the mortality rate increases
- Risk increases with regard to symptomatic haemorrhages

Blood pressure (BP) monitoring during treatment administration and up to 24 hours is necessary. Intravenous antihypertensive therapy is recommended if systolic BP > 180 mm Hg or diastolic BP > 105 mm Hg.

The therapeutic benefit is reduced in patients who had a prior stroke or in whom an uncontrolled diabetes is known, thus the benefit/risk ratio is considered less favourable, but still positive in these patients.

In patients with very mild stroke, the risks outweigh the expected benefit (see CONTRAINDICATIONS).

Patients with very severe stroke are at higher risk of intracerebral haemorrhage and death and should not be treated with ACTILYSE (see CONTRAINDICATIONS).

Patients with extensive infarctions are at greater risk of poor outcome including severe haemorrhage and death. In such patients, the benefit/risk ratio should be thoroughly considered.

In stroke patients the likelihood of a favourable outcome decreases with increasing age, increasing stroke severity and increased levels of blood glucose on admission; while the likelihood of severe disability and death or relevant intracranial bleeding increases, independently from treatment. The use of ACTILYSE in patients over 80 years of age should be weighed carefully against anticipated risks on an individual basis (see CLINICAL TRIALS). Patients with severe stroke (as assessed clinically and/or by appropriate imaging techniques) and patients with blood glucose levels < 50 mg/dL (< 2.8 mmol/L) or > 400 mg/dL (> 22.2 mmol/L) at baseline should not be treated with ACTILYSE (see CONTRAINDICATIONS).

Reperfusion of ischaemic area may induce cerebral oedema in the infarcted zone. Due to an increased haemorrhagic risk, treatment with platelet aggregation inhibitors should not be initiated within the first 24 hours following thrombolysis with ACTILYSE (see DOSAGE AND ADMINISTRATION).

General

ACTILYSE should be administered in a setting where the appropriate diagnostic and monitoring techniques are readily available.

Routine management of myocardial infarction should not be deferred after evidence of successful thrombolysis is seen. Evaluation for presence of underlying artherosclerotic heart disease should be carried out as clinically indicated.

The diagnosis of acute pulmonary embolism should be confirmed whenever possible by objective means such as pulmonary angiography or non-invasive procedures such as lung scanning.

It should be realised that the treatment of pulmonary embolism with ACTILYSE has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of re-embolisation due to the lysis of underlying deep venous thrombi should be considered.

Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimised. In the event of serious bleeding, ACTILYSE and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Current data generally do not support the use of thrombolytic therapy in patients when the ECG shows only ST depression (with the exception of those patients with a “true posterior” infarct, as indicated by tall R waves and marked ST depression in leads V_1 - V_3).

Hypersensitivity

There has been little experience with re-administration of ACTILYSE. Re-administration should be undertaken with caution. Less than 0.5% of patients receiving single courses of ACTILYSE therapy have experienced transient antibody formation. No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systemic experience with re-administration of ACTILYSE. Anaphylactoid reactions associated with

the administration of ACTILYSE are rare and can be caused by hypersensitivity to the active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients. The stopper of the glass vial with ACTILYSE powder contains natural rubber (a derivative of latex) which may cause allergic reactions. If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment should be initiated.

Effects on Fertility

Studies with ACTILYSE have not been performed to determine effect on fertility or reproduction.

Use in Pregnancy Category B1

Studies have shown that ACTILYSE is not teratogenic in the rat and rabbit and does not cross the placental barrier in the pregnant rat. In the rabbit, however, a dose-related increase in abortions and resorption rate was seen in the dose range 3-10 mg/kg/day. ACTILYSE should be given to pregnant women only if the need clearly outweighs the potential risk.

Use in Lactation

It is not known whether ACTILYSE is excreted in human milk. Because many drugs are excreted by this route, caution should be exercised when ACTILYSE is administered to breastfeeding women.

Use in Children

Safety and effectiveness of ACTILYSE in children has not been established. Therefore treatment of such patients is not recommended. ACTILYSE is not indicated for treatment of acute stroke in patients less than 18 years of age.

Use in the Elderly

The risks of therapy may be increased in the elderly. In a pooled analysis of randomised controlled clinical trials, patients over 80 years was associated with an increased risk of haemorrhage (both ICH and symptomatic ICH), mortality and decreased efficacy compared to younger patients (see CLINICAL TRIALS). For use in patients above 80 years of age, see PRECAUTIONS.

Carcinogenicity

Studies with ACTILYSE have not been performed to determine carcinogenicity.

Genotoxicity

Studies with ACTILYSE have not been performed to determine genotoxicity.

Interactions with Other Medicines

The risk of haemorrhage may be increased with the use of coumarin derivatives, antiplatelet aggregation agents, heparin or any other agent which influences haemostasis (before, during or within the first 24 hours after treatment with ACTILYSE). The concomitant use of GP IIb/IIIa antagonists increases the risk of bleeding.

The interaction of ACTILYSE with other drugs has not been studied. Data on adjunctive pharmacotherapy during thrombolysis with ACTILYSE (e.g. calcium channel blockers, beta adrenergic blockers etc) are inadequate to exclude any possible drug interactions.

Concomitant treatment with Angiotensin Converting Enzymes (ACE) inhibitors may enhance the risk of suffering an anaphylactoid reaction (see ADVERSE EFFECTS). Monitoring is recommended particularly for patients receiving concomitant ACE inhibitors.

Effects on Laboratory Tests

During ACTILYSE infusion, coagulation tests and/or measures of fibrinolytic activity may be performed if desired. However, routine measurements of fibrinogen as well as fibrinogen degradation products are unreliable, and should not be undertaken unless specific precautions are taken to prevent *in vitro* artifacts. ACTILYSE is a serine protease that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions.

This can lead to degradation of fibrinogen in a blood sample removed for analysis. Collection of blood samples on aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Effects on ability to drive and use machines

Not applicable.

ADVERSE EFFECTS

The most frequent adverse reaction associated with ACTILYSE is bleeding (>1%, ≤10% major bleeds; >10% any haemorrhage) which may result in a fall in haematocrit and/or haemoglobin values. Haemorrhage at any site or body cavity can occur and may result in life-threatening situations, permanent disability or death.

Neurological symptoms such as somnolence, aphasia, hemiparesis, convulsion, epileptic seizure, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression and psychosis may be associated with intracranial haemorrhage.

The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding at any site or body cavity;
- Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g. venous cutdowns, arterial punctures, sites of recent surgical intervention).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTILYSE therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Death and permanent disability are not uncommonly reported in patients that have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

The overall in-hospital mortality in myocardial infarction patients from all causes receiving ACTILYSE averaged 5-6%.

The following adverse reactions have been reported among patients receiving ACTILYSE in clinical trials and in post-marketing experience. The frequencies given below are based on adverse events reported for one or all three indications which may be causally related to ACTILYSE treatment.

The number of patients treated in clinical trials in the indications pulmonary embolism and stroke (within the 0 - 4.5 hours time window) is smaller than the number in trials for myocardial infarction (see CLINICAL TRIALS). Except for intracranial haemorrhage as side effect in the stroke indication as well as for reperfusion arrhythmias in the myocardial infarction indication, there is no medical reason to assume that the qualitative/quantitative side effect profile of ACTILYSE would differ between the three indications.

a) Adverse events related specifically to one or more indications

Cardiac disorders (related to myocardial infarction indication only):

>10%: reperfusion arrhythmias, such as

- arrhythmia
- extrasystoles
- atrial fibrillation
- first degree atrioventricular block to complete atrioventricular block
- bradycardia
- tachycardia
- ventricular arrhythmia
- ventricular fibrillation
- ventricular tachycardia occur in close temporal relationship to treatment with ACTILYSE

Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional anti-arrhythmic therapies.

Nervous system disorders (related to myocardial infarction and pulmonary embolism indications):

>0.1% and ≤1%: intracranial haemorrhage, such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation of stroke
- intracranial haematoma
- subarachnoid haemorrhage

Nervous system disorders (related to acute ischaemic stroke indication only):

>1% and ≤10%: intracranial haemorrhage, such as

- cerebral haemorrhage
- cerebral haematoma
- haemorrhagic stroke
- haemorrhagic transformation of stroke
- intracranial haematoma
- subarachnoid haemorrhage

Symptomatic intracerebral haemorrhages represents the major adverse events (up to 10% of patients). However, this had not shown an increased overall morbidity or mortality.

b) Adverse events related to all three indications

Gastrointestinal disorders:

>1% and ≤10%: gastrointestinal haemorrhage, such as

- gastric haemorrhage
- gastric ulcer haemorrhage
- rectal haemorrhage
- haematemesis
- melaena
- mouth haemorrhage
- nausea
- vomiting

Nausea and vomiting can also occur as symptoms of myocardial infarction.

>0.1% and ≤1%: retroperitoneal haemorrhage, such as
- retroperitoneal haematoma
- gingival bleeding

General disorders and administration site conditions:

>10%: injection site haemorrhage, puncture site haemorrhage, such as
- catheter site haematoma
- catheter site haemorrhage

Immune system disorders:

>0.1% and ≤1%: anaphylactoid reactions, which are usually mild, but can be life threatening in isolated cases

They may appear as
- rash
- urticaria
- bronchospasm
- angio-oedema
- hypotension
- shock or any other symptom associated with hypersensitivity

If they occur, conventional anti-allergic therapy should be initiated. In the cases reported, a relatively larger proportion of patients were receiving concomitant ACE inhibitors. No definite anaphylactic (IgE mediated) reactions to ACTILYSE are known. Transient antibody formation to ACTILYSE has been observed in rare cases and with low titres, but a clinical relevance of this finding could not be established.

Injury and poisoning and procedural complications

>0.01% and ≤0.1%: fat embolism, which may lead to corresponding consequences in the organs concerned

The classification of fat embolism, which was not observed in the clinical trial population, was based on spontaneous reporting.

Eye disorders:

≤0.01%: eye haemorrhage

Cardiac disorders:

>0.1% and ≤1%: pericardial haemorrhage

Investigations:

>10%: blood pressure decreased

>1% and ≤10%: body temperature increased

Renal and urinary disorders:

>1% and ≤10%: urogenital haemorrhage, such as
- haematuria
- haemorrhage urinary tract

Respiratory, thoracic and mediastinal disorders:

>1% and ≤10%: respiratory tract haemorrhage, such as
- pharyngeal haemorrhage
- haemoptysis
- epistaxis

Surgical and medical procedures:

>1% and ≤10%: transfusion

Skin and subcutaneous tissue disorders:

>1% and ≤10%: ecchymosis

Vascular disorders:

>10%: haemorrhage (such as haematoma)

>0.1% and ≤1%: embolism, which may lead to corresponding consequences in the organs concerned

>0.01% and ≤0.1%: bleeding of parenchymatous organs, such as
- hepatic haemorrhage
- pulmonary haemorrhage

As with other thrombolytic agents, the following events have been reported as sequelae of the underlying disease and/or thrombolytic administration and the effect of ACTILYSE on the incidence of these events is unknown. These events may be life threatening and may lead to death.

Use in acute myocardial infarction: recurrent ischemia / angina, heart failure, cardiogenic shock, myocardial re-infarction, myocardial rupture, electromechanical dissociation, pericardial effusion, pericarditis, mitral regurgitation, cardiac tamponade, pulmonary oedema, ventricular septal defect

Use in pulmonary embolism: pulmonary re-embolisation, pulmonary oedema, pleural effusion, hypotension

Use in acute ischemic stroke: cerebral oedema, cerebral herniation, seizure, new ischemic stroke

DOSAGE AND ADMINISTRATION

Administer ACTILYSE as soon as possible after onset of symptoms. ACTILYSE is intended for intravenous use only. It should be given via a dedicated intravenous line with an infusion pump.

A total dose *exceeding 100 mg* of ACTILYSE should not be used for the treatment of acute myocardial infarction or pulmonary embolism because it has been associated with an increase in intracranial bleeding. For the same reason, the total dose used for the treatment of acute ischaemic stroke should not exceed *90 mg*.

Myocardial Infarction

a) Accelerated Infusion

The accelerated dosage regimen is based on the results from the GUSTO Study (See PHARMACOLOGY).

For patients weighing over 65 kg, the recommended total dose is 100 mg administered as follows:

- 15 mg intravenous bolus
- 50 mg infusion over the first 30 minutes
- 35 mg infusion over the following 60 minutes.

For patients weighing less than or equal to 65 kg, the dose is adjusted on the basis of bodyweight as follows:

- 15 mg intravenous bolus
- 0.75 mg/kg infusion over the first 30 minutes
- 0.5 mg/kg infusion over the following 60 minutes.

b) 3 Hour Infusion

For a description of the trials this dosage regimen is based on, see PHARMACOLOGY.

For patients weighing over 65 kg, the recommended total dose is 100 mg administered as follows:

- 10 mg intravenous bolus
- 50 mg infusion over the first hour
- 40 mg infusion over the following 2 hours.

For patients weighing less than or equal to 65 kg, the dose is adjusted on the basis of bodyweight so that the total dose does not exceed 1.5 mg/kg.

Adjunctive Therapy:

Antithrombotic adjunctive therapy is recommended according to the current international guidelines for the management of patients with ST-elevation myocardial infarction.

For the antithrombotic adjunctive therapy regimen used in the GUSTO study, see CLINICAL TRIALS.

Pulmonary Embolism

A total dose of 100 mg should be administered over 2 hours. The most experience available is with the following dose regimen:

- 10 mg as an intravenous bolus over 1-2 minutes,
- 90 mg as an intravenous infusion over two hours.

The total dose should not exceed 1.5 mg/kg in patients with a body weight below 65 kg.

Adjunctive Therapy:

After treatment with ACTILYSE, heparin therapy should be initiated (or resumed) when aPTT values are less than twice the upper limit of normal. The infusion should be adjusted to maintain aPTT 1.5 to 2.5 fold of the reference value (50-70 seconds).

Acute Ischaemic Stroke

Treatment must be performed by a physician specialised in neurological care. (See PRECAUTIONS – Additional Warnings in Acute Ischaemic Stroke)

The recommended dose is 0.9 mg/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus.

Treatment with ACTILYSE should be initiated as early as possible within 4.5 hours of symptom onset. The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome.

Adjunctive therapy:

The safety and efficacy of this regimen with concomitant administration of heparin and aspirin within the first 24 hours of onset of the symptoms have not been sufficiently investigated. Administration of aspirin or intravenous heparin should be avoided in the first 24 hours after treatment with ACTILYSE. If heparin is required for other indications (e.g. prevention of deep vein thrombosis) the dose should not exceed 10,000 IU per day, administered subcutaneously.

RECONSTITUTION AND DILUTION

Reconstitution

Do not use vial if vacuum is not present.

ACTILYSE should be reconstituted to a concentration of 1 mg alteplase per mL by aseptically adding the appropriate volume of sterilised Water for Injections into the ACTILYSE dry powder vial:

ACTILYSE 10 mg vial

- Reconstitute the ACTILYSE 10 mg vial with 10 mL sterilised Water for Injections in the accompanying vial.
- Reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterilised Water for Injections into the lyophilised cake.
- When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

ACTILYSE 20 mg vial

- Reconstitute the ACTILYSE 20 mg vial with 20 mL sterilised Water for Injections in the accompanying vial by use of the transfer cannula (provided with the pack). The transfer cannula must always be introduced vertically into the stopper and through the mark at its centre.
- As an alternative to the use of the transfer cannula, reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterilised Water for Injections into the lyophilised cake.
- When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

ACTILYSE 50 mg vial

- Reconstitute the ACTILYSE 50 mg vial with 50 mL sterilised Water for Injections in the accompanying vial by use of the transfer cannula (provided with the pack). The transfer cannula must always be introduced vertically into the stopper and through the mark at its centre.
- As an alternative to the use of the transfer cannula, reconstitution can be carried out using a large bore needle (e.g. 18 gauge), directing the stream of sterilised Water for Injections into the lyophilised cake.
- When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

It is important that ACTILYSE be reconstituted only with sterilised Water for Injections without preservatives. Do not use bacteriostatic Water for Injections.

The reconstituted lyophilised preparation results in a colourless to pale yellow transparent solution containing ACTILYSE 1.0 mg/mL at a pH of 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

ACTILYSE should not be mixed with other drugs, neither in the same infusion vial nor the same venous line (not even with heparin). Before dilution or administration, parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration whenever solution and container permit.

Dilution

The reconstituted solution (1 mg alteplase per mL) may be diluted further, immediately before administration, with sterilised physiological saline solution (0.9% Sodium Chloride for Injection) up to a minimal concentration of 0.2 mg alteplase per mL. Further dilution of the reconstituted solution with sterile physiological saline solution (0.9% Sodium Chloride for Injection) below a minimal concentration of 0.2 mg alteplase per mL is not recommended since the occurrence of turbidity of the reconstituted solution cannot be excluded.

A dilution of the reconstituted solution with sterilised Water for Injections, carbohydrate infusion solutions (e.g. glucose), or preservative containing solutions is not recommended due to increasing formation of turbidity of the reconstituted solution.

Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion.

No other medication should be added to ACTILYSE solution. Because ACTILYSE contains no preservatives, it should be reconstituted immediately before use.

STABILITY AND STORAGE CONDITIONS

Lyophilised ACTILYSE is stable up to the expiration date stamped on the vial.

Store below 30°C.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for up to 24 hours at 2-8°C. From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

For single use in only one patient. Discard any unused solution.

Protect the lyophilised material during storage from light. During the period of reconstitution and infusion, protection from light is not necessary.

OVERDOSAGE

In case of overdose, advice can be obtained from the Poisons Information Centre (telephone 13 11 26).

Symptoms and Treatment

Should serious bleeding occur in a critical location, in particular cerebral haemorrhage, the infusion of ACTILYSE and any other concomitant anticoagulant therapy should be discontinued immediately. Most patients can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement and manual pressure applied to the bleeding vessel if accessible. Protamine should be

considered if heparin has been administered within 4 hours of the onset of bleeding. If necessary, blood loss and reversal of the bleeding tendency can be managed with fresh whole blood or packed red blood cells. In the event of clinically significant fibrinogen depletion, fresh frozen plasma or cryoprecipitate can be infused with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents may be used as a last option.

PRESENTATION

ACTILYSE 10 mg

Box containing 1 vial of ACTILYSE 10 mg in up to 466.6 mg dry powder, 1 vial of sterilised Water for Injections, 10 mL.

The quantitative composition of the lyophilised products is:

- Alteplase 10 mg
- L-Arginine 348.4 mg
- Phosphoric acid 107.2 mg
- Polysorbate 80 700 μg to 1.0 mg

ACTILYSE 20 mg

Box containing 1 vial of ACTILYSE 20 mg in 933.2 mg dry powder, 1 vial of sterilised Water for Injections, 20 mL, and 1 transfer cannula for preparing a sterile solution of ACTILYSE.

The quantitative composition of the lyophilised products is:

- Alteplase 20 mg
- L-Arginine 696.8 mg
- Phosphoric Acid 214.4 mg
- Polysorbate 80 1.4-2 mg

ACTILYSE 50 mg

Box containing 1 vial of ACTILYSE 50 mg in 2333 mg dry powder, 1 vial of sterilised Water for Injections, 50 mL, and 1 transfer cannula for preparing a sterile solution of ACTILYSE.

The quantitative composition of the lyophilised products is:

- Alteplase 50 mg
- L-Arginine 1.742 g
- Phosphoric Acid 536 mg
- Polysorbate 80 3.5-5 mg

Phosphoric acid and/or sodium hydroxide may be used prior to lyophilisation for pH adjustment.

Not all strengths are being distributed in Australia.

POISON SCHEDULE

Schedule 4

NAME AND ADDRESS OF SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

NORTH RYDE NSW 2113

Text approved by the Therapeutic Goods Administration (TGA) on 22 September 2010