EWG 2014

EXPERT WORKING GROUP

ACTILYSE (ALTEPLASE) BA LANCE O F BEN EFITS AND RISKS WH EN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of paper: Paper 1: Introduction to the papers.

Product: Actilyse 10, 20, 50mg	**Assessors:** Medical assessor: Dr [redacted] Scientific assessor: Dr [redacted] Statistical assessor: Dr [redacted] Epidemiological assessors: Dr [redacted] Dr [redacted]
MAHs: Boehringer Ingelheim Limited	**Previous Assessments:** CHM May 2014
Active constituents: Alteplase (rt-PA)	**Legal status:** **POM**
Therapeutic classification: Antithrombotic agent, ATC code B01AD02	

1. Issue

The MHRA was contacted by Dr [redacted] a retired stroke physician, who has concerns regarding the balance of benefits and risks of alteplase (rt-PA) when used in acute ischaemic stroke. Dr [redacted] viewpoint that an updated independent evaluation of rt-PA when used in the treatment of ischaemic stroke was necessary was supported by the then president of the Royal College of Physicians (Sir Richard Thompson), the National Medical Director of the NHS Commissioning Board (Sir Bruce Keogh) and a number of other influential physicians. In light of these concerns, the public health importance of stroke services and rt-PA, and the availability of new data that had not been previously reviewed, the MHRA sought initial advice from the Commission on Human Medicines (CHM) on whether the issues raised impacted the balance of benefits and risks of rt-PA when used in accordance with the licence in the treatment of stroke.

In May 2014 the CHM carefully considered the MHRA assessment of the new data and the specific concerns raised at that time. CHM concluded that the data presented did not change the favourable balance of benefits and risks for rt-PA in the treatment of acute ischaemic stroke. The May CHM paper has already been circulated to the group by way of background. However, in order to be assured that all relevant sources of evidence had been taken into consideration, CHM also advised that an expert working group should be set up. The proposed Terms of Reference for the group are provided in Annex 1.

This paper is intended to provide a brief reminder of the regulatory background to rt-PA and a guide to the assessment reports provided.

2. Background

rt-PA is a recombinant human tissue-type plasminogen activator (t-PA). It is produced by expression of the human gene for t-PA in CHO cells. The mechanism of action of rt-PA is understood to be the enzymatic cleavage of plasminogen to plasmin with subsequent increase in fibrinolysis. In the indication of acute ischaemic stroke the recommended dose is 0.9 mg rt-PA/kg body weight (maximum of 90 mg) infused intravenously over 60 minutes with 10% of the total dose administered as an initial intravenous bolus. Product information currently includes a negative benefit:risk statement for administration beyond the 4.5 hour window, and a reminder that treatment must be started as early as possible within the 4.5 hours.

2.1. Regulatory background

rt-PA was first approved in the UK for fibrinolysis in coronary artery occlusion and massive pulmonary embolism in 1988. It was authorised via the European mutual recognition procedure, with Germany acting as the lead member state (Reference Member State, RMS).

In 2002, rt-PA received a conditional licence in the indication of treatment of acute ischaemic stroke from 0-3 hours following symptom onset. Several member states expressed divergent opinions during this procedure, and the UK expressed a negative view. The extension of indication was eventually granted following a lengthy arbitration procedure on condition that the company conducted:

- A further randomised placebo-controlled trial (ECASS III) to assess efficacy and safety within 3-4 hours of symptom onset [later revised to 3-4.5 hours]
- A post-marketing surveillance study (SITS-MOST)

In 2012, the treatment time-window for rt-PA was extended from 0-3 hours to 0-4.5 hours post-symptom onset. The UK raised Major Objections during this procedure with a particular concern related to the apparent increase in death rates in the rt-PA group compared with the placebo group. This was resolved when it transpired that data on deaths had been collected for unequal lengths of follow-up in the two groups which, when corrected, demonstrated that rt-PA did not have an adverse effect on mortality in this time-window.

Both the initial application for the indication in the treatment of acute ischaemic stroke and the variation to extend the time-window for treatment up to 4.5 hours were extensively discussed both at CHM and within Europe. All data that were available and considered relevant at these times were comprehensively reviewed in the European procedures, and all of the MHRA/CHM's concerns were addressed via the appropriate means, which included further data submissions/analyses and oral explanations by the company at the meetings of the Committee for Medicinal Products for Human Use (CHMP, previously CPMP).

2.2. Current situation

The use of rt-PA for the treatment of acute ischaemic stroke continues to generate strong, polarised viewpoints, despite the considerable length of time that has elapsed since the indication was first approved. The reasons for this are understandable, when the consequences both of treating and of not treating any individual patient are considered – the risk of leaving a patient with a potentially devastating ischaemic stroke untreated must be weighed against the risk of causing a potentially devastating intracranial haemorrhage in a patient who might otherwise have had a reasonable outcome if left untreated. Furthermore, the lengthy European licensing procedures that have preceded both initial approval of the indication and the extension to the time-window reflect the complexities of the discussions leading up to the final decision on the balance of benefits and risks, and are demonstrative of the fact that randomised clinical trial data have not shown a very substantial beneficial effect.

On this background, it is particularly important that any new data or new major concerns regarding data that were critical to the current licence approval are thoroughly assessed.

The May CHM review therefore carefully considered the concerns raised by Dr [redacted] at that time, together with additional data that had become available since the approval of the extension to the time-window for treatment in 2012, or that had not previously been reviewed. These data were:

- IST-3 trial
- Published re-analysis of the NINDS trial data
- Observational cohort data from the Oxfordshire community stroke project, the Lothian stroke register and the first international stroke trial (in the UK)
- Unpublished data from a meta-analysis presented recently at the American Stroke Association meeting

Since then we have received further submissions from the following stakeholders and these will be considered in this set of papers:

1. the marketing authorisation holder (Boehringer Ingleheim)
2. Dr [redacted] UK
3. Dr Mandava, US
4. Professors Fatovitch and Brown, Australia

3. Explanation of papers provided to the group

It is intended that the expert working group will meet twice, in November 2014 and January 2015 to consider the balance of benefits and risks of rt-PA in the treatment of acute ischaemic stroke. In order to facilitate the discussions and in accordance with the proposed Terms of Reference of the group (annex 1), the following papers will be provided to the group:

Paper 2: Stroke care in the UK and a wider perspective since 2000

This paper is intended to provide a description of the changes in stroke care in the UK that have taken place during the current and last decade, and the impacts that these changes have had on morbidity and mortality of stroke patients. The paper then considers whether there is evidence for a learning-curve within stroke centres with respect to the use of rt-PA and outcomes achieved, which could potentially have implications for appropriate risk minimisation measures. Finally, paper 2 considers the imaging techniques used in the diagnosis of acute stroke patients and whether there is evidence to support any change to the current product information or to clinical guidelines.

Paper 3: Usage of rt-PA

This paper provides information relating to the level of use of rt-PA in the UK and more widely, including level of off-label use.

Paper 4: Benefits and risks: new study data

This paper provides a summary of the main clinical trial data that supported the initial approval of the indication in acute ischaemic stroke and the extension of the time-window to 0-4.5 hours post-symptom onset. These trials include NINDS parts 1 and 2, ECASS I, II, and III, and ATLANTIS A and B. In addition, a summary of the published re-analysis of the NINDS trials, the IST-3 study, and the meta-analysis by Emberson *et al* are provided. These data were initially discussed by CHM in May and Dr Jonathan Emberson will be presenting further details on the meta-analysis at the November meeting. Finally the paper will discuss relevant data that have not previously been considered within regulatory procedures, including the latest data from SITS-ISTR, the SITS-UTMOST cohort, the Get With The Guidelines-Stroke registry, the Bade-Wuerttemberg Stroke registry, and the Canadian Alteplase for Stroke Effectiveness Study.

In November Professor Gary Ford will discuss his experience with rt-PA and in particular with respect to the SITS Registry.

Paper 5: Discussion of individuals' concerns on specific aspects of the supporting clinical evidence

This paper addresses specific concerns that have been raised with MHRA in three separate submissions, from Dr [redacted] Dr Mandava and Professors Fatovich and Brown. The submissions have already been provided to the group. Dr [redacted] and Professors Fatovich and Brown have raised a wide variety of concerns relating to the key clinical trials, and Dr Mandava has provided data regarding the analysis methods used in clinical trials of acute stroke. In addition this paper discusses the definitions of symptomatic intracerebral haemorrhage used in clinical trials and the choice of primary endpoint and analysis method.

January 2015 meeting

Additional papers will be provided for the group's consideration in advance of the January meeting. These papers will focus on the balance of benefits and risks of rt-PA used in normal clinical practice, including in off-label use. This will include further consideration of the IST-3 trial, which was conducted nearly exclusively in patients

treated off-label, including a presentation by Professor Peter Sandercock. Following discussion of the balance of benefits and risks of treatment in off-label populations, the feasibility of using rt-PA within the current UK marketing authorisation will be considered, together with the adequacy of current risk minimisation measures and the need for/practicality of further measures to improve the balance of benefits and risks.

Annex 1: Proposed Terms of Reference

The Expert Working Group on rt-PA will:

- review all sources of evidence on safety of alteplase in clinical use in ischaemic stroke
- advise whether these data have implications for the benefit:risk of alteplase in clinical use for the treatment of ischaemic stroke
- consider whether further measures are necessary to minimise harm in stroke patients
- advise on a communication strategy

EWG 2015

EXPERT WORKING GROUP

ACTILYSE (ALTEPLASE) BA LANCE O F BENEFITS A ND RISKS WH EN USED IN THE TREATMENT OF ACUTE ISCHAEMIC STROKE

Title of p aper: Paper 1A : For In formation: Regulatory h istory of al teplase us e i n acute ischaemic stroke.

Product: Actilyse 10, 20, 50mg	**Assessors:** Dr [redacted]
MAHs: Boehringer Ingelheim Limited	**Previous Assessments:** CHM May 2014, EWG Nov 2014
Active constituents: Alteplase (rt-PA)	**Legal status:** **POM**
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Contents

1. Issue

This paper has been provided following feedback from the first meeting of the EWG on 20 November 2014. It is intended to provide further context to the current regulatory position for rt-PA in acute ischaemic stroke in the UK in light of the emerging data, and is therefore not a full discussion of benefits and risks.

2. Initial approval of the indication in acute ischaemic stroke

rt-PA was first approved for fibrinolysis in coronary artery occlusion and massive pulmonary embolism, with the initial UK licence granted in 1988.

The US FDA approved rt-PA for the treatment of acute ischaemic stroke within 3 hours of the onset of symptoms in 1996. An application for this indication was submitted to the German regulatory authorities in 1997, and approval of the indication was granted in Germany in 2000. As a result a mutual recognition procedure (where other EU member states are asked to recognise a national marketing authorisation) was initiated in 2000. This procedure was led by Germany, as Reference Member State (RMS). The assessments of the data submitted and the responses from the company were extensively discussed on several occasions both nationally in the UK (at the Committee on Safety of Medicines (CSM) - now CHM) and within Europe at the Committee for Proprietary Medicinal Products (CPMP, predecessor of the Committee for Medicinal Products for Human Use CHMP).

The clinical trials that were identified as relevant at this time were NINDS part 1 and 2 (NINDS, 1995), ECASS I (Hacke *et al*, 1995) and II (Hacke *et al*, 1998) and ATLANTIS A (Clark *et al*, 2000) and B (Clark *et al*, 1999). The NINDS part 2 study was the pivotal trial in the application. A summary of the results of these studies was provided in paper 4: Benefits and risks: new study data. For convenience, this has also been included as annex 1 to this paper.

The headline results from these initial trials were that the pivotal NINDS part 2 trial was positive in its primary endpoint of favourable clinical outcome at 3 months, a global measure encompassing scores on the mRS (0-1), BI (95-100), NIHSS (0-1), and GOS (1); OR: 1.7, 95% CI [1.2-2.6].

NINDS part 1 was similarly favourable for this global outcome at 3 months (OR 2.1, 95% CI [1.3-3.2]). However, part 1failed in its primary outcome measure which was improvement in NIHSS score at 24 hours following stroke (by 4 or more points, or complete resolution of symptoms), RR 1.2, 95% CI [0.9-1.6].

The ECASS I and II and ATLANTIS A and B studies also all failed in their primary endpoints.

During the authorisation procedure a number of possible reasons for the differences between the results of the NINDS part 2 trial and the other clinical trials were identified, summarised as follows:

NINDS part 1: the primary outcome chosen for part 1 (NIHSS at 24 hours) was concluded to be less clinically relevant than the day 90 outcomes on functional measures. The outcomes at day 90 were measured as secondary endpoints and were consistent with the part 2 results.

ECASS I: the dose studied in ECASS I was 1.1mg/kg body weight, higher than that used in NINDS and the now licensed dose (0.9mg/kg body weight). Time from onset to treatment in ECASS I was 0-6 hours, compared with 0-3 hours in NINDS. The primary endpoints differed from NINDS: a difference of 15 points on the BI scale, and a difference of 1 grade in the mRS at 90 days [see paper 5 for a discussion on choice of endpoints].

ECASS II: the time window for enrolment was also 0-6 hours post symptom onset, whilst the dose was 0.9mg/kg body weight and the same as that used in NINDS. The primary endpoint was mRS at day 90, with a favourable outcome defined as 0-1. Of the 800 patients randomised, only 158 were treated between 0-3 hours (n=81 for rt-PA, n=77 for placebo).

ATLANTIS A and B: the time window for enrolment was initially 0-6 hours, which was then amended to 0-5 hours due to safety concerns, and the trial restarted as part B (part A included 142 patients). The time-window for treatment in part B was later modified to 3-5 hours, in light of the NINDS trial results for the 0-3 hour window. Only 31 patients in part B had been enrolled from 0-3 hours at the time of this change.

During the initial authorisation procedure the UK's main concerns were the heterogeneity of the data: that although NINDS part 2 showed benefit, the other trials did not – whilst acknowledging the differences between the studies and their potential impact on the results. In addition, the differences between the trials meant that of the 2647 patients randomised into all 6 trials, only 1341 received rt-PA, and of these only 405 patients had received the proposed marketed dose (0.9mg/kg) within 3 hours of stroke onset (the time-window initially approved). For a common condition, this was considered to be too few patients.

A potential serious risk to public health[1] was therefore raised by the UK during the procedure, as follows: *"There are insufficient data at the dose and time-window proposed for reassurance that the risk-benefit assessment is positive. The benefits appear modest and there is concern regarding the frequency of ICH. Further adequately powered randomised clinical trials are required."* Other potential serious risks to public health that were raised by the UK at the same time included:

- the optimum dose should be better defined
- data were missing from the original dossier (including the ATLANTIS study)
- the practicalities of treating patients within 3 hours.

The UK's assessment of the available data at this time was in fact similar to the RMS (Germany), as Germany had granted the indication in stroke nationally under "exceptional circumstances", with the condition that the company would conduct a further placebo-controlled trial in the EU which replicated the NINDS study. If the outcome of that study were negative, the licence for treatment of acute ischaemic stroke would be revoked. The main difference between the UK and the German assessment therefore lay in the country's final position – with Germany proposing that the study should be conducted post-licensing, and the UK concluding that the study should be conducted before the indication was approved. Other Concerned Member States were also not willing to grant a marketing authorisation on the basis of this benefit-risk evaluation.

The disagreement between member states led to an arbitration procedure, prompted by Netherlands, Spain, Greece and the UK. The main basis for the procedure was:

"the need to establish whether there are sufficient clinical data with reference to efficacy as well as safety to grant a Marketing Authorisation for the new indication 'for fibrinolytic treatment of acute ischaemic stroke' without putting public health at risk. In particular, the major concern for most of the Concerned Member States was the lack of replication of the favourable results of the pivotal US trial (NINDS part 2) in

[1] This regulatory category is defined in 'Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC – March 2006' [http://ec.europa.eu/health/files/eudralex/vol-1/com_2006_133/com_2006_133_en.pdf] as "a situation where there is a significant probability that a serious hazard resulting from a human medicinal product in the context of its proposed use will affect public health" that is, they are issues raised considered to be serious enough to prevent approval if unresolved, i.e. risk:benefit is negative (lesser concerns are referred to as 'points for clarification').

the European studies (ECASS I and II) as well as another US trial (ATLANTIS). Concerns were raised that the data in support of the dose and time window proposed are insufficient for reassurance that the risk-benefit assessment is positive. The benefit appears modest and there was concern regarding the frequency of intracranial haemorrhage. Moreover the modest observed benefits are only apparent if the product is used less than 3 hours after the onset of symptoms. There is concern about the risk-benefit, which is markedly reduced outside this time frame. The basis for selecting the optimal dose should be better defined and the rational for the selected dose further justified."

Netherlands and France were appointed to take the lead in the assessment of the arbitration referral procedure.

The arbitration referral procedure was initiated in January 2001, and resulted in several rounds of assessment, an oral explanation by the applicant and an Ad Hoc expert meeting. At the end of this process the UK remained negative; however, the Committee for Proprietary Medicinal Products (CPMP, now CHMP) concluded that:

- The results from NINDS may be extrapolated to some extent to the EU setting, and the results from the EU trials (ECASS I and II) are explained by differences in trial designs and inclusion criteria. The published meta-analysis also tended towards a positive result (numbers too small to be significant)
- It is possible to use rt-PA in accordance with the SmPC restrictions, to maximise benefit.
- A placebo-controlled trial in an EU setting with a population defined by the SmPC and enrolment up to 3 hours would likely face difficulties with recruitment and may not be feasible. However a study in this population between 3-4 hours may be acceptable to HCPs.
- Placebo-controlled randomised trials in high-risk groups of patients would be of interest and be considered both ethical and feasible. However, it would be difficult to extrapolate the results from these trials to the overall stroke population – a population similar to NINDS would be required for this.

A conditional licence was granted for the indication of acute ischaemic stroke in September 2002, with commitments to conduct a confirmatory randomised placebo controlled trial in the time-window 3-4 hours (later revised to 3-4.5 hours), with a patient population as defined by the SmPC (ECASS III; Hacke *et al*, 2008); and to conduct a post-marketing surveillance study (SITS-MOST; Wahlgren *et al*, 2007). In addition, Periodic Safety Update Reports (PSURs) were to be submitted every 6 months for two years, and then annually for three years.

3. Information from Periodic Safety Update Reports (PSURs)

[from the period prior to initial licensing of the indication to fulfilment of licensing conditions]

PSURs are used to routinely monitor medicines at regular intervals in the post-marketing period. Between November 1998 and May 2009 the subject of haemorrhage and specifically ICH was discussed within the PSURs. Headline results, where available, from these PSURs are provided in this section.

Usage

Worldwide usage reported for clinical trial and for marketed use is provided in the following tables. These data are based on sales data for all indications for rt-PA, including myocardial infarction and pulmonary embolism as well as acute ischaemic stroke.

Nov '98 – Jan '02		**Jan '02 – Mar '03**		**Mar '03 – Sept '03**		**Sept '03 – Nov '03**	
Clinical trial	Marketed use	Clinical trial	Marketed use	Clinical trial	Marketed use	Clinical trial	Marketed use
9,020	817,233	280	209,143	310	130,438	0	32,896
	*256,387**		*176,120**		*260,876**		*263,168**

May '04 – May '05		**May '06 – May '07**		**May '07 – May '08**		**May '08 – May '09**	
Clinical trial	Marketed use	Clinical trial	Marketed use	Clinical trial	Marketed use	Clinical trial	Marketed use
1918	263,987	555	367,420	530	382,182	510	477,631
	*263,987**		*367,420**		*398,798**		*440,890**

*Table: No. of patients treated in clinical trials and for marketed use (estimated based on sales data, assuming a dose of 90 mg, i.e. 1 vial = 1 patient). Note that some data are missing. *equivalent usage (no. of patients) in one year, as not all data intervals are equal.*

Total use of rt-PA appeared to remain fairly static between November 1998 and May 2004, and then increased between about May 2004 and May 2009.

Adverse reactions

The MAH states that: "patient safety is a paramount concern for Boehringer Ingelheim. Collecting pharmacovigilance data is therefore an important means of gathering ongoing insights in to our medicines. However, there are well recognised limitations in the data contained in the global drug safety database (GDSD), which is where this information is collected.

For example, insights on a medicine's safety profile gained from this database can be limited because by definition it looks at those patients who have experienced an adverse event (in other words it does not record all the patients who have not had an adverse event).

Also the database is subject to variability in the quality of information reported, particularly from spontaneous reporting. This is because it relies heavily on the accuracy and completeness of the data supplied.

Consequently, a degree of caution should be applied when drawing conclusions from this data, and it should always be evaluated in conjunction with the results of controlled clinical trial data sets."

The number of case reports of adverse reactions, including cases with a fatal outcome, from worldwide sources received by the marketing authorisation holder (MAH) overall for each of these time periods is provided in the following tables. These numbers represent cases received for all indications, including myocardial infarction and pulmonary embolism as well as acute ischaemic stroke.

Nov '98 – Jan '02		**Jan '02 – Mar '03**		**Mar '03 – Sept '03**		**Sept '03 – Nov '03**	
Cases (total)	Fatal cases	Cases (total)	Fatal cases	Cases (total)	Fatal cases	Cases (total)	Fatal cases
1,141	349 (31%)	442	139 (31%)	349	108 (31%)	159	14 (9%)
*358**		*372**		*698**		*1272**	
*14***		*21***		*27***		*48***	

May '04 – May '05		**May '06 – May '07**		**May '07 – May '08**		**May '08 – May '09**	
Cases (total)	Fatal cases	Cases (total)	Fatal cases	Cases (total)	Fatal cases	Cases (total)	Fatal cases
424	115 (27%)	877	275 (31%)	840	268 (32%)	830	282 (34%)
*424**		*877**		*877**		*766**	
*16***		*24***		*22***		*17***	

*Table: Total no. of case reports received and no. of fatal cases (% of total). Note that some data are missing. *equivalent no. of cases in one year as not all data intervals are equal in duration. **no. of cases per 10,000 patients treated (sales data from above).*

Reporting rates overall per 10,000 patients treated can be seen to have fluctuated, ranging from ~14 to ~27 (the figure of 48/10,000 patients relates to a very short time interval and is therefore unlikely to be accurate), with no clear trend for an increase or decrease over time. The proportion of reported cases that were fatal has remained relatively consistent at around 30%.

Number of cases of ICH

The numbers of cases of ICH have been provided according to indication for treatment, and are given in the following tables. These data are from worldwide sources.

15 Nov 1998 – 21 Jan 2002 (prior to approval of the indication in acute ischaemic stroke in the EU):

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***
Ischaemic stroke	274	24.0	180	65.7
Myocardial infarction	514	45.0	167	32.5
Pulmonary embolism	48	4.2	18	37.5
Off-label use	271	23.8	58	21.4
Not reported	32	3.0	9	29.5
Total	1141	100	452	39.6

*% of cases received in specific indication that describe ICH

The reporting rate for all cases of ICH, in any indication, is 5.5/10,000 patients. The proportion of cases of ICH that were fatal was not provided per indication, however overall a fatal outcome was recorded in ~55% of ICH cases (~3/10,000 patients).

22 Jan 2002 – 29 Mar 2003 (covering the period prior to and post approval of the indication in acute ischaemic stroke in the EU):

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***	**No. of cases of fatal ICH**	**%****
Ischaemic stroke	171	38.7	132	77.2	36	27.3
Myocardial infarction	87	19.7	16	18.4	8	50.0
Pulmonary embolism	27	6.11	4	14.8	3	75.0
Off-label use	151	34.2	20	13.2	10	50.0
Not reported	6	1.36	3	50.0	3	100
Total	442	100	175	39.6	60	34.3

*% of cases received in specific indication that describe ICH; **% of ICH cases received in specific indication that describe fatal ICH.

The reporting rate for all cases of ICH, in any indication, is 8.4/10,000 patients; the reporting rate for fatal ICH is 2.9/10,000 patients.

30 Mar 2003 – 29 Sept 2003:

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***	**No. of cases of fatal ICH**	**%****
Ischaemic stroke	280	80.2	145	51.8	27	18.6
Myocardial infarction	18	5.16	8	44.4	3	37.5
Pulmonary embolism	6	1.72	2	33.3	2	100
Off-label use	43	12.3	5	11.6	0	0
Not reported	2	0.57	1	50.0	0	0
Total	349	100	161	46.1	32	19.9

*% of cases received in specific indication that describe ICH; **% of ICH cases received in specific indication that describe fatal ICH.

The reporting rate for all cases of ICH, in any indication, is 12.3/10,000 patients; the reporting rate for fatal ICH is 2.5/10,000 patients.

30 Sept 2003 – 15 Nov 2003:

In this short reporting period, a total of 6 cases of ICH were reported (3.8% of the total number of reports received). 3 of the cases occurred in the indication of MI, and 1 in lower extremity arterial occlusion. In the other 2 cases, the indication was not reported.

16 May 2004 – 15 May 2005:

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***	**No. of cases of fatal ICH**	**%****
Ischaemic stroke	227	53.5	174	76.7	63	36.2
Myocardial infarction	33	7.8	9	27.3	2	22.2
Pulmonary embolism	18	4.2	7	38.9	2	28.6
Off-label use	126	29.7	22	17.5	8	36.4
Not reported	20	4.7	6	30.0	4	66.6
Total	424	100	218	51.2	79	36.4

*% of cases received in specific indication that describe ICH; **% of ICH cases received in specific indication that describe fatal ICH.

The reporting rate for all cases of ICH, in any indication, is 8.3/10,000 patients; the reporting rate for fatal ICH is 3.0/10,000 patients.

16 May 2006 – 15 May 2007:

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***	**No. of cases of fatal ICH**	**%****

Ischaemic stroke	673	78.9	419	62.3	141	33.7
Myocardial infarction	43	5.1	5	11.6	1	20.0
Pulmonary embolism	19	2.2	4	21.1	2	50.0
Off-label use	99♠	11.6	1	1.0	0	0
Not reported	19	2.2	4	21.1	2	50.0
Total	853	100	433	50.8	146	33.7

*% of cases received in specific indication that describe ICH; **% of ICH cases received in specific indication that describe fatal ICH. ♠ includes 21 cases treated for a local application in a catheter.

The reporting rate for all cases of ICH, in any indication, is 11.8/10,000 patients; the reporting rate for fatal ICH is 4.0/10,000 patients.

16 May 2007 – 1 May 2008:

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***	**No. of cases of fatal ICH**	**%****
Ischaemic stroke	587	70.3	343	58.4	121	35.3
Myocardial infarction	35	4.2	4	11.4	1	25
Pulmonary embolism	35	4.2	2	5.6	1	50
Off-label use	146♠	17.5	12	8.3	6	50
Not reported	32	3.8	12	37.5	7	58.3
Total	835	100	373	44.6	136	36.5

*% of cases received in specific indication that describe ICH; **% of ICH cases received in specific indication that describe fatal ICH. ♠ includes 21 cases treated for a local application in a catheter.

The reporting rate for all cases of ICH, in any indication, is 9.8/10,000 patients; the reporting rate for fatal ICH is 3.6/10,000 patients.

2 May 2008 – 31 May 2009:

Indication for use	**Total no. of cases received**	**%**	**No. of cases of ICH**	**%***	**No. of cases of fatal ICH**	**%****
Ischaemic stroke	501	61.2	237	47.3	81	34.2
Myocardial infarction	28	3.4	2	7.1	2	100
Pulmonary embolism	74	9.0	8	10.8	5	62.5
OCVAD	26	3.2	1	3.8	0	0
Off-label use	158	19.3	19	12.0	11	57.9
Not reported	31	3.8	13	41.9	2	15.4
Total	818	100	280	34.2	101	36.1

OCVAD Occluded central venous access device. *% of cases received in specific indication that describe ICH; **% of ICH cases received in specific indication that describe fatal ICH.

The reporting rate for all cases of ICH, in any indication, is 5.9/10,000 patients; the reporting rate for fatal ICH is 2.1/10,000 patients.

Summary comments

PSURs were used to monitor the safety of rt-PA in normal clinical use following the approval of the indication in acute ischaemic stroke.

For the time periods covered by these PSURs, overall reporting rates for ICH cases occurring in any indication varied between ~5.5 to ~12.3 per 10,000 patients and reporting rate of fatal ICH varied between ~2.1 to ~4.0 per 10,000 patients. No trend in these rates with time was noted.

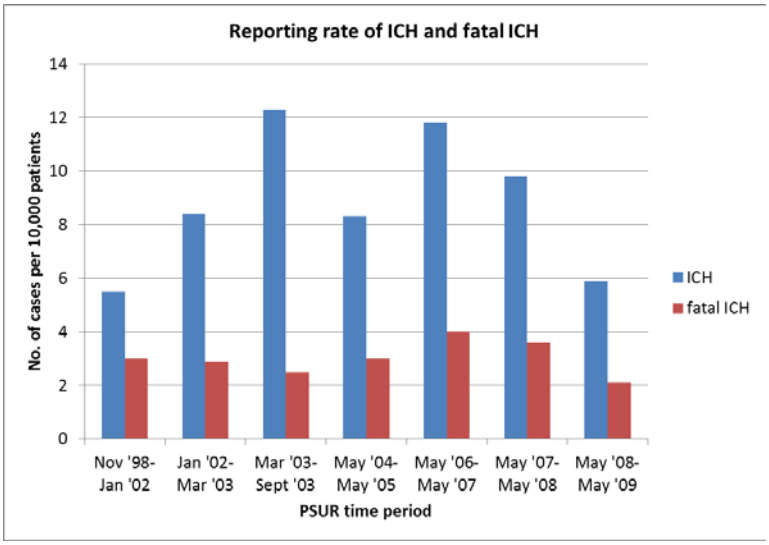

Figure: estimated worldwide reporting rates per 10,000 patients, of cases of ICH and fatal ICH reported in all indications for rt-PA in PSURs (note differing reporting intervals and non-sequential information)

The proportion of cases received for the stroke indication that reported ICH varied between 47.3% and 77.2%, with no clear trend. The proportion of the ICH cases received for the stroke indication that had a fatal outcome seemed to stabilise around ~34% by 2009.

It should be noted that these data are based on spontaneous reporting/literature cases and are subject to well-known limitations, in particular including under-reporting of cases, inadequate information provided in some cases and that cases are of suspected adverse drug reactions and therefore causality in any individual case is not definitive.

Despite the obvious limitations, the PSUR data submitted did not raise signals of concern regarding the rate of ICH or fatal ICH with the use of rt-PA in the treatment of stroke outside of clinical trials conditions.

4. Progress reports on SITS-MOST and ECASS III

The MAH provided updates on the progress of the SITS-MOST registry and ECASS III as summaries in PSURs and in dedicated progress reports following the approval of the indication in acute ischaemic stroke. The following information has been summarised from these two sources:

22 Jan 2002 – 29 Mar 2003: SITS-MOST (patients treated within the licence i.e. 0.9mg/kg body weight and 0-3 hours) had enrolled 14 patients at this point, none of whom had reached the D90 endpoint. Data were available at D7 for ten patients, with 8 having improved by 4 points or more on the NIHSS scale. There were no reports of sICH at this stage.

ECASS III was yet to begin randomisation.

30 Mar 2003 – 29 Sept 2003: SITS-MOST had enrolled 300 patients in total. Day 7 outcome data were available for 225 patients, with beneficial outcomes reported in 55% of patients. Nine patients had died, two had evidence of ICH.

ECASS III had recruited 9 patients by the cut-off date of this PSUR.

16 May 2004 – 15 May 2005: SITS-MOST had exceeded the initial recruitment target of 1000 patients, with 2885 patients entered by 31 May 2005.

ECASS III had recruited 202 patients at this point.

September 2005 (5th trial progress report on ECASS III and SITS-MOST): Following a signal of increased mortality in the relatively inexperienced centres that was identified in the 4th progress report, enrolment into SITS-MOST was continuing, and the licence conditions were revised to state that SITS-MOST would continue as a formal study until this signal had been resolved, to confirm whether the mortality rate would decrease as experience increased.

A total of 3180 patients had been registered at the time of the 5th report. The report concluded that the death rates and sICH (as defined in the RCTs) were comparable with the results from RCTs. The proportion of patients with a favourable outcome was slightly less than that observed in RCTs (38% vs. 42%), though it is stressed by the Rapporteur that as SITS-MOST is a non-comparative, open study the data cannot be considered to provide confirmatory efficacy data. The finding of increased mortality in the inexperienced centres compared with the experienced centres remained. The difference at day 7 (6.5% in previous ECASS sites[2] vs. 5.9% in non-ECASS sites with ≥5 patients vs. 9.3% in non-ECASS sites with <5 patients) was less than the difference at day 90 (11.8% vs. 13.9% vs. 20.7% respectively). As a result it was suggested that the centres likely differed in more ways than simply the logistic experience with rt-PA.

This 5th report also explains that in the 4th progress report, concerns were raised by CHMP regarding the recruitment rate of ECASS III and an action plan was put in place to improve enrolment, including increasing the percentage of active sites, initiating new sites and targeting new countries, as well as expanding the time window for recruitment to 3-4.5 hours (expected to increase recruitment rate 2 fold).

February 2006 (6th trial progress report on ECASS III and SITS-MOST): SITS-MOST had enrolled 4543 patients at the cut-off for this report. The finding of an increased rate of death in the 'inexperienced centres' remained, with mortality rates at day 90 of 11.0%, 12.9% and 17.4% for previous ECASS sites, non-ECASS sites with ≥5 patients and non-ECASS sites with <5 patients respectively. Evidence for a learning curve was not convincing. Overall mortality rate was found to be stabilising for the day 90 results (12.9% at the cut-off date of 15 Nov 2005):

[2] 'ECASS sites' are sites that have previously participated in either ECASS I or ECASS II (but not ECASS III, as this trial enrolled patients treated outside of the then licensed time-window of 0-3 hours following symptom onset).

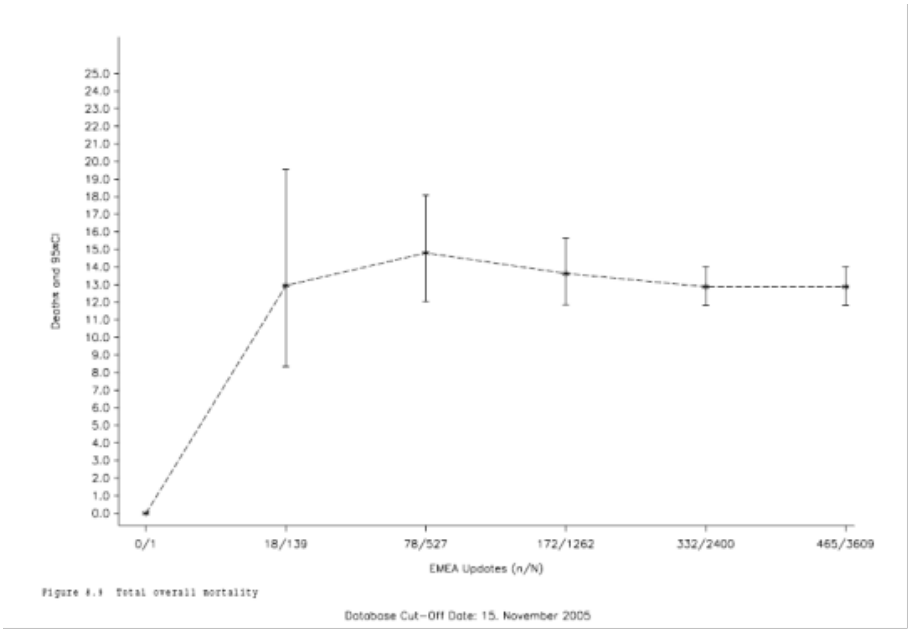

Figure: Total overall mortality at 3 months, % and 95% CI (data-points are results at successive progress reports)

It was agreed to close the SITS-MOST registry, as it was concluded that further data would not impact on the results.

ECASS III recruitment rate had increased, with 287 patients enrolled in the 6 months to November 2005, compared with 207 patients enrolled during the first 22 months of the study. The DSMB met in October 2005 and considered safety data for 253 patients, concluding there was no reason to stop enrolment.

16 May 2006 – 15 May 2007: SITS-MOST enrolment ended on 30 April 2006, with a total of 6483 patients, and the results were published in the Lancet.

At this point ECASS III was recruiting patients between 3-4.5 hours following symptom onset (previously specified as 3-4 hours), and had recruited a total of 672 patients.

August 2007 (9th trial progress report on ECASS III and SITS-MOST): The final study report for SITS-MOST was presented in this update. Differences in mortality rates at 3 months in previous ECASS sites, non-ECASS sites ≥5 patients treated, and non-ECASS sites <5 patients treated were no longer considered an issue, as the data from these categories were found to be converging in the 8th progress report (10.6%, 11.1% and 13.4% respectively). Data were therefore expressed as overall findings, and not expressed separately according to centre experience.

Overall mortality was 11.3%, reported to be lower than that observed in RCTs. ICH incidence varied depending on the definition used, between 1.7% and 7.3%. Independence defined as mRS 0-1 was found in 39% and defined as mRS 0-2 in 55%, which compared with functional independence rate of 50% in RCTs. However the Rapporteur emphasised that SITS-MOST was primarily a safety study and that the lack of a control arm limits any conclusion on efficacy. It is not possible to determine the relative contributions of thrombolytic therapy vs. the development of stroke units/improvements in care to apparent improvements in outcomes.

ECASS III recruitment was progressing satisfactorily, with 685 patients enrolled at this time-point.

16 May 2007 – 1 May 2008: ECASS III stopped recruiting in November 2007, after 821 patients had been enrolled.

February 2009 (12th trial progress report on ECASS III): The final study report for ECASS III was presented in this update. The headline results from this study are provided in section 6 below and annex 2.

2 May 2008 – 31 May 2009: ECASS III was submitted in June 2009 as part of an MR variation to extend the time window for treatment to 4.5 hours post-symptom onset.

5. Impact of ECASS III and SITS-MOST on Marketing Authorisation for rt-PA

As previously mentioned, the rt-PA licence was originally granted as a conditional licence with the MAH obliged to conduct a confirmatory, placebo controlled trial (ECASS III) and an observational safety study (SITS-MOST), in order to allow the balance of benefits and risks to be re-assessed in the EU setting.

The rationale for the commitment to conduct the ECASS III study was to remove uncertainty regarding the efficacy of rt-PA in the EU indication. Whilst a placebo controlled trial in the approved indication was considered to be unethical, a trial in the licensed population in the later time-window of 3-4 hours (initially, later revised to 3-4.5 hours) was considered to be acceptable because initial analyses had suggested there may be a benefit in this time window as well.

It was considered by CHMP that success of the ECASS III trial, with demonstration of efficacy for this later time window (3-4.5 hours) would by definition provide confirmatory evidence that the balance of benefits and risks in the licensed indication (0-3 hours) was positive, because of the understanding that efficacy diminishes with increasing time to onset of treatment.

Meanwhile, the SITS-MOST registry was set up to provide re-assurance that the safety profile of rt-PA when used within the licenced population in normal clinical practice was consistent with that observed during the RCTs.

Biannual assessments of the progress of these two studies were conducted (see above) until these two commitments were completed. The final results from SITS-MOST were presented in progress report 9, and outstanding questions resulting from these data were discussed and concluded in the later reports, with the final conclusion that rt-PA can be used safely in an experienced clinical setting, reached in September 2008. Final results from ECASS III were presented in progress report 12.

The twelfth and final progress report was discussed by CHMP in February 2009 and **CHMP concluded that the positive balance of benefits and risks of rt-PA in the treatment of acute ischaemic stroke between 0-3 hours of symptom onset had been indirectly confirmed**, fulfilment of the conditions meant that the referral procedure should be closed – and the was licence no longer subject to any conditions.

The UK was in agreement with this conclusion, and sent comments agreeing that the commitment could be finalised, and that the ECASS III results gave indirect confirmation of the efficacy for rt-PA in the licensed posology – that is, the balance of benefits and risks of rt-PA in the treatment of acute ischaemic stroke from 0-3 hours post-symptom onset was positive.

The UK additionally commented that it could not be concluded from these results that the balance of benefits and risks in the 3-4.5 hour timeframe was positive, because this would require a fuller consideration of the data, including comparison with the 0-3

hour time-window and an integrated analysis of all data available in the 3-4.5 hour time-window.

6. Extension of time window to 4.5 hours (approved 2012)

The MAH applied in 2009 to extend the time window for treatment to 4.5 hours following symptom onset. The application was based mainly on the ECASS III data (Hacke *et al*, 2008), with some supporting data from SITS-ISTR (Wahlgren *et al*, 2008) and a pooled analysis carried out by the MAH. The review was led by Germany as RMS.

A summary of the data supporting the application was provided in the May CHM paper and in paper 4 (for ECASS III). For convenience, this summary has also been included as annex 2 to this paper.

As the ECASS III trial was conducted as a condition of the original approval of the indication in acute ischaemic stroke, to provide confirmatory data of a positive balance of benefits and risks in this indication, aside from the time-window for treatment (3-4.5 hours), the exclusion/inclusion criteria reflected the EU SmPC.

The primary endpoint in ECASS III was mRS 0-1 at day 90, and the resulting odds ratio for a favourable outcome in the intention to treat population was 1.34 95% CI [1.02-1.76].

A total of 113 patients (27%) in the rt-PA group had intracranial haemorrhages of which 3 were fatal. This compares with 71 patients (17.6%) with ICH in the placebo group of which 0 were fatal. The OR for any ICH was 1.73 95% CI [1.24-2.42].

The SITS-ISTR (Safe Implementation of Thrombolysis in Stroke –International Stroke Thrombolysis Register) is an inclusive international registry of stroke patients treated with thrombolysis, whilst the SITS-MOST registry was embedded within SITS-ISTR and included patients treated in the EU (and Norway/Iceland), within the conditions of the licence at that time (i.e. up to 3 hours post-symptom onset and complying with the contraindications to treatment). The SITS-ISTR data available at that time found that patients treated in the later time window (3-4.5 hours) had a median age that was 3 years younger and a stroke severity that was 1 point lower on the NIHSS compared with those treated from 0-3 hours. No significant differences were found in the rates of sICH, mortality or independence (mRS ≤2 at day 90) between the two treatment groups (0-3 hours vs. 3-4.5 hours).

The pooled analysis (ECASS III, ECASS II, ATLANTIS A and B and NINDS part 1 and 2) had a primary outcome of mRS 0-1 at day 90 and found a benefit in favour of rt-PA for the 3-4.5 hour time window, OR 1.31; 95% CI [1.06-1.63] p=0.014.

Whilst other Member States agreed with the RMS's conclusion that the time-window for treatment should be increased to 0-4.5 hours, subject to the MAH addressing some questions on the data submitted, the UK initially considered that the balance of benefits and risks between 3-4 hours was weak, and between 4-4.5 hours was negative and therefore raised a potential serious risk to public health.

In particular the UK had concerns about a number of issues regarding the ECASS III trial, including

- Baseline imbalances in NIHSS favouring rt-PA for the whole 3-4.5 hour period
- More marked baseline imbalance at the 4-4.5 hour time-point
- More deaths in the rt-PA group at the 4-4.5 hour time-point, increasing mortality with increasing onset to treatment time
- More ICH and cerebral oedema in the rt-PA group
- Inconsistent benefit, with more subjects with mRS = 5 in the rt-PA group. Benefit was evident across the whole mRS in the NINDS trial.

- Larger increase in mRS 5 and 6 in patients >65 years in ECASS III
- Deaths from haemorrhage 0.8% for rt-PA vs. 0 for placebo
- For the 4-4.5 time-point the mRS of 0-1 for 56.3% in the rt-PA vs. 43.2% in the placebo group is not considered to demonstrate sufficient benefit, when for the same group there is an increase of 3.3% for mRS 5 and higher death rates were seen in the rt-PA group at 4-4.5 hrs (12/174 [6.9%] rt-PA vs. 8/148 [5.4%] placebo)

In response to the UK's concerns the MAH presented a series of further data and analyses. In particular the company provided further information on the mortality data from ECASS III. A particular concern had been the apparent increase in mortality with rt-PA between 4-4.5 hours compared with placebo (rt-PA: 12/174 (6.9%) vs. placebo 8/148 (5.4%)). It was established that the mortality data that had originally been presented by the company included additional deaths reported after day 90, and that deaths were not collected over an equal duration of follow-up in the two arms of the trial. When these additional deaths were excluded, rt-PA was not found to have an unfavourable effect on mortality, as shown in the table below (NB the data presented on mortality at different time points in the ECASS III trial in annex 2 are the original, uncorrected data).

Treatment	**Time window (min)**	**n/N**	**Point estimate (%)**	**95% CI (%)**
Placebo	Overall	33/403	8.2	5.9 - 11.3
	181-210	4/42	9.5	3.8 - 22.1
	211-240	18/193	9.3	6.0 - 14.3
	241-270	8/148	5.4	2.8 - 10.3
rt-PT	Overall	28/418	6.7	4.7 - 9.5
	181-210	1/40	2.5	0.4 - 12.9
	211-240	17/191	8.9	5.6 - 13.8
	241-270	10/174	5.7	3.2 - 10.3

Table: Day 90 mortality in ECASS III (ITT), in 30 minute intervals

An additional argument made at this time by the MAH was that although there is no difference in the worst outcomes (severe disability and death), the patient will be willing to accept the risk if they have even a small chance of recovering completely.

The additional information and analyses provided were discussed by the CHM, who agreed that the concerns raised had been satisfactorily addressed and the variation to extend the time-window for treatment to 4.5 hour could be approved. The variation was granted in March 2012.

7. Conclusion

Though the UK was initially negative about the balance of benefits and risks for rt-PA when used up to 3 hours post symptom onset of acute ischaemic stroke, the data that became available following the initial approval of the indication in the treatment of acute ischaemic stroke provided reassurance with regards to the safety of rt-PA in normal clinical practice (data from SITS-MOST, for example and to some extent from PSURs) and in terms of benefit, in particular the results from the ECASS III trial.

In particular the UK considered that a positive benefit:risk balance of treatment up to 3 hours was indirectly confirmed by the success of the ECASS III trial, which demonstrated efficacy for the later time window of 3-4.5 hours, and the understanding that efficacy diminishes with increasing time to onset of treatment.

Since the approval of the variation to extend the time-window for treatment with rt-PA up to 4.5 hours in 2012, the results of the IST-3 trial (IST-3 collaborative group, 2012 and 2013) have become available, as well as an updated Cochrane review (Wardlaw *et al*, 2014) and an updated meta-analysis from the STT collaborative group (Emberson *et al*, 2014). The impact of these data on the balance of benefits and risks in the current indication will be considered by the group at the third meeting.

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Annex 1: Summary of trials available at the time of initial licensing approval

NINDS part 1 and 2 (0-3 hours of symptom onset) (NINDS, 1995)

These two studies were conducted in the US by the US National Institute of Neurological Disorders and Stroke (NINDS). Both studies were placebo-controlled, used a dose of 0.9mg/kg and treatment was within 0-3 hours of symptom onset. NINDS part 1 was a phase II study (n=291), and NINDS part 2 was phase III (n=333).

The primary endpoint for NINDS part 1 was neurological outcome after 24 hours measured as an improvement from baseline in the NIH stroke scale (NIHSS) of 4 or more points or complete resolution of neurologic deficit. The primary endpoint was not reached as there was no significant difference between the rt-PA and the placebo groups at 24 hours. However there was a benefit observed at 3 months after treatment in the rt-PA group.

NINDS part 2 was the pivotal randomised, placebo controlled trial supporting the application. The primary endpoint was clinical outcome at 3 months, according to scores on the Barthel index (BI), modified Rankin scale (mRS), Glasgow outcome scale (GOS) and NIHSS. The odds ratio for a favourable outcome (minimal or no disability at 3 months) in the rt-PA group compared with placebo was 1.7 (95% CI [1.2-2.6]). The absolute increase in number of patients with minimal disability was 12% at 90 days. Symptomatic intracranial haemorrhage (ICH) within 36 hours of stroke onset occurred in 6.4% of rt-PA treated patients vs. 0.6% of placebo patients. This did not translate into an increase in mortality. Overall mortality in the rt-PA group was 17%, vs. 21% in the placebo group. Stratifying patients by the time window for treatment suggested that the benefit of rt-PA over placebo is greater in the first 1.5 hours compared with the second 1.5 hours.

ECASS I (0-6 hours of symptom onset) (Hacke *et al*, 1995)

The European Co-operative Acute Stroke Study (ECASS I) was a randomised double-blind placebo controlled trial in 14 European countries, designed to evaluate efficacy and safety of rt-PA in patients with acute ischaemic stroke with moderate to severe neurological deficit and with none or minimal early infarct signs on the initial CT scan. This was a phase III study, n=610.

The primary endpoints included BI and mRS at 90 days. Secondary endpoints included combined BI, mRS and Scandinavian stroke scale (SSS) at 90 days and 30 days mortality. The dose of rt-PA used was 1.1 mg/kg body weight within 6 hours of symptom onset.

There was no difference between the groups in the intention to treat (ITT) analysis of the primary endpoints. The secondary endpoint of combined BI and mRS demonstrated a difference in favour of rt-PA treatment. Mortality at 90 days was higher in the rt-PA population (22.4% vs. 15.8% for placebo) and parenchymal haemorrhages were significantly more frequent in the rt-PA group (ITT: n=62 for rt-PA vs. n=20 for the placebo group).

ECASS II (0-6 hours of symptom onset) (Hacke *et al*, 1998)

The European-Australasian Acute Stroke Study (ECASS II) used a lower dose of rt-PA (0.9mg/kg body weight) to match that used in NINDS. This was a phase III study, n= 800. Treatment was given within 6 hours of symptom onset, stratified into 0-3 hours and 3-6 hours. Due to issues with patients receiving early treatment such as the time taken between onset of symptoms and arrival at hospital, only 81 out of 409 rt-PA treated patients were included in the early stratum.

The primary endpoint was the proportion of patients with a favourable outcome (score 0 or 1) on the mRS at day 90 after treatment. No significant difference was found between rt-PA and placebo for the primary endpoint. The study found no

evidence that efficacy depends upon administration within 3 hours of symptom onset, however there were only a small number of patients in the 0-3 hour time window.

Symptomatic ICH occurred in 8.8% of rt-PA patients and in 3.4% of placebo patients, but no increase in morbidity or mortality at day 90 was observed in the rt-PA group compared with placebo.

ATLANTIS part B (3-5 hours of symptom onset) (Clark *et al*, 1999)

The Alteplase ThromboLysis for Acute Non-interventional Therapy in Ischaemic Stroke (ATLANTIS) study was a placebo-controlled, double-blind, randomised study conducted in North America. It was initially designed to assess rt-PA administered from 0-6 hours following onset of symptoms. Two years into the study the DSMB halted enrolment and the time-window for treatment was changed to 0-5 hours due to safety concerns in the 5-6 hour group. At this point the trial was re-started as part B, with the previously enrolled patients to be considered separately as part A (Clark *et al*, 2000). Part B was further modified 2 years later to a time window of 3-5 hours in light of the NINDS trial results for the 0-3 hour window. 31 patients in part B had been enrolled from 0-3 hours at the time of this change.

Part B was a phase III study, n=613. The dose of rt-PA used was 0.9mg/kg, as used in NINDS. This study was not included in the initial submission by the applicant for this indication. The trial endpoints were changed during the study[3] (for reasons unknown to this assessor), at the time of publication of part B the primary endpoint was the number of patients with an excellent neurological recovery at day 90 (score 0-1 on the NIHSS). Secondary endpoints were excellent recovery on BI, mRS and GOS scales at days 30 and 90.

For the primary outcome, 32% of placebo and 34% of rt-PA patients had an excellent recovery at 90 days. There were no differences in secondary outcome measures.

In the first 10 days following treatment, the rate of ICH was higher in the rt-PA treated group than in the placebo group (symptomatic ICH: 11.4% rt-PA vs. 4.7% placebo). Mortality at 90 days was 11% in the rt-PA group, vs. 6.9% in the placebo group.

This trial was stopped prematurely after a pre-planned interim analysis, as the DSMB considered a beneficial effect seemed unlikely.

Part A included 142 patients and also found no significant benefit for any of the planned efficacy endpoints, and an increased risk of ICH.

[3] The ATLANTIS part A publication states primary hypotheses as: 1. Significant difference between rt-PA and placebo groups in clinical improvement, (decrease of ≥4 points on the NIHSS or complete resolution of symptoms from baseline to 24 hours/30 days); 2. Significant difference between rt-PA and placebo groups in volume of cerebral infarction as measured by CT scanning at 30 days.

Annex 2: Summary of trials/data included in the variation to extend the time-window for treatment to 4.5 hours

ECASS III (3 - 4.5 hours of symptom onset) (Hacke *et al*, 2008)

The European Cooperative Acute Stroke Study III (ECASS III) was a randomised, multi-national, double-blind, placebo controlled trial in patients treated with rt-PA between 3 and 4.5 hours after stroke onset. The study took place between 2003 and 2008 and enrolled 821 patients. Inclusion and exclusion criteria were identical to the EU SmPC for rt-PA in ischaemic stroke, except for the time-window for treatment.

rt-PA was administered at a dose of 0.9 mg/kg body weight (the licensed dose). The primary outcome was mRS 0-1 at Day 90. The secondary outcome was a global measure combining Day 90 results for the mRS score 0-1, the BI score ≥95, the NIHSS score of 0-1 and the GOS score of 1.

The safety endpoints included overall mortality at day 90, stroke-related and neurological deaths, all ICH, symptomatic ICH, and symptomatic brain oedema.

ECASS III results

Treatment with rt-PA was significantly associated with a favourable primary outcome (mRS = 0-1 at day 90) compared with placebo in the intention to treat population:

OR 1.34; 95% CI [1.02-1.76]
RR 1.16; 95% CI [1.01-1.34]

The more global secondary endpoint for the intention to treat population was also found to have a statistically significant difference in favour of rt-PA treatment:

OR 1.28; 95% CI [1.00-1.65].

The per-protocol results found similar, slightly greater ratios. The effect on the distribution of mRS scores is shown in the following figure.

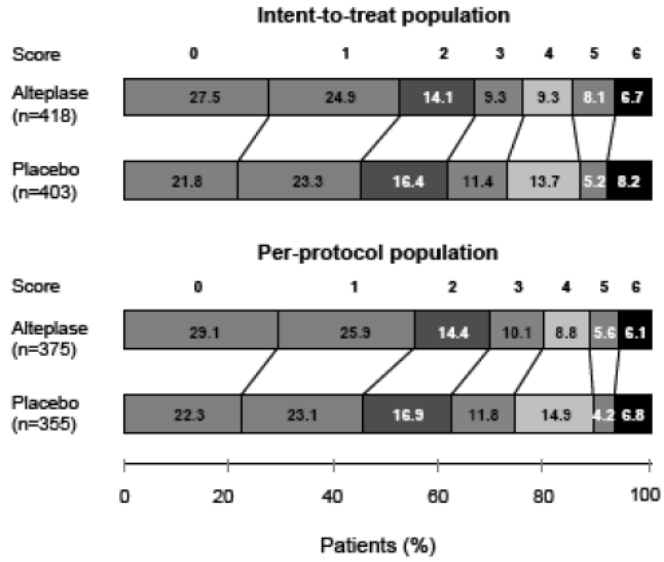

Figure 1: Overall distribution of scores on the mRS at the day 90 visit

A total of 113 patients (27%) in the rt-PA group had intracranial haemorrhages of which 3 were fatal. This compares with 71 patients (17.6%) with ICH in the placebo group of which 0 were fatal. Most ICH occurred within 24 hours of receiving treatment. The OR for any ICH was 1.73 95% CI [1.24-2.42]. Symptomatic ICH was defined as any blood in the brain or intracranial associated with a clinical deterioration of ≥4 points of the NIHSS for which haemorrhage has been identified as the dominating cause. All symptomatic ICH occurred within the first 22 to 36 hours

after initiation of treatment. Symptomatic ICH frequencies were also estimated using definitions from previous studies[4].

	Alteplase n (%)	Placebo n (%)	Odds Ratio (95% CI)	p value[1]
ITT population	418 (100.00)	403 (100.00)		
As per ECASS III definition	10 (2.39)	1 (0.25)	9.85 (1.26-77.32)	0.0076
As per ECASS II definition	22 (5.26)	9 (2.23)	2.43 (1.11-5.35)	0.0228
As per SITS-MOST definition	8 (1.91)	1 (0.25)	7.84 (0.98-63.00)	0.0219
As per NINDS definition	33 (7.89)	14 (3.47)	2.38 (1.25-4.52)	0.0064
PP population	375 (100.00)	355 (100.00)		
As per ECASS III definition	7 (1.87)	1 (0.28)	6.73 (0.82-55.01)	0.0398
As per ECASS II definition	19 (5.07)	9 (2.54)	2.05 (0.92-4.60)	0.0751
As per SITS-MOST definition	5 (1.33)	1 (0.28)	4.78 (0.56-41.15)	0.1157
As per NINDS definition	28 (7.47)	14 (3.94)	1.97 (1.02-3.80)	0.0410

Table 1: Overall incidence of symptomatic ICH in ECASS III (according to different definitions).

The percentage of patients with symptomatic ICH was found to remain the same for the rt-PA treated group across the three time periods of treatment (3-3.5, 3.5-4 and 4-4.5 hours) using NINDS criteria. For the placebo group, the rate of symptomatic ICH reduced with longer time to treatment.

Overall mortality rates were similar between the two groups, in the ITT population a total of 32 (7.7%) of patients in the rt-PA arm died whilst 34 (8.4%) in the placebo group died. A trend for increasing mortality with increasing time to treatment was found.

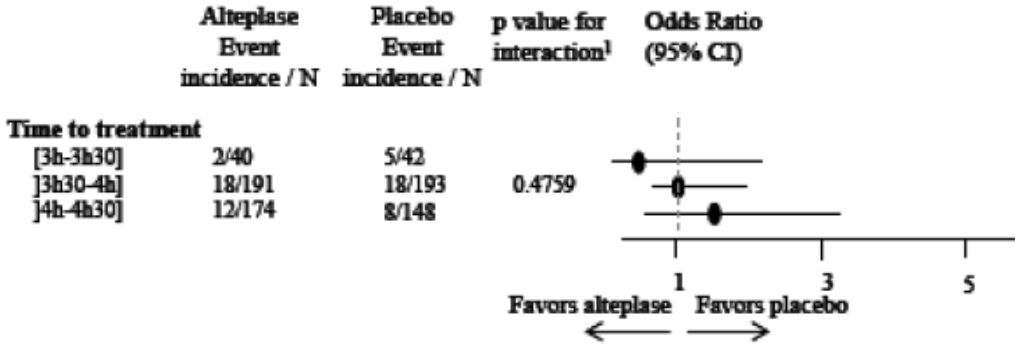

Figure 2: Subgroup analysis (time to treatment) for mortality (ITT population)

Elderly patients (≥65 years) were found to have a trend for increased mortality, an increased risk for symptomatic ICH and a trend to lower efficacy.

[4] Definition of sICH according to:
ECASS II: Any intracranial bleed and at least 4 points worsening on the NIHSS score (the same as the **ECASS III** protocol definition except that the causal relationship between haemorrhage and clinical deterioration was not required).
SITS-MOST: Local or remote parenchymal haematoma type 2 on the 22- to 36-hour posttreatment imaging scan, combined with a neurological 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.
NINDS: 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 neurological 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-ISTR (observational registry) (Wahlgren *et al*, 2008)

SITS-ISTR was a prospective multi-national registry study for patients given rt-PA following stroke. Data were collected from 2002 to 2007, and a later update to 2008. Two cohorts were compared, patients treated between 0-3 hours of symptom onset (n=11,865) and those treated between 3-4.5 hours (n=664). The main efficacy endpoint was functional independence (mRS ≤2) at day 90. Safety endpoints were symptomatic ICH within 24 hours and mortality at day 90.

SITS-ISTR results

Patients in the later time period had a median age that was 3 years younger than the earlier treatment time-point and a stroke severity 1 point lower on the NIHSS. In the 3-4.5 hour cohort, ~60% of patients were treated in the first 20 minutes, and only ~8% in the last 30 minutes. For the 3-4.5 hour cohort compared with the 3 hour cohort:

Rate of sICH (SITS-MOST definition) 2.2% vs. 1.6%; OR 1.18 [95% CI 0.89–1.55], p=0.24; adjusted OR 1.32 [95% CI 1.00–1.75], p=0.052;

Rate of sICH (ECASS II definition): 5.3% vs. 4.8%; OR 1.06 [95% CI 0.89–1.26], p=0.54;

Rate of sICH (NINDS definition): 8.0% vs. 7.3%; OR 1.06 [95% CI 0.91–1.22], p=0.46.

Mortality rate: 12.7% vs. 12.2%; OR 1.02 [95% CI 0.90–1.17], p=0.72; adjusted OR 1.15 [95% CI 1.00–1.33]; p=0.053.

Independence (mRS ≤2 at day 90): 58.0% vs. 56.3%, OR 1.04 [95% CI 0.95–1.13], p=0.42; adjusted OR 0.93 [95% CI 0.84–1.03], p=0.18.

Pooled analysis

This pooled analysis combined data from ECASS III with ECASS II, ATLANTIS A and B, NINDS 1 and 2. ECASS I was not included as it used a higher dose. Overall a total of 2958 patients (1490 rt-PA and 1468 placebo) treated within the 0-6 hour time window were included. Of these, 1355 patients were treated in the 3-4.5 hour time window.

The primary efficacy endpoint was mRS 0-1 at day 90. A benefit in favour of rt-PA was observed for the 3-4.5 hour time window, OR 1.31; 95% CI [1.06-1.63] p=0.014. For the subset of patients who fulfilled the inclusion/exclusion criteria other than time to treatment, according to the SmPC, a significant benefit was also found, n=1251; OR 1.42; 95% CI [1.13-1.78], p=0.002.

Rates of symptomatic ICH in the 3-4.5 hour cohort were comparable with those from ECASS III, according to the SITS-MOST definition. The pooled analysis found the excess risk with rt-PA compared with placebo was slightly smaller for 0-3 hours compared with 3-4.5 hours, and was markedly higher for patients treated after 4.5 hours. Results from ECASS III also found a numeric trend of increasing risk of sICH with increasing time to treatment onset.

No difference was found in the rate of all-cause mortality in the rt-PA compared with the placebo arms, and mortality rate was similar to that in the ECASS III trial. Risk of mortality in the rt-PA arm increased with increasing time to treatment.