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Protocol for non-interventional studies based on existing data

Document Number:	**c30353958-01**
BI Study Number:	0135-0344
BI Investigational Product(s):	Actilyse
Title:	Safe Implementation of Treatments in Stroke (SITS) - Intravenous thrombolysis in acute ischaemic stroke patients over 80 years, SITS-IVT>80 years study
Protocol version identifier:	*1.0*
Date of last version of protocol:	na
PASS:	Yes
EU PAS register number:	Study not yet registered
Active substance:	Alteplase
Medicinal product:	Actilyse: Powder and solvent for solution for injection and infusion, 10 mg, 20 mg, and 50 mg
Product reference:	*DE/H/0015/004*
Procedure number:	*DE/H/0015/004/IB/135*
Joint PASS:	*No*
Research question and objectives:	Pooled analysis of randomized controlled trials (RCTs) of intravenous thrombolysis (IVT) with Alteplase, a recombinant tissue plasminogen Activator (rt-PA) for acute ischemic stroke, has shown that patients >80 years treated with IVT versus control derived equal benefit compared to patients 18-80 years. The SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register)-VISTA analysis demonstrated benefit of IVT in patients >80 years compared to control, and found no difference in the slope of benefit versus treatment delay for younger versus elderly patients[3], a finding that was confirmed in the RCT dataset. The European guideline recommends use of IVT within 4.5h of symptom onset also in the elderly. Until recently, most European regulatory agencies

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	had not approved marketing of IVT with Alteplase for use in ischemic patients >80 years. A recently published SITS study showed that unselected patients >80-years treated with IVT after 3h versus earlier, had a slightly higher rate of SICH but similar unadjusted functional outcome and poorer adjusted outcome. IVT with Alteplase in >80 years old patients treated within 4.5h of symptom onset is now approved in a number of European and non-European countries. Safety and outcome of a treatment in acute ischaemic stroke may be different in the RCT settings in patients over 80 years. Although IVT in patients >80 years has been used off-label in many countries prior to approval, use of IVT in patients>80 years will probably be more frequent after approval. The proposed SITS-ISTR provides an opportunity for continuous monitoring of thrombolysis treatment in stroke, and provides a technical foundation for the SITS->80 years post-approval study. The SITS-IVT>80 years is a retrospective study based on data collected in the SITS-ISTR setting from acute ischemic stroke patients > 80 years of age. The study aims to evaluate the incidence rate with 95% CI of SICH, death and functional independence/favourable outcome within 90 days for ischaemic stroke patients treated with rt-PA in clinical routine settings. In the proposed SITS-IVT>80 years study using the SITS registry we plan to identify approximately 1000 patients older than 80 years treated with IV Alteplase otherwise fulfilling SmPC criteria in the post-approval period of 3 years (from 1 July 2018 to 30 June 2021) and also to identify 1000 patients older than 80 years treated with IV Alteplase otherwise fulfilling SmPC criteria in the pre-approval period of 3 years (from June 2015 to June 2018). In both periods, at least 500 patients should be registered from centres of European countries being part of the mutual recognition. The objective of the SITS-IVT>80 years is to compare the safety and other outcome parameters between the post-approval >80 years and pre-approval >80 years AIS patients using the data already collected in SITS-ISTR.
Country(-ies) of study:	Austria, Belgium, Cyprus, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Iceland, Italy, Luxemburg, Malta, Netherland, Norway, Portugal, Sweden, United Kingdom
Author:	[redacted] Phone [redacted]

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MAH contact person:	[redacted]
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Signature of EU-QPPV:	
Date:	25 Nov 2019

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
AUC	Area under the Curve
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computer Tomogram
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
ICO	International Coordinating Office
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
MedDRA	Medical Dictionary for Drug Regulatory Activities
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
MST	Medical Subteam
NIHSS	National Institute of Health's Stroke Scale
OPU	Operative Unit
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PH	Parenchymal Haemorrhage
q.d.	quaque die (once a day)
SAE	Serious Adverse Event
s.c.	Subcutaneous
SICH	Symptomatic Intracerebral Haemorrhage
SmPC	Summary of Product Characteristics
SPC	Summary of Product Characteristics
SITS-ISTR	Safe Implementation of Treatments in Stroke- International Stroke Thrombolysis Registry
TCM	Trial Clinical Monitor

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TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
t-PA	Tissue plasminogen activator, alteplase, Actilyse®
TMM	Team Member Medicine
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

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3. RESPONSIBLE PARTIES

SITS ORGANISATION

SITS International:	Responsibility:	Representatives:
SITS Scientific Committee	• Scientific responsibility • Data evaluation • Monitoring SITS Scientific activities, e.g. projects, reports and publications	[redacted]
Data management	Data management and statistical analysis	[redacted] Statistical support will also be sought from [redacted]
SITS ICO (International Coordination Office)	Manage centre application, coordinate, maintain and online monitoring of SITS registry, development and maintenance of database	[redacted]

On behalf of SITS International:

[redacted]

Phone [redacted]

On behalf of Boehringer Ingelheim International GmbH:

[redacted]

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: If applicable, list centrally-authorised medicinal product(s) subject to the study.			
Name of active ingredient: List pharmacotherapeutic group(s){ACT codes} and active substance(s) subject to the study **Alteplase**			
Protocol date: 25 Nov 2019	**Study number:** 0135-0344	**Version/Revision:** 1.0	**Version/Revision date:**
Title of study:	SITS-IVT>80 years Safe Implementation of Treatments in Stroke (SITS) - Intravenous thrombolysis in acute ischaemic stroke patients over 80 years, SITS-IVT>80 years study. A non-interventional post-approval study on SITS-ISTR existing data of intravenous rt-PA (0.9 mg/kg) in acute ischaemic stroke patients over 80 years, treated according to the Summary of Product Characteristics (SmPC) of European countries being part of the mutual recognition procedure within the academic SITS-ISTR (International Stroke Thrombolysis Registry).		
Rationale and background:	Pooled analysis of randomized controlled trials (RCTs) of intravenous thrombolysis (IVT) with Alteplase, a recombinant tissue plasminogen Activator (rt-PA) for acute ischemic stroke, has shown that patients >80 years treated with IVT versus control derived equal benefit compared to patients 18-80 years.[9] Effectiveness of IVT diminished as the treatment delay increased across the first 6 hours without a corresponding increase in the relative risk of symptomatic intracerebral hemorrhage (SICH).[9] Real world registry experience supports these RCT data in patients >80 years treated within 3h.[35,36] The SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register)-VISTA analysis demonstrated benefit of IVT in patients >80 years compared to control, and found no difference in the slope of benefit versus treatment delay for younger versus elderly patients,[36] a finding that was confirmed in the RCT dataset.[37] Until recently, most European regulatory agencies had not approved marketing of IVT with Alteplase for use in ischemic patients >80 years, whereas the American regulatory agency supports promotion of IVT in patients >80 years within 3h of symptom onset. A recently published SITS study showed that unselected patients >80-years treated with IVT after 3h versus earlier, had a slightly higher rate of SICH but similar unadjusted functional outcome and poorer adjusted outcome.[40] The European guideline[38] recommends use of IVT within 4.5h of symptom onset also in the elderly and IVT		

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	with Alteplase within 4.5h of symptom onset is now approved in a number of European and non-European countries. Safety and outcome of a treatment in acute ischaemic stroke may be different in the RCT settings in patients over 80 years. Although IVT in patients >80 years has been used off-label in many countries prior to approval, use of IVT in patients>80 years will probably be more frequent after approval. The SITS-ISTR setting provides an opportunity for continuous monitoring of thrombolysis treatment in stroke, and provides a technical foundation for the SITS->80 years post-approval registry. The SITS-IVT>80 years is a retrospective study of existing data in the SITS-ISTR on acute ischaemic patients treated with IVT according to the Summary of Product Characteristics (SmPC) criteria. The study aims to evaluate the incidence rate of SICH, death and independence/favourable outcome within 90 days for ischaemic stroke patients over 80 years treated with rt-PA in clinical routine settings. At least 2000 patients overall from approximately 60 European sites are planned to be identified for the SITS-IVT>80 years study. Safety and other outcome parameters will be compared between post-approval >80 years and pre-approval >80 years patients.		
Research question and objectives:	Safety and outcome of a treatment in acute ischaemic stroke may be different in the RCT settings in patients over 80 years. Although IVT in patients >80 years has been used off-label in many countries prior to approval, use of IVT in patients>80 years will probably be more frequent after approval. The study aims to evaluate the incidence rate of SICH, death and independence/favourable outcome within 90 days for ischaemic stroke patients treated with rt-PA in clinical routine settings. The SITS-IVT>80 years Study will primarily investigate the safety and outcome of IVT in acute ischaemic stroke in patients >80 years collected during the post-approval period and to compare the safety outcome with existing pre-approval patients >80 years collected in routine clinical practice and recorded in the SITS registry.		

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Protocol date: 25 Nov 2019	**Study number:** 0135-0344	**Version/Revision:** 1.0	**Version/Revision date:**
Study design:	This is a retrospective observational study using existing data from the SITS registry.		
Population:	Post-approval: Patients over 80 years old presenting with acute ischaemic stroke symptoms for which thrombolysis treatment was initiated within 4.5 hours after stroke onset according to the SmPC during the study period July 2018 to June 2021. Pre-approval: Patients aged over 80 years presenting with acute ischaemic stroke symptoms for which thrombolysis treatment was initiated within 4.5 hours after stroke onset otherwise according to SmPC during the period of approximately 3 years prior to approval (June 2015 to June 2018)		
Variables:	Standard SITS-ISTR safety parameters: • Symptomatic intracerebral haemorrhage (SICH): Intracerebral haemorrhage (parenchymatous haemorrhage type 2), at post-treatment scan combined with neurological deterioration leading to an increase of 4 points on the NIH Stroke Scale (SITS-MOST definition) • Mortality: Death (mRS = 6) at day 90 • Independence / favourable outcome: Independence for the activities of daily living at day 90. Good functional outcome is defined as a modified Rankin Scale (mRS) score of both 0-2 (independence) and 0-1 (favourable) • Baseline and demographic variables available in the SITS registry for describing patient characteristics. • Patient management variables o Time from onset to door o Door to needle (treatment) time		

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Protocol date: 25 Nov 2019	**Study number:** 0135-0344	**Version/Revision:** 1.0	**Version/Revision date:**
	○ Onset to treatment time		
Data sources:	The SITS-ISTR		
Study size:	Approximately 1000 patients above 80 years treated with IV Alteplase according to SmPC after approval of indication and approximately 1000 patients above 80 years treated with IV Alteplase within 4.5 hours otherwise according to SmPC before the approval of the indication. Of these at least 500 patients each from the pre-approval and post-approval period from centres of European countries being part of SITS registry. The sample size of the study is not based on any formal power calculation, but chosen in consultation with authorities, based on numbers considered to be achievable within a 3-year period.		
Data analysis:	Descriptive and exploratory analyses in the unmatched and propensity score matched groups. Multivariable analysis with adjustment for differences or imbalances in prognostic variables for outcome comparisons.		
Milestones:	Planned milestones	Estimated timelines	
	Post approval data collection is planned after the majority of the participating countries received approval of the label change for >80 years with acute ischaemic stroke	Q3 2018 or Q2 2021 Last patient out October 2021	
	Interim reports	Yearly	
	Final report to be available within 6 months of the database lock	April 2022	
	Final report to be submitted two months after its availability	June 2022	

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	Re-assessment of the timelines will be performed as study progresses		

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5. AMENDMENTS AND UPDATES

None

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6. MILESTONES

Planned milestones	Estimated timelines
Post approval data collection is planned after the majority of the participating countries received approval of the label change for >80 years with acute ischaemic stroke	Q3 2018 or Q2 2021 Last patient out October 2021
Interim reports	Yearly
Final report to be available within 6 months of the database lock	April 2022
Final report to be submitted two months after its availability	June 2022

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7. RATIONALE AND BACKGROUND

Stroke – a growing disease

Stroke is the third leading cause of death and the number one cause of neurological disability in adults globally, not only in the elderly, but also in younger age groups.[1]
About one million strokes occur annually within the European Union. Stroke patients often require extended hospital stays followed by rehabilitation, ongoing support from the community, and nursing-home care.[2]

Alarmingly, stroke incidence is expected to increase considerably over the next decades because of an increase in the elderly population. The proportion of people over the age of 70, which was 13% in year 2000, is expected to be 20% in year 2050. It is predicted that stroke will account for 6.2% of the total burden of illness in 2020. Thus, without major advances to improve prevention and treatment, the cost of this disease will increase dramatically.[3,4]

Treatment strategies for stroke

Stroke unit care[5,6] and reperfusion therapy by iv thrombolysis within 4.5 hours of symptom onset[7-12], and/or endovascular thrombectomy within 6 hours of symptom onset in anterior circulation stroke[13-19], are the only evidence-based treatments for acute ischemic stroke, and are recommended by national and international practice guidelines.[20-21]

Stroke unit care

Stroke unit care is the evidence-based treatment for patients with all types of acute stroke in all ages and severity grades. The aggregate of multidisciplinary treatment, monitoring and care measures in dedicated stroke units prevents complications, improves functional outcomes, and reduces stroke mortality. Stroke unit care increases chance of independent survival by an absolute of 5-6 % compared to treatment in general medical wards, and the effect is sustainable for 10 years or more.[5,6] In Sweden, approximately 91 % of all stroke patients are admitted to a stroke unit.[1]

Intravenous thrombolysis

Intravenous thrombolysis with tissue plasminogen activator (tPA) within 4.5 hours of ischaemic stroke onset is an established and approved treatment[7-12]. The effect of iv thrombolysis is time-dependent. Among patients treated within one hour, every second patient is expected to fully recover within three months, among those treated within 90 minutes, every third, and within 3 hours every seventh patient. For patients treated within the time interval of 3-4.5 hours, 14 patients need to be treated for one additional patient to recover fully.[8,9] IV thrombolysis given within three hours from stroke onset increases the chance of reaching good functional outcome (defined as having exactly the same functional level as before the stroke) from 23% to 33%, and when given between 3 and 4.5 hours from onset, by a more modest but still substantial absolute 5%.[8,9] The use of iv thrombolysis is increasing but still used in only 10-15% of all ischaemic stroke patients. Meanwhile, 2-7% of patients treated with iv thrombolysis suffer symptomatic intracerebral haemorrhage (ICH) as a complication, leading to death in 1.5-2%, and worsening functional outcome in survivors.[8,9]

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Endovascular thrombectomy
Endovascular thrombectomy,[13-19] although highly effective in reducing stroke disability and potentially mortality, is only indicated in large artery occlusion, feasible in a minority of patients, and is most commonly used in addition to iv thrombolysis.

The rationale for thrombolytic treatment
Thromboembolic occlusion of an artery leading to the brain or in the brain, is a major cause of stroke. An occlusion of an artery leads to immediate drop of blood flow into the corresponding arterial territory. The size and site of the occlusion, and the efficiency of compensatory flow through collateral arteries determine the amplitude and the extension of the drop in the blood flow. If the flow is reduced to about 20 ml/100 g/minute (about 40% of the normal value), neurological symptoms occur. A blood flow below 10 ml/100 g/min is not compatible with cell survival, and the brain tissue is infarcted. Brain tissue with a blood flow between 10 and 20 ml/100g/min may survive for a few hours, but is likely to die if blood flow is not re-established.[22]
Spontaneous reperfusion may occur through endogenous release of plasminogen activator, which stimulates plasmin formation from plasminogen. For larger occlusions, this release seems insufficient to induce reperfusion in time to avoid a cerebral lesion.
Administration of plasminogen activator as an intravenous infusion is thus a method to enhance this endogenous procedure. Reperfusion should of course be done as early as possible to avoid a cerebral lesion, and to avoid complications caused by ischaemic injury to blood vessel walls and the blood-brain barrier.

Evidence from randomised controlled trials
In total, 17 randomised trials with 5,216 patients form the evidence base for thrombolysis in stroke. Of the data derived from these trials, 42% relate to streptokinase, 3% to intravenous urokinase and 5% to intra-arterial pro-urokinase. 50% of the data comes from trials using intravenous rt-PA. The results of these trials and agents are frequently discussed together, which may give a more unfavourable impression of the effect of thrombolysis than if only intravenous rt-PA is studied. Whether there is true heterogeneity between thrombolytic agents is still not quite clarified, but there are differences between e.g. streptokinase and rt-PA in the effect on blood pressure (streptokinase reduces blood pressure) which may cause differential effects on collateral blood flow to the ischaemic area of the brain.
A meta-analysis[9] of individual patient data from 6756 patients in 9 randomised trials [7,11,23-27] comparing intravenous thrombolysis with Alteplase with placebo or open control in acute ischemic stroke shows that Alteplase significantly improves the overall odds of a good stroke outcome (defined by a modified Rankin score (mRS) of 0–1) when given within 4·5 h of stroke onset. The earlier treatment is associated with higher proportional benefits. Although Alteplase treatment significantly increased the odds of symptomatic intracranial haemorrhage and of fatal intracranial haemorrhage within 7 days but by 3–6 months this risk was offset by an average absolute increase in disability- free survival of about 10% for patients treated within 3 hours and about 5% for patients treated between >3 and 4.5 hours.
For rt-PA, data from 2,955 patients are available for analysis. Of these, 869 were included within three hours after onset of clinical symptoms. The results are more favourable for patients included within three hours compared to those included between three and six hours. The number needed to treat to get one more favourable outcome increases from 4.5, during the first 90 minutes, to 9 between 1.5 and 3 hours, and to 14 between 3 and 4.5 hours.[28]

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Pooled analysis of randomized controlled trials (RCTs) of intravenous thrombolysis (IVT) with Alteplase, a recombinant tissue plasminogen Activator (rt-PA) for acute ischemic stroke, has shown that patients >80 years treated with IVT versus control derived equal benefit compared to patients 18-80 years.[9] Effectiveness of IVT diminished as the treatment delay increased across the first 6 hours without a corresponding increase in the relative risk of symptomatic intracerebral haemorrhage (SICH).[9] Real world registry experience supports these RCT data in patients >80 years treated within 3h.[35,36] The SITS-ISTR (Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register)-VISTA analysis demonstrated benefit of IVT in patients >80 years compared to control, and found no difference in the slope of benefit versus treatment delay for younger versus elderly patients,[36] a finding that was confirmed in the RCT dataset.[37]

Experiences from post-trial treatments

Several open studies have been performed to address the issue of safety and efficacy of routine thrombolysis in acute stroke[29-34]. In the absence of control groups, the outcome of these studies must be compared with the results of randomised controlled trials. Such comparisons have been difficult since the baseline characteristics in most of the studies have not been comparable. This is illustrated by Katzan et al[31] who reported the highest rate of cerebral haemorrhages of all studies. Initial stroke severity, the most important predictor of haemorrhagic complication risk was reported in only 40 % of all patients and in only 27 % of those with haemorrhage.

Guideline recommendation and approval status

The European guideline[38] recommends use of IVT within 4.5h of symptom onset also in the elderly, but North American guidance does not recommend IVT in the >3-4.5h window in patients >80 years.[39] Until recently, most European regulatory agencies had not approved marketing of IVT with Alteplase for use in ischemic patients >80 years, whereas the American regulatory agency supports promotion of IVT in patients >80 years within 3h of symptom onset. A recently published SITS study showed that unselected patients >80-years treated with IVT after 3h versus earlier, had a slightly higher rate of SICH but similar unadjusted functional outcome and poorer adjusted outcome.[40] IVT with Alteplase within 4.5h of symptom onset is now approved in a number of European and non-European countries.

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8. RESEARCH QUESTION AND OBJECTIVES

Safety and efficacy of a treatment in acute ischaemic stroke may be different in the RCT settings in patients over 80 years. Although IVT in patients >80 years has been used off-label in many countries prior to approval, use of IVT in patients>80 years will probably be more frequent after approval. The SITS-ISTR provides an opportunity for continuous monitoring of thrombolysis treatment in stroke, and provides a technical foundation for the SITS->80 years post-approval registry. The proposed SITS-IVT>80 years is a retrospective study of existing data in the SITS-ISTR for the ischaemic stroke patients treated with IVT according to the Summary of Product Characteristics (SmPC) criteria. The study aims to evaluate the incidence rate of SICH, death and independence/favourable outcome within 90 days for ischaemic stroke patients treated with rt-PA in clinical routine settings. At least 2000 (1000 in the post-approval and 1000 in the pre-approval) patients overall from approximately 60 European sites are planned to be identified in the SITS-IVT>80 years study. Safety and other outcome parameters will be compared between post-approval >80 years and pre-approval >80 years patients.

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9. RESEARCH METHODS

9.1 STUDY DESIGN

The SITS-IVT>80 years is an observational, multinational, multicenter study in patients with acute ischaemic stroke treated with IV thrombolysis according to SmPC. This is a retrospective study based on existing data collected in the registry for patients treated according to the revised and approved Summary of Product Characteristics (SmPC) of IVT>80 years in European countries.

Approximately 1000 patients older than 80 years treated with IV Alteplase are expected to be identified for the proposed SITS-IVT>80 year study in the post-approval period of 3 years (1 July 2018 to 30 June 2021) and also approximately 1000 patients above 80 years treated with IV Alteplase within 4.5 hours otherwise according to SmPC in the pre-approval period (June 2015 to June 2018). Of these, at least 500 patients each should be registered from European centers (see list of European countries being part of the mutual recognition procedure) during the pre-approval as well as in the post-approval period. If the target 1000 patient is not reached during the 3 year period (post-approval phase), the data exchange will stop provided at least 500 patients registered from European centers have been included into the analysis.

The aim is to investigate the incidence rate of SICH, death and functional independence (mRS) / favorable outcome (primary endpoints) at day 90 in post-approval registered group of >80 year old patients and to compare with pre-approval registered group of >80 year old patients, comparison will be in both unmatched and the propensity score matched groups in the SITS-ISTR registry.

Additional analyses will be made with regards to patient's characteristics, management time (secondary endpoints): onset of symptoms to time of treatment initiation, and its components: onset of symptoms to door; door to treatment initiation.

9.2 SETTING

The SITS-IVT>80 years Study is driven by the SITS International according to SITS policy, and data will be provided to the Regulatory Authorities as needed. Acute ischaemic stroke patients aged >80 years who received IV thrombolysis according to SmPC during the period June 2015 to June 2021 were considered. Of these, pre-approval sample will consist at least 1000 patients from June 2015 to June 2018 and post-approval sample of 1000 patients from July 2018 to June 2021.

9.2.1 Level of care

- Thrombolysis treatment should be given at a semi-intensive care unit within a stroke unit, or an intensive care unit or semi-intensive care unit in close collaboration with the stroke unit, under the responsibility of an experienced stroke neurologist/stroke

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physician. This stroke neurologist/stroke physician should have personal experience from thrombolysis treatment in stroke.

Inclusion criteria

- Patients over 80 years old presenting with acute ischaemic stroke symptoms for which thrombolysis treatment was initiated within 4.5 hours after stroke onset according to SmPC are included.
- Patients over 80 years who received thrombolysis according to SmPC for AIS within 4.5 hours after stroke onset during the period (approximately 3 years) prior to July 2018 are included.

Exclusion criteria

- Contraindication(s) to the use of IV thrombolysis per local SmPC.
- Documentation that the patient was enrolled or is planned to be enrolled in an investigational clinical trial at the time of the onset of index event and for the duration of the data collection.

9.3 VARIABLES

9.3.1 Exposures

Intravenous thrombolysis

Index date is defined as the date of initiation of IV thrombolysis with alteplase (Actilyse®).

Intravenous thrombolysis with tissue plasminogen activator (tPA) within 4.5 hours of ischaemic stroke onset is an established and approved treatment.[7-12] The effect of iv thrombolysis is time-dependent. Among patients treated within one hour, every second patient is expected to fully recover within three months, among those treated within 90 minutes, every third, and within 3 hours every seventh patient. For patients treated within the time interval of 3-4.5 hours, 14 patients need to be treated for one additional patient to recover fully.[8,9] IV thrombolysis given within three hours from stroke onset increases the chance of reaching good functional outcome (defined as having exactly the same functional level as before the stroke) from 23% to 33%, and when given between 3 and 4.5 hours from onset, by a more modest but still substantial absolute 5%.[8,9] The use of iv thrombolysis is increasing but still used in only 10-15% of all ischaemic stroke patients. Meanwhile, 2-7% of patients treated with iv thrombolysis suffer symptomatic intracerebral haemorrhage (ICH) as a complication, leading to death in 1.5-2%, and worsening functional outcome in survivors.[8,9]

Administration of plasminogen activator as an intravenous infusion is thus a method to enhance this endogenous procedure. Reperfusion should of course be done as early as possible to avoid a cerebral lesion, and to avoid complications caused by ischaemic injury to blood vessel walls and the blood-brain barrier.

Treatment with Actilyse must be started as early as possible within 4.5 hours of the onset of symptoms. Beyond 4.5 hours after onset of stroke symptoms there is a negative benefit risk ratio associated with Actilyse administration and so it should not be administered.

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The recommended total dose is 0.9 mg alteplase/kg body weight (maximum of 90 mg) starting with 10% of the total dose as an initial intravenous bolus, immediately followed by the remainder of the total dose infused intravenously over 60 minutes.

Patients in general will be exposed once to Actilyse for the treatment of the acute ischemic index event.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Primary outcome

- Safety: SICH per SITS-MOST definition
- Mortality (mRS=6) within 90 days
- Outcome: Functional Independency as defined by mRS 0-2 within 90 days

A modified Rankin score, mRS, is used to evaluate daily activity of the patient at day 90 (described in Attachment 8.3). The scores are entered in the on-line entry form. The score 0-1 is defined as favourable outcome and 0-2 as independence of the patient.

Symptomatic intracerebral haemorrhage, SICH, is defined as 'Intracerebral haemorrhage' (parenchymatous haemorrhage type 2, PH2), at the 22-36 hours post-treatment scan combined with neurological deterioration leading to an increase of 4 points on the NIH Stroke Scale' (SITS-MOST definition).

The evaluation of post-treatment haemorrhage is done using the CT/MRI scan performed between 22-36 hours after start of treatment or earlier if clinically indicated.

Death within 90 days as classified by the investigator according to cause: cerebral infarct, cerebral haemorrhage, cerebral infarct and haemorrhage unspecified, myocardial infarct, pulmonary embolism, pneumonia, other vascular cause, unknown and other cause of death (ICD 10 to be provided).

9.3.2.2 Secondary outcomes

Secondary outcomes

- Patient characteristics at baseline including stroke severity (NIHSS)
  - Outcomes: Favourable outcome as defined by mRS 0-1 within 90 days
  - Secondary safety: SICH per ECASS 2 within 90 days
  - Delays of management
    - Time from onset of symptoms – start of treatment
    - Time from onset of symptoms – door (or as captured in the registry arrival at hospital)
    - Door – needle time

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[redacted]

9.3.3 Covariates

Specification of data collection from the index stroke event

At baseline: Demographic data (age, sex, weight), NIHSS and pre-stroke mRS, blood pressure, laboratory values (plasma glucose, cholesterol) medical history including comorbidities and concomitant medication, results of imaging scans, time logistics

At 24 hours: NIHSS score, blood pressure, laboratory and imaging scans if performed.
During hospital stay: details of concomitant medications, additional imaging scans

At 7 day or discharge if occurred earlier than 7 days: Date/time discharge, NIHSS scores, blood pressure, type of stroke and AF, medications

At 3-months follow up: mRS scale, any events including recurrent stroke (haemorrhagic or ischaemic), major extracranial haemorrhage

The analysis will include standard covariates.
Standard SITS-ISTR safety parameters:

- Baseline and demographic variables available in SITS for describing patient characteristics such as but not limited to stroke severity, age, gender etc. (standard covariates)

- Symptomatic intracerebral haemorrhage (SICH):

Intracerebral haemorrhage (parenchymatous haemorrhage type 2), at post-treatment scan combined with neurological deterioration leading to an increase of 4 points on the NIH Stroke Scale (SITS-MOST definition)

- Mortality:

Death (mRS = 6) at day 90

- Independence / favourable outcome:

Independence for the activities of daily living at day 90. Good functional outcome is defined as a modified Rankin Scale (mRS) score of both 0-2 (independence) and 0-1 (favourable)and independency / favourable outcome at 90 days (mRS 0-2, mRS 0-1

Patient management variables

- Time from onset to door
- Door to needle (treatment) time
  Onset to treatment time

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9.4 ONSET TO TREATMENT TIME DATA SOURCES

Data is collected within the SITS-ISTR registry according to their standard procedures.

SITS is an academic-driven, non-profit, international collaboration. It is an initiative by the medical profession aimed at driving excellence in acute and secondary stroke treatment, and to develop new knowledge and leading research. SITS-ISTR is an ongoing, prospective, multinational and academic driven registry for centres using thrombolysis for the treatment of acute ischaemic stroke patients. The registry contains data about alteplase treatment independent of the time since stroke onset. Information related to patient demographics, baseline characteristics, stroke severity at baseline, onset to treatment time, risk factors, drug treatment history, admission time and data on baseline and follow-up imaging scans are collected in SITS-ISTR

9.5 STUDY SIZE

The sample size was not based on any formal power calculation, rather chosen pragmatically in consultation with authorities and based on numbers achievable within a 3-year period. Approximately 2000 acute ischaemic patients who were treated with IV thrombolysis within 4.5 hours within symptom onset constitute the main analysis population. Data from a minimum of 500 European patients are expected within the database during post approval phase as well as equal number during the pre-approval phase in patients > 80 years old acute ischemic stroke patients.

9.6 DATA MANAGEMENT

Data in the SITS registry are entered on-line through the SITS website.
SITS uses the two-factors authentication to login to the registry, i.e. first by username and password and then by a code which is sent to the user either by SMS or by e-mail. Each investigator/study nurse has a personal access code which must be kept secret and used only by the owner. All data entry from a centre can be made by each member of the local team, but once the data entry is confirmed (i.e. cannot be changed), the person who made the confirmation will be identified on the data entry form.

For the purpose of analysis, a download will be made in Excel/ CSV format which will then be transferred in the appropriate advance data analysis software such as STATISTICA/ SAS.

Data collection in this study is approved as part of the SITS-ISTR study framework by the Regional Research Ethics Committee in Stockholm, Sweden. Data analyses are performed according to SITS policy and under the responsibility of the Scientific Committee.

9.7 DATA ANALYSIS

A non-interventional post-approval study on SITS-ISTR existing data of intravenous rt-PA (0.9 mg/kg) in acute ischaemic stroke patients over 80 years, according to the Summary of

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Product Characteristics (SmPC) of European countries being part of the mutual recognition procedure within the academic SITS-ISTR (International Stroke Thrombolysis Registry, ongoing since December 2002).

Descriptive statistics (absolute and relative frequencies, means, standard deviations, medians, inter quartile ranges, minimum and maximum values, 95% confidence intervals and proportions, as appropriate) for baseline and demographic characteristics for all included patients will be provided. To compare demographic and clinical baseline characteristics between pre-approval and post-approval patients over >80years, standardized differences will be used. Multivariable analyses (exploratory) with adjustment for differences or imbalances in prognostic variables for outcome comparison will be performed.

9.7.1 Main analysis

We will compare the outcome of interest both in unmatched and propensity score matched patient sets as described below. The primary analysis will be on propensity score matched patient sets and we will compare the post-approval >80 year old patients with the pre-approval retrospective >80 year olds regarding baseline demographics, clinical and radiological parameters, as well as treatment logistics, safety outcomes, functional outcome and death. Secondary analysis will be on unmatched patient sets, i.e. all patients fulfilling the inclusions-exclusions criteria will be included in this analysis. A sensitivity analysis restricted to European and non-European patients might be considered if minimum sample size required for analysis is met in the matched patient set.

Patient sets analysed includes “unmatched” and “matched”. “Unmatched” patients set composed of IV thrombolysis treated patients >80 years from both pre-approval and post-approval phase those who fulfil the inclusions-exclusions criteria. Matched patient set constitute propensity score matched pair (1:1 greedy nearest neighbour matching using calipers equal to 0.2*SD of the logit of the propensity score).

The incidence rate and corresponding 95% CI of patients with primary and secondary outcome events will be calculated within the following cohorts:

a) Patients >80 years after approval

b) Patients >80 years before approval

The incidence rate for the outcome of interest using as-treated approach will be calculated on the unmatched (all eligible patients) and the matched patient sets.

In the primary analysis, post-approval >80 year old patients will be matched to pre-approval >80 year old patients using a structured, iterative propensity score model with the primary objective to maximize the balance in the distribution of possible confounders between these two groups [9].

In the propensity score-matching algorithm, all baseline characteristics will be included. The corresponding propensity score of the post-approval >80 years group will be calculated for

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each subject and a nearest neighbour matching algorithm will then be used to match patients in the post-approval >80 years group to patients in the pre-approval >80 years group within 0.2*SD of the logit of the propensity score. To determine whether the propensity score approach achieved balance in all potential confounders, we will compare all baseline characteristics of patients in the post-approval >80 years group to their propensity score matched pre-approval >80 year old patients using standardized difference.

We will also compare baseline characteristics between the unmatched and propensity matched subgroups to detect potential imbalances between the two populations. Differences of outcome between post-approval >80 years and pre-approval >80 years will be evaluated with univariable and multivariable binary logistic regression models adjusting for potential confounders. In these models the factors that contribute to the outcome of interest in the initial univariable analyses at p values <0.1, will be included in the multivariable model as candidate variables. The final variables that will be independently associated in the multivariable logistic regression analyses with the outcome of interest will be selected by backward stepwise selection procedures using a p value <0.05.

[redacted]

9.8 QUALITY CONTROL

European Stroke Centres (approx. 60) continuously registering patients into SITS-ISTR having

- a typical experience from acute stroke treatment
- high quality (at least 90% complete data entered at acute phase and 70% data entered at 3m follow up) in both prospective and retrospective groups
- a willingness to participate in SITS-IVT>80 years registry

9.8.1 Investigators and local procedures

According to the current processes in SITS described on the SITS web site (www.sitsinternational.org) the following persons are involved;

National Coordinator
A National Coordinator (NC) is appointed by SITS as to be the responsible person for the SITS activity in the specific country. The NC has an overview of the infrastructure in regards to stroke care treatments in the country. The role of NC is to coordinate among the different centers in the country. SITS has engaged leading stroke scientists as National Coordinators in each participating country.

Local coordinator/ Centre coordinator
The Local Coordinator (LC) is responsible for the centre activity and ultimate responsibility of the data entered in the SITS registry from the hospital. The LC must be a doctor authorised by the medical head of the department.

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Local user
The Local User (LU) is responsible for entering data in the SITS registry. The LU must be appointed by the LC and operating within the stroke unit.

Internal data quality controls will be done by the SITS Coordinating Office, which will include:

1. Validation rules for key data parameters so that impossible data will not be possible to enter
2. Online monitoring to find out inconsistent data entry, data completeness
3. In addition to online data monitoring, inconsistency and completeness check every 6 months. Normally investigators are informed by newsletter regarding the completeness of data entry for overall registry and asked to complete the missing data. In case of major inconsistency or high rate of missing data investigators are contacted personally by e-mail.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Non-interventional study based on existing data

The quality of a study based on existing data relies on accuracy of recorded data. Important data may not be available.

Selection bias
There is a risk of selection bias at the patient level. Sites might preferentially include "interesting" cases to the SITS study. To minimize selection bias at the patient level, centres were reminded by e-mail every 3 months that all consecutive patients from each site who meet entry criteria must be included in the SITS-Registry.

Lost to follow up
As with all observational studies a loss to follow up can occur. In this study this will affect the patients with a pre-planned follow up (patients initiating IV thrombolysis within the 3 months after the index event). However, considering the short time period of the follow up and the lost to follow up at 3 months in the general SITS Registry being 20%, a similar percentage of lost to follow up is expected in this study as well.

For the analysis of clinical outcome events we do not exclude patients lost to follow-up after IV thrombolysis initiation and before the 3 months after index event, which could lead to underidentification of clinical outcome events.

9.10 OTHER ASPECTS

Not applicable.

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9.11 SUBJECTS

Patients over 80 years old presenting with acute ischaemic stroke symptoms for which thrombolysis treatment was initiated within 4.5 hours after stroke onset according to the SmPC during the study period June 2015 to June 2021 divided into pre-approval (June 2015 to June 2018) and post-approval (July 2018 to June 2021).

9.11.1 Cases

Not applicable.

9.11.2 Controls

Please refer to Section 9.7.1

9.12 BIAS

To assess potential channeling bias, baseline characteristics of all patients fulfilling the in/exclusion criteria and were included in SITS-ISTR registry in the defined time period will be described based on the IV thrombolysis treatment they receive for ischemic stroke within 4.5 hours from symptoms onset.

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10. PROTECTION OF HUMAN SUBJECTS

Regulated under the SITS ISTR registry. All data entered into the SITS International Thrombolysis registry are encrypted in order to maintain patient data privacy. The individual patient and its research data is identified by a unique registry identification number. Access to data is strictly controlled by permitting two-way authentication, i.e. each user a unique username and password and a code received by sms or e-mail. Additionally, each user has restrictions in viewing data sets, depending on their activity role in the database. Each data entry is centrally monitored by internal quality checks, such as automatic range checks and a full audit trail is maintained**.**

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), Adverse Event (AE) reporting is not required for Non-Interventional Study (NIS) which is based on secondary data use.

12. AS AN OBSERVATIONAL STUDY, BASED ON EXISTING DATA, ALL PATIENT DATA IS DE-IDENTIFIED AND WILL BE ANALYSED IN AGGREGATE. INDIVIDUAL PATIENT SAFETY RELATED INFORMATION WILL NOT BE CAPTURED DURING THIS STUDY. THUS, INDIVIDUAL SAFETY REPORTING IS NOT APPLICABLE. SAFETY REPORTING WILL BE DONE CUMULATIVELY IN AGGREGATE IN THE STUDY REPORT.PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results will be disclosed on EnCEPP, Publications will be prepared and the full study report will be submitted to the authorities.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	not applicable	September 2019	common-combined-Actilyse-en-clean-September 2019
2	not applicable	September 2019	SITS- IVTP Standard data entry form_2019 September

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ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

A copy of the ENCePP Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Safe Implementation of Treatments in Stroke (SITS) -

Intravenous thrombolysis in acute ischaemic stroke patients over 80 years, SITS-IVT>80 years study

EU PAS Register® number:
Study reference number (if applicable): n/a

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Section 1: Milestones	Yes	No	N/A	Section Number
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1
4.2.2 Age and sex	☒	☐	☐	9.1

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.3 Country of origin	☒	☐	☐	9.1
4.2.4 Disease/indication	☒	☐	☐	9.1
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	7
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	7
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

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Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.6 and 9.8
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.6 and 9.8
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.6 and 9.8
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

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Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.7
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	9.5

Comments:

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Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.7
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	9.5

Comments:

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ANNEX 3. ADDITIONAL INFORMATION

National Institute of Health Stroke Scale, NIHSS
The NIH stroke scale, NIHSS, is described in Attachment 1.1. The scores are entered in the on-line entry form.

Global Evaluation Scale, GES
The Global Outcome Evaluation Scale, is described in Attachment 1.2 and the questions to answer are specified at the on-line entry form.

Modified Rankin Scale (Mrs)
mRS **is described in Attachment 1.3 and the questions to answer are specified at the on-line entry form**

Brain CT/MR scan
All CT/MR scans are reviewed at the participating centre according to the local routine procedure and the outcome of the evaluation is entered in the database.

- **Baseline readings**

The CTs will be evaluated with respect to haemorrhage, any sign of acute cerebral ischemic injury in the symptomatic vascular territory, or other pathology. Preferably, CTA (CT angiography) imaging will be used for identification of cerebral artery occlusion.

- **Day 2 readings (22-36 hours after start of treatment)**

Intracerebral haemorrhage, ICH, will be classified according to the SITS-ISTR data collection format.

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1a.Level of consciousness	**0**	Alert	
	1	Not alert, but arousable with minimal stimulation	
	2	Not alert, requires repeated stimulation to attend	
	3	Coma	
1b. Ask patient the month and their age	**0**	Answers both correctly	
	1	Answers one correctly	
	2	Both incorrect	
1c.Ask patient to open/close eyes and form/release fist	**0**	Obeys both correctly	
	1	Obeyrs one correctly	
	2	Both incorrect	
2.Best gaze (only horisontal eye movements)	**0**	Normal	
	1	Partial gaze palsy	
	2	Forced gaze deviation	
3. Visual field testing	**0**	No visual field loss	
	1	Partial hemianopia	
	2	Complete hemianopia	
	3	Bilateral hemianopia (blind, incl. Cortical blindness)	
4. Facial paresis (Ask patient to show teeth or raise eyebrows and close eyes tightly)	**0**	Normal symmetrical movement	
	1	Minor paralysis (flattened nasolabial fold, asymmetry on smiling),	
	2	Partial paralysis (total or near total paralysis of lower face)	
	3	Complete paralysis of one or both sides (abscence of facial movement in the upper and lower face)	
5a. Motor function - right arm	**0**	Normal (extends arm 90 or 45 for 10 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
5b. Motor Function - left arm	**0**	Normal (extends arm 90 or 45 for 10 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
6a. Motor Function - right leg	**0**	Normal (holds leg in 30 position for 5 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
6b. Motor Function – left leg	**0**	Normal (holds leg in 30 position for 5 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Untestable (joint fused or limb amputated)	
7. Limb ataxia	**0**	No ataxia	
	1	Present in one limb	
	2	Present in two limbs	
8. Sensory (use pinprick to test arms, legs trunk and face, compare side to side)	**0**	Normal	
	1	Mild to moderate decrease in sensation	
	2	Severe to total sensory loss	
9. Best language (describe picture, name items)	**0**	No aphasia	
	1	Mild to moderate aphasia	
	2	Severe aphasia	
	3	Mute	
10. Dysarthria (read several words)	**0**	Normal articulation	
	1	Mild to moderate slurring of words	
	2	Near unintelligible or unable to speak	
	9	Intubated or other physical barrier	
11. Extinction and inattention (use visual double stimulation or sensory double stimulation)	**0**	Normal	
	1	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	
	2	Severe hemi-inattention or hemi-inattention to more than one modality	

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1.2 Global evaluation scale, GES

Has a change in the patient's clinical condition occurred after treatment?

Check one alternative:

Much better	+2
Better	+1
Unchanged	0
Worse	-1
Much worse	-2
Dead	-3

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1.3 Modified Rankin Scale, mRS

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Total (0-6): _____

APPROVAL / SIGNATURE PAGE

Document Number: c30353958 **Technical Version Number:1.0**

Document Name: ctp-safe-implementation-of-treatments-in-stroke-sits

Title: CTP-Safe Implementation of Treatments in Stroke (SITS) - Intravenous thrombolysis in acute ischaemic stroke patients over 80 years, SITS-IVT>80 years study

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-[redacted] Established Core Products	[redacted]	25 Nov 2019 12:15 CET
Approval-[redacted] Safety Evaluation Therapeutic Area		25 Nov 2019 12:24 CET
Approval-Team Member Medical Affairs		25 Nov 2019 13:35 CET
Approval-EU Qualified Person Pharmacovigilance		25 Nov 2019 13:41 CET
Approval-Pharmacovigilance		25 Nov 2019 14:17 CET
Approval-On behalf of [redacted] or [redacted] or [redacted]		25 Nov 2019 15:12 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed