

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse®			
Name of active ingredient: Alteplase			
Report date: 11 Nov 2022	Study number: 0135-0344	Version/Revision: 1.0	Version/Revision date:
Title of study:	Safe Implementation of Treatments in Stroke (SITS) - Intravenous thrombolysis in acute ischaemic stroke patients over 80 years, SITS-IVT>80 years study.		
Keywords:	ischaemic stroke, intravenous thrombolysis, elderly, safety, outcome		
Rationale and background:	Intravenous thrombolysis (IVT) with alteplase in >80 years old patients treated within 4.5h of symptom onset has been approved in a number of European and non-European countries. Pooled analysis of randomized controlled trials (RCTs) of IVT with alteplase, a recombinant tissue Plasminogen Activator (rt-PA) for acute ischaemic stroke, has shown that patients >80 years treated with IVT versus control derived equal benefit compared to patients 18-80 years. Results from 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 time delay for younger versus elderly patients, 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. This study, the SITS-IVT>80 years, was a retrospective study based on data collected in the SITS-ISTR setting from acute ischaemic stroke patients > 80 years of age. The study aimed 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 alteplase in clinical routine settings.		
Research question and objectives:	The objective of the SITS-IVT>80 years study was to compare the safety and other outcome parameters between the post-approval >80 years and pre-approval >80 years acute ischaemic stroke patients using the data already collected in SITS registry.		
Study design:	This is a retrospective observational study using existing data from the SITS registry; SITS-ISTR (International Stroke Thrombolysis Registry).		
Setting:	A non-interventional post-approval study on SITS-ISTR existing data of intravenous alteplase (0.9 mg/kg) in acute ischaemic stroke patients over 80 years, treated according to the Summary of Product Characteristics		

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse®			
Name of active ingredient: Alteplase			
Report date: 11 Nov 2022	Study number: 0135-0344	Version/Revision: 1.0	Version/Revision date:
	(SmPC) of European countries being part of the mutual recognition procedure.		
Subjects and study size, including dropouts:	Post-approval patients: Patients over 80 years old presenting with acute ischaemic stroke symptoms for which thrombolysis treatment (Actilyse®) was initiated within 4.5 hours after stroke onset according to the SmPC during the study period July 2018 to December 2021. Pre-approval patients: 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). In both periods, the plan was to include at least 500 patients from centres of European countries being part of the mutual recognition process (MRP).		
Variables and data sources:	Standard SITS-ISTR baseline, safety and outcome 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 (modified Rankin Scale [mRS] score = 6) at day 90 • Independence / favourable outcome for the activities of daily living at day 90: Functional Independence is defined as a modified Rankin Scale (mRS) score of both 0-2 and favourable as mRS 0-1 • Baseline and demographic variables available in the SITS registry for describing patient characteristics. • Patient management variables		

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse®			
Name of active ingredient: Alteplase			
Report date: 11 Nov 2022	Study number: 0135-0344	Version/Revision: 1.0	Version/Revision date:
	• Time from onset of symptoms–start of IVT treatment/ needle time • Time from onset of symptoms–door (or as captured in the registry arrival at hospital) • Door to needle time • Baseline stroke severity		
Results:	Final study population is 662 patients in the post-approval period and 993 in the pre-approval period. After propensity score matching, 614 patients remained in each group. The primary analyses were propensity score matched that compared post-approval patients to pre-approval patients. There were no statistically significant differences in the primary outcomes (SICH per SITS-MOST: 2.5% vs. 2.3%, RR: 1.064 [0.345-1.784], p=1.0; death within 3 months: 25.3% vs. 28.4%, RR 0.889 [0.699-1.08], p=0.25; functional independence as measured by modified Rankin scale score 0-2 at 90 days: 40.3% vs. 37%, RR 1.089 [0.942-1.237], p=0.28), and the secondary outcomes (SICH per ECASS 2: 5% vs. 4%, RR 1.231 [0.707-1.756], p=0.52; favourable outcome as defined by mRS 0-1 at 90 days: 27.3% vs. 25.6%, RR 1.066 [0.872-1.261], p= 0.56; NIHSS score at baseline: 11 vs. 10.5, standardized mean difference 0.016 [–0.096-0.128], p= 0.92; stroke onset to IVT start time: 151 vs. 153 minutes, standardized mean difference – 0.021 [–0.133-0.091], p= 0.81). In the secondary analysis, post-approval patients had a statistically higher chance of achieving functional independence at 3 months follow up (RR: 1.11 (1.0-1.23), p= 0.048) than pre-approval patients. There were no statistically significant differences for favourable outcome (RR 1.14 (0.98-1.31), p= 0.09), death and SICH per any definitions between post- and pre-approval periods.		
Discussion:	In this observational study, we did not find any difference in the primary and secondary outcomes between pre- and post-approval periods for IVT treatment with Actilyse® in AIS patients over 80 years old in the matched population. In the regression analysis, we observed an increased chance for functional independence in the post-approval cohort as compared to the		

BOEHRINGER INGELHEIM

Study report for non-interventional studies based on existing data

Page 8 of 45

BI Study number 0135-0344

Document number: c40616085-01

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse®			
Name of active ingredient: Alteplase			
Report date: 11 Nov 2022	Study number: 0135-0344	Version/Revision: 1.0	Version/Revision date:
	pre-approval cohort. However, we also observed some delay in patients' management in the post-approval cohort compared to the pre-approval cohort. Based on results of previous studies in non-elderly patients, our results support the similar safety and benefit of IVT treatment with alteplase in AIS patients older than 80 years in the post-approval compared with pre-approval period.		
Marketing Authorisation Holder(s):	[REDACTED] Boehringer Ingelheim Corporate Boehringer Ingelheim International GmbH [REDACTED]		
Names and affiliations of principal investigators:	[REDACTED] [REDACTED] [REDACTED]		