Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	c36563700-01
BI Study Number:	0135-0349
BI Investigational Product(s):	Actilyse® (Alteplase)
Title:	Effectiveness and safety of IV rt-PA treatment in Chinese AIS patients aged above 80 years: a real-world study
Brief lay title:	Alteplase treatment in elderly AIS patients
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	No
EU PAS register number:	EUPAS41540
Active substance:	Alteplase
Medicinal product:	Actilyse® (Alteplase)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	Primary objective: • To compare the 1-year favourable neurological functional outcome (as measured by modified Rankin Scale [mRS] score , defined as mRS 0-1) of Chinese AIS patients aged > 80 years who received IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion therapy.

	Secondary objectives: • To compare in-hospital and other 1-year clinical outcomes (including any intracranial haemorrhage (ICH), all-cause mortality during hospitalisation, independence (mRS 0-2) at 1 year, distribution of mRS score at 1 year, and all-cause mortality at 1 year. Detailed description of these outcomes are provided in the section "secondary outcomes") of elderly AIS patients who received IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion therapy. • To compare the baseline characteristics of AIS patients aged > 80 years treated with IV rt-PA within 4.5 hours of symptom onset versus AIS patients aged >80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion treatment in Zhejiang Stroke Quality Control Centre (ZSQCC) platform to evaluate potential channelling bias. [redacted]
Country(-ies) of study:	China
Author:	[redacted]
In case of PASS, add: **MAH contact person:**	Not applicable
In case of PASS, add: **<EU-QPPV:>**	Not applicable
In case of PASS, add: **<Signature of EU-QPPV:>**	Not applicable
Date:	2 Sep 2021

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2. LIST OF ABBREVIATIONS

AIS	Acute Ischaemic Stroke
ASD	Absolute Standardised Difference
BI	Boehringer Ingelheim
CDE	Centre for Drug Evaluation
CSCA	Chinese Stroke Centre Alliance
DMRP	Data Management and Review Plan
GPP	Good Pharmacoepidemiology Practice
ICH	Intracranial Haemorrhage
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
IVT	Intravenous Thrombolysis
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NIS	Non-Interventional Study(ies)
PS	Propensity Score
PSM	Propensity Score Matching
RCT	Randomised Controlled Trials
RR	Relative Risk
rt-PA	Recombinant Tissue Plasminogen Activator
RWE	Real-World Evidence
SOP	Standard Operation Procedure
ZSQCC	Zhejiang Stroke Quality Control Centre

3. RESPONSIBLE PARTIES

Boehringer Ingelheim Contact Person:

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Contact details: [redacted]

[redacted] Investigator:

[redacted]

Contact details: [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Actilyse®			
Name of active ingredient: Alteplase			
Protocol date: 2 Sep 2021	**Study number:** 0135-0349	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Effectiveness and safety of IV rt-PA treatment in Chinese AIS patients aged above 80 years: a real-world study		
Rationale and background:	Actilyse® was first approved for the treatment of acute ischaemic stroke (AIS) for patients aged 18-80 years. Data from recent studies have shown that patients aged > 80 years may also benefit from intravenous (IV) recombinant tissue plasminogen activator (rt-PA) when given within 4.5 hours of symptom onset. All countries in the European Union including Germany, Austria and Belgium have successively approved Actilyse® to remove the age restriction of 80 years since Jun 2018. Most of the data supporting this clinical overview came from western countries. As there is limited data regarding the safety or effectiveness of IV rt-PA among Chinse AIS patients aged > 80 years, the age restriction has not been removed yet by National Medical Products Administration. However, Chinese Guidelines for Diagnosis and Treatment of AIS 2014 and 2018 removed the age restriction of 80 years in the recommendations for intravenous thrombolysis (IVT) with alteplase within 3 hours and 3 to 4.5 hours of stroke onset, respectively. In addition, Chinese AIS patients aged > 80 years have been treated with IV thrombolytic therapy in clinical practice according to local guidelines. We propose to use the Zhejiang Stroke Quality Control Centre (ZSQCC) platform data to conduct a retrospective study comparing the 1-year clinical outcome of IV rt-PA treated patients versus non-reperfusion elderly (> 80 years) AIS patients.		
Research question and objectives:	Research question: Can Chinese AIS patients older than 80 years benefit from IV rt-PA treatment within 4.5 hours of symptom onset in a real-world clinical setting? Primary objective: • To compare the 1-year favourable neurological functional outcome (as measured by modified Rankin Scale [mRS] score, defined as mRS 0-1) of Chinese AIS patients aged > 80 years receiving IV rt-PA treatment within 4.5 hours of symptom onset versus those who		

Name of company: Boehringer Ingelheim			
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	arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion therapy. Secondary objectives: • To compare in-hospital and other 1-year clinical outcomes (including any intracranial haemorrhage (ICH), all-cause mortality during hospitalisation, independence (mRS 0-2) at 1 year, distribution of mRS score at 1 year, and all-cause mortality at 1 year. Detailed description of these outcomes are provided in the section "secondary outcomes") of elderly AIS patients receiving IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion therapy. • To compare the baseline characteristics of AIS patients aged > 80 years treated with IV rt-PA within 4.5 hours of symptom onset versus AIS patients aged > 80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion treatment in ZSQCC platform to evaluate potential channelling. [redacted]
Study design:	This is a NIS based on existing data from the ZSQCC platform.
Population:	Inclusion criteria: • Patients registered in the ZSQCC platform from Jan 2017 to Mar 2020 • > 80 years of age • Diagnosed with AIS at admission

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	• Arrived or admitted to the hospital within 4.5 hours of symptom onset • If treated with IV rt-PA: received IV rt-PA within 4.5 hours of symptom onset Exclusion criteria: • Documented IVT contraindication except age to IV rt-PA treatment according to the SmPC. • Missing any one of the key data (age, gender, baseline National Institutes of Health Stroke Scale [NIHSS], time of symptom onset, time of hospital arrival or admission, IVT status, time of IV rt-PA treatment) • Received thrombolysis agents other than rt-PA (urokinase, tenecteplase, recombinant plasminogen activator, prourokinase, streptokinase) • Received endovascular treatment • Received IV rt-PA after 4.5 hours of symptom onset Eligible patients from the ZAQCC platform will be divided into 2 cohorts: • IV rt-PA cohort: AIS patients aged > 80 years who received IV rt-PA within 4.5 hours of symptom onset • Non-reperfusion cohort: AIS patients aged > 80 years who arrived or were admitted to the hospital and did not receive any reperfusion treatments		
Variables:	Primary outcome: • Favourable outcome (mRS 0-1) at 1 year Secondary outcomes: • Any intracranial haemorrhage (ICH) during hospitalisation • All-cause mortality during hospitalisation • Independence (mRS 0-2) at 1 year • Distribution of mRS score at 1 year • All-cause mortality at 1 year		

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- Baseline characteristics (age, gender, NIHSS, etc.)

[redacted]

Covariates:

- Demographic and sociological characteristics
  - Age
  - Gender (male, female)
  - Body weight
  - Medical insurance status (urban employee basic medical insurance, urban resident basic medical insurance, new rural cooperative medical insurance, other insurance, no insurance)
- Lifestyle related characteristics
  - Smoking status (current smoker, former smoker, never smoker)
- Stroke severity (baseline NIHSS)
- Time from symptom onset to hospital admission
- For patients in the IV rt-PA cohort:
  - Time from symptom onset to treatment
  - Time from hospital admission to treatment
  - rt-PA dosage (dichotomised as standard dosage and low dosage)
- Comorbidities at baseline
  - Diabetes
  - Coronary artery disease
  - Atrial fibrillation
  - Prior stroke/transient ischaemic attack

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	○ Hypertension • Co-medication at baseline (anti-platelet, oral anticoagulation, lipid lowering) • Hospital level ○ Grade 2 ○ Grade 3 • Duration of hospitalization • Reasons for not being treated with rt-PA for rt-PA non treatment group
Data sources:	ZSQCC platform
Study size:	Approximately 1301 or 1146 patients, calculated by 2:1 or 1:1 treatment ratio, respectively.
Data analysis:	*To account for potential confounding, the study cohorts (patients who received IV rt-PA and patients who did not receive reperfusion treatment) will be matched by baseline characteristics using the propensity score matching (PSM) method. The PSM aims to balance the 2 treatment cohorts on baseline covariates. The feasibility of PSM will be evaluated based on available sample size and descriptive results. If patient characteristic between the 2 cohorts are significantly different, the study design will be re-evaluated before proceeding to analysis. The Nearest Neighbour method of PSM will be used to select the matched samples. The final list of baseline characteristics in the PSM will be decided in conjunction with Boehringer Ingelheim. All the variables listed in the section covariates will be considered. Covariables including duration of hospitalization and reasons for untreated with rt-PA are only for descriptive analysis. The distribution of baseline characteristics will be presented before and after the matching process.* Absolute standardized difference (ASD) between the compared groups will be calculated, in which a $\geqslant$10% ASD will be considered a meaningful difference. For baseline covariates that are not sufficiently balanced after PSM, the covariates will be included in an appropriate multivariate model to adjust for those differences. Main Analysis: A comparison of 1-year favourable outcome between the propensity score

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	(PS)-matched cohorts will be calculated using a chi-square test. A logistic regression model will be used to calculate odds ratios between cohorts. For the secondary outcomes, descriptive summaries will be conducted in the PS-matched cohorts separately. For categorical variables including any ICH and mortality during hospitalisation, independence (mRS 0-2) at 1 year, the percentage and 95% confidence interval will be calculated. A logistic regression model will be used to calculate odds ratios. For time to death up to 1 year and time to ICH during hospitalisation, a Kaplan-Meier curve will be used to analyse the data. Cox regression will be used to estimate hazard ratio for 1-year all-cause mortality between cohorts. For the distribution of mRS, an ordinal logistic regression model will be used to calculate the common odds ratio between the matched cohorts. For baseline characteristics of patients, the absolute standardised difference (ASD) between the PS-matched cohorts will be calculated, where an ASD of at least 10% ASD will be considered a meaningful difference. [redacted]
Milestones:	Protocol Approval: Oct 2021 Start of data collection: NA End of data collection: NA Statistical and epidemiological analysis plan completion: Apr 2022 Final report of study results: Jul 2022

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Protocol Approval	Oct 2021
IRB/IEC approval	Dec 2021
Statistical and epidemiological analysis plan completion	Apr 2022
Final report of study results:	Jul 2022

7. RATIONALE AND BACKGROUND

Stroke is the leading cause of mortality and disability among adults in China, which is characterized by high morbidity, disability and mortality. With the aging of society, the acceleration of urbanization, and popular unhealthy lifestyle among residents, the stroke burden in China displayed an explosive growth trend and elderly patients with AIS are becoming common in China. [R19-3903], [R21-1796], [R21-04631] According to the 2018 data in Chinese acute ischaemic stroke (AIS) patients, it was deduced that there were 12.42 million Chinese AIS patients and 1.96 million patients died due to AIS.[R19-3903] In addition, according to the report of the Chinese Stroke Centre Alliance (CSCA) from 2015 to 2017, about one fourth of the AIS patients recorded in the CSCA platform were elderly patients aged > 75 years.[P21-04633] Therefore, the prevention and treatment of stroke is still facing huge challenges in China, and further strengthening the prevention and treatment system and improving the prognosis of stroke patients are urgent needs in stroke management.

The benefit of intravenous thrombolysis (IVT) within 4.5 hours of symptom onset for AIS patients has been well proven and recommended by international/national guidelines.[P19-10385], [P21-02289], [P19-10855] A meta-analysis of randomised controlled trials (RCTs) demonstrated a positive benefit-risk ratio for alteplase when used according to label criteria.[P20-06029] The benefit–risk ratio changed with time to treatment: earlier treatment was associated with better outcomes, while delayed treatment was associated with reduced benefit.

When Actilyse® was first approved for the treatment of AIS, it was indicated only for patients aged 18 to 80 years. Recent studies suggested that patients aged > 80 years may also benefit from intravenous (IV) recombinant tissue plasminogen activator (rt-PA) when given within 4.5 hours of symptom onset.[P14-16838] Data from both RCTs and observational studies showed consistent results: patients aged > 80 years who received IV rt-PA within 4.5 hours of symptom onset had improved outcomes without increasing haemorrhage rates, although this elderly patient population had a higher mortality rate and poorer functional outcomes than younger patients do. In addition, the international guidelines recommend the IV thrombolysis with alteplase within 3 hours and 3 to 4.5 hours of stroke onset in suitable AIS patients aged >80 years.[P19-10385]

All countries in the European Union including Germany, Austria, and Belgium have successively approved Actilyse® to remove the age restriction of 80 years since Jun 2018. Until now, there is limited data regarding the safety or effectiveness of IV rt-PA among Chinse AIS patients aged > 80 years. Therefore, in China the age restriction of 80 years has not been removed yet by National Medical Products Administration. However, Chinese Guidelines for Diagnosis and Treatment of AIS 2014[P21-04636] and 2018[P19-10855] removed the age restriction of 80 years in the recommendations for IV thrombolysis with alteplase within 3 hours and 3 to 4.5 hours of stroke onset, respectively. In addition, it is common to give IV thrombolytic therapy to Chinese AIS patients aged > 80 years in clinical practice according to local guidelines.[P19-10855], [P21-04637]

In January 2020, the Chinese Centre for Drug Evaluation (CDE) released Guidelines for Real-World Evidence to Support Drug Development and Review (Interim). In this guideline, China CDE listed several scenarios demonstrating how real-world evidence (RWE) can be

used to support drug development and regulatory decision making. One of the scenarios was to use RWE to provide evidence for changing leaflets of approved drugs, including adding new applicable populations.

We propose to use the Zhejiang Stroke Quality Control Centre (ZSQCC) platform data to conduct this retrospective study comparing the 1-year clinical outcome of IV rt-PA treated patients versus non-reperfusion elderly (> 80 years) AIS patients.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: Can Chinese AIS patients older than 80 years benefit from IV rt-PA treatment within 4.5 hours of symptom onset in a real-world clinical setting?

Primary objective:

- To compare the 1-year neurological favourable functional outcome (as measured by modified Rankin Scale [mRS] score, defined as mRS 0-1) of Chinese AIS patients aged > 80 years who received IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion therapy.

Secondary objectives:

- To compare in-hospital and other 1-year clinical outcomes (including any intracranial haemorrhage (ICH), all-cause mortality during hospitalisation, independence (mRS 0-2) at 1 year, distribution of mRS score at 1 year, and all-cause mortality at 1 year. Detailed description of these outcomes are provided in the section "secondary outcomes") of elderly AIS patients who received IV rt-PA treatment within 4.5 hours of symptom onset versus those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion therapy.
- To compare the baseline characteristics of AIS patients aged > 80 years treated with IV rt-PA within 4.5 hours of symptom onset versus AIS patients aged > 80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion treatment in the ZSQCC platform to evaluate potential channelling.

[redacted]

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a NIS based on existing data. We will analyse data of AIS patients aged > 80 years in China collected from the ZSQCC platform.[P21-04780], [P21-04783], [P21-04784], [P21-04779], [P21-04782] In this study, the index date for the IV rt-PA cohort is defined as the date when rt-PA treatment is initiated. For the non-reperfusion cohort, index date is defined as the date when the patient arrived at the hospital.

Approximately 1301 or 1146 AIS patients in total are planned to be included to this study, calculated by 2:1 or 1:1 treatment ratio, respectively.

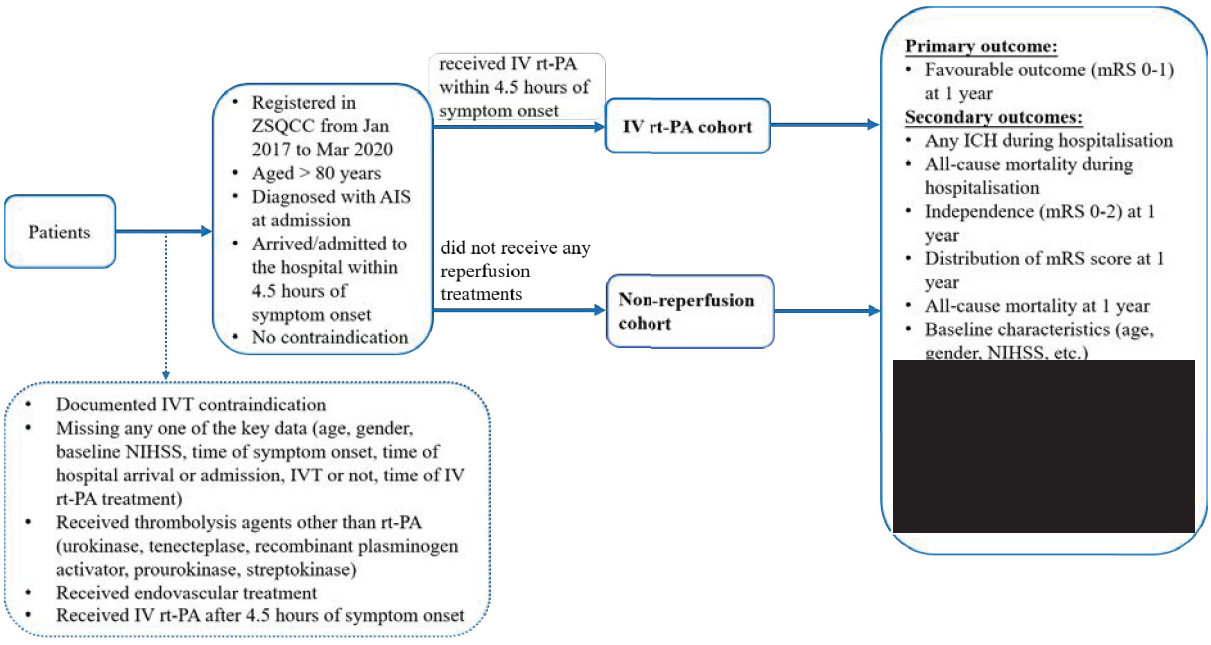
Patients meeting the inclusion/exclusion criteria will be divided into 2 cohorts:

- IV rt-PA cohort: AIS patients aged > 80 years who received IV rt-PA within 4.5 hours of symptom onset
- Non-reperfusion cohort: AIS patients aged > 80 years who arrived or admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion treatments

Propensity score matching (PSM) will be used to match the baseline characteristics between the above 2 cohorts. Clinical outcomes and baseline characteristics will be compared between the matched cohorts.

The flow of data selection for each of the 2 reporting patient cohorts is depicted in Figure 1 below.

Figure 1 Patient cohorts selected for the non-interventional study



Note: dotted lines: excluded

9.2 SETTING

9.2.1 Study sites

In this study, AIS patient data from 80 stroke centres in the ZSQCC platform from January 2017 to March 2020 will be used.

9.2.2 Study population

No sampling will be undertaken and all patients who meet all the inclusion criteria and none of the patients presenting with at least one exclusion criterion will be included.

The inclusion and exclusion criteria are listed below:

Inclusion criteria:

- Patients registered in the ZSQCC platform from Jan 2017 to Mar 2020
- > 80 years of age
- Diagnosed with AIS at admission
- Arrived or admitted to the hospital within 4.5 hours of symptom onset
- If treated with IV rt-PA: received IV rt-PA within 4.5 hours of symptom onset

Exclusion criteria:

- Documented IVT contraindication except age to IV rt-PA treatment according to the SmPC.
- Missing any one of the key data (age, gender, baseline National Institutes of Health Stroke Scale [NIHSS], time of symptom onset, time of hospital arrival or admission, IVT or not, time of IV rt-PA treatment)
- Received thrombolysis agents other than rt-PA (urokinase, tenecteplase, recombinant plasminogen activator, prourokinase, streptokinase)
- Received endovascular treatment
- Received IV rt-PA after 4.5 hours of symptom onset

9.2.3 Study visits

Not applicable.

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study at any time for the following reason:

- Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by study site, investigator or research collaborator, disturbing the appropriate conduct of the study

9.3 VARIABLES

9.3.1 Exposures

The exposure of this study is IV rt-PA treatment within 4.5 hours of symptom onset.

9.3.2 Outcomes

9.3.2.1 Primary outcome

- Favourable outcome (mRS 0-1) at 1 year

9.3.2.2 Secondary outcomes

- Any intracranial haemorrhage (ICH) during hospitalisation
- All-cause mortality during hospitalisation
- Independence (mRS 0-2) at 1 year
- Distribution of mRS score at 1 year
- All-cause mortality at 1 year
- Baseline characteristics (age, gender, NIHSS, etc.)

[redacted]

9.3.3 Covariates

The covariates to be collected at baseline as follows:

- Demographic and sociological characteristics
  - Age
  - Gender (male, female)
  - Body weight
  - Medical insurance status (urban employee basic medical insurance, urban resident basic medical insurance, new rural cooperative medical insurance, other insurance, no insurance)
- Lifestyle related characteristics
  - Smoking status (current smoker, former smoker, never smoker)
- Stroke severity (baseline NIHSS)
- Time from symptom onset to hospital admission
- For patients in the IV rt-PA cohort:
  - Time from symptom onset to treatment
  - Time from hospital admission to treatment
  - rt-PA dosage (dichotomised as standard dosage and low dosage)
- Comorbidities at baseline
  - Diabetes

  - Coronary artery disease
  - Atrial fibrillation
  - Prior stroke/transient ischaemic attack
  - Hypertension
- Co-medication at baseline
  - Anti-platelet
  - Oral anticoagulation
  - Lipid lowering
- Hospital level
  - Grade 2
  - Grade 3

Other covariates including:

- Duration of hospitalization
- Reasons for not being treated with rt-PA for rt-PA non treatment group

9.4 DATA SOURCES

9.4.1 ZSQCC platform

The current study will be conducted based on data from the ZSQCC platform, which is a continuous comprehensive reporting system that collects 100000 patient-level data from 80 stroke centres from January 2017 to March 2020.

All printed medical documents for consecutive AIS patients admitted in the stroke centre will be provided and scanned by investigators from ZSQCC. Only the de-identified scanned documents will be preserved as images in a safe information database. The local infrastructure and characteristics of each recruited centre will also be recorded.

The database includes patient demographic information, baseline clinical characteristics, indicators related to diagnosis and treatment during hospitalisation and follow-up after discharge. The platform staffs tried to follow up all discharged patients by a phone call at 1-year discharge. In addition, patients who received rt-PA treatments were followed up by a phone call at 3-month after discharge. Telephone follow-up of the platform was conducted by platform staffs. The follow-up standards were unified, and telephone recordings were all kept. Neurologists conducted trainings at regular intervals for platform staffs and randomly checked the telephone recordings. Several studies based on this dataset were approved by the Second Affiliated Hospital of Zhejiang University Institutional Review Board (IRB) and were published in peer-reviewed journals.[P21-04780], [P21-04783], [P21-04784], [P21-04779], [P21-04782]

9.4.2 CSCA platform

The CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative, launched by Chinese Stroke Association in 2015. This programme is made available to all Chinese grade 2 and 3 hospitals. Hospitals continued to join the programme in a staggered manner. By Jul 2019, 1476 hospitals (720 grade 2 hospitals, 756 grade 3 hospitals) had participated into this programme. Hospital characteristics, including geographic region, teaching status, hospital volume (grade 2 and 3) and annual stroke volume, are surveyed. Data were collected via the web-based patient data

collection and management tool ([redacted]), abstracted via chart review, coded, de-identified and transmitted in a secure manner to maintain patient confidentiality compliant with national privacy standards. The following data were collected for each hospitalization: patient demographics, history of disease and medication, hospital presentation, initial neurological status, medications and interventions, reperfusion strategy and in-hospital outcomes and complications.

9.5 STUDY SIZE

A feasibility assessment was conducted in June 2020. The results showed that there were approximately 1561 elderly AIS patients who were treated with IV rt-PA and 1037 patients who were admitted to the hospital within 4.5 hours of symptom onset without IVT contraindication and did not receive reperfusion treatment from Jan 2017 to Mar 2020 according to the ZSQCC platform database.

A meta-analysis of RCTs showed that the 3-month favourable outcome (mRS 0-1) with IV rt-PA versus the placebo arm in patients above 80 years of age was 19.1% versus 13.1% (relative risk [RR]: 1.46). In safe implementation of thrombolysis in upper time window monitoring study, the 3-month favourable outcome for IV rt-PA treated elderly patients was 26.6%. In this study, we assume the 1-year favourable outcome for IV rt-PA treated elderly patients is 28%, with the same RR (1.46) observed in RCTs, and the 1-year favourable outcome for non-reperfusion cohort is 19.2%. With the treatment ratio 2:1 between the IV rt-PA cohort and the non-reperfusion cohort, 1106 patients in total are needed to detect the treatment difference of 8.8% with 90% power and a 2-sided alpha of 0.05. Considering a 15% rate of loss to visit, 1301 patients in total are needed. If a 2:1 match cannot reach good match in terms of the major potential confounders, we may conduct a 1:1 match instead. Considering a treatment ratio 1:1 with the same assumption described above with power of 90% at a 2-sided, 974 patients are needed to detect 8.8% treatment difference, considering 15% loss to visit, 1146 patients are needed in total.

9.6 DATA MANAGEMENT

The data will be managed by ZSQCC. The source codes for data management and data analyses will be kept for inspection for at least 5 years after publication of the results.

Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

9.7 DATA ANALYSIS

For the purpose of this study, analyses will generally be descriptive in nature and will be conducted using SAS statistical software (version 9.3 or higher). Descriptive data regarding patient demographic and clinical characteristics will be calculated. For categorical measures, data will include the frequency (number of cases [n]) and percentage (%) of total study patients observed in each category (N). All variables will be summarised descriptively by tabular displays of mean, median, ranges, and standard deviations of continuous variables and frequency distributions of categorical variables. When necessary, continuous variables also

will be categorised into intervals, with the distribution of patients (n, N, %) for each interval provided.

The statistical analysis plan for the study is summarised below. Full details of the statistical analysis will be documented in the statistical and epidemiological analysis plan, which will be finalised before the end of data extraction.

As this is a NIS based on existing data, no formal hypothesis testing or comparisons between treatment cohorts are planned.

9.7.1 Main analysis

To account for potential confounding, the study cohorts (patients who received IV rt-PA and patients who did not receive reperfusion treatment) will be 1:1 or 1:2 matched by baseline characteristics using the PSM method. The PSM aims to balance the 2 treatment cohorts on baseline covariables. The feasibility of PSM will be evaluated based on available sample size and descriptive results. If patient characteristic between the 2 cohorts are significantly different, i.e., less than 50% of patients in the IV rt-PA cohort can be matched to the non-reperfusion cohort based on PSM, the study design will be re-evaluated before proceeding to analysis. The Nearest Neighbour method of PSM will be used to select the matched samples. The final list of baseline characteristics in the PSM will be decided in conjunction with BI. All variables listed in the covariates will be considered. Covariables including duration of hospitalization and reasons for untreated with rt-PA are only for descriptive analysis. The distribution of baseline characteristics will be presented before and after the matching process. Absolute standardized difference (ASD) between the compared groups will be calculated, in which a $\geqslant$10% ASD will be considered a meaningful difference. For baseline covariates that are not sufficiently balanced after PSM which is assessed using ASD, the covariates will be included in an appropriate multivariate model to adjust for those differences.

For the primary outcome, a comparison of 1-year mRS 0-1 score between the 2 propensity score (PS)-matched cohorts will be calculated using a chi-square test. A logistic regression model will be used to calculate odds ratios between 2 matched cohorts.

For the secondary outcomes, descriptive summaries will be conducted in the PS-matched cohorts separately. For categorical variables including any ICH during hospitalisation, mortality during hospitalisation, and mRS 0-2 at 1 year, the percentage and 95% confidence interval will be calculated. A logistic regression model will be used to calculate the odds ratios.

For time to death up to 1 year and time to ICH during hospitalisation, a Kaplan-Meier curve will be used to analyse the data. Cox regression will be used to estimate hazard ratio for 1-year all-cause mortality between PS-matched cohorts.

For the distribution of mRS, an ordinal logistic regression model will be used to calculate the odds ratio between the PS-matched cohorts.

9.7.3 Safety analysis

This is a NIS based on existing data. From safety information collecting and reporting perspective, this study will not involve individual medical record review, thus no adverse event/adverse drug reaction information is required to collect. The analysis refers to Section 9.7.2.

9.8 QUALITY CONTROL

The study will strictly follow BI standard operation procedures (SOPs). In addition, this study will follow key elements of the Guideline for GPP. The statistical analytic approach will be reviewed/repeated by a second analyst. The study report will be reviewed, approved and archived per BI SOP.

All the data cleaning, integration, and analysis will be conducted under the guidance and supervision of ZSQCC.

Greater details are documented in the NIS-DMRP.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This is a NIS based on existing data. Although PSM is used, we cannot rule out the influence of unmeasured confounding factors. In this study, potential limitations of the study design can be listed as:

- Zhejiang is an economically advanced province in China. Patients in this study may not be fully representative to all AIS patients in China. We plan to compare the

baseline characteristics of patients in this study with those from CSCA to evaluate the representativeness of the population in this study.
- AIS patient data from the ZSQCC platform were reported by the stroke centre without external monitoring.
- The treatment adapted for AIS patients may be different among stroke centres.
- The completeness of the captured data and potential for misclassification of data could differ among stroke centres.
- Some important variables may not be collected in the database. For example, patients' education level was not available in the database. Another example is that patients who did not receive rt-PA treatments were not followed up at 3 months after discharge. Therefore, for outcomes at 3 months we could only describe them in the rt-PA treated cohort.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the investigator or by IRBs / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to the investigator's study-related files and correspondence of this study.

9.10.2 Study records

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data extracted.

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related audits, IRB/IEC review and regulatory inspection, providing direct access to all related database/documents. All source documents, including progress notes must be available at all times for review by the inspection by health authorities.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice, guidelines for GPP, and the relevant BI SOPs.

10.1 STUDY APPROVAL AND PATIENT INFORMATION

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/IEC and Competent Authority according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the study need to be available for inspection upon request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology[R11-4318] and the European Medicines Agency[R13-1970], NIS such as the one described in this proposal, conducted using health care records, do not require expedited reporting of suspected adverse events/reactions. Specifically, as stated in section VI.C.1.2.1 of Guideline on Good Pharmacovigilance Practices, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, for NIS designs, which are based on use of secondary data, reporting of adverse reactions is not required. Not applicable based on the secondary use of data without any potential that any employee of BI or agent working on behalf of BI will asceses individually identifiable patient data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalisation of the study report.

Boehringer Ingelheim intends to use data from this study to prepare peer-reviewed publications and other scientific communications such as abstracts, posters, and podiums presentations.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R19-3903 Wang LD, Liu JM, Yang Y, Peng B, Wang YL, and others on behalf of the compiling group of the Report on Stroke Prevention and Treatment in China 2018. The Prevention and Treatment of Stroke Still Face Huge Challenges—Brief Report on Stroke Prevention and Treatment in China 2018. Chin Circ J. 2019; 34(2):105–119.

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P19-10385 Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019; 50(12):e344-e418.

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13 September 2011); Bethesda: International Society for Pharmacoepidemiology (ISPE); 2007. [B(MB1]

R13-1970 European Medicines Agency (EMA), Heads of Medicines Agencies (HMA); 2012.Guideline on good pharmacovigilance practices (GVP): module VI - management and reporting of adverse reactions to medicinal products (22 June 2012, EMA/873138/2011).

13.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

1.	**Study title:** Effectiveness and safety of IV rt-PA treatment in Chinese AIS patients aged above 80 years: a real-world study

2.	**EU PAS Register® number:**
3.	**Study reference number (if applicable):**

4. Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection1	☐	☐	☒	6
1.1.2 End of data collection2	☐	☐	☒	6
1.1.3 Progress report(s)	☐	☒	☐	NA
1.1.4 Interim report(s)	☐	☒	☐	NA
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	NA
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

5. Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 and 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)	☒	☐	☐	7
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)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	NA

Comments:

[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.

6. 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 and 9.3.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☒	☐	NA
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))	☐	☒	☐	NA
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)	☒	☐	☐	9.7.3 and 11

Comments:

7. Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2.2
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.4.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

8. 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)	☒	☐	☐	9.3.1

8. Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	NA
5.3 Is exposure categorised according to time windows?	☐	☒	☐	NA
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	NA
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	NA

Comments:

9. 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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
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)	☐	☐	☒	NA
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)	☐	☒	☐	NA

Comments:

10. Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.1, 9.7, and 9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7

Comments:

11. **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, subgroup analyses, anticipated direction of effect)	☐	☒	☐	NA

Comments:

12. 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)	☒	☐	☐	9.3.1 and 9.4.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
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)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	NA
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	NA
9.3.3 Covariates and other characteristics?	☐	☐	☒	NA
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	NA

Comments:

13. 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?	☐	☐	☒	NA
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	NA
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	NA
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2

Comments:

14. 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)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10.1
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	NA

Comments:

15. 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).	☐	☐	☒	NA

15. Section 12: Limitations	Yes	No	N/A	Section Number
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)	☒	☐	☐	9.1 and 9.2

Comments:

16. Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

17. Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

18. Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year 2021. 9. 2

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

None.

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA			
Global PVWG Chair	X		
GPV SC			
Global CTIS representative			
Local Medical Director /Market Access	X (if local study)		X
Local Head MAcc / HEOR Director			
Global TA Head Epi*			
Global TA Head Clinical Development / Medical Affairs / Market Access*			
Global TA Head PV RM*			
RWE CoE (for NISnd only)	X	X	X
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM			
Local Head MA/Clinical Development			

** After review by Global TM for function*

Study Title: Effectiveness and safety of IV rt-PA treatment in Chinese AIS patients aged above 80 years: a real-world study

Study Number: 0135-0349

Protocol Version: 1.0

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____