# Protocol for non-interventional study

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| **Document Number:** | c36696074-01 |
| **BI Study Number:** | 0135-0348 |
| **BI Investigational Product(s):** | Actilyse® (Alteplase) |
| **Title:** | Characteristics and in-hospital outcomes of Chinese elderly (>80 years) patients with acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator treatment within 4.5 hours of symptom onset |
| **Brief lay title:** | Alteplase in elderly AIS during hospitalization |
| **Protocol version identifier:** | 1.0 |
| **Date of last version of protocol:** | Not applicable |
| **PASS:** | No |
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| **Active substance:** | Alteplase |
| **Medicinal product:** | Actilyse® (Alteplase) |
| **Product reference:** | Not applicable |
| **Procedure number:** | Not applicable |
| **Marketing authorisation holder(s):** | Boehringer Ingelheim (China) Investment Co., Ltd |
| **Joint PASS:** | No |
| **Research question and objectives:** | Primary objective:<br>• To describe all-cause mortality during hospitalization of acute ischemic stroke (AIS) patients who were treated with intravenous recombinant tissue plasminogen activator (IV rt-PA) within 4.5 hours of symptom onset, among those aged 18 to 80 years and >80 years, respectively.<br>Secondary objectives:<br>• To describe other in-hospital clinical outcomes (including proportion of patients with hemorrhagic stroke during |

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| | hospitalization, change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatment, mRS score at discharge, proportion of patients with stroke recurrence during hospitalization, and length of hospitalization) of AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, among those aged 18 to 80 years and >80 years, respectively<br>• To describe the characteristics of AIS patients who arrived or were admitted to the hospital within 4.5 hours of symptom onset and were treated with or without IV rt-PA among different age groups (18 to 80 years and above 80 years).<br>• To describe the percentage of patients receiving IV rt-PA treatment within 4.5 hours of symptom onset among AIS patients aged 18 to 80 years and above 80 years who arrived at or were admitted to the hospital within 4.5 hours of symptom onset. |
| | [redacted] |
| **Country(-ies) of study:** | China |
| **Author:** | [redacted]<br>Medical Advisor |
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| *In case of PASS, add:* **<Signature of EU-QPPV:>** | Not applicable |
| **Date:** | 22 Sep 2021 |
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# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AIS | Acute Ischemic Stroke |
| ASD | Absolute Standardized Difference |
| BI | Boehringer Ingelheim |
| CDE | Chinese Centre for Drug Evaluation |
| CI | Confidence Intervals |
| CSA | Chinese Stroke Association |
| CSCA | Chinese Stroke Centre Alliance |
| eCRF | Electronic Case Report Form |
| EVT | Endovascular Treatment |
| IEC | Independent Ethics Committee |
| INR | International Normalized Ratio |
| IQR | Interquartile Range |
| IRB | Institutional Review Board |
| IV | Intravenous |
| IVT | Intravenous Thrombolysis |
| NIHSS | National Institutes of Health Stroke Scale |
| NIS | Non-interventional Study |
| NIS-DMRP | Non-interventional Study-data Management and Review Plan |
| PT | Prothrombin Time |
| RCTs | Randomized Controlled Trials |
| rt-PA | Recombinant Tissue Plasminogen Activator |
| RWE | Real-world Evidence |
| SEAP | Statistical and Epidemiological Analysis Plan |
| SOPs | Standard Operation Procedures |
| TIA | Transient Ischemic Attack |
| ZSQCCP | Zhejiang Stroke Quality Control Center Platform |

# 3. RESPONSIBLE PARTIES

Boehringer Ingelheim Contact Person:

[redacted]

Contact details: [redacted]

Principal Investigator:

[redacted]

Contact details: [redacted]

# 4. ABSTRACT

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| **Name of company:** Boehringer Ingelheim | | | |
| **Name of finished medicinal product:** Actilyse | | | |
| **Name of active ingredient:** Alteplase | | | |
| **Protocol date:** 22 Sep 2021 | **Study number:** 0135-0348 | **Version/Revision:** 1.0 | **Version/Revision date:** |
| **Title of study:** | Characteristics and in-hospital outcomes of Chinese elderly (>80 years) patients with acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator treatment within 4.5 hours of symptom onset | | |
| **Rationale and background:** | Actilyse® was first approved for the treatment of acute ischaemic stroke (AIS) for patients aged 18 to 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. 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.<br><br>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 IV thrombolysis 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.<br><br>In this study, we propose to use the Chinese Stroke Centre Alliance (CSCA) data to describe the in-hospital clinical outcomes regarding safety and effectiveness for AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, aged above 80 years, as well as between 18 and 80 years. We plan to apply and incorporate the results of this study (providing in-hospital outcomes), together with another non-interventional study in China (providing 1-year clinical outcomes), as well as results from randomized controlled trials conducted in other countries, to support local label update: to remove the age restriction (>80 years) from the label of Actilyse in China. | | |
| **Research question and objectives:** | **Research question:** What are the in-hospital clinical outcomes among Chinese AIS patients, who were treated with IV rt-PA within 4.5 hours of symptom onset in different age groups (18 to 80 years and above 80 years). | | |

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| | **Primary objective:**<br>• To describe all-cause mortality during hospitalization of AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, among those aged 18 to 80 years and >80 years, respectively.<br><br>**Secondary objectives:**<br>• To describe other in-hospital clinical outcomes (including proportion of patients with hemorrhagic stroke during hospitalization, change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatment, mRS score at discharge, proportion of patients with stroke recurrence during hospitalization, and length of hospitalization) of AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, among those aged 18 to 80 years and >80 years, respectively<br>• To describe the characteristics of AIS patients who arrived or were admitted to the hospital within 4.5 hours of symptom onset and were treated with or without IV rt-PA among different age groups (18 to 80 years and above 80 years).<br>• To describe the percentage of patients receiving IV rt-PA treatment within 4.5 hours of symptom onset among AIS patients aged 18 to 80 years and above 80 years who arrived at or were admitted to the hospital within 4.5 hours of symptom onset.<br><br>[redacted] |
| **Study design:** | This is a non-interventional study based on existing data from CSCA platform. |
| **Population:** | **Inclusion Criteria:**<br>• Patients registered in the CSCA platform from Aug 2015 to Jul 2019<br>• ≥18 years old |

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| | • Diagnosed as AIS at admission<br>• Arrived or admitted to hospital within 4.5 hours of symptom onset<br>• For patients in the IV rt-PA groups only: received IV rt-PA within 4.5 hours of symptom onset<br><br>**Exclusion Criteria:**<br>• Documented intravenous thrombolytics (IVT) absolute contraindication except age to IV rt-PA treatment according to the SmPC.<br>• Key data missing (age, gender, baseline National Institutes of Health Stroke Scale [NIHSS], time of symptom onset, IVT treated or not, time of IV alteplase treatment)<br>• Received thrombolysis agents other than IV rt-PA (urokinase, tenecteplase, recombinant plasminogen activator, prourokinase, streptokinase)<br>• Received endovascular treatment<br>• Received IV rt-PA after 4.5 hours of symptom onset<br><br>**Patient groups:**<br>Patients in this study will be divided into 4 groups:<br>• Group 1: AIS patients aged >80 years who received IV rt-PA within 4.5 hours of symptom onset<br>• Group 2: AIS patients aged 18 to 80 years who received IV rt-PA within 4.5 hours of symptom onset<br>• Group 3: AIS patients aged >80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive thrombolysis treatment<br>• Group 4: AIS patients aged 18 to 80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive thrombolysis treatment |
| **Variables:** | **Covariates** include the following variables at baseline:<br>• Age<br>• Gender (male, female)<br>• Stroke severity (baseline NIHSS)<br>• Time from symptom onset to hospital arrival or admission<br>• Smoking (current smoker, former smoker, never smoker) |

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- Alcohol consumption (yes, no)
- Comorbidities at baseline (diabetes, prior coronary heart disease /myocardial infarction, atrial fibrillation/flutter, prior heart failure, carotid stenosis, peripheral vascular disease, prior stroke/transient ischemic attack, hypertension, dyslipidaemia)
- Comedication at baseline (antiplatelet, anticoagulation, antidiabetics, antihypertensive drug, lipid-lowering drug)
- For IV rt-PA treated patients: time from symptom onset to treatment, time from hospital arrival or admission to treatment (door-to-needle time), dosage of rt-PA
- For No IV rt-PA treated patients: Reasons for not being treated with IV rt-PA
- Education (primary school or below, junior high school, senior high school, junior college or above)
- Medical insurance status (urban employee basic medical insurance, urban resident basic medical insurance, new rural cooperative medical insurance, other medical insurance, no insurance)
- Hospital level (Grade 2, Grade 3).

Variables collected during hospitalization:

- Lab values: blood-glucose, C-reactive protein;
- Clinical symptoms: evaluation of swallowing ability, pneumonia;

**Primary outcomes:**

- All-cause mortality during hospitalization of patients in Group 1 and Group 2.

**Secondary outcomes:**

- Proportion of patients with hemorrhagic stroke during hospitalization
- Change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatment
- mRS score at discharge
- Proportion of patients with stroke recurrence during hospitalization
- Length of hospitalization;
- All the above in-hospital secondary outcomes will be observed in Group 1 and Group 2.
- Percentage of IV rt-PA treatment among AIS patients arrived or were

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| | admitted to the hospital within 4.5 hours of symptom onset.<br>• Percentage of IV rt-PA treatment within 4.5 hours of symptom onset among eligible AIS patients (3.5-hour arrival or admission)<br>The percentage of IV rt-PA treatment will be calculated based on age groups (18-80 years and > 80 year).<br>[redacted] |
| **Data sources:** | Data for this study will come from the CSCA platform.The CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative, launched by Chinese Stroke Association (CSA) in 2015. This programme is made available to all Chinese Grade 2 and Grade 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 (Medicine Innovation Research Center, Beijing, China), 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. |
| **Study size:** | A feasibility check showed that by Jul 2019, according to the key inclusion and exclusion criteria, there were roughly 31,400 ( 28,100 aged 18 to 80 years, 3,300 above 80 years) AIS patients treated with IV rt-PA and 84,000 (72,000 aged 18 to 80 years; 12,000 above 80 years) AIS patients arrived at hospital within 4.5 hours of symptom onset but did not receive reperfusion treatment.<br><br>Previous studies showed that the incidence of symptomatic intracerebral hemorrhage for IVT treated patients was 2.4% among 18 to 80 years age group |

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and 3.7% among >80 years age group. Table 1 showed the 95% confidence intervals (CI) with the current sample size and the incidence rates from previous studies:

Table 1 Estimated rates of in-hospital hemorrhage stroke and 95% CI

| Age Group | Current Sample Size | Incidence Based on Previous Studies | 95%CI |
|---|---|---|---|
| ⩾18 years | N=31400 | 3.6% | 3.40%, 3.82% |
| 18-80 years | N=28100 | 2.4% | 2.22%, 2.59% |
| >80 years | N=3300 | 3.7% | 3.07%, 4.41% |

**Data analysis:**

The primary and secondary outcomes will be analysed by using descriptive statistics for group 1 and group 2. The baseline characteristics (covariates) will be described descriptively for all 4 groups in this study.

To evaluate the potential channelling, the baseline characteristics of AIS patients aged >80 years treated with iv rtPA within 4.5 hours of symptom onset (group 1) will be compared with the following 2 groups:

Patients aged >80 years who did not receive reperfusion and who arrived at or admitted to the hospital within 4.5 hours of symptom onset (group 3)

Patients aged 18-80 years who received iv rtPA and who arrived at or admitted to the hospital within 4.5 hours of symptom onset (group 2)

Absolute standardized difference (ASD) between the compared groups will be calculated, in which a ⩾10% ASD will be considered a meaningful difference.

[redacted]

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| **Protocol date:** 22 Sep 2021 | **Study number:** 0135-0348 | **Version/Revision:** 1.0 | **Version/Revision date:** |
| | For general statistical considerations, the descriptive statistics for continuous variables will include mean, standard deviation, 95% CI of mean,median, interquartile range; for categorical variables, counts, percentages and 95% CI will be included. For categorical variables, 95% Clopper-Pearson confidence interval will be used.<br>[redacted] | | |
| **Milestones:** | Protocol finalisation: Oct 2021<br>Start of data collection: NA<br>End of data collection: NA<br>Statistical and epidemiological analysis plan completion: Apr 2022<br>*Final report of study results: Jul 2022* | | |

# 5. AMENDMENTS AND UPDATES

Not applicable.

# 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],[P21-04631] 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 Alliance from 2015 to 2017, about one fourth of the AIS patients recorded in the China Stroke Centre Alliance (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 IV recombinant tissue plasminogen activator (rt-PA) when given within 4.5 hours of symptom onset. [P21-04636] 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 recommends 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.

In this study, we propose to use the Chinese Stroke Centre Alliance (CSCA) data to describe the in-hospital clinical outcomes regarding safety and effectiveness for AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, aged >80 years, as well as between 18 and 80 years.

# 8. RESEARCH QUESTION AND OBJECTIVES

**Research question:**
What are the in-hospital clinical outcomes among Chinese AIS patients, who were treated with IV rt-PA within 4.5 hours of symptom onset in different age groups (18 to 80 years and above 80 years).

**Primary objective:**
To describe all-cause mortality during hospitalization of AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, among those aged 18 to 80 years and >80 years, respectively.

**Secondary objectives:**

- To describe other in-hospital clinical outcomes (including proportion of patients with hemorrhagic stroke during hospitalization, change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatment, mRS score at discharge, proportion of patients with stroke recurrence during hospitalization, and length of hospitalization) of AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, among those aged 18 to 80 years and >80 years, respectively.
- To describe the characteristics of AIS patients who arrived or were admitted to the hospital within 4.5 hours of symptom onset and were treated with or without IV rt-PA among different age groups (18 to 80 years and above 80 years).
- To describe the percentage of patients receiving IV rt-PA treatment within 4.5 hours of symptom onset among AIS patients aged 18 to 80 years and above 80 years who arrived at or were admitted to the hospital within 4.5 hours of symptom onset.

# 9. RESEARCH METHODS

## 9.1 STUDY DESIGN

This is a non-interventional study based on existing data from CSCA platform.

Patients in this study will be divided into 4 groups:

- Group 1: AIS patients aged >80 years who received IV rt-PA within 4.5 hours of symptom onset
- Group 2: AIS patients aged 18 to 80 years who received IV rt-PA within 4.5 hours of symptom onset
- Group 3: AIS patients aged >80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive thrombolysis treatment
- Group 4: AIS patients aged 18 to 80 years who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive thrombolysis treatment.

The baseline characteristics will be described in groups 1 to 4.

The clinical outcomes during hospitalization will be observed in groups 1 to 2.

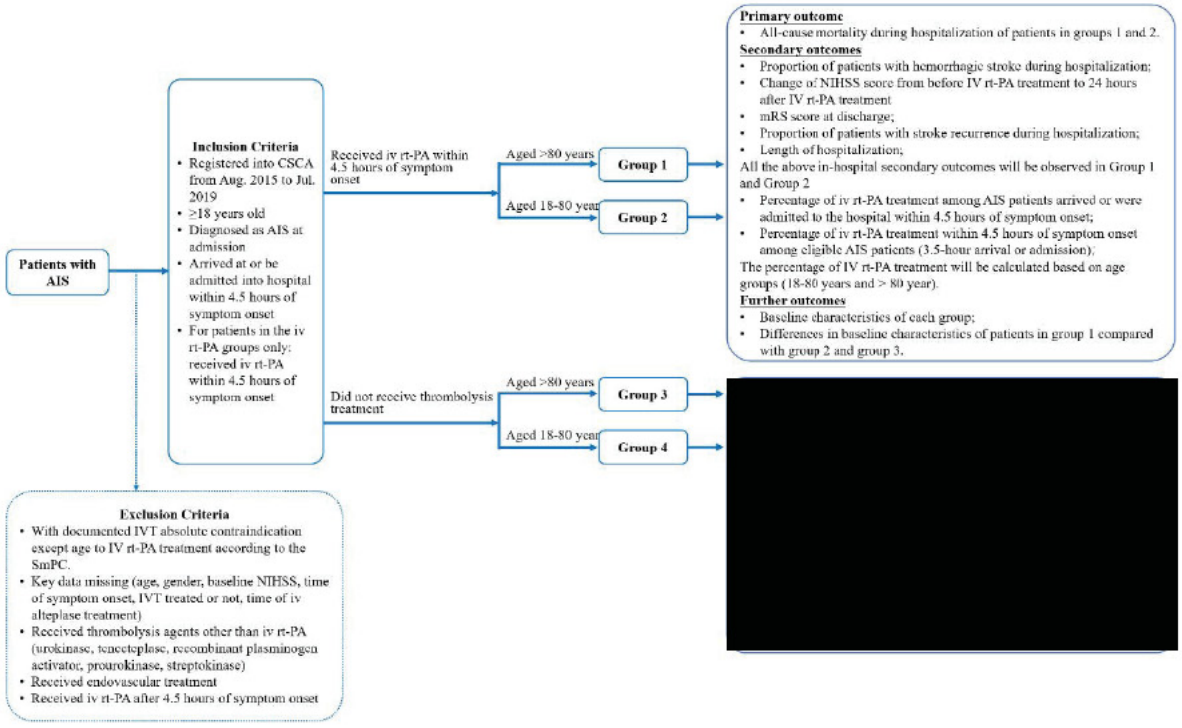
In addition, the percentage of AIS patients who received IV rt-PA treatment within 4.5 hours of onset will be calculated among 4.5 hours hospital arrival AIS patients, and IVT eligible patients (3.5 hours hospital arrival or admission and without IVT absolute contraindication), in each age group of 18 to 80 years and >80 years, respectively.

In China, rt-PA is only indicated in AIS patients aged 18 to 80 years. Therefore, it is possible that AIS patients aged >80 years who received IV rt-PA are different from other patients in terms of their baseline characteristics (channeling). To evaluate the potential channeling, in this study we will compare the baseline characteristics of AIS patients aged >80 years treated with IV rt-PA within 4.5 hours of symptom onset (Group 1) with those in Group 2 and Group 3.

[redacted]

The flow of data selection for each of the 4 reporting patient groups is depicted in Figure 1 below.

Figure 1 Patient groups for the non-interventional study




Note: AIS, Acute Ischemic Stroke; CSCA, Chinese Stroke Centre Alliance; iv, Intravenous; rt-PA, Recombinant Tissue Plasminogen Activator; IVT, Intravenous Thrombolysis.

## 9.2 SETTING

### 9.2.1 Study sites

In this study, AIS patients from 1476 hospitals (720 Grade 2 hospitals and 756 Grade 3 hospitals)in the CSCA platform from Aug 2015 to Jul 2019 will be used.

### 9.2.2 Study population

Acute ischemic stroke (AIS) patients who were treated with IV rt-PA or did not receive thrombolysis treatment within 4.5 hours of symptom onset, aged ≥18 years old.

No sampling will be undertaken and all patients who meet all the inclusion criteria and none of the exclusion criteria will be included.

The inclusion and exclusion criteria are listed below:

Inclusion Criteria:

- Patient registered in the CSCA platform from Aug 2015 to Jul 2019
- ≥18 years old
- Diagnosed as AIS at admission
- Arrived or admitted into hospital within 4.5 hours of symptom onset
- For patients in the iv rt-PA groups only: received IV rt-PA within 4.5 hours of symptom onset.

Exclusion Criteria:

- Documented IVT absolute contraindication
- Key data missing (age, gender, baseline National Institutes of Health Stroke Scale [NIHSS], time of symptom onset, IVT treated or not, time of IV alteplase treatment)
- Received thrombolysis agents other than IV 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 in this study is the use of IV rt-PA among AIS patients within 4.5 hours of symptom onset.

### 9.3.2 Outcomes

9.3.2.1 Primary outcome

- All-cause mortality during hospitalization of patients in Group 1 and Group 2.

9.3.2.2 Secondary outcomes

- Proportion of patients with hemorrhagic stroke during hospitalization
- Change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatment
- mRS score at discharge
- Proportion of patients with stroke recurrence during hospitalization
- Length of hospitalization;

All the above in-hospital secondary outcomes will be observed in Group 1 and Group 2.

- Percentage of IV rt-PA treatment among AIS patients arrived or were admitted to the hospital within 4.5 hours of symptom onset
- Percentage of IV rt-PA treatment within 4.5 hours of symptom onset among eligible AIS

patients (3.5-hour arrival or admission)

The percentage of IV rt-PA treatment will be calculated based on age groups (18-80 years and > 80 year).

[redacted]

### 9.3.3 Covariates

Covariates include the following variables at baseline:

- Age
- Gender (male, female)
- Stroke severity (baseline NIHSS)
- Time from symptom onset to hospital arrival or admission
- Smoking (current smoker, former smoker, never smoker)
- Alcohol consumption (yes, no)
- Comorbidities at baseline:
    - Diabetes
    - Prior coronary heart disease /myocardial infarction
    - Atrial fibrillation/flutter
    - Prior heart failure
    - Carotid stenosis
    - Peripheral vascular disease
    - Prior stroke/Transient Ischemic Attack (TIA)
        - Prior stroke
        - Prior TIA
    - Hypertension
    - Dyslipidaemia
- Comedication at baseline (antiplatelet, anticoagulation, antidiabetics, antihypertensive drug, lipid-lowering drug)
- For IV rt-PA treated patients:
    - Time from symptom onset to treatment
    - Time from hospital arrival or admission to treatment (door-to-needle time)
    - Dosage of rt-PA
- For No IV rt-PA treated patients:
    - Reasons for not being treated with IV rt-PA
- Education
    - Primary school or below
    - Junior high school
    - Senior high school

  - Junior college or above
- Medical insurance status (urban employee basic medical insurance, urban resident basic medical insurance, new rural cooperative medical insurance, other medical insurance, no insurance)
- Hospital level
  - Grade 2
  - Grade 3

Variables collected during hospitalization:

- Lab values: blood-glucose, C-reactive protein;
- Clinical symptoms: evaluation of swallowing ability, pneumonia;

## 9.4 DATA SOURCES

The CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative, launched by Chinese Stroke Association (CSA) in 2015. This programme is made available to all Chinese Grade 2 and Grade 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 check showed that by Jul 2019, according to the key inclusion and exclusion criteria, there were roughly 31,400 (28,100 aged 18-80 years, 3,300 above 80 years) AIS patients treated with IV rt-PA and 84,000 (72,000 aged 18 to 80 years; 12,000 above 80 years) AIS patients arrived at hospital within 4.5 hours of symptom onset but did not receive reperfusion treatment.

Previous studies showed that the incidence of symptomatic intracerebral hemorrhage for IVT treated patients was 2.4% among 18 to 80 years age group and 3.7% among > 80 years age group. [P14-16838] Table 1 showed the 95% confidence intervals with the current sample size and the incidence rates from previous studies:

Table 1 Estimated rates of in-hospital hemorrhage stroke and 95% CI

| Age Group | Current Sample Size | Incidence Based on Previous Studies | 95%CI |
|---|---|---|---|
| ⩾18 years | N=31,400 | 3.6% | 3.40%, 3.82% |
| 18-80 years | N=28,100 | 2.4% | 2.22%, 2.59% |

| | | | |
|---|---|---|---|
| >80 years | N=3,300 | 3.7% | 3.07%, 4.41% |

## 9.6 DATA MANAGEMENT

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

Routine operations of the CSCA are conducted and managed by the CSA staff. These operations are as follows: update and maintain the CSCA web-based data collection and management tool; develop and run site feedback reports and execute research analyses as part of its role as the CSCA data coordinating centre. The CSCA's data coordinating centre resides at the [redacted] Hospital.

All statistical analysis will be using SAS version 9.3 or above.

## 9.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the SEAP, which will be finalized before the end of data collection.

### 9.7.1 Main analysis

The baseline characteristics (covariates) as listed in Section 9.3.3 will be analysed by using descriptive statistics for all 4 groups in this study, where Group 1 is compared against group 2 and Group 1 is compared against Group 3 to evaluate the potential channeling. Absolute standardized difference (ASD) between the compared groups will be calculated, in which a ≥10% ASD will be considered a meaningful difference.

The primary outcome is the all-cause mortality during hospitalization. The primary outcome will be described using descriptive statistics for Group 1 and Group 2. The secondary outcome as listed in Section 9.3.2.2 will also be described using descriptive statistics for Group 1 and Group 2. Additionally, if the baseline characteristics of patients in group 1 are comparable to patients in group 3 (ASD<10%), then we will describe the in-hospital outcomes for group 3 patients, including all-cause mortality during hospitalization, proportion of patients with hemorrhagic stroke during hospitalization, mRS score at discharge, proportion of patients with stroke recurrence during hospitalization, and length of hospitalization. If the baseline characteristics of patients in group 1 and group 3 are not comparable, then we will not describe the above outcomes in group 3.

For general statistical considerations, the descriptive statistics for continuous variables will include mean, standard deviation, 95% confidence interval (CI) of mean, median, interquartile range (IQR); for categorical variables, counts, percentages, and 95% CI will be included. For categorical variables, 95% Clopper-Pearson confidence interval will be used.

In terms of the display of decimal places, mean, median, and IQR will be reported to one more decimal place than the raw data recorded in the database. Standard deviation and 95% confidence interval will be reported to two more decimal places than the raw data recorded in the database. P-value will be reported to fourth decimal place if available.

### 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 please refer to Section 9.7.2.

## 9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

The study will strictly follow BI standard operation procedures (SOPs). In addition, this study will follow key elements of the Guideline for GPP.[R16-5416] The statistical analytic approach will be reviewed/repeated by a second analyst. The study report will be reviewed, approved and archived per BI SOP.

## 9.9 LIMITATIONS OF THE RESEARCH METHODS

Hospital participation in the CSCA is voluntary. As a result, the current participating hospitals are more likely to be larger, tertiary centers with a myriad of resources to which smaller hospitals do not have access. Although hospital recruitment remains ongoing, the findings from CSCA may not be generalizable to patients who present with acute stroke/TIA to hospitals outside of the CSCA. Data collected by hospitals were not independently audited by external chart review. Data reliability depends on training for data abstractors and built-in automated checks to identify erroneous, illogical data entries.

The CSCA data only collected in-hospital outcomes for AIS patients. Therefore, in this study it is not possible to look at the clinical outcomes at relatively long-term follow-up period, e.g., 3 months or 1 year. However, we will have another non-interventional study (NIS) in parallel based on the Zhejiang Stroke Quality Control Center Platform (ZSQCCP) data which include AIS patients in Zhejiang province aged >80 years who received and who did not receive IVT with 12-month follow-up.

## 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 and 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[R16-5416] 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 secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access 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.

R21-1796 Gao Y, Jiang B, Sun H, Ru X, Sun D, Wang L, Wang L, Jiang Y, Feigin VL, Wang Y, Wang W. The burden of stroke in China: Results from a nationwide population-based epidemiological survey. PLoS One. 2018; 13(12):e0208398.

P21-04631 Wang YJ, Li ZX, Gu HQ, Zhai Y, Jiang Y, Zhao XQ, Wang YL, Yang X, Wang CJ, Meng X, Li H, Liu LP, Jing J, Wu J, Xu AD, Dong Q, Wang D, Zhao JZ; China Stroke Statistics 2019 Writing Committee. China Stroke Statistics 2019: A Report From the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. Stroke Vasc Neurol. 2020; 5(3):211-239.

P21-04633 Wang YJ, Li ZX, Wang YL, Zhao XQ, Liu LP, Yang X, Wang CY, Gu HQ, Zhang FY, Wang CJ, Xian Y, Wang DZ, Dong Q, Xu AD, Zhao JZ, on behalf of Chinese Stroke Center Alliance investigators. Chinese Stroke Center Alliance: a national effort to improve healthcare quality for acute stroke and transient ischaemic attack: rationale, design and preliminary findings. Stroke Vasc Neurol. 2018; 3:256-262.

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.

P21-02289 Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C, de la Ossa NP, Strbian D, Tsivgoulis G, Turc G. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. 2021; 6(1):I-LXII.

P19-10855 Society of Neurology, Chinese Stroke Society. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. Chin J Neurol. 2018; 51(9):666-682.

P20-06029 Bluhmki E, Danays T, Biegert G, Hacke W, Lees KR. Alteplase for Acute Ischemic Stroke in Patients Aged >80 Years: Pooled Analyses of Individual Patient Data. Stroke. 2020; 51(8):2322-2331.

P14-16838 Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014; 384(9958):1929-1935.

P21-04636 Society of Neurology, Chinese Stroke Society. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2014. Clin J Neurol. 2015; 48(4):246-257.

P21-04637 Liu LP, Chen WQ, Duan WY, Huo XC, Xu WH, Li SJ, Li ZX, Huang LA, Wang CX, Zheng GH, Wang YJ. Chinese Stroke Association Guidelines for Clinical Management of Cerebrovascular Disorders (Excerpts)-Clinical Management of Ischemic Cerebrovascular Disorders. Chin J Stroke. 2019; 14(7):709-726.

R16-5416 International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP), Pharmacoepidemiol Drug Saf. 2015;25(1):2-10.

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

**Study title:** Characteristics and in-hospital outcomes of Chinese elderly (>80 years) patients with acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator treatment within 4.5 hours of symptom onset

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

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | 6 |
| 1.1.1 Start of data collection[1] | ☐ | ☐ | ☒ | |
| 1.1.2 End of data collection[2] | ☐ | ☐ | ☒ | |
| 1.1.3 Progress report(s) | ☐ | ☒ | ☐ | |
| 1.1.4 Interim report(s) | ☐ | ☒ | ☐ | |
| 1.1.5 Registration in the EU PAS Register® | ☐ | ☒ | ☐ | |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | |

Comments:

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| **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? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no a priori hypothesis? | ☐ | ☐ | ☒ | |

Comments:

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| **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? | ☒ | ☐ | ☐ | 9.4 |

[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.

| Section 3: Study design | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☐ | ☒ | ☐ | |
| 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)) | ☒ | ☐ | ☐ | 9.7.2 |
| 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) | ☐ | ☒ | ☐ | |

Comments:

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| Section 4: Source and study populations | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.4 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.2.1 |
| 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 | ☒ | ☐ | ☐ | 9.3.2 |
| 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:

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| 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 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☒ | ☐ | |
| 5.3 Is exposure categorised according to time windows? | ☐ | ☒ | ☐ | |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.7.2 |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☒ | ☐ | |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☐ | ☒ | ☐ | |

Comments:

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| 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) | ☐ | ☒ | ☐ | |
| 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) | ☒ | ☐ | ☐ | 9.9 |
| 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) | ☒ | ☐ | ☐ | 9.9 |

Comments:

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| 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) | ☒ | ☐ | ☐ | 9.3.3 |

Comments:

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| 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) | ☒ | ☐ | ☐ | 9.4 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.4 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 9.4 |
| 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) | ☐ | ☐ | ☒ | |

Comments:

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| 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? | ☐ | ☒ | ☐ | |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☒ | ☐ | |
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☒ | ☐ | |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 9.7 |

Comments:

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

Comments:

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| 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). | ☐ | ☐ | ☒ | |
| 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:

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| Section 13: Ethical/data protection issues | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 9.10.1 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☒ | ☐ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10.2 |

Comments:

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

Comments:

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| 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)? | ☐ | ☒ | ☐ | |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

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

Date: dd/Month/year 202|.9.22

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: Characteristics and in-hospital outcomes of Chinese elderly (>80 years) AIS patients receiving IV rt-PA treatment within 4.5 hours of symptom onset**

**Study Number: 0135-0348**

**Protocol Version: 1.0**

**I here with 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**:** _____