Non-Interventional Study (NIS) Protocol

Document Number:	c36821715-01
BI Study Number:	0135-0350
BI Investigational Product(s):	Actilyse® (Alteplase)
Title:	1-year clinical outcomes after intravenous rt-PA for Chinese AIS patients
Brief lay title:	1-year clinical outcomes in rt-PA treated Chinese AIS patients
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	NO
EU PAS register number:	EUPAS41543
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: • To compare the 1-year mortality of AIS patients treated with IV rt-PA 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 treatment. Secondary objective: • To compare the 1-year neurological functional outcome (as measured by Modified Rankin Scale [mRS]) of AIS patients treated with IV rt-PA 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.
Country(-ies) of study:	China
Author:	[redacted] Medical Advisor
In case of PASS, add: **MAH contact person:**	*NA*
In case of PASS, add: **<EU-QPPV:>**	***NA***
In case of PASS, add: **<Signature of EU-QPPV:>**	***NA***
Date:	2 Sep 2021

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2. LIST OF ABBREVIATIONS

AIS	Acute Ischaemic Stroke
ASD	Absolute Standardised Difference
BI	Boehringer Ingelheim
CI	Confidence Interval
DMRP	Data Management and Review Plan
GPP	Good Pharmacoepidemiology Practice
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
rt-PA	Recombinant Tissue Plasminogen Activator
SOP	Standard Operation Procedure
tPA	Tissue-type Plasminogen Activator
ZSQCC	Zhejiang Stroke Quality Control Centre

3. RESPONSIBLE PARTIES

Boehringer Ingelheim Contact Person:

[redacted]

Contact details: [redacted]

Principal 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:** 0135-0350	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	1-year clinical outcomes after intravenous rt-PA for Chinese AIS patients		
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. According to the Global Burden of Disease study 2019, data for acute ischaemic stroke (AIS) patients in China, it is deduced that there were 12.42 million Chinese AIS patients with 2.87 million new cases every year, and 1.03 million patients died due to AIS in 2019. The benefit of intravenous thrombolysis (IVT) treatment within 4.5 hours of symptom onset for AIS patients has been well proven and recommended by international/national guidelines. Recent real-world studies from western countries indicated that intravenous (IV) recombinant tissue plasminogen activator (rt-PA) treatment of AIS patients was associated with decreased long-term mortality. However, there are very limited data in terms of the effectiveness of IV rt-PA treatment on the long-term clinical outcomes, especially, mortality among AIS patients in China. In this study, we plan to evaluate the 1-year clinical outcomes comparing IV rt-PA treated patients versus non-reperfusion AIS patients (≥ 18 years) based on Zhejiang Stroke Quality Control Centre (ZSQCC) platform data.		
Research question and objectives:	Research question: In a real-world clinical setting, what are the 1-year clinical outcomes among AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset compared with those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion treatment? Primary objective: • To compare the 1-year mortality of AIS patients treated with IV rt-PA 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 treatment.		

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	Secondary objective: • To compare the 1-year neurological functional outcome (as measured by Modified Rankin Scale [mRS]) of AIS patients treated with IV rt-PA 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.
Study design:	This is a non-interventional study based on existing data from the ZSQCC platform.
Population:	Inclusion Criteria: • Patients registered in the ZSQCC platform from Jan 2017 to Mar 2020 • ≥ 18 years of age • Diagnosed with AIS at admission • Arrived or admitted to 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 Eligible patients from the ZSQCC platform will be divided into 2 cohorts: • IV rt-PA cohort: AIS patients who received IV rt-PA within 4.5 hours of symptom onset

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	• Non-reperfusion cohort: AIS patients who arrived or were admitted to the hospital and did not receive any reperfusion treatments		
Variables:	Primary outcomes: • All-cause mortality at 1 year (mRS=6) Secondary outcomes: • Functional independence (mRS 0-2) at 1 year • Favourable clinical outcome (mRS 0-1) at 1 year • mRS 5-6 at 1 year • Distribution of mRS score at 1 year Covariates: • Demographic and sociological characteristics o Age o Gender (male, female) o Body weight o 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 o Smoking status (current smoker, former smoker, never smoker) • Stroke severity (baseline NIHSS) • Pre-stroke mRS • Time from symptom onset to hospital admission • For patients in the IV rt-PA cohort: o Time from symptom onset to treatment o Time from hospital admission to treatment o rt-PA dosage (dichotomised as standard dosage and low dosage) • Comorbidities at baseline o Diabetes		

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	○ 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 • Duration of hospitalization • Reasons for not being treated with rt-PA for rt-PA non treatment group
Data sources:	ZSQCC platform
Study size:	Approximately 11700 patients; There are roughly8500 AIS patients≥ 18 years of age who have been treated with IV rtPA and 3200 patients who admitted to hospital within 4.5 hours of onset and did not receive reperfusion treatment from Jan 2017 to Mar 2020. In the China National Stroke Registry I (2007-2008) the 12-month mortality rate for post-stroke patients is around 14%. For this study, it is assumed that 1-year mortality is 12% and 15% for the rt-PA treatment group and the group who did not receive reperfusion. In total, 6069 patients with treatment ratio 2:1are needed to observe 855 events and to detect the difference (HR=0.79) with 2-sideded alpha of 0.05 and 90% power. In addition, considering a treatment ratio 1:1 with the same assumption described above with power of 90% at a 2-sided, 5% significant level, roughly 5400 patients are needed to observe 756 events to detect the difference.

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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 using the propensity score matching (PSM) method. Propensity score will be derived from predicted probabilities of treatment initiation. 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 two groups are significantly different, i.e., less than 50% of patients in the iv. rt-PA group can be matched to the non-reperfusion group based on PSM, then 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. All the 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. 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: Baseline characteristics of patients who received IV rt-PA and who didn't receive reperfusion treatments will be described, both before and after PSM. Absolute standardised difference (ASD) between the propensity score (PS)-matched cohorts will be calculated, in which a ≥ 10% ASD will be considered a meaningful difference. In the primary analysis, all patients who received endovascular treatment will be excluded. For the primary outcome, all-cause mortality at 1-year (mRS=6), will be evaluated using Kaplan-Meier curve. The percentage of 1-year mortality with 95% confidence intervals (CIs) in the 2 PS-matched cohorts will be calculated separately. Cox regression models will be used to estimate the hazard ratio for the primary outcome between PS-matched cohorts. For the secondary outcomes, descriptive summaries will be conducted in the PS-matched cohorts separately. For categorical variables including functional independence (mRS 0-2), favourable clinical outcome (mRS 0-1) and outcome of mRS 5-6, the percentage and 95% CI will be calculated. A logistic regression model will be used to calculate odds ratios. For the		

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	distribution of mRS at 1 year, an ordinal logistic regression model will be used to calculate the odds ratio and 95% CI. The primary and secondary outcomes will be analysed using the same method for subgroups (baseline NIHSS score, onset to treatment time, age and rt-PA dose).Subgroup analyses will be conducted only when the patient number of each subgroup is equal to or exceeds 6069 or 5400 based on 2:1 or 1:1 treatment ratio assumption, respectively. [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], [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] Therefore, the prevention and treatment of stroke is still facing huge challenges in China, 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) treatment 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 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.

Past randomised studies have demonstrated that recombinant tissue plasminogen activator (rt-PA) thrombolysis treatment did not affect 3-month mortality, and the clinical benefit mainly focuses on reducing the disability.[P14-16838] Recent real-world studies from western countries indicated that intravenous (IV) rt-PA treatment of AIS patients is associated with decreased long-term mortality: 1) Survival was higher in the IV alteplase treated group (median, 5.72 years) compared with control group (4.98 years). After Cox regression analysis, thrombolysis reduced risk of mortality by 37% (hazard ratio, 0.63; 95% confidence interval [CI], 0.48-0.82) at 10 years; however, after introducing a multiplicative interaction term into the model, mortality risk reduction was 42% (hazard ratio, 0.58; 95% CI, 0.40-0.82) at 10 years for those arriving within 3 hours to the hospital. On average, in a 10-year period, treated patients lived 1 year longer than controls. There was no difference in stroke recurrence.[P18-01688] 2) Treatment with IV tissue-type plasminogen activator (tPA) was associated with a lower risk of long-term mortality (adjusted hazard ratio, 0.66; 95% CI, 0.49-0.88). The long-term risk of recurrent ischemic stroke (adjusted hazard ratio, 1.05; 95% CI, 0.68-1.64) and major bleeding (adjusted hazard ratio, 0.59; 95% CI, 0.24-1.47) did not differ significantly between the IV tPA-treated and non-treated patients.[P14-13950] 3) The median length of the stroke admission was 9 days in the thrombolysed group and 13 days in the non-thrombolysed group (adjusted geometric mean ratio, 0.88; 95% CI: 0.78-1.00). The median all-cause hospital bed day use within the first year was 12 days in the thrombolysed group and 19 days in the non-thrombolysed group (adjusted geometric mean ratio, 0.82; 95% CI: 0.73-0.92). There was no significant difference in the overall risk of readmission (adjusted hazard ratio, 0.91; 95% CI: 0.79-1.04); however, thrombolysis was associated with reduced risk of pneumonia (adjusted hazard ratio, 0.59; 95% CI: 0.35-0.97).[P16-12462]

However, there are very limited data in terms of the effectiveness of IV rt-PA treatment on the long-term clinical outcomes, especially, mortality among AIS patients in China. In this study, we plan to evaluate the 1-year clinical outcomes comparing IV rt-PA treated AIS

patients versus non-reperfusion AIS patients (≥ 18 years) based on the Zhejiang Stroke Quality Control Centre (ZSQCC) platform data.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: In a real-world clinical setting, what are the 1-year clinical outcomes among AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset compared with those who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion treatment?

Primary objective:

- To compare the 1-year mortality of AIS patients treated with IV rt-PA 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 treatment.

Secondary objective:

- To compare the 1-year neurological functional outcome (as measured by Modified Rankin Scale [mRS]) of AIS patients treated with IV rt-PA 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.

9. RESEARCH METHODS

A) STUDY DESIGN

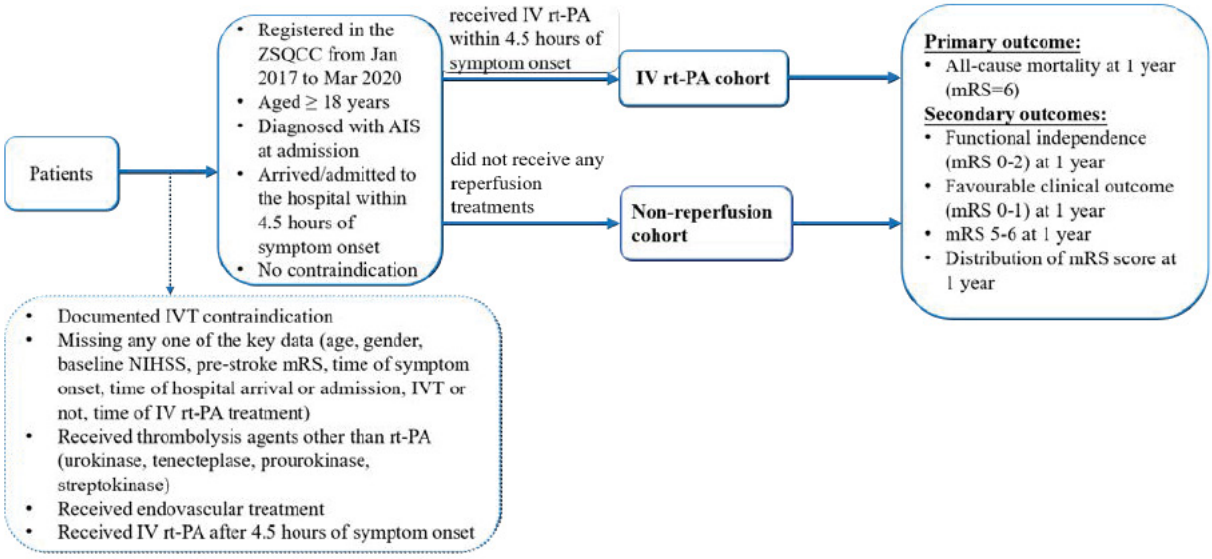
This study is a non-interventional study (NIS) based on existing data. We will analyse data of AIS patients aged ≥ 18 years in China collected from the ZSQCC platform.[P21-04780], [P21-04783], [P21-04784], [P21-04779], [P21-04782]

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

- IV rt-PA cohort: Patients who received IV rt-PA within 4.5 hours of symptom onset
- Non-reperfusion cohort: Patients who arrived or were admitted to the hospital within 4.5 hours of symptom onset and did not receive any reperfusion treatment

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

B) SETTING

i. 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.

ii. Study population

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:

- Patients registered in the ZSQCC platform from Jan 2017 to Mar 2020
- ≥ 18 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

iii. Study visits

Not applicable.

iv. Study discontinuation

Boehringer Ingelheim (BI) 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

C) VARIABLES

i. Exposures

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

ii. Outcomes

1. Primary outcome:

- All-cause mortality at 1 year (mRS=6)

2. Secondary outcomes:

- Functional independence (mRS 0-2) at 1 year
- Favourable clinical outcome (mRS 0-1) at 1 year
- mRS 5-6 at 1 year
- Distribution of mRS score at 1 year

iii. Covariates

The covariates to be collected at baseline are as follows:

- Demographic and sociological characteristics
  - Age
  - Gender (male, female)
  - 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)
- Pre-stroke mRS
- 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

D) DATA SOURCES

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

All medical documents for consecutive acute stroke patients admitted in the stroke centre will be provided 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. 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]

E) STUDY SIZE

There were approximately 8500 AIS patients (≥ 18 years of age) who were treated with IV rt-PA and 3200 patients who were admitted to the hospital within 4.5 hours of symptom onset and did not receive reperfusion treatment from Jan 2017 to Mar 2020.

In the China National Stroke Registry I (2007-2008), the 12-month mortality rate for post-stroke patients was approximately 14%.[R21-1852] For this study, it is assumed that 1-year mortality is 12% and 15% for the rt-PA treatment cohort and the cohort who did not receive reperfusion, respectively. In total, 6069 patients with a treatment ratio 2:1 are needed to observe 855 events and to detect the difference (hazard ratio=0.79) with a 2-sided alpha of 0.05 and 90% power. In addition, considering a treatment ratio 1:1 with the same assumption described above with power of 90% at a 2-sided, 5% significant level, roughly 5400 patients are needed to observe 756 events to detect the difference.

F) 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).

G) 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 through 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.

i. 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 2:1 matched by baseline characteristics using the propensity score matching (PSM) method. Propensity score (PS) will be derived from predicted probabilities of treatment initiation. 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 characteristics 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. All the 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. 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.

Baseline characteristics of patients who received IV rt-PA and who didn't receive reperfusion treatments will be described, both before and after PSM. 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.

In the primary analysis, all patients who received endovascular treatment will be excluded. For the primary outcome, all-cause mortality at 1-year (mRS=6), will be evaluated using from the Kaplan-Meier curve. The percentage of 1-year mortality with 95% CIs in the 2 PS-matched cohorts will be calculated separately. Cox regression models will be used to estimate the hazard ratio for the primary outcome between PS-matched cohorts.
For the secondary outcomes, descriptive summaries will be conducted in the PS-matched cohorts separately. For categorical variables including functional independence (mRS 0-2), favourable clinical outcome (mRS 0-1) and outcome of mRS 5-6, the percentage and 95% CI will be calculated. A logistic regression model will be used to calculate odds ratios for functional independence (mRS 0-2), favourable clinical outcome (mRS 0-1) and outcome of mRS 5-6. For the distribution of mRS at 1 year, an ordinal logistic regression model will be used to calculate the odds ratio and 95% CI.

The primary and secondary outcomes will be analysed using the same method described above in following subgroups:

- Baseline NIHSS score (0-4, 5-10, 11-15, 16-21 and ≥ 22)
- Onset to treatment time (≤ 90 mins, 91-180 mins, and 181-270 mins)
- Age (18-80 years, > 80 years)
- rt-PA dose (low dose of ~0.6 mg/kg, standard dose 0.9 mg/kg)

Subgroup analyses will be conducted only when the patient number of each subgroup is equal to or exceeds 6069 or 5400 based on 2:1 or 1:1 treatment ratio assumption, respectively.

[redacted]

iii. Safety analysis

This study 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 ii.

H) 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, analysis will be conducted under the guidance and supervision of ZSQCC.

Greater details are documented in the NIS-DMRP.

I) LIMITATIONS OF THE RESEARCH METHODS

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

- Zhejiang is an economically advanced province in China. In this study, AIS patients who received treatment or arrived or were admitted to the hospital within 4.5 hours of symptom onset in this study will be analysed and may not be fully representative to all AIS patients in China.
- AIS patient data from the ZSQCC platform were reported by the stroke centres 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.

J) OTHER ASPECTS

i. 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.

ii. Study records

1. Source documents

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

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.

A) 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.

B) 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 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

A) 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.

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.

P18-01688 Walter Muruet, Anthony Rudd, Charles D.A. Wolfe, and Abdel Douiri. Long-Term Survival After Intravenous Thrombolysis for Ischaemic Stroke. A Propensity Score-Matched Cohort With up to 10-Year Follow-Up. Stroke. 2018; 49:607–613.

P14-13950 Marie Louise Schmitz, Claus Z. Simonsen, Heidi Hundborg, Hanne Christensen, Karsten Ellemann, Karin Geisler, Helle Iversen, Charlotte Madsen, Mary-Jette Rasmussen, Karsten Vestergaard, Grethe Andersen, and Soeren P. Johnsen. Acute Ischemic Stroke and Long-Term Outcome After Thrombolysis Nationwide Propensity Score–Matched Follow-Up Study. Stroke. 2014; 45:3070–3072.

P16-12462 Terkelsen T, Schmitz ML, Simonsen CZ, Hundborg HH, Christensen HK, Gyllenborg J, et al. Thrombolysis in acute ischaemic stroke is associated with lower long-term hospital bed day use: a nationwide propensity score-matched follow-up study. Int J Stroke. 2016 Oct;11(8):910-916.

P21-04780 Zhang CC, Lou M, Chen ZC, Chen HF, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT. Analysis of intravenous thrombolysis time and prognosis in patients with in-hospital stroke. J Zhejiang Univ (Med Sci). 2019; 48(3):260-266.

P21-04783 Chen HF, Gong XX, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT, Lou M, Chen ZC. Advanced treatment time improves outcomes of patients with ischaemic stroke undergoing reperfusion therapy. J Zhejiang Univ (Med Sci). 2019; 48(3):247-253.

P21-04784 Zhong WS, Chen ZC, Chen HF, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT, Lou M. Effects of emergency medical service on prognosis of ischaemic stroke patients treated with intravenous thrombolysis. J Zhejiang Univ (Med Sci). 2019; 48(3):241-246.

P21-04779 Pan FH, Lou M, Chen ZC, Chen HF, Xu DJ, Wang ZM, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT. Effect of different working time on the prognosis of ischemic stroke patients undergoing intravenous thrombolysis. J Zhejiang Univ (Med Sci). 2019; 48(3):267-274.

P21-04782 Tao AY, Wang ZM, Chen HF, Xu DJ, Hu HF, Wu CL, Zhang XL, Ma XD, Wang YX, Hu HT, Lou M. Association of atrial fibrillation with hemorrhagic transformation after intravenous thrombolysis in patients with ischaemic stroke. J Zhejiang Univ (Med Sci). 2019; 48(3): 254-259.

R21-1852 Zhan Wang, Jingjing Li, Chunxue Wang, Xiaomei Yao, Xingquan Zhao, Yilong Wang,Hao Li, Gaifen Liu, Anxin Wang, Yongjun Wang. Gender Differences in 1-Year Clinical Characteristics and Outcomes after Stroke: Results from the China National Stroke Registry. PLoS ONE 8(2): e56459. doi:10.1371/journal.pone.0056459.

R11-4318 Guidelines for Good Pharmacoepidemiology Practices (GPP) (revision 2: April 2007). Source: http://www.pharmacoepi.org/resources/guidelines_08027.cfm (access date: 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).

B) UNPUBLISHED REFERENCES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

1.	**Study title:** 1-year clinical outcomes after intravenous rt-PA for Chinese AIS patients

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®	☒	☐	☐	6
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)	☒	☐	☐	9.2.2
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?	☒	☐	☐	9.3.1
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, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.1

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
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 Director	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 NISed 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: 1-year clinical outcomes after intravenous rt-PA for Chinese AIS patients

Study Number: 0135-0350

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**:** _____

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