

## Clinical Trial Protocol

<b>Document Number:</b>		<b>c08776773-03</b>
<b>BI Trial No.:</b>	135.331	
<b>BI Investigational Products:</b>	Actilyse®, Alteplase (rt-PA)	
<b>Title:</b>	An open label, multicenter, single-arm trial to assess safety and efficacy of alteplase (rt-PA) in Chinese patients with acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4.5 hours after stroke onset	
<b>Lay Title:</b>	Stroke-Ampoule	
<b>Clinical Phase:</b>	IIIb	
<b>Trial Clinical Monitor:</b>	Tel : Email:	
<b>Coordinating Investigator:</b>	Tel: Fax: Email:	
<b>Status:</b>	Final Protocol (Revised Protocol based on Global Amendment 2)	
<b>Version and Date:</b>	<b>Version:</b>	<b>Date:</b>
	3.0	15 Feb 2017

## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Name of company:</b>		<b>Boehringer Ingelheim</b>	
<b>Name of finished product:</b>		Actilyse®	
<b>Name of active ingredient:</b>		Alteplase (rt-PA)	
<b>Protocol date:</b> 25 Apr 2016	<b>Trial number:</b> 135.331		<b>Revision date:</b> 15 Feb 2017
<b>Title of trial:</b>	An open label, multicenter, single-arm trial to assess safety and efficacy of alteplase (rt-PA) in Chinese patients with acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4.5 hours after stroke onset		
<b>Coordinating investigator :</b>			
Tel: Fax: Email:			
<b>Trial sites:</b>	Multi-center trial conducted in China (will be conducted at neurology clinics or stroke units and with 24 hours access to an adequate imaging scanner and lab tests) About 15 sites		
<b>Clinical phase:</b>	III b		
<b>Objectives:</b>	To evaluate the safety and efficacy of alteplase when administered between 3 and 4.5 hours after onset of stroke symptoms in Chinese patients with acute ischemic stroke		
<b>Methodology:</b>	Multi-center, open label, single arm study		
<b>No. of patients: total entered:</b>	120		
<b>Diagnosis :</b>	Acute Ischemic Stroke (AIS)		
<b>Main criteria for inclusion:</b>	<p>To be eligible, patients must fulfil the following criteria:</p> <p><b>Main inclusion criteria:</b></p> <ol style="list-style-type: none"> <li>Age <math>\geq</math> 18 years at screening(visit 1A) but <math>\leq</math> 80 years</li> <li>Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial</li> <li>Diagnosis of ischemic stroke with a measureable neurological deficit on National Institute of Health Stroke Scale (NIHSS)</li> <li>Thrombolytic therapy can be initiated within 3 to 4.5 hours of stroke onset</li> </ol>		

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<b>Main exclusion criteria</b> <ol style="list-style-type: none"> <li>1. Evidence of intracranial haemorrhage (ICH) on the CT/MRI-scan or symptoms suggestive of subarachnoid haemorrhage, even if the CT/MRI-scan is normal</li> <li>2. Acute bleeding diathesis</li> <li>3. Severe stroke as assessed clinically( e.g. NIHSS&gt;25) and/ or imaging demonstrates multi-lobar infarction (hypodensity &gt;1/3 cerebral hemisphere)</li> <li>4. Severe uncontrolled arterial hypertension, e.g. systolic blood pressure&gt;185 mmHg or diastolic blood pressure&gt;110mmHg, or aggressive management (IV medication) necessary to reduce BP to these limits</li> <li>5. Blood glucose &lt;50mg/ dL or &gt;400 mg/dL</li> <li>6. Any history of prior stroke in previous 3 months, or any history of prior stroke with concomitant diabetes</li> <li>7. Seizure at stroke onset</li> </ol>			
<b>Test product:</b>		Alteplase	
<b>dose:</b>		0.9 mg/kg (Maximum dose 90 mg)	
<b>mode of administration:</b>		(10% bolus+90% infusion/60minutes) 10% of total dose administered as a bolus over 1-2 minutes and remaining 90% given by continuous IV infusion over 60 minutes if no allergic reaction within 5 minutes following administration of test dose.	
<b>Comparator products:</b>		NA	
<b>dose:</b>		NA	
<b>mode of administration:</b>		NA	
<b>Duration of treatment:</b>		Bolus plus one hour infusion	
<b>Efficacy Endpoints</b>		<b>Primary Efficacy Endpoint:</b> <ul style="list-style-type: none"> <li>• The percentage of mRS 0-1 (favourable outcome) responder at visit 5 (i.e., day 90)</li> </ul> <b>Secondary Efficacy Endpoint:</b> <ul style="list-style-type: none"> <li>• The percentage of global outcome responder at visit 5 (i.e., day 90) if he/she obtains the following results at visit 5 (i.e., day 90) (for all of the 4 endpoints)</li> </ul>	

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		mRS score of 0 to 1 Barthel Index score $\geq 95$ NIHSS score of 0 to 1 Glasgow Outcome Scale score of 1	
<b>Safety criteria:</b>	<b>Primary Safety endpoints:</b> <ul style="list-style-type: none"> <li>The percentage of patients with symptomatic intracranial haemorrhage (sICH) within the whole study period centrally evaluated by DMC consultants, according to ECASSIII criteria, details refer to section 5.3.1.</li> </ul> <b>Secondary Safety Endpoints:</b> <ul style="list-style-type: none"> <li>Patient survival probability at visit 5 (censoring at 90 days)</li> </ul>		

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	<ul style="list-style-type: none"> <li>• Frequency of death related to stroke or of neurological causes</li> <li>• Frequency and severity of adverse events</li> <li>• The percentage of patients with cerebral herniation and symptomatic edema</li> </ul>		
<b>Statistical methods:</b>	<p>The sICH rate will be estimated as the proportion of patients with sICH event within the whole study period and its exact 95% confidence interval will be calculated.</p> <p>Efficacy endpoints will be assessed in the treated set. The proportion of mRS 0-1 (favourable outcome) responders will also be calculated along with its 95% CI. From the historical literature review, the best guess of the response rate is around 50%. It is assumed that the primary efficacy endpoint in this study will be comparable with this number.</p> <p>Descriptive statistics of demographic, safety and efficacy data will be presented as appropriate.</p>		

## FLOW CHART

Visit	1A (Screening)	Trial Drug Admin	1B	1C	2	3	4	5
Day	0				1	7	30	90
	≤4.5 Hrs		1 Hr #	2 Hrs #				
Time Window			± 15Mins	±30Mins	±2Hrs	±3Days	±3Days	±7Days
Informed consent <sup>1</sup>	X							
Demographics	X							
Medical History	X							
Cerebral imaging and interpretation	X <sup>2</sup>				X <sup>3</sup>	X <sup>4</sup>	X <sup>4</sup>	
Physical Exam , vital signs	X		X	X	X	X	X	X
In- / Exclusion Criteria	X							
Lab Test	X <sup>5</sup>				X <sup>6</sup>	X		X <sup>6</sup>
Pregnancy Test(blood or urine)	X <sup>7</sup>				X <sup>6</sup>			X <sup>6</sup>
Concomitant Therapy	X		X	X	X	X	X	X
Administration of Alteplase		← dminis tr						
Adverse Events	X	X	X	X	X	X	X	X
12-Lead ECG	X		X	X		X		
NIHSS <sup>8</sup>	X			X	X	X	X	X
Glasgow Outcome Score <sup>8</sup>								X
Modified Rankin Scale <sup>8</sup>							X	X

Barthel Index <sup>8</sup>							X	X
Conclude subject participation <sup>9</sup>								X

1. Informed consent needs to be signed before any procedure related to the study. When it is signed, all AEs and concomitant treatment occurring after Informed Consent have to be recorded. Procedures which are performed as part of routine clinical care prior to obtaining the informed consent could be used for screening if they are within the allowed time window (after stroke onset and before drug administration). (considered by investigator).
2. Either CT or MRI is mandatory before Alteplase administration to exclude ICH (absolute contraindication) or mimic stroke (e.g. cerebral tumor) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present. The brain imaging should be interpreted by a physician with expertise in reading CT and MRI. Investigator could make decision whether or not an imaging outside the site could be used for evaluation of inclusion/exclusion criteria.
3. Cerebral image: between 22 and 36 hours after starting the infusion of trial medication.
4. Optional in case of clinical deterioration (considered by investigator)
5. For some lab results used for eligibility evaluation, e.g., random blood glucose, coagulation items, platelet, it is mandatory to get their results before drug administration. For other lab results, it is recommended but not mandatory (considered by investigator).
6. Optional in case of clinical deterioration or clinical demand (considered by investigator)
7. It is acceptable whether it is test with blood or urine (considered by investigator), but it is mandatory to have the test result verified by investigator before administration, since it might impact eligibility evaluation, too.
8. Strongly recommended, the same person should conduct all neurological questionnaires for each individual patient.
9. Trial completion:
  - At the end of visit 5 (Day 90 per protocol) for patients who have completed the trial on treatment and came to future visits as planned.
  - After early discontinuation, if a patient refuses to attend future visits as originally planned.

# Time after the start of infusion of study drug

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## ABBREVIATIONS

ADL	Activity Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIS	Acute ischaemic stroke
aPTT	Activated Partial Thromboplastin Time
AUC	Area under the Curve
B.I.	Boehringer Ingelheim
BI	Barthel Index
b.i.d.	bis in die (twice daily dosing)
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BP	Blood Pressure
CCDS	Company Core Data Sheet
CDE	Center of drug evaluation
CFDA	China Food and Drug Administration
CI	Confidence Interval
CML	Local Clinical Monitor
CNS	Central Nervous System
CNSR	Chinese National Stroke Registry
CPK	Creatinphosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CTSU	Clinical Trial Supply Unit
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECASS III	European Cooperative Acute Stroke Study III
ECG	Electrocardiogram
ED	Emergency Department
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
GCP	Good Clinical Practice
r-GT	Gamma-Glutamyl Transpeptidase
HPC	Human Pharmacology Center
IB	Investigator's Brochure
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology

ISF	Investigator Site File
i.v.	Intravenous
LDH	Lactate Dehydrogenase
LoEE	List of Essential Element
MedDRA	Medical Dictionary for Drug Regulatory Activities
MCA	Middle Cerebral Artery
mRS	Modified Rankin Scale
MST	Medical Sub team
NA	Not applicable
ND	Not done
NIHSS	National Institute of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OPU	Operative Unit
PD	Pharmacodynamics
PIL	Patient Information Leaflet
PK	Pharmacokinetics
p.o.	per os (oral)
PT	Prothrombin Time
PCC	Protocol Challenge Committee
q.d.	quaque die (once a day)
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
rt-PA	Recombinant Tissue Plasminogen Activator
SAE	Serious Adverse Event
s.c.	subcutaneous
SPC	Summary of Product Characteristics
SDV	Source Data Verification
sICH	Symptomatic intracranial haemorrhage
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TIMS-China	Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China
TMF	Trial Master File
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan
UNK $\beta$ HCG	Unknown $\beta$ Human Chorionic Gonadotropin

## 1. INTRODUCTION

### 1.1 MEDICAL BACKGROUND

Stroke is a major cause of death and morbidity. More than 80% of the strokes are acute ischaemic strokes (AIS). It has been estimated that stroke causes over 4 million deaths in the world each year, about 3 million of these are in developing countries, thus, stroke is the second most common single cause of death after ischaemic heart disease [[R09-0863](#), [R09-0864](#)]. In China, stroke has become the number 1 fatal disease, with ischemic stroke being the dominant type. Whereas stroke mortality in Europe and the USA ranges from 30 to 60 per 100 000, it is estimated to be between 120 and 240 per 100 000 in Russia, China, and large parts of Africa [[R12-4499](#)]. Globally, the burden of stroke is still increasing. Economic studies conducted in developed countries showed that Recombinant Tissue Plasminogen Activator (rt-PA ) given within 4.5 hours is cost-effective or even cost-saving in the long term [[P00-00952](#), [P11-09116](#), [P11-09575](#), [P13-09520](#)].

The ideal therapy of acute ischemic stroke is achieved by quick restoration of the blood flow to brain areas that are blocked by a vessel occlusion with good clinical outcome, in order to reduce death and dependency on others for activities of daily living.

So far, Alteplase is the only approved thrombolytic for acute ischemic stroke within 4.5 hours after stroke onset and the overall benefit from alteplase is substantial [[P10-05924](#), [P95-3793](#), [P06-00786](#), [P98-10052](#), [P00-01176](#)]. Guidance and practice address opportunities for optimal stroke care in the acute phase of the ischemic stroke.

Stroke accounts for 301 million disability-adjusted life-years, which makes it the first leading cause of death and imposing significant disease and economic burden in China [[P14-10421](#)].

Between May, 2007, and April, 2012, a total of 1440 patients who received IV-tPA were registered in the Thrombolysis Implementation and Monitor of Acute Ischemic Stroke in China (TIMS-China). Final analysis demonstrated 2 important facts regarding IV-tPA dosages. First, the standard-dose IV-tPA treatment protocol was safe for Chinese patients with stroke, without any increased rate of symptomatic intracranial haemorrhage (sICH) according to ECASS III definition or mortality compared with the low dose group. The sICH mentioned below is all according to ECASS III definition unless other specified. Second, patients with stroke receiving standard dose IV-tPA may have more favorable outcome than those receiving low doses of IV-tPA [[P13-12586](#)].

The 2013 version of Chinese IV rt-PA consensus was published based on previous version of China guideline and all new publications on the use of IV rt-PA for AIS. The Chinese Stroke Therapy Expert Panel concluded that Intravenous rt-PA is currently the most effective therapy for acute ischemic stroke and there is clinical evidence supporting the use of IV rt-PA between 3 and 4.5 hours after the onset with several exclusion criteria. After years of stroke quality care improvement, incidence of stroke has not decreased as expected. Part of the reasons might be due to the gap between clinical guidance and real practice.

From the Chinese National Stroke Registry (CNSR), among 11675 acute ischemic stroke patients with documented acute onset time, only 189 patients finally were treated with

alteplase [[P11-07866](#)]. In the last five years, proportion of thrombolysis within early hours increased from 7% to 20%, data from the United States is around 80%, the gap is still there. As of June 2014, MOST data demonstrated periodical analysis: totally 5049 cases were reported, within which 3872 cases (77%) were administered with IV rt-PA. Of all the patients who received early IV rt-PA thrombolysis, 67% of the patients showed functional improvement measured by NIHSS score, sICH rate was 4.1%, observed death rate was 4.3% [[Other Reference](#)]. The prognosis of Chinese patients with thrombolytic therapy is better than other Asian countries, however, Europe and the United States are even better. Therefore, it is encouraged to be more active in early thrombolysis in China.

## 1.2 DRUG PROFILE

For a more detailed description of the Alteplase profile please refer to the current Investigator's Brochure (IB), version 1.0, 30<sup>th</sup> Nov 2001, company core data sheet (CCDS), 04<sup>th</sup> Sep 2012 and approved patient information leaflet (PIL), 29Dec2014 by China Food and Drug Administration CFDA.

### Chemistry

The discovery of thrombolytic agents goes back to the 1930s, when it was shown that substances derived from bacteria with plasmin was recognized, but it was not until 1958 that its first use in acute ischaemic stroke (AIS) was described. However, since computer tomography (CT) was not available until the middle 1970s, the potential to treat optimal selection of patients was not possible. Early studies with streptokinase in AIS showed an increased risk of intracranial haemorrhage and lack of efficacy, which was associated with low fibrin specificity. The search for new agents with a better risk-benefit profile continued until 1979 when tissue plasminogen activator (t-PA) was purified [[P84-97880](#), [P05-03664](#)].

Tissue plasminogen activator is a serine protease which is pharmacologically classified as a thrombolytic enzyme. Alteplase, a recombinant single-chain human tissue-type-plasminogen activator (rt-PA), is an enzyme which has the property of fibrin-enhanced conversion of plasminogen to plasmin. When introduced into the systemic circulation at pharmacologic levels, alteplase binds preferentially to fibrin in a thrombus and converts the fibrin-associated plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. It produces limited conversion of plasminogen in the absence of fibrin.

Actilyse® (Alteplase, recombinant; recombinant tissue plasminogen activator, rt-PA) is commercially available as a lyophilized powder for reconstitution in 50- mg vial (see [section 4](#) for additional product information).

### Pharmacology

Zivin et al. [[P00-01176](#)] were the first to report on the use of rt-PA in an animal model of stroke. Small blood clots were injected into the carotid circulation of rabbits. Immediately thereafter, alteplase was given intravenously. A significant reduction in neurological damage was seen after alteplase while drug-induced hemorrhages were not observed. Zivin and colleagues have subsequently extended their analyses of alteplase in the rabbit model of embolic stroke. They reported that alteplase administration could be delayed for at least 15

minutes after embolus injection and significant neurological tissue protection was observed in the treated versus control animals. No alteplase induced hemorrhages were noted on neuropathological examination and documented significant neuronal protection in rabbits treated with alteplase versus control animals as long as 45 minutes after embolus injection [P87-31520, P10-08848]. Zivin and colleagues have also attempted to address the question whether or not post-stroke alteplase administration lead to an increase in the incidence of intracranial hemorrhages [P10-08848]. In their initial analyses, a large clot model was used to assess whether alteplase altered the frequency of intraparenchymal hemorrhages. No statistically significant differences were noted in "grossly apparent hemorrhages" at 4 hours post embolus injection in control versus alteplase- treated animals. In another study Lyden and colleagues [P08-12177], studied hemorrhage rates following rt-PA in their rabbit stroke model. The rates of hemorrhage were similar in all groups, regardless of treatment. However, a significant association was observed between stroke severity and cerebral hemorrhage. Most recently, Lyden et al. [P08-11746] performed a study using rt-PA in rabbits. The rabbits received doses of 3 - 10 mg/kg rt-PA or saline. Each brain was examined for "grossly apparent cerebral hemorrhages". Hemorrhage occurred with equal frequency in animals treated with both rt-PA and saline. In addition, treatment with rt-PA was not associated with an increase in the size of visible hemorrhages seen. Other investigator groups have analyzed the efficacy and safety of alteplase in animal models of stroke. Papadopoulos et al. [P87-31520] evaluated alteplase effects in an acute thromboembolic stroke model in rats. Post-mortem angiography revealed significantly more middle cerebral artery occlusions in control versus alteplase treated animals. Kissel et al. [P10-08848] also reported that alteplase significantly improved angiographic and post-mortem anatomical parameters in an embolic stroke model in rabbits. Finally, del Zoppo et al. [P10-05924] concluded that the incidence and severity of hemorrhage following alteplase as well as alteplase are not related to infarction size. In addition, they found that rt-PA did not increase the incidence or severity (i.e., volume) of hemorrhage when given within 3.5 hours of the onset of focal cerebral ischemia in the baboon.

#### Pharmacokinetic properties

Alteplase is cleared rapidly from the circulating blood and metabolised mainly by the liver (plasma clearance 550-680ml/min.) The relevant plasma half-life  $t_{1/2}$  alpha is 4-5 minutes. This means that after 20 minutes less than 10% of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured.

#### Preclinical safety data

In subchronic toxicity studies in rats and marmosets no unexpected undesirable effects were found. No indications of a mutagenic potential were found in mutagenic tests.

In pregnant animals no teratogenic effects were observed after intravenous infusion of pharmacologically effective doses. In rabbits embryotoxicity (embryo lethality, growth retardation) was induced by more than 3mg/kg/day. No effects on peri-postnatal development or on fertility parameters were observed in rats with doses up to 10mg/kg/day.

Toxicology: See IB, CCDS and PIL approved by CFDA

**Clinical data:**

In 1996, the Food and Drug Administration approved rt-PA in AIS patients, mainly based on the outcome of the NINDS-2. The safety and efficacy of rt-PA in AIS was further investigated between 1998 and 2008 in the ECASS-1/2/3, ATLANTIS-A/B and EPITHET trials [[P95-3793](#), [P98-10052](#), [P08-12177](#), [P00-00047](#), [P00-01176](#), [P08-02933](#)]. A pooled analysis, performed by Lees et al. [[P10-04547](#)] in 2010, showed that rt-PA is moderately beneficial between 3 and 4.5 h, with the greater benefit with earlier treatment [[P11-02890](#)]. This was confirmed by the findings in a Canadian rt-PA registry [[P11-02891](#)]. To date, rt-PA is still the only licensed thrombolytic agent for AIS; a dose of 0.9 mg/kg is administered starting with an intravenous bolus of 10% of dose, followed by intravenous infusion of the rest of the dose over 60 min, according to the NINDS study criteria. In 2009, the advice from the American Heart Association Stroke Council was published, recommending that patients can be treated with rt-PA within the time period of 3–4.5 h after onset of ischaemic stroke when additional criteria are taken into account [[P09-10649](#)]. This advice was mainly based on the results of the ECASS-III trial [[P05-03664](#)], the outcome of the pooled analysis performed by Lees et al, and the publications from the SITS-ISTR registry [[P08-11746](#), [P10-08848](#)]. In 2011, these findings led to the approval of rt-PA by the European Medical Agency for its use up to 4.5 h after onset. However, there is recent evidence supporting the use of intravenous thrombolysis in patients aged over 80 years as well as in patients with diabetes and prior stroke if they otherwise fulfil treatment criteria [[P10-14128](#), [P10-12678](#), [P11-00417](#), [P12-07668](#)]. The Food and Drug Administration has not extended the license time window beyond 3 h. In Japan, rt-PA (0.6 mg/kg i.v.) was approved in 2005 for use up to 3 h after onset [[P11-00579](#)], extended to 4.5 h in 2012.



## 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

### 2.1 RATIONALE FOR PERFORMING THE TRIAL

The main aim of this trial is to examine the safety and efficacy of alteplase between 3 to 4.5 hours of onset of ischemic stroke symptoms for Chinese population.

Advances had been made in China during the last several years. However, still many patients are left untreated due to the narrow time window, unknown onset time, delayed door to needle, lack of awareness, and a high number of exclusion criteria for currently approved label indication and/ or treatment.

#### **Trial needs for thrombolysis with Alteplase in China**

The extension of time window from 0~3 hours to 0~4.5 hours had been approved in EU and several other non-European countries like Australia, Latin-American, etc.

In domestic and international guidelines, thrombolysis with Alteplase 3~4.5 hours after onset is recommended, which is already performed in clinical practice in China. Although thrombolysis ratio is low at present in China, thrombolysis is usually performed 3~4.5 hours after onset with positive evaluation for patients. Extension of time window meets the demand of clinical practice and patients and is socially valuable.

However, according to label of Alteplase approved in China, thrombolysis for ischemic stroke with alteplase can only be given within 3 hours after symptom onset. There is the gap between treatment guidance and label, which put clinical physician in risk of the off-label use Alteplase. There is the registration need to extend time window of the product. ECASS III was a clinical study only for European patients without any data of Chinese patients.

In TIMS-China, 409 patients were thrombolysed between 0 and 3 h, and 165 patients were treated between 3 and 4.5 h. Functional outcomes (independence and excellent recovery) by Modified Rankin Scale (mRS) at day 90 were similar to those of ECASS III. And there were no significant differences in sICH at 24- to 36-h post-intravenous rtPA therapy, or mortality between the 0- to 3-h group and the 3- to 4.5-h group in Chinese patients with AIS [[P07-01580](#)].

### 2.2 TRIAL OBJECTIVES

The objective of the trial is to assess the efficacy and safety of alteplase (rt-PA) in Chinese patients with acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4.5 hours after stroke onset.

The primary efficacy outcome is functional independence as measured by the mRS (score of 0-1). It will be assessed at visit 5 ( Day 90 ) after stroke onset.

The primary safety outcome measures for the trial is symptomatic intra-cerebral haemorrhage (sICH), assessed for the whole study period centrally evaluated by DMC consultants. As for the protocol, sICH is defined as the same with ECASS III criteria, details refer to [section 5.3.1](#).

## 2.3 BENEFIT - RISK ASSESSMENT

Stroke care quality improvement should be a continuous effort. There are established database to capture the achievement of stroke care quality improvement [[P06-03224](#), [P11-05168](#), [P07-00880](#)]. The reason for these advances was multifactorial and included improved prevention and improved care within the first hours of acute stroke, within which intravenous fibrinolytic therapy increased and it is still recommended as the first-line treatment by most national and international association [[P01-09325](#), [P07-06240](#), and [P04-01702](#)]. Its high efficacy and safety have been proved in randomized controlled clinical trials (RCTs) when the treatment is given within 3 hours after onset of neurological symptoms in selected patients with acute ischemic stroke [[P95-4908](#), [P95-3793](#), [P98-10052](#), [P00-00047](#), [P00-01176](#)]. Subsequent additional trials and analysis suggest that patient can still benefit from thrombolysis with alteplase after extending the treatment up to 4.5 [[P08-12177](#), [P08-11746](#), [P10-08848](#), [P10-05924](#)]. Overall, the results were consistent, which indicated that intravenous rtPA can be given safely to, and can improve outcomes for, carefully selected patients treated 3 to 4.5 hours after stroke.

In clinical practice, rt-PA is not always beneficial, since it sometimes fails in achieving rapid reperfusion, delivers poor recanalization rates in some vessels, and is associated with bleeding risk. For more details of reported adverse reaction of the product please refer to [appendix 10.6](#). Adverse reaction per the local approved label, dated as 29Dec 2014.

The major risk of intravenous rtPA treatment remains sICH. Although the presence of edema or mass effect on baseline CT scan was associated with higher risk of sICH, patients with these findings were more likely to have an excellent outcome if they received fibrinolytic therapy [[P97-10211](#)].

Approaches for safety management: predefine etiology criteria for some predictors. eg. mRS score, baseline NIHSS score and platelet count. 3 out of 17 clinical parameters were identified as independent predictors of sICH: prestroke mRS score (OR 1.54, P = 0.02), baseline NIHSS score (OR 1.13, P = 0.002), and platelet count (OR 0.99, P = 0.04) [[P15-10504](#)].

Given the narrow therapeutic windows of treatment of acute ischemic stroke, timely emergency department ED evaluation and diagnosis of ischemic stroke are paramount. Hospitals and EDs should create efficient processes and pathways to manage stroke patients in the ED and inpatient settings. This should include the ability to receive, identify, evaluate, treat, and/or refer patients with suspected stroke, as well as to obtain access to stroke expertise when necessary for diagnostic or treatment purposes.

All centers should be able to offer 24/7 (24 hours per day, 7 days per week) comprehensive stroke care to acute stroke patients. The hospitals must be acute stroke hospitals ready to

organize effectively and efficiently evaluate, diagnose, and treat acute stroke. Besides key principle, guideline and procedures for site selection of clinical trials, the centers should fulfill below elements as,

- Ability to administer intravenous rtPA
- Ability to perform emergency brain imaging (eg, CT/MRI scan) at all times
- Ability to conduct emergency laboratory testing at all times
- Maintenance of a stroke patient notes

### **3. DESCRIPTION OF DESIGN AND TRIAL POPULATION**

#### **3.1 OVERALL TRIAL DESIGN AND PLAN**

##### **3.1.1 Administrative structure of the trial**

The trial is sponsored by

A Coordinating Investigator is responsible to coordinate Investigators at different centers participating in this multicenter trial. Tasks and responsibilities are defined in investigator agreement.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in Investigator Study File (ISF).

A data-monitoring committee (DMC), independent of the sponsor will be established to assess the progress of the clinical trial, focusing on the safety outcomes for the benefit-risk evaluation at pre-specified time points, and to recommend to the sponsor whether to continue, modify, or stop the trial. DMC is constructed by three DMC members mainly monitoring the overall number of sICH events judged by investigators, and two DMC consultants for centrally evaluating sICH event. The detailed tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

. has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

The organization of the trial in China will be performed by the respective local BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will be agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistics evaluation will be done by BI according to BI SOPs and CRO SOPs. The final executed contract must state the duties within the scope of work.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

#### **3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP**

##### **An open label, prospective, single arm study**

Study design has been fully discussed with center of drug evaluation (CDE) in CFDA with support from several external neurologists. This study is designed as an open label single arm

study for the following reasons. The new version of Chinese Intravenous rt-PA consensus was published in 2013 regarding the usage of IV rt-PA on patients with acute ischemic stroke. The Chinese Stroke Therapy Expert Panel concluded that IV rt-PA is currently the most effective therapy and clinical evidence supports the use of IV rt-PA between 3 and 4.5 hours after the onset with several exclusion criteria. Therefore it is not ethical to design a placebo-controlled randomization study as ECASS III in China with current available evidence.

Although urokinase is recommended in Chinese guideline, it's only for patients that alteplase cannot be given.

Furthermore, patients need to be treated immediately after AIS onset. It is impractical and not ethical to randomize patients to two groups as 0-3 hours and 3-4.5 hours after AIS onset for comparison. Without randomization, it does not add much scientific value to design the study including 0-3hours patients for the comparison and evaluation of safety and evaluation of 3-4.5 hours due to the uncontrolled confounding factors.

### 3.3 SELECTION OF TRIAL POPULATION

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

#### 3.3.1 Main diagnosis for trial entry

Please refer to [section 8.3.1](#) (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

#### 3.3.2 Inclusion criteria

1. Age  $\geq$  18 years at screening (visit 1A) but  $\leq$  80 years
2. Male or female patients. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception <methods meeting these criteria is provided in the patient information
3. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial
4. Diagnosis of ischemic stroke with a measureable neurological deficit on National Institute of Health Stroke Scale (NIHSS)  
Stroke symptoms should be have been present for at least 30 minutes without significant improvement prior treatment
5. Thrombolytic therapy can be initiated within 3 to 4.5 hours of stroke onset
6. Willingness and ability to comply with protocol

#### 3.3.3 Exclusion criteria

1. Stroke onset >4.5 hours prior to infusion start or when time of symptom onset is unknown

2. Evidence of intracranial haemorrhage (ICH) on the CT/MRI-scan or symptoms suggestive of subarachnoid haemorrhage, even if the CT/MRI-scan is normal
3. Patients who must or wish to continue the intake of restricted medications (see [section 4.2.2.1](#)) or any drug considered likely to interfere with the safe conduct of the trial
4. Acute bleeding diathesis, including but not limited to
  - a. Known genetic predisposition to bleeding or significant bleeding disorder at present or within the past 6 months
  - b. Administration of heparin within the previous 48 hours and aPTT exceeding the upper limit of normal for laboratory
  - c. Platelet count of below 100,000/mm<sup>3</sup>
  - d. Taking oral anticoagulant
  - e. Any history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
  - f. Recent traumatic external heart massage, obstetrical delivery, within the past 10 days, recent puncture of a non-compressive blood-vessel (e.g. subclavian or jugular vein puncture)
  - g. Known history of suspected intracranial haemorrhage or suspected subarachnoid haemorrhage from aneurysm
  - h. Neoplasm with increased hemorrhagic risk
  - i. Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial-aneurysm, arterial/venous malformations
  - j. Any known disorder associated with a significant increased risk of bleeding
5. Bacterial endocarditis, pericarditis
6. Acute pancreatitis
7. Severe hepatic dysfunction, including hepatic failure, cirrhosis, portal hypertension (oesophageal varices) and active hepatitis
8. Significant trauma or major surgery (according to the investigator's assessment) in past 3 months
9. Severe stroke as assessed clinically (e.g. NIHSS>25) and/ or imaging demonstrates multi-lobar infarction (hypodensity >1/3 cerebral hemisphere)
10. Minor neurological deficit or symptoms rapidly improving before start of infusion
11. Severe uncontrolled arterial hypertension, e.g. systolic blood pressure>185 mmHg or diastolic blood pressure>110mmHg, or aggressive management (IV medication) necessary to reduce BP to these limits
12. Blood glucose <50 mg/dL or >400 mg/dL
13. Any history of prior stroke in previous 3 months, or any history of prior stroke with concomitant diabetes
14. Seizure at stroke onset
15. Known hypersensitivity to active substance alteplase, gentamicin (a trace residue from the manufacturing process) or to any of the excipients.
16. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s)
17. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

### 3.3.4 Removal of patients from therapy or assessments

#### 3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

An individual patient is to be withdrawn from trial treatment if:

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication
- The patient, who had discontinued the treatment for any reasons (such as surgery, adverse events, other diseases), can no longer be treated with trial medication again. The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the [Flow Chart](#).

For all patients the reason for withdrawal (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

#### 3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial

The Investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

## 4. TREATMENTS

### 4.1 INVESTIGATIONAL TREATMENTS

#### 4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product: Alteplase

Substance:	Alteplase (rt-PA)
Brand name:	Actilyse®
Pharmaceutical formulation:	Lyophilisate and solvent for injection The powder is presented as a colourless to pale yellow lyophilizate cake
Source:	BI Pharma GmbH & Co. KG
Unit strength:	50mg
Posology	Actilyse® 50 mg, vial containing 50 mg Alteplase lyophilisate plus vial of solvent containing 50 mL sterile water for injection. The reconstituted solution contains 1 mg alteplase per mL.
Route of administration:	IV

Under aseptic conditions the content of injection vial of Alteplase lyophilisate (50mg) dry substance is dissolved with 50ml sterile water for injection to obtain a final concentration of 1mg alteplase per mL.

For this purpose a transfer cannula should be managed at each site. When reconstituting the product from the respective amount of powder and solvent, the mixture should only be agitated gently until complete dissolution. Any vigorous agitation should be avoided to prevent foam formation.

The reconstituted preparation is a clear and colourless to pale yellow solution. Prior to administration it should be inspected visually for particles and colour. It may be diluted further with sterile sodium chloride 9 mg/mL (0.9%) solution for injection up to a minimal concentration of 0.2 mg/mL.

A dilution of the reconstituted solution with sterilised water for injections or in general, the use of carbohydrate infusion solutions, e.g. dextrose is not used.

Actilyse® should not be mixed with other drugs, neither in the same infusion-vial nor the same venous line.



#### 4.1.2 Dosage and treatment schedule

The study drug will be administered as a total single dose of 0.9 mg/kg per patient. The upper dose limit is set to 90 mg per patient. Ten percent of the total dose will be administered as a bolus over 1 - 2 minutes. The remaining 90% of the dose will be given by continuous IV infusion over 60 minutes if there is no evidence of an allergic reaction within 5 minutes following the administration of the test dose.

The dose is weight adjusted, therefore investigator should try every effort to take the actual body weight of the patient. If it is hard to have an actual body weight due to certain reasons, an estimated body weight by investigator is acceptable.

The treatment effect is time-dependent; therefore earlier treatment increases the probability of a favourable outcome [[P08-12177](#)], so patients eligible in the 3-4.5 hrs time window should be treated without delay.

#### 4.1.3 Method of assigning patients to treatment

It is an open label trial.

At visit 1A, after assessment of all in- and -exclusion criteria, each eligible patient will be assigned with medication manually. Site personnel will enter the medication number in the CRF.

#### 4.1.4 Blinding and procedures for unblinding

It is an open label trial. Blinding concern and unblinding procedure are not applicable for this trial.

#### 4.1.5 Packaging, labelling, and re-supply

The investigational products will be provided by Clinical Trial Supply Unit (CTSU). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

The clinical trial supply kit consists of two vials of alteplase lyophilisate and two vials of sterile water. Details of packaging and description of the label will be provided in the ISF.

Initial supply and further re-supplies will be managed by an IRT, inventory needs to be monitored/maintained manually. To facilitate the use of the IRT, the investigator will receive all necessary instructions for using the IRT. Details please refer to user manual in the ISF.

#### 4.1.6 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. The vials have to be stored at room temperature (not above 25°C) and have to be protected from light. Freeze is not allowed. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

#### **4.1.7 Drug accountability**

The Investigator and/or Pharmacist will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator

The Investigator and/or Pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return, including the unused product returned back to local depot. If applicable, the sponsor and the distributional partner will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. All used product will be destructed at sites. All unused products will be return to the local depot, At the time of return the Investigator / Pharmacist must verify that no remaining supplies are in the Investigator's possession.

### **4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS**

#### **4.2.1 Other treatments and emergency procedures**

Actilyse should be used by physician experienced in the use of thrombolytic treatment and with the facilities to monitor that use. As with other thrombolytics, it is recommended that when Actilyse is administered, standard resuscitation equipment and medication be available in all circumstances.

##### **Recommendation of managing bleeding**

The most common complication encountered during Actilyse therapy is bleeding. The concomitant use of heparin anticoagulation may contribute to bleeding. As fibrin is lysed during Actilyse therapy, bleeding from recent puncture sites may occur. Thrombolytic therapy requires careful attention to all possible bleeding sites (including those following catheter insertion, arterial and venous puncture cutdown and needle puncture). The use of rigid catheters, intramuscular injections and non-essential handling of the patient should be avoided during treatment with Actilyse.

Should serious bleeding occur, in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued and concomitant heparin administration should be terminated

immediately. Administration of protamine should be considered if heparin has been administered within 4 hours before the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated.

Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/L is desirable with cryoprecipitate infusion. Antifibrinolytic agents should also be considered.

#### Recommendation of managing hypersensitivity

No sustained antibody formation to the recombinant human tissue-type plasminogen activator molecule has been observed after treatment. There is no systematic experience with re-administration of Actilyse. Anaphylactoid reactions associated with administration of Actilyse are rare.

If an anaphylactoid reaction occurs, the infusion should be discontinued and appropriate treatment should be initiated. Monitoring is recommended particularly for patients receiving ACE-inhibitors concomitantly.

#### Recommendation of managing other AEs

During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial.

### **4.2.2 Restrictions**

#### **4.2.2.1 Restrictions regarding concomitant treatment**

Additional thrombolytic medication (e.g. urokinase or streptokinase) is forbidden.

Heparin: In exceptional circumstances, low dose subcutaneous heparin may be given concomitantly during the first 24 hours in order to prevent deep venous thrombosis provided that the aPTT will not be prolonged for more than 2 times over the baseline value. APTT must be determined regularly during the subcutaneous (SC) administration of heparin. The SC heparin dose must not exceed 10,000 IU of sodium heparin during 24 hours or equivalent doses of low molecular weight heparin. Simultaneous administration of heparin and other antithrombotic drugs is strongly discouraged.

IV heparin at any dose is forbidden before and during the study drug administration and during the initial 24 hours after completion of administration of study drug.

Thereafter intravenous heparin must not be started before the second CT is evaluated and reveals no signs of intracranial bleeding.

Other medication:

Administration of oral anticoagulants, antiplatelet agents (i.e. aspirin), hemorrheologic agents, and brain protective drugs (e.g. calcium channel blockers) is prohibited during the first 24 hours after completion of the study drug administration.

The use of volume expanders, such as dextran and hydroxyethyl starch, is prohibited within the first 24 hours after completion of study drug infusion.

Traditional Chinese medicine which had been demonstrated with evidence of effect as anticoagulants, antiplatelet agent, hemorrheologic agents and brain protective agents is prohibited during the first 24 hours after completion of the study administration [P14-16668](#).

Other drug therapy may be given according to patient needs. Osmotic agents (mannitol, glycerol) may be given if the intracranial pressure is increased.

#### 4.2.2.2 Restrictions on diet and life style

Not applicable

#### 4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

### 4.3 TREATMENT COMPLIANCE

The investigator will maintain accurate records of receipt of all study medication, including the date, exact time point of receipt. In addition, accurate records will be kept regarding the total dosage administered to each individual patient in the study.

Actual weighing of the patient is preferred when it can be performed without inducing delays. The treatment effect is time-dependent; therefore treatment must be started as early as possible within 4.5 hours after onset of stroke symptoms.

## **5. VARIABLES AND THEIR ASSESSMENT**

### **5.1 TRIAL ENDPOINTS**

#### **5.1.1 Endpoints of efficacy**

##### **5.1.1.1 Primary Efficacy Endpoint**

The primary efficacy endpoint is the percentage of patients with mRS 0-1 (favourable outcome) at visit 5 (i.e., day 90) after stroke onset by face-to-face interview with patient.

##### **5.1.1.2 Secondary Efficacy Endpoint**

The percentage of global outcome responder at visit 5 (i.e., day 90) if he/she obtains the following results at visit 5 (i.e., day 90) (for all of the 4 endpoints)

- mRS score of 0 to 1

- Barthel Index score  $\geq 95$

- NIHSS score of 0 to 1

- Glasgow Outcome Scale score of 1

## 5.1.2 Endpoints of safety

### 5.1.2.1 Primary Safety endpoints

The percentage of patients with symptomatic intracranial haemorrhage (sICH) centrally evaluated by DMC consultants according to ECASS III definition within the whole study period.

### 5.1.2.2 Secondary Safety Endpoints

- Patient survival probability at visit 5 (censoring at day 90)
- Frequency of death related to stroke or of neurological causes
- Frequency and severity of adverse events
- Incidence of cerebral herniation and symptomatic edema

## 5.2 ASSESSMENT OF EFFICACY

The primary study endpoint is functional independence as measured by the mRS (score of 0-1) assessed at 90 days after stroke onset by face-to-face interview with patient.

Functional outcome (day 90) is defined by mRS, excellent (mRS 0-1) vs. unfavourable outcome (mRS 2-6), which is the primary study endpoint.

The secondary efficacy endpoint will be global outcome analysis of four neurological and disability scores combined.

### Modified Rankin Scale:

The mRS is a tool used to evaluate disability after a stroke and will be collected at day 30 and at day 90.

The grading of the score is as follows:

Grade 0: no symptoms at all

Grade 1: no significant disability despite symptoms;  
able to carry out all usual duties and activities

Grade 2: slight disability: unable to carry out all previous activities but able to look after own affairs without assistance

Grade 3\*: moderate disability: requiring some help but able to walk without assistance

Grade 4: moderate-severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance

Grade 5: severe disability: bedridden, incontinent, and requiring constant nursing care and attention.

Grade 6: Dead

**Barthel Index score**

It will be used to evaluate the recovery of neurological functions at day 30 and day 90.

**Glasgow Outcome Scale score**

The Glasgow Outcome Scale applies to patients with brain damage allowing the objective assessment of their recovery in five categories. This allows a prediction of the long-term course of rehabilitation to return to work and everyday life. It will be collected at day 90.

The Glasgow Outcome Scale is a 5-level score:

1. Good Recovery
2. Moderately Disabled
3. Severely Disabled
4. Vegetative State
5. Dead

**National Institutes of Health Stroke Scale (NIHSS)**

The NIHSS will be recorded, if it had been collected at the time of qualifying (index) stroke. In patients, where NIHSS has not been done at the time of index stroke, it will be performed at study entry (at Visit 1). It is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, and for each item a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0. Clinical outcome will also be assessed by NIHSS scoring at 2 hours, 24 hours, and on day 7, 30 and 90.

**5.3 ASSESSMENT OF SAFETY**

Patients are monitored in the stroke unit or Intensive Care Unit (ICU). For assessment of safety, incidence and severity of adverse events including mortality at day 90, stroke-related and neurological, including cerebral herniation rate and symptomatic oedema, deaths, and symptomatic cerebral bleeding will be evaluated. Intracranial haemorrhage will be assessed separately.

Safety monitoring is performed by an independent Data Monitoring Committee (DMC). The details will be described in the DMC Charter.

**5.3.1 Assessment of symptomatic intracranial haemorrhage (sICH)**

According to this protocol, sICH (ECASS III criteria) is defined as: any apparently extravascular blood in the brain or within the cranium that was associated with clinical

deterioration (defined by an increase in the NIHSS score of 4 or more points), or that led to death and that was identified as the predominant cause of the neurological deterioration. sICH event will be firstly evaluated by investigator. The DMC consultants will evaluate all the patients with NIHSS score increase of at least 4 any time after treatment (including all the sICH events evaluated by investigator).

### 5.3.2 Physical examination

A physical examination will be performed for all patients at screening visit (Visit 1A) and repeated at all predefined treatment time points (Visit 1B and Visit 1C) as of the administration day and visit 2,3,4, and 5. All abnormal findings at baseline will be recorded on the Medical History/Baseline Condition page in the patient's electronic case report form (eCRF). New abnormal findings or worsening of baseline conditions detected at follow-up physical examinations will be recorded as adverse events on the appropriate eCRF page. The measurement of height (in cm) and body weight (in kg) will only be performed at the screening visit.

### 5.3.3 Vital Signs

Vital signs include blood pressure, pulse rate, respiratory rate and armpit temperature (the locations should be specified in the medical notes and the same location should be used at each time point when body temperature is measured).

The measurements of blood pressure will always be obtained with the patient seated and rested for a minimum of five minutes. Vital signs will be measures every 30 minutes for 6 hours, then hourly until 24 hours after the start of infusion.

### 5.3.4 Safety laboratory parameters

An abbreviated hematology and chemistry panel including liver and renal function testing will be analysed for safety at specific time-points throughout the trial by a certified laboratory. The laboratory tests will include:

Category	Laboratory test
Haematology	Red blood cell count (RBC) Haemoglobin (Hb) Haematocrit (HCT) Mean corpuscular volume White blood cell count including differential Platelet count
Biochemistry	Aspartate aminotransferase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Alkaline phosphatase (ALP) Total bilirubin



	Creatinine Glucose Uric acid (optional) β- Human Chorionic Gonadotropin(HCG)*
Electrolytes	Sodium Potassium Calcium Inorganic phosphorus
Coagulation	International normalized ratio (INR) Partial thromboplastin time (ptt) Prothrombin time (PT)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite (semi quantitative measurements; (-, +, ++, +++), pregnancy test*

Both of the two types of pregnancy tests are acceptable for this trial, whatever test it may be, it should be carried out appropriately, according to the routine practice of local lab of selected sites.

Note: for the urgent indication, if patient could not provide urine at the time point of screening for the routine urine test, investigator should judge, according to the baseline condition of the patients, to decide whether the missing data of routine urine test will impact patients' participate in the clinical trial. Urine test should be conducted at the earliest time when it is available afterwards for safety consideration.

### 5.3.5 Electrocardiogram

Printed paper traces from 12 lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected at visit 1 and 3 for all patients. In the event of any cardiac symptoms (i.e. suspicion of heart rhythm disorders or cardiac ischemia), an additional ECG will be recorded. All ECGs will be evaluated, (signed, dated and commented upon) by the treating physician/investigator and stored locally. Any clinically relevant changes in the ECG will be reported as AEs and followed up and/or treated locally until normal or stable condition.

### 5.3.6 Other safety parameters

For further safety parameters see [section 5.1.2](#)

### 5.3.7 Assessment of adverse events

#### 5.3.7.1 Definitions of AEs

#### Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

#### Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

#### Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
  - is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
  - requires inpatient hospitalisation or
  - prolongation of existing hospitalisation,
  - results in persistent or significant disability or incapacity, or
  - is a congenital anomaly / birth defect,
- or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

#### AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as given above.

The latest list of “Always Serious AEs” can be found in the RDC system. These events should always be reported as SAEs as described above.

### **Intensity of AEs**

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

### **Causal relationship of AEs**

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).

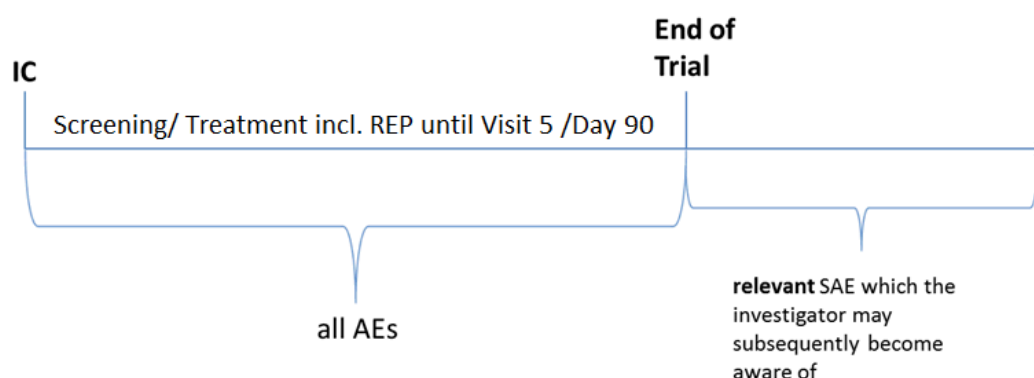
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

### 5.3.7.2 Adverse event collection and reporting

#### **AE Collection**

The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial (per protocol: Visit 5, Day 90).  
-all AEs (serious and non-serious).
- After the individual patient's end of trial:  
the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs of which the Investigator may become aware of.



\*The REP is defined as the number of days after the last trial medication application. According to CCDS of the product, after 20 minutes less than 10% of the initial value is present in the plasma. For the residual amount remaining in a deep compartment, a beta-half-life of about 40 minutes was measured. The REP is quite short. To be consistent with statistical analysis plan in previous trial, e.g. ECASSIII, REP is defined as 7 days after the last trial medication application in this protocol.

All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please see [section 7.3.4](#).

Events which occurred after the REP will be considered as post treatment.

#### **AE reporting to sponsor and timelines**

The Investigator must report SAEs, and non-serious AEs which are relevant for the reported SAE, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator

could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

### **Information required**

For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

### **Pregnancy**

In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

## **5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS**

### **5.4.1 Assessment of Pharmacokinetics**

Not applicable since no pharmacokinetic data will be collected or analysed in this trial.

#### **5.4.2 Methods of sample collection**

Not applicable

#### **5.4.3 Analytical determinations**

Not applicable

#### **5.4.4 Pharmacokinetic – Pharmacodynamic Relationship**

Not applicable since no pharmacodynamics data will be collected or analysed in this trial

### **5.5 ASSESSMENT OF BIOMARKER**

Not applicable since no biomarker data will be collected and analysed in this trial

#### **5.5.1 Biobanking**

Not applicable since no sample will be collected and analysed for biobanking in this trial.

### **5.6 OTHER ASSESSMENTS**

Not applicable since there is no other assessments will be done.

### **5.7 APPROPRIATENESS OF MEASUREMENTS**

All measurements conducted in the trial are using standard methods.

## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

Informed consent of all study patients will be obtained in compliance with ICH and GCP guidelines and the principles stipulated in the Declaration of Helsinki prior to any study related procedure.

After informed consent procedure, a patient may be enrolled into the study when entering the clinic with acute stroke symptoms and being liable to be treated between 3 and 4.5 hours after stroke onset. All inclusion and exclusion criteria have to be checked prior to administration of the test dose of study medication. The cerebral imaging scan and its evaluation has to be done with due diligence. Investigator and/or co-investigator must agree with the radiologist that there are no imaging exclusion criteria prior to administration of the test dose of study medication.

The study will consist of 5 visit days. The visits will be conducted during the study, among which, the visit 1 is divided into three sub-visits, the schedule for trial visits is summarized in the study [Flow Chart](#) including time windows for study visits.

All visit dates are calculated from the date of drug administration. In the event that visits are missed or out of sequence, subsequent visits will be planned according to the date of visit 1.

No protocol waivers will be given (e.g. Sponsor will not grant permission to include a known ineligible patient). In the case of medical emergencies, prior approval from the Sponsor for protocol deviations (e.g. visit schedule) will not be required, but BI should be notified as soon as possible. The relevance of any such protocol deviation will be assessed prior to analysing the data.

The procedures to be conducted at each visit are provided in the Flow Chart and further described below.

### 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

#### 6.2.1 Screening period

At visit 1A (baseline) the documentation of demographics, medical history, physical examination, vital signs, resting 12-lead ECG, concomitant therapy, NIH Stroke Scale, and a cerebral imaging scan will be performed.

#### 6.2.2 Treatment period

After consent procedure had been completed, eligibility has been confirmed and all Visit 1A procedures completed, drug administration can be conducted.

The test dose of rt-PA will be administered. Ten percent of the total dose will be administered as a bolus over 1 - 2 minutes. The remaining 90% of the dose will be given by continuous IV

infusion over 60 minutes if there is no evidence of an allergic reaction within 5 minutes following the administration of the test dose.

### 6.2.3 Observation Period and Trial Completion

A physical examination, the documentation of adverse events and of concomitant medication will be performed for all patients at all predefined treatment time points (Visit 1B and Visit 1C) as of the administration day and visit 2,3,4, and 5.

Lab test at visit 1A and visit 3 are mandatory. It will be optional at visit 2 and visit 5 in case of clinical deterioration (considered by investigator)

At visit 1B (i.e., 1 hour after the start of infusion of study drug), vital signs will be measured every 30 minutes until Hour 2. An 12-lead ECG recording will be made.

At visit 1C (i.e., 2 hours after the start of infusion of study drug), the NIH Stroke Scale will be performed. Vital signs will be measured every 30 minutes for 6 hours, then hourly until 24 hours. An 12-lead ECG recording will be made.

At visit 2 (24 hours), vital signs will be measured. The NIH Stroke Scale will be performed. A second imaging (CT/MRI) scan will be done within Hour 22 and Hour 36 after start of infusion of study drug.

At visit 3 (on day 7), vital signs will be measured. The NIH Stroke Scale will be performed. An 12-lead ECG recording will be made. A CT/MRI scan will be performed in case of clinical deterioration

At visit 4 (on day 30), vital sign will be measured. The NIH Stroke Scale, the modified Rankin Scale, and the Barthel Index will be performed. A CT/MRI scan will be performed in case of clinical deterioration.

At visit 5 (on day 90), vital sign will be measured. The NIH Stroke Scale, the Glasgow Outcome Score, the modified Rankin Scale, and the Barthel Index will be performed. A physical examination takes place. The patient termination record will be filled in. Length of stay in hospital will be assessed as well.

The trial completion (end of the trial) eCRF page has to be filled-in when patient has terminated the trial.

The end of the trial is:

- At the end of visit 5 (Day 90 per protocol) for patients who have completed the trial on treatment and came to future visits as planned.
- After early discontinuation, if a patient refuses to attend future visits as originally planned.

If a patient discontinues from the trial after treatment, this will be documented and the reason for discontinuation will be recorded in the eCRFs. At the time of discontinuation, a completed end-of-trial evaluation (Visit 5, Day 90) will be performed whenever possible and the data collected from these patients will be included in the trial database and will be reported.



## **6.3 VISIT WINDOW AND TRIAL COMPLETION**

### **6.3.1 Visit schedule**

For visit 1A (D0) there is no time window.

For visit 1B, a window between +15 and - 15 minutes is acceptable.

For visit 1C, a window between +30 and -30 minutes is acceptable.

For visit 2 (D1), a window between +2 and -2 hours is acceptable. The second cerebral CT/MRI may be done between Hour 22 and Hour 36 after start of infusion of study drug.

For visit 3 (D7), a window between +3 and -3 days is acceptable.

Visit 4 (D30) may take place between 27 and 33 days.

Visit 5 (D90) may take place between 83 and 97 days.

### **6.3.2 Criteria and rules for stopping subject treatment**

Each patient may terminate the study prematurely without giving any reason. If possible, the patient should discuss her/his decision with the investigator. The investigator may terminate the administration of study drug prematurely for any medical reason. Reason, date, and clock time of terminating have to be documented. Each of these patients must be followed up for 90 days if possible. Drop-outs and withdrawals will not be replaced.

## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN - MODEL

This is an open-label, single-arm, multi-center. Phase III trial that is designed to assess the safety and efficacy on alteplase (rt-PA) of 0.9 mg/kg rt-PA (intravenously infused over 1 hour) in acute ischemic stroke patients within 3-4.5 hrs from onset of symptoms in the Chinese population. Considering the design of single-arm study and binary nature of primary endpoints, the point estimators will be mainly presented along with the corresponding 95% confidence intervals.

### 7.2 NULL AND ALTERNATIVE HYPOTHESES

Alteplase (rt-PA) has been approved and widely used in more than 100 countries for about 20 years. Many studies were conducted by the sponsors and researchers to understand the efficacy and safety profiles of the drug for patients treated within 3-4.5 hours after AIS onset in both controlled clinical studies and real world setting. The percentage of mRS 0-1 responder at day 90 was 40.9% in SITS-ISTR [[P15-11922](#)] 52.4% in ECASS III (ITT population) and 60.9% in TIMS-China [[P13-12586](#)]. The estimation from historical review varies from 40% to 60%.

In this study, we are aiming to rule out a response rate of 40% or lower, which is considered as insufficient level of efficacy for alteplase treated within 3-4.5 hrs from stroke onset in Chinese acute ischemic stroke patients [[P13-12586](#)]. Therefore, a null hypothesis of  $p \leq 40\%$  versus an alternative hypothesis of  $p > 40\%$  will be tested using a one sample test at two-sided significance level of 0.05, where  $p$  denotes the response rate in Chinese patients who are treated within 3-4.5 hrs after stroke onset.

### 7.3 PLANNED ANALYSES

All enrolled patients who received Actilyse treatment at any dose will be included in the treated set (TS). This is also the full analysis set (FAS) since all treated patients will be evaluated. The primary efficacy analysis and the safety analysis will be performed on the TS.

#### 7.3.1 Primary endpoint analyses

The primary efficacy endpoint is the percentage of mRS 0-1 (favourable outcome) responder at day 90 after stroke onset by face-to-face interview with patient. The proportion of patients with mRS 0-1 will be presented with corresponding 95% confidence intervals (CIs).

The primary safety endpoint is the percentage of patients with symptomatic intracranial haemorrhage (sICH) centrally evaluated by DMC consultants according to ECASS III definition within the whole study period. The proportion of patients with sICH will also be presented along with corresponding 95% CIs.

Regarding the safety endpoint, the event rate of sICH observed from these studies arranged from 2.4% to 4.9% using ECASS III definition [[P05-03664](#)].

### 7.3.2 Secondary endpoint analyses

The secondary efficacy endpoint is the percentage of global outcome at day 90. A global outcome responder is defined as patient with outcomes at day 90 of a score of 0 or 1 on the mRS, a score of 95 or higher on the Barthel Index, a score of 0 or 1 on the NIHSS, and a score of 1 on the Glasgow Outcome Scale. The proportion of global outcome responders will be displayed along with corresponding 95% CIs.

Each item of the composite criteria global outcome responder will be evaluated separately as well.

### 7.3.4 Safety analyses

Safety analysis will be performed based on full analysis set.

Patient's survival at Day 90 (censoring at 90 days) will be analysed using the Kaplan-Meier method. The median survival along with 95% confidence interval, using Greenwood's standard error estimate, will be presented. The Kaplan-Meier estimates will also be plotted over the observation period of 90 days.

The frequency of death related to stroke or of neurological causes and the incidence of cerebral herniation and symptomatic edema will be analysed descriptively.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The frequency, severity and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to MedDRA. Because this study is a single dose drug administration (duration of approximately one hour), the incidence and severity of adverse events will be displayed by treatment periods. All AEs which occurred through the single dose treatment phase and throughout the REP will be considered as on treatment. Events which occurred after the REP will be considered as post treatment. The frequency of on-treatment AEs will be summarized as primary interest. The frequency of all AEs collected until the end of the study will also be summarized. More

details will be specified in Statistical Analysis Plan. Standard BI summary tables and listings will be produced.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

### 7.3.5 Pharmacokinetic and pharmacodynamic analyses

Not applicable.

## 7.4 INTERIM ANALYSES

An interim analysis will be performed when 60 patients enter and complete the study. All the first 60 patients who complete the study will be included in this interim analysis. Both safety and efficacy will be evaluated at interim analysis.

For efficacy, a predictive probability approach in the Bayesian setting is used to help to make the decision whether the study should continue to the full enrolment and whether an early application should be submitted to CFDA upon the promising interim results.

We target  $p_s = 55\%$  as a promising response rate in the end of study. The Bayesian analysis will be performed to estimate predictive probability (PP), which is the probability that the response rate reaches  $p_s$  or above in the final study result, given the data observed at interim time-point. If the predictive probability is greater than 90%, it shows the high potential of reaching promising result in the end given interim data.

In addition, we also consider a futile response rate lower than  $p_f = 40\%$  in the end of study for early stop at the interim. We estimate the predictive probability of observing the response rate lower than  $p_f$  in the end of study given interim data. If the predictive probability is greater than 90%, it shows high potential of futility in the end. [Appendix 10.5](#) elaborates how the predictive probability is calculated.

In summary, there are 3 scenarios suggested by the interim results as below,

- Scenario A - Early submission upon promising efficacy (i.e., promising zone): PP ( $\hat{p} \geq 55\%$ )  $\geq 90\%$ , equivalently, 37 or more responders among 60 patients at interim;
- Scenario B - Early stopping upon futile efficacy (i.e., Futility zone): PP ( $\hat{p} \leq 40\%$ )  $\geq 90\%$ , equivalently, 20 or fewer responders among 60 patients at interim;
- Scenario C - Competitive zone: the rest other than promising and futility zones;

For both scenarios A and C, if there is no safety alert from independent Data Monitoring Committee (DMC), the trial will continue for the completion of recruitment of 120 patients to the end as planned to collect the sufficient safety information.

In addition to the efficacy evaluation, an independent Data Monitoring Committee (DMC) will be constituted for continuously monitoring and reviewing the safety data during the study conduction. The details of the safety monitoring scheme will be specified in DMC SAP.

At the interim, it is envisioned that the DMC may make two types of recommendations, namely:

1. No safety issues or concerns, ethical to continue the trial as planned
2. Warning of significant safety concerns and recommendation of stopping the trial for patients' safety.

Table 7.4:1 Guidance for decision making at interim analysis

Timing and Results			Action
First 60 patients complete study			
Efficacy		Safety	
Promising Zone: $\geq 37$ patients with favourable outcome	AND	DMC declare no safety issues	Continue enrolment and early submission
Competitive Zone: $< 37$ but $> 20$ patients with favourable outcome	AND	DMC declare no safety issues	Continue enrolment without early submission
Futility Zone: $\leq 20$ patients with favourable outcome	OR	DMC declare warning of significant safety issues	early trial stopping

The guidance described in the Table 7.4.1 serves as decision base for early trial stopping or early submission to CFDA. The interim analysis in conjunction with other safety and efficacy data will be used to allow BI, in consultation with the investigators and DMC, to make a joint decision on whether the benefit and risk support continuation of the trial to the full enrolment up to 120 patients, and will help BI to make the decision on whether an early application should be submitted to CFDA.

The interim analysis will not lead to sample size recalculations and adjustment of enrolment targets.

## 7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete information according to the protocol. No missing values regarding vital status and intracranial bleeds are expected. However, for functional outcome parameters of surviving patients missing values might occur. The last observation carried forward (LOCF) method will be applied in the sense that data from the previous visit or measurement will substitute the missing data. In case of missing values due to death, the worst score principle will be applied.

## 7.6 RANDOMISATION

No randomisation is required since all patients will be treated with rt-PA.

## 7.7 DETERMINATION OF SAMPLE SIZE

The study will enrol approximately 120 patients. The sample size calculation takes account into both safety and efficacy considerations.

Regarding the primary safety endpoint, an observed sICH rate of 2.4%, i.e., 3 sICH events out of 120 patients, will result in an exact binomial 95% CI (0.48%, 6.99%) with the confidence width as 6.51%, which is considered as reasonable estimation precision.

The percentage of mRS 0-1 (favourable outcome) responder at day 90 is the primary efficacy endpoint. The range of the response rate from historical review was from 40% to 60% [[P05-03664](#)]. If assuming an underlying response rate of 55% of rt-PA treatment in Chinese patients, for the planned sample size of 120 patients, a power of 91.5% can be achieved. The sample size calculations in Table 7.7.1 have been performed based on a one sample test for proportion with a two-sided significance level of 0.05 and power ranging from 80% to 90%. Calculations were performed using ADDPLAN version 6.

Table 7.7:1 Sample size calculations based on a one sample test with a two-sided significance level of 0.05 and various assumptions of percentages of mRS 0-1 responders (n=120)

Assumed mRS response rate	Number of mRS 0-1 responders	Power(%)
52.5%	63	79.4
53.3%	64	84.2
<b>55.0%</b>	<b>66</b>	<b>91.5</b>

## **8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY**

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and local GCP regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP\*.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: [trials.boehringer-ingelheim.com](http://trials.boehringer-ingelheim.com). The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the Investigator and the patients, and is stored in the ISF (Investigator Site File).

### **8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT**

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial

collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

## **8.2 DATA QUALITY ASSURANCE**

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

## **8.3 RECORDS**

Case Report Forms (CRF) for individual patients will be provided by the sponsor.

### **8.3.1 Source documents**

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))



- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

### 8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in [section 8.3.1](#). The sponsor will also monitor compliance with the protocol and ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to subject safety and data quality.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to subject safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results

The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in [section 8.3.1](#). The sponsor will also monitor compliance with the protocol and ICH GCP.

### 8.3.3 Storage period of records

#### Trial sites:

The trial sites must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

#### Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs. Details will be defined in investigator agreement.

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

## 8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

### 8.5.1 Collection, storage and future use of biological samples and corresponding data

Not applicable

## 8.6 TRIAL MILESTONES

**The start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

**The end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPO at their site.

**Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

**Temporary halt of the trial** is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

**Suspension of the trial** is defined as an interruption of the trial based on a Health Authority request.

A final report of the clinical trial data will be written only after all patients have completed the trial to incorporate and consider all data in the report.

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## 10. APPENDICES

### 10.1 NATIONAL INSTITUTE OF HEALTH STROKE SCOR, NIHSS

1a. Level of consciousness	0	Alert	
	1	Not alert, but arousable with minimal stimulation	
	2	Not alert, requires repeated stimulation to attend	
	3	Coma	
1b. Ask patient the month and their age	0	Answers both correctly	
	1	Answers one correctly	
	2	Both incorrect	
1c. Ask patient to open/close eyes and form/release fist	0	Obeys both correctly	
	1	Obeys one correctly	
	2	Both incorrect	
2. Best gaze (only horizontal eye movements)	0	Normal	
	1	Partial gaze palsy	
	2	Forced gaze deviation	
3. Visual field testing	0	No visual field loss	
	1	Partial hemianopsia	
	2	Complete hemianopsia	
	3	Bilateral hemianopsia (blind, incl. Cortical blindness)	
4. Facial paresis (Ask patient to show teeth or raise eyebrows and close eyes tightly)	0	Normal symmetrical movement	
	1	Minor paralysis (flattened nasolabial fold, asymmetry on)	
	2	Partial paralysis (total or near total paralysis of lower face)	
	3	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	
5a. Motor Function - right arm	0	Normal (extends arm 90° or 45° for 10 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Unstable (joint fused or limb amputated)	
5b. Motor Function - left arm	0	Normal (extends arm 90° or 45° for 10 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Unstable (joint fused or limb amputated)	
6a. Motor Function - right leg	0	Normal (holds leg in 30° position for 5 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Unstable (joint fused or limb amputated)	
6b. Motor Function - left leg	0	Normal (holds leg in 30° position for 5 sec without drift)	
	1	Drift	
	2	Some effort against gravity	
	3	No effort against gravity	
	4	No movement	
	9	Unstable (joint fused or limb amputated)	
7. Limb ataxia	0	No ataxia	
	1	Present in one limb	
	2	Present in two limbs	
8. Sensory (use pinprick to test arms, legs trunk and face, compare side to side)	0	Normal	
	1	Mild to moderate decrease in sensation	
	2	Severe to total sensory loss	

<b>9. Best language (describe picture, name items)</b>	<b>0</b>	No aphasia	
	<b>1</b>	Mild to moderate aphasia	
	<b>2</b>	Severe aphasia	
	<b>3</b>	Mute	
<b>10. Dysarthria (read several words)</b>	<b>0</b>	Normal articulation	
	<b>1</b>	Mild to moderate slurring of words	
	<b>2</b>	Near unintelligible or unable to speak	
	<b>9</b>	Intubated or other physical barrier	
<b>11. Extinction and inattention (use visual double stimulation or sensory double stimulation)</b>	<b>0</b>	Normal	
	<b>1</b>	Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities	
	<b>2</b>	Severe hemi-inattention or hemi-inattention to more than one modality	

**10.2 MODIFIED RANKIN SCALE, MRS**

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

**10.3 BARTHEL INDEX**

Item	Score	Categories
Bowels	0	Incontinent or needs enemas
	5	Occasional incontinence (< once per week)
	10	Continent
Bladder	0	Incontinent / unable to manage catheter
	5	Occasional accident (< once per day)
	10	Continent
Grooming	0	Needs help with shaving, washing, hair or teeth
	5	Independent
Toilet use	0	Dependent
	5	Needs some help
	10	Independent on, off, dressing and cleaning
Feeding	0	Dependent
	5	Needs some help (e.g. with cutting, spreading)
	10	Independent if food provided within reach
Transfer (e.g. bed to chair)	0	Unable and no sitting balance
	5	Needs major help
	10	Needs minor help
	15	Independent
Mobility	0	Unable
	5	Wheelchair independent indoors
	10	Walks with help or supervision
	15	Independent (but may use aid)
Dressing	0	Dependent
	5	Needs some help
	10	Independent including fasteners
Stairs	0	Unable
	5	Needs some help or supervision
	10	Independent up and down
Bathing	0	Dependent
	5	Independent in bath or shower
<b>Total</b>	<b>100</b>	

**10.4 GLASGOW OUTCOME SCALE**

<b>Grade</b>	<b>Description</b>	<b>Definition</b>
1	Good recovery	Patient can lead an independent life, with or without minimal neurological deficit
2	Moderately disabled	Patient has neurological or intellectual impairment but is independent
3	Severely disabled	Patient conscious but totally dependent on others to get through daily activities
4	Vegetative survival	Patient is unresponsive, but alive; a "vegetable" in lay language
5	Dead	

#### **10.6        ACCORDING TO THE LOCAL APPROVED LABEL, EFFECTIVE DATE: 29 DEC 2014**

Adverse reactions listed below are classified according to frequency and system organ class. Frequency groupings are defined according to the following convention: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $<1/10$ ), Uncommon ( $\geq 1/1,000$  to  $<1/100$ ), Rare ( $\geq 1/10,000$  to  $<1/1,000$ ), Very rare ( $<1/10,000$ ), Not known (cannot be estimated from the available data).

Except for intracerebral/intracranial haemorrhage as adverse reaction in the indication stroke as well as for reperfusion arrhythmias in the indication myocardial infarction, there is no medical reason to assume that the qualitative and quantitative adverse reaction profile of Actilyse in the indications pulmonary embolism and acute ischaemic stroke is different from the profile in the indication myocardial infarction.

**Haemorrhage**

The most frequent adverse reaction associated with Actilyse is bleeding in different forms resulting in a fall in haematocrit and/or haemoglobin values.

very common	intracerebral haemorrhage represents the major adverse reaction in the treatment of acute ischaemic stroke (up to 15 % of patients without any increase of overall mortality and without any relevant increase in overall mortality and severe disability combined, i.e. mRS of 5 and 6).
	bleeding from damaged blood vessels (such as haematoma)
common	intracerebral haemorrhage (such as cerebral haemorrhage, cerebral haematoma, haemorrhagic stroke, haemorrhagic transformation of stroke, intracranial haematoma, subarachnoid haemorrhage) in the treatment of acute myocardial infarction and acute pulmonary embolism
	pharyngeal haemorrhage
	gastrointestinal haemorrhage (such as gastric haemorrhage, gastric ulcer haemorrhage, rectal haemorrhage, haematemesis, melaena, mouth haemorrhage, gingival bleeding)
	ecchymosis
	urogenital haemorrhage (such as haematuria, haemorrhage urinary tract)
	injection site haemorrhage (puncture site haemorrhage, catheter site haematoma, catheter site haemorrhage)
uncommon	pulmonary haemorrhage (such as haemoptysis, hemothorax, respiratory tract haemorrhage)
	epistaxis
	ear haemorrhage
rare	eye haemorrhage
	pericardial haemorrhage
	retroperitoneal bleeding (such as retroperitoneal haematoma)
not known***	bleeding in parenchymatous organs (such as hepatic haemorrhage)

Death and permanent disability are reported in patients who have experienced stroke (including intracranial bleeding) and other serious bleeding episodes.

If a potentially dangerous haemorrhage occurs in particular cerebral haemorrhage, the fibrinolytic therapy must be discontinued. In general, however, it is not necessary to replace the coagulation factors because of the short half-life and the minimal effect on the systemic coagulation factors. Most patients who have bleeding can be managed by interruption of thrombolytic and anticoagulant therapy, volume replacement, and manual pressure applied to an incompetent vessel. Protamine should be considered if heparin has been administered within 4 hours of the onset of bleeding. In the few patients who fail to respond to these conservative measures, judicious use of transfusion products may be indicated. Transfusion of cryoprecipitate, fresh frozen plasma, and platelets should be considered with clinical and laboratory reassessment after each administration. A target fibrinogen level of 1 g/l is desirable with cryoprecipitate infusion. Antifibrinolytic agents are available as a last alternative.

#### Immune system disorders\*

rare	hypersensitivity / anaphylactoid reactions (e.g. allergic reactions including rash, urticaria, bronchospasm, angio-oedema, hypotension, shock or any other symptom associated with hypersensitivity)
very rare	serious anaphylaxis

If they occur, conventional anti-allergic therapy should be initiated. In such cases a relatively larger proportion of patients were receiving concomitant Angiotensin Converting Enzymes inhibitors. No definite anaphylactic (IgE mediated) reactions to ACTILYSE® are known. Transient antibody formation to ACTILYSE® has been observed in rare cases and with low titres, but a clinical relevance of this finding could not be established.

#### Nervous system disorders

very rare	events related to the nervous system (e.g. epileptic seizure, convulsion, aphasia, speech disorder, delirium, acute brain syndrome, agitation, confusion, depression, psychosis) often in association with concurrent ischaemic or haemorrhagic cerebrovascular events
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#### Cardiac disorders\*\*

As with other thrombolytic agents, the events described above under the respective section have been reported as sequelae of myocardial infarction and / or thrombolytic administration.

very common	recurrent ischaemia / angina pectoris, hypotension and heart failure / pulmonary oedema,
common	cardiogenic shock, cardiac arrest and reinfarction



uncommon	reperfusion arrhythmias (such as arrhythmia, extrasystoles, AV block first degree to atrioventricular block complete, atrial fibrillation / flutter, bradycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia / fibrillation, electromechanical dissociation [EMD])
	mitral regurgitation, pulmonary embolism, other systemic embolism / cerebral embolism, ventricular septal defect

These cardiac events can be life-threatening and may lead to death.

Reperfusion arrhythmias may lead to cardiac arrest, can be life threatening and may require the use of conventional antiarrhythmic therapies.

### Vascular disorders

rare	Embolism, which may lead to corresponding consequences in the organs concerned
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### Gastrointestinal disorders

rare	Nausea (can also occur as symptoms of myocardial infarction)
not known***	Vomiting (can also occur as symptoms of myocardial infarction)

### Investigations

uncommon	blood pressure decreased
not known***	body temperature increased

### Injury and poisoning and procedural complications

not known***	fat embolism (cholesterol crystal embolisation), which may lead to corresponding consequences in the organs concerned
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### Surgical and medicinal procedures

not known***	Blood transfusions (necessary)
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\*\*\*This adverse reaction has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than “rare”, but might be lower. Precise frequency estimation is not possible as the adverse drug reaction did not occur in a clinical trial database of 8299 patients.



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[illegible]





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[illegible]



**APPROVAL / SIGNATURE PAGE****Document Number:** c08776773**Technical Version Number:**3.0**Document Name:** clinical-trial-protocol-revision-02

**Title:** An open label, multicentre, single-arm trial to assess safety and efficacy of alteplase (rt-PA) in Chinese patients with acute ischemic hemispheric stroke where thrombolysis is initiated between 3 and 4.5 hours after stroke onset

**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor		17 Feb 2017 08:47 CET
Approval-Biostatistics		17 Feb 2017 08:48 CET
Approval-Therapeutic Area		19 Feb 2017 11:34 CET
Approval-Team Member Medicine		24 Feb 2017 11:55 CET

**(Continued) Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
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