BI Study Number:	0135-0348
Title:	Characteristics and in-hospital outcomes of Chinese elderly (>80 years) patients with acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator treatment within 4.5 hours of symptom onset
NCT number:	NCT05395351
Date:	January 28, 2022

This page has been added to the Statistical and Epidemiological Analysis Plan (SEAP) to reflect the requirements by ClinicalTrials.gov. This information is not part of the standard document.

STATISTICAL AND EPIDEMIOLOGICAL ANALYSIS PLAN (SEAP) FOR NON-INTERVENTIONAL STUDIES (NIS)

Document Number:	c37691036-01
BI Study Number:	0135-0348
BI Investigational Product(s)	Actilyse® (Alteplase)
Title:	Characteristics and in-hospital outcomes of Chinese elderly (>80 years) patients with acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator treatment within 4.5 hours of symptom onset
Brief lay title:	Alteplase in elderly AIS during hospitalization
SEAP version identifier:	1.0
Date of last version of SEAP:	
NIS Statistician [SEAP author]	[redacted]
NIS [redacted] [SEAP reviewer]	
NIS Data [redacted] [SEAP reviewer]	

1. TABLE CONTENTS

2. LIST OF ABBREVIATIONS

AIS	Acute Ischemic Stroke
ASD	Absolute Standardized Difference
BI	Boehringer Ingelheim
CI	Confidence Intervals
CSA	Chinese Stroke Association
CSCA	Chinese Stroke Centre Alliance
EVT	Endovascular Treatment
IQR	Interquartile Range
IV	Intravenous
IVT	Intravenous Thrombolysis
NIHSS	National Institutes of Health Stroke Scale
NIS	Non-interventional Study
NIS-DMRP	Non-interventional Study-data Management and Review Plan
RCTs	Randomized Controlled Trials
rt-PA	Recombinant Tissue Plasminogen Activator
RWE	Real-world Evidence
SEAP	Statistical and Epidemiological Analysis Plan
SOPs	Standard Operation Procedures
TIA	Transient Ischemic Attack

3. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]

[redacted]

SEAP reviewers are:

- BI NIS [redacted]
- NIS Data [redacted]
- RWE [redacted]
- TSTAT

NA

- TM Epi

[redacted]

4. PURPOSE AND SCOPE

Using the Chinese Stroke Centre Alliance (CSCA) data to describe the in-hospital clinical outcomes regarding safety and effectiveness for AIS patients who were treated with IV rt-PA within 4.5 hours of symptom onset, aged above 80 years, as well as between 18 and 80 years. We plan to apply and incorporate the results of this study (providing in-hospital outcomes), together with another non-interventional study in China (providing 1-year clinical outcomes), as well as results from randomized controlled trials conducted in other countries, to support local label update: to remove the age restriction (>80 years) from the label of Actilyse in China.

5. AMENDMENTS AND UPDATES

Not applicable.

6. RESEARCH QUESTION AND OBJECTIVE

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

Primary objective:

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

Secondary objectives:

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

7. RESEARCH METHODS

7.1 STUDY DESIGN

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

Patient groups:
Patients in this study will be divided into 4 groups:

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

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

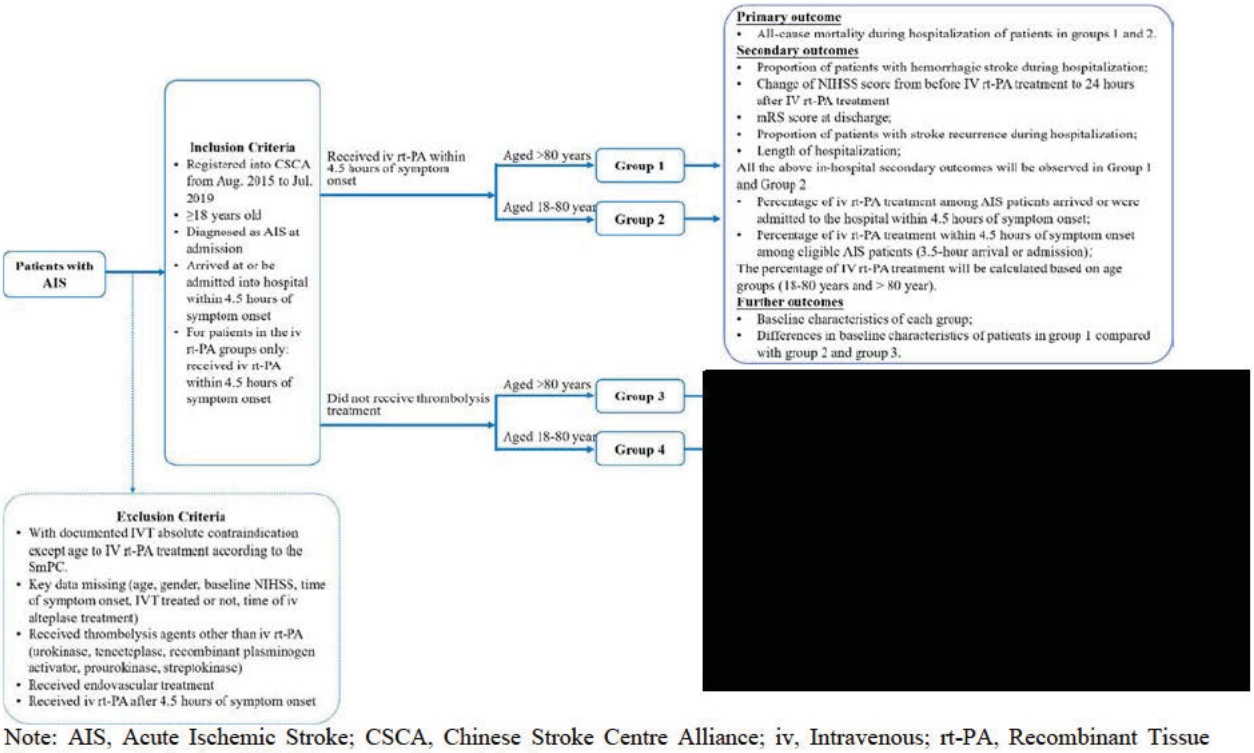
The clinical outcomes during hospitalization will be observed in groups 1 to 2.

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

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

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

Figure 1 Patient groups for the non-interventional study



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

7.2 SETTING

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

7.3 STUDY POPULATION

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

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

The inclusion and exclusion criteria are listed below:

Inclusion Criteria:

- Patient registered in the CSCA platform from Aug 2015 to Jul 2019
- ≥18 years old
- Diagnosed as AIS at admission
- Arrived or admitted into hospital within 4.5 hours of symptom onset

- For patients in the iv rt-PA groups only: received IV rt-PA within 4.5 hours of symptom onset.

Exclusion Criteria:

- Documented IVT absolute contraindication
- Key data missing (age, gender, baseline National Institutes of Health Stroke Scale [NIHSS], time of symptom onset, IVT treated or not, time of IV alteplase treatment)
- Received thrombolysis agents other than IV rt-PA (urokinase, tenecteplase, recombinant plasminogen activator, prourokinase, streptokinase)
- Received endovascular treatment
- Received IV rt-PA after 4.5 hours of symptom onset.

7.4 STUDY VISITS

Not applicable.

8. VARIABLES

8.1 EXPOSURES

The exposure in this study is the use of IV rt-PA among AIS patients within 4.5 hours of symptom onset.

8.2 OUTCOMES

8.2.1 Primary outcomes

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

8.2.2 Secondary outcomes

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

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

- Percentage of IV rt-PA treatment among AIS patients arrived or were admitted to the hospital within 4.5 hours of symptom onset
- Percentage of IV rt-PA treatment within 4.5 hours of symptom onset among eligible AIS patients (3.5-hour arrival or admission)

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

8.3 COVARIATES

Covariates include the following variables at baseline:

- Age
- Gender (male, female)
- Stroke severity (baseline NIHSS)
- Time from symptom onset to hospital arrival or admission
- Smoking (current smoker, former smoker, never smoker)

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

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

9. DATA SOURCES

The CSCA is a national, hospital-based, multicentre, voluntary, multifaceted intervention and continuous quality improvement initiative, launched by Chinese Stroke Association (CSA) in 2015. This programme is made available to all Chinese Grade 2 and Grade 3 hospitals. Hospitals continued to join the programme in a staggered manner. By Jul 2019, 1476 hospitals (720 Grade 2 hospitals, 756 Grade 3 hospitals) had participated into this programme. Hospital characteristics, including geographic region, teaching status, hospital volume (grade 2 and 3) and annual stroke volume, are surveyed. Data were collected via the web-based patient data collection and management tool [redacted], abstracted via chart review, coded, de-identified and transmitted in a secure manner to maintain patient confidentiality compliant with national privacy standards. The following data were collected for each hospitalization: patient demographics, history of disease and medication, hospital presentation, initial neurological status, medications and interventions, reperfusion strategy and in-hospital outcomes and complications.

10. DATA MANAGEMENT AND SOFTWARE/TOOLS

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

10.1 SOFTWARE/TOOLS

All statistical analyses were performed using SAS Version 9.4 software [redacted]. All ASD>10 were considered significant.

10.2 HANDLING OF MISSING VALUES

Every reasonable attempt have been undertaken to ensure completeness of data collection. In general, missing data will be treated as missing. No data imputation will be performed for the missing data. Due to the nature of existing data, the interpretation is based on non-missing data.

10.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

Missing and erroneous values in patient cases can significantly impact the ability to perform research for identifying risk factors and disease distribution, treatment progression. This study is mainly based on review of data collected from CSCA and aims at evaluating differences in clinical practice of IV-rtPA treatment among AIS patients from 2015 to 2019. Data follow-up period has already been finished. Thus, data cannot meet the criteria of this study will be excluded.

Exclusion criteria:

1. Missing key data including
   - Contraindications to venous thrombolysis within a time window
   - symptom onset time (or last known well time);
   - baseline NIHSS;
   - whether received IVT treatment or not;
   - the time of IVT treatment (For patients in the IV rt-PA groups only);
   - Received thrombolysis agents other than IV rt-PA（Urokinase）;
   - Received endovascular treatment:
   - Received IV rt-PA after 4.5 hours of symptom onset (For patients in the IV rt-PA groups only):
   - age and gender
2. Contradiction of time period:
   - IVT treatment time earlier than symptom onset time (or last known well time);
   - treatment time earlier than hospital arrival time;
   - hospital arrival time earlier than symptom onset time

3. Diagnosed with intracranial hemorrhage (ICH), Transient Ischemic Attack (TIA), subarachnoid hemorrhage (SAH), or unspecific stroke

11. DATA ANALYSIS

The study is descriptive in nature. The calculation will be based on the available data. Selected outcomes will be analyzed with data from hospital participated in CSCA. Selected outcomes will also be standardized by hospital (based on CSCA).
For continuous data, descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, interquartile range, and maximum) will be presented. Categorical data will be presented as frequency and proportion with 95% CI as appropriate.

11.1 MAIN ANALYSIS

The baseline characteristics (covariates) as listed in Section 8.3 will be analysed by using descriptive statistics for all 4 groups in this study, where Group 1 is compared against group 2 and Group 1 is compared against Group 3 to evaluate the potential channeling. Absolute standardized difference (ASD) between the compared groups will be calculated, in which a ≥10% ASD will be considered a meaningful difference.

The primary outcome is the all-cause mortality during hospitalization. The primary outcome will be described using descriptive statistics for Group 1 and Group 2. The secondary outcome as listed in Section 8.2.2 will also be described using descriptive statistics for Group 1 and Group 2. Additionally, if the baseline characteristics of patients in group 1 are comparable to patients in group 3 (ASD<10%), then we will describe the in-hospital outcomes for group 3 patients, including all-cause mortality during hospitalization, proportion of patients with hemorrhagic stroke during hospitalization, mRS score at discharge, proportion of patients with stroke recurrence during hospitalization, and length of hospitalization. If the baseline characteristics of patients in group 1 and group 3 are not comparable, then we will not describe the above outcomes in group 3.

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

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

11.1.1 Primary outcomes

All-cause mortality during hospitalization of patients in Group 1 and Group 2 (Table 1)

- Proportion of died AIS patients during hospitalization who were treated with IV rt-PA within 4.5 hours of symptom onset among those aged 18 to 80 years(Group 2) and >80 years(Group 1);

11.1.2 Second outcomes

Among all AIS patients during hospitalization who were treated with IV rt-PA within 4.5 hours of symptom onset (patients Group 1 and Group 2) (Table 2)

- Proportion of patients with hemorrhagic stroke during hospitalization
- Change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatment
- mRS score at discharge
  a) Discharge MRS score classification
  b) Discharge MRS score (0-1)
- Proportion of patients with stroke recurrence during hospitalization
- Length of hospitalization;

Among all AIS patients during hospitalization on 18-80 years age groups (Group 2 and Group 4) and > 80 year age groups (Group 1 and Group 3)(Table 3)

- Percentage of IV rt-PA treatment among AIS patients arrived or were admitted to the hospital within 4.5 hours of symptom onset
- Percentage of IV rt-PA treatment within 4.5 hours of symptom onset among eligible AIS patients (3.5-hour arrival or admission)

11.3 SAFETY ANALYSIS

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

12. QUALITY CONTROL

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

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

13. REFERENCES

13.1 PUBLISHED REFERENCES

NA

13.2 UNPUBLISHED REFERENCES

NA

ANNEX 1. ADDITIONAL INFORMATION

1. DEFINITION OF VARIABLES

(1) Patients characteristics
--Smoke including current smoking & cessation of smoking within previous year
(2) Medical history
--DM including self-reported history of diabetes or current use of hypoglycemic drugs
--Hypertension including self-reported history of hypertension or current use of antihypertensive drugs

	Variable Name	Type	Label & Value
1	pid	character	Patient ID
2	hunitID	character	Hospital ID
3	Hlevel	numerical	Hospital Grade
4	hname	character	Hospital Name
5	gender	numerical	Gender:1=Male;2=Female
6	Agen	numerical	Age At Admission
7	d_diag	character	Final diagnosis: 1= Ischemic stroke;2=TIA;3=ICH;4=SAH;5=Other
8	A_NIHSSn	numerical	Fisrt Time Nihss After Hospital Arrival
9	H_SMK	numerical	History Of Smoke: 1-never smoker;2- former smoker; 3-current smoker; other-unclear) :
10	H_DRINK	numerical	History Of Drink (Including Past Habit of Drinking But Not In Last Year; Or Still Drinking) :0=No;1=Yes
11	H_DM1	numerical	History Of Diabetes: Selfreport History or Medication Use: 0=No;1=Yes
12	H_HYPT1	numerical	History Of Hypertentsion: Selfreport History or Medication Use: 0=No;1=Yes
13	Stt_lipid	numerical	History Of Hypelipidemia: Selfreport History or Medication Use: 0=No;1=Yes
14	H_AFIB	character	History of atrial Fibrillation: 0=No;1=Yes
15	H_HF	character	History of heart failure: 0=No;1=Yes
16	H_CHDMI	numerical	History of chronic heart disease or Myocardial Infarction: 0=No;1=Yes
17	H_PVD	character	History of peripheral vascular disease: 0=No;1=Yes
18	H_CSTENO	character	History of carotid artery stenosis: 0=No;1=Yes
19	H_StrokeTIA	numerical	History of stroke or TIA
20	onset_door_time	numerical	Hours from onset to hospital arrival
21	onset_needle_time	numerical	Hours from onset to rt-PA Treatment
22	Door_needle_time	numerical	Hours from hospital arrival to rt-PA Treatment
23	TPA	numerical	Treatment wtih Tpa: 0=No;1=Yes
24	H_PLT	character	History of medication of Antiplatelet agent: 0=No;1=Yes
25	H_COAG	character	History of medication of Anticoagulant drugs: 0=No;1=Yes
26	TPA_R	character	Reasons for not being treated with IV rt-PA:1= Beyond the rt-PA intravenous thrombolysis time window;2= ontraindications to intravenous thrombolysis within a time window;3= Hospital related or other reasons;4= Economic reasons;5= The patient or family refused; other=unclear.
27	DYS_RESULTFMT	numerical	1= Function good;0 or 2= Function of difficult; other=unclear

	Variable Name	Type	Label & Value
28	EDUcat	numerical	1=college;2=high school ;3=below elementary; other=unclear
29	Insurance	character	1=UEBMI;4=URBMI;5=NRCMS;6=Self-pay; other=other medical insurance
30	I_FGn	numerical	blood-glucose
31	I_CRP_UNITn	numerical	C-reactive protein

--CHD or MI including Chronic Heart Disease or self-report history of myocardial infarction
--AF including self-report history of Atrial fibrillation
--Previous stroke including self-report history of ischemic stroke, intracranial hemorrhage or subarachnoid hemorrhage
--TIA including self-report history of transient ischemic attack
--Dyslipidaemia including self-report history of lipid metabolism disorders or current use of lipid-lowering drugs

2. DICTIONARY OF VARIABLES

3. MOCK TABLE&FIGURE

Primary outcomes:

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

Variables	Group 1 (N= [%])	Group 2 (N= [%])
All-cause mortality	n (%) (95%CI)	n (%) (95%CI)

Secondary outcomes:

Table 2. Secondary outcomes during hospitalization of patients in Group 1 and Group 2**.**

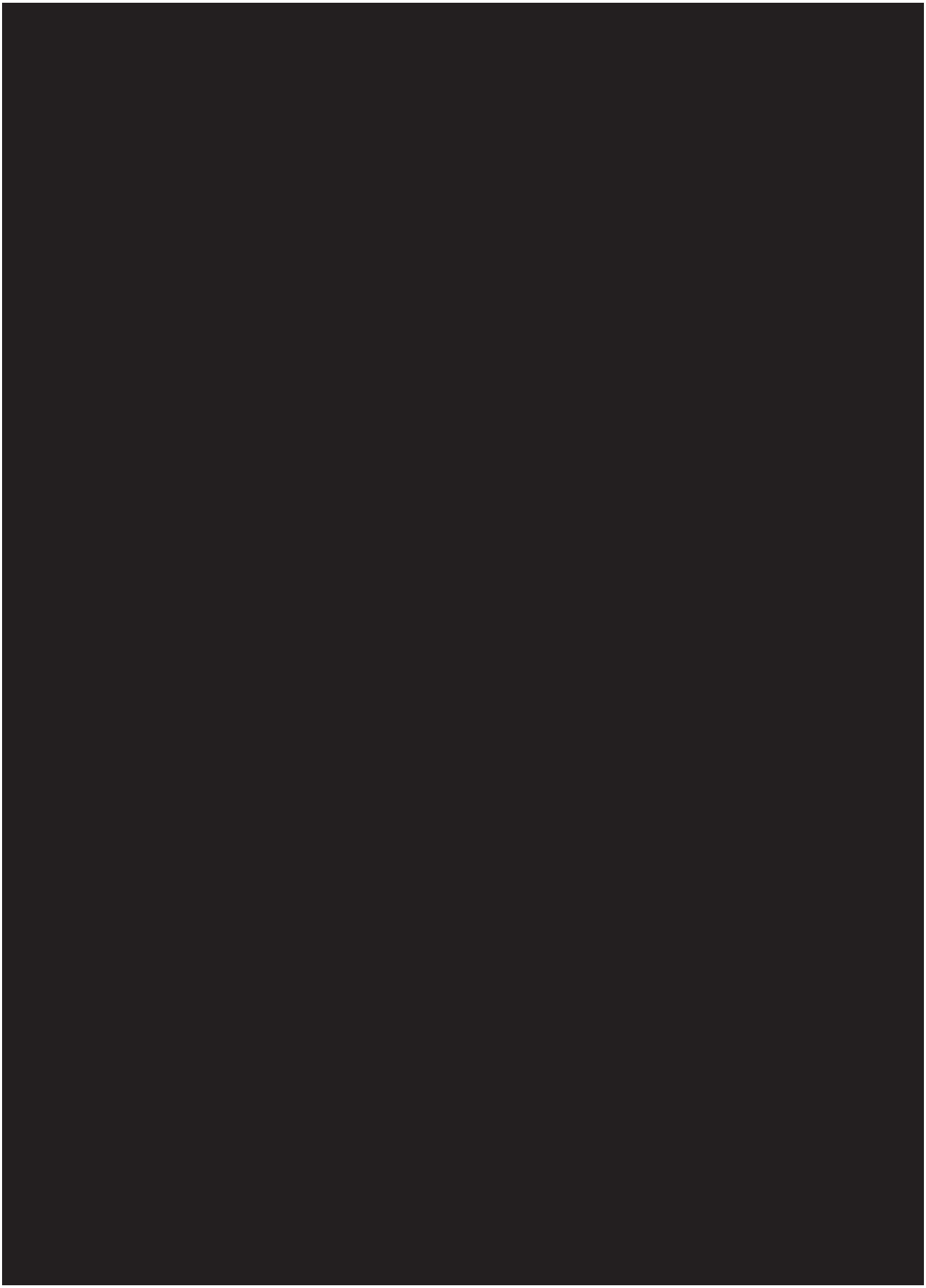
Variables	Group 1 (N= [%])	Group 2 (N= [%])
Proportion of patients with hemorrhagic stroke during hospitalization	n (%) (95%CI)	n (%) (95%CI)
Change of NIHSS score from before IV rt-PA treatment to 24 hours after IV rt-PA treatments		
	Nmiss (%)	Nmiss (%)
	Mean±SD	Mean±SD
	Min–Max	Min–Max
	Median (IQR)	Median (IQR)
mRS score at discharge		
Discharge mRS score classification		
Missing	n (%) (95%CI)	n (%) (95%CI)
0	n (%) (95%CI)	n (%) (95%CI)
1	n (%) (95%CI)	n (%) (95%CI)
2	n (%) (95%CI)	n (%) (95%CI)
3	n (%) (95%CI)	n (%) (95%CI)
4	n (%) (95%CI)	n (%) (95%CI)
5	n (%) (95%CI)	n (%) (95%CI)
Discharge mRS score (0-1)	n (%) (95%CI)	n (%) (95%CI)

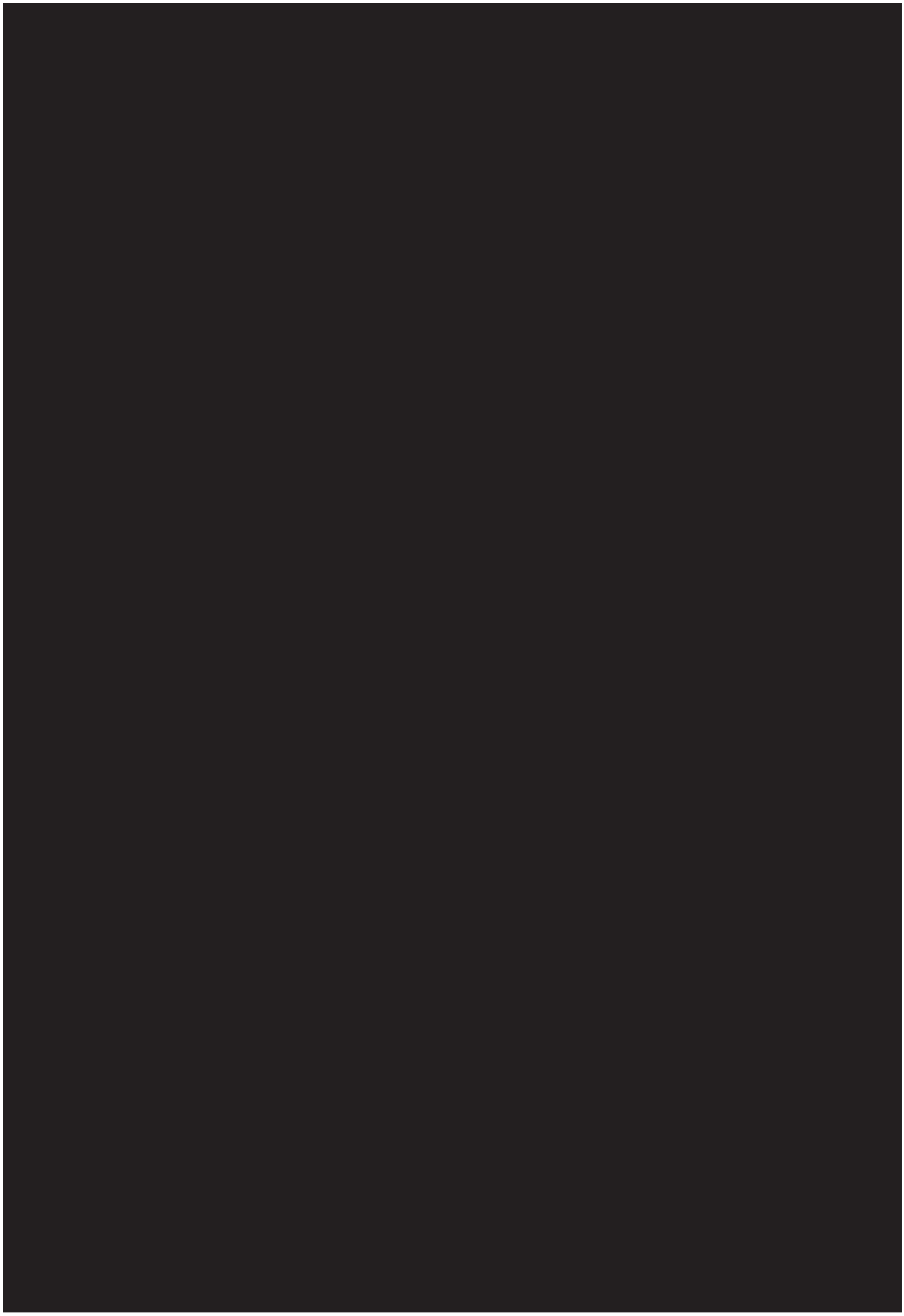
Variables	Group 1 (N= [%])	Group 2 (N= [%])
Proportion of patients with stroke recurrence during hospitalization	n (%) (95%CI)	n (%) (95%CI)
Length of hospitalization, d	Nmiss (%) Mean±SD Min–Max Median (IQR)	Nmiss (%) Mean±SD Min–Max Median (IQR)

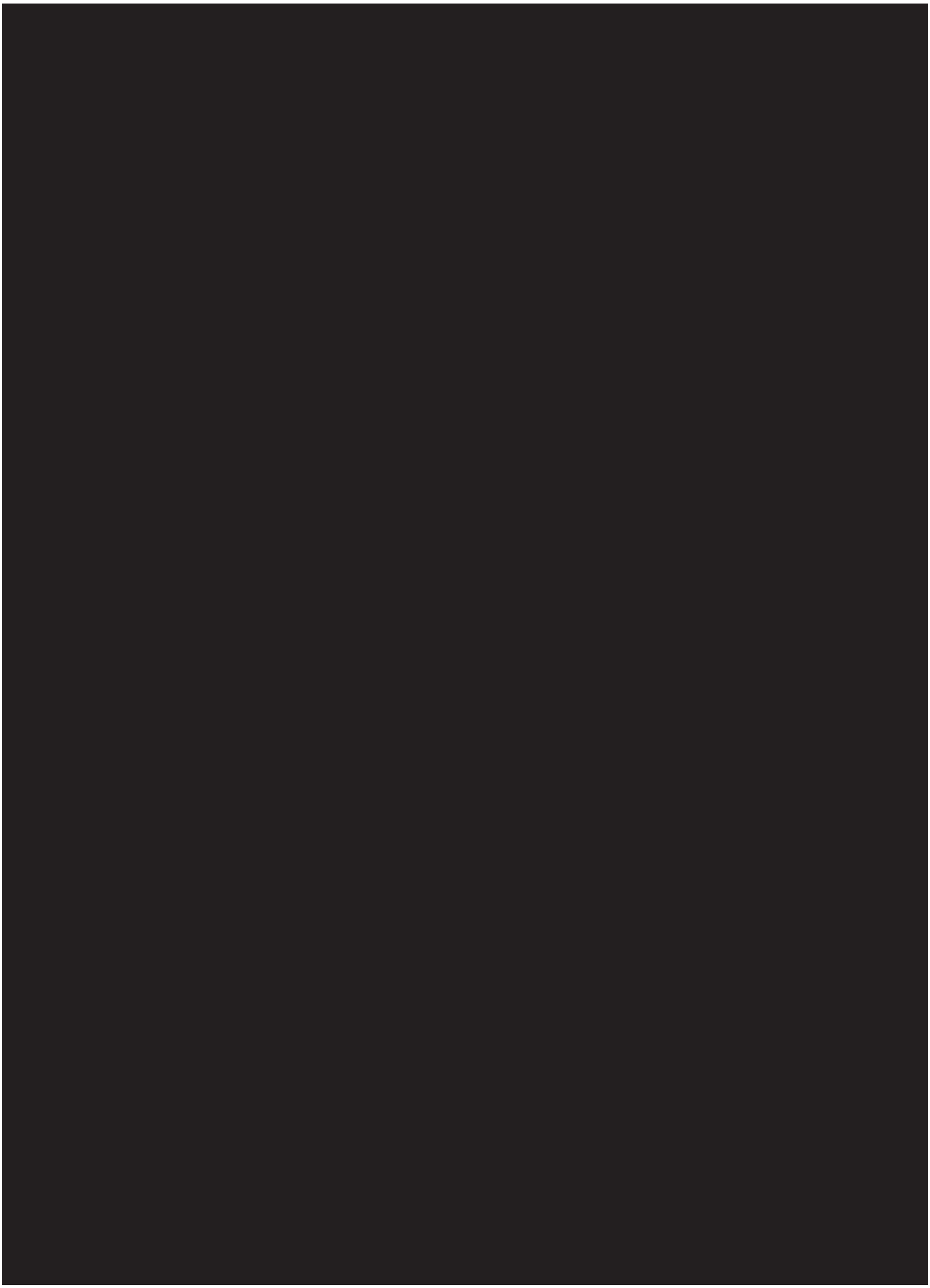
Table 3. Proportion of 4.5 h IV-rtPA treatment among all AIS patients (arrived or admitted within 4.5 hours of symptom onset) based on age groups & Proportion of 4.5h IV-rtPA treatment among 3.5h IVT eligible patients.

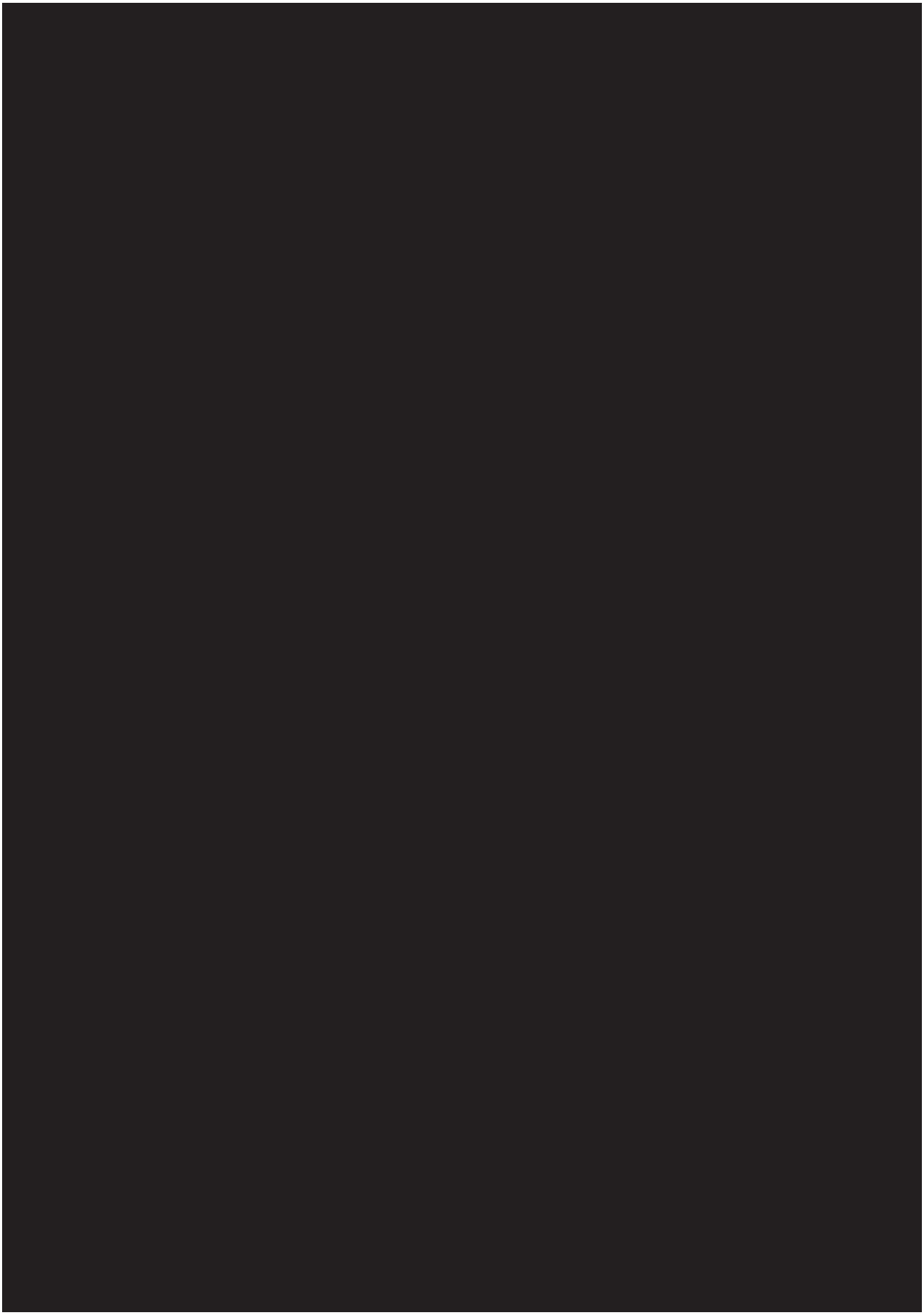
Proportion	18-80 years (N= [%])	> 80 years (N= [%])
4.5h IV-rtPA / all AIS patients	n (%) (95%CI)	n (%) (95%CI)
4.5h IV-rtPA / 3.5h IVT eligible	n (%) (95%CI)	n (%) (95%CI)

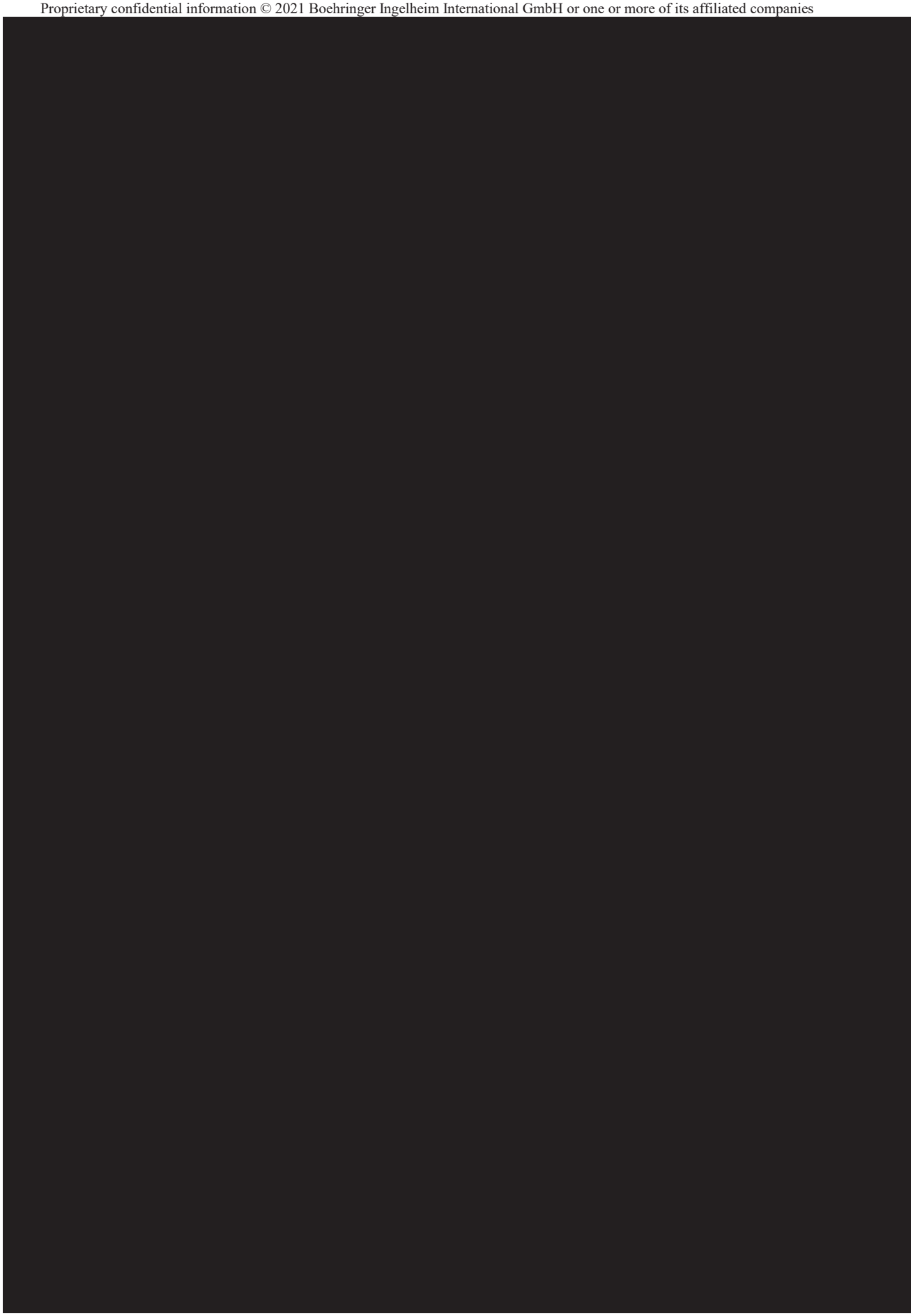
[redacted]

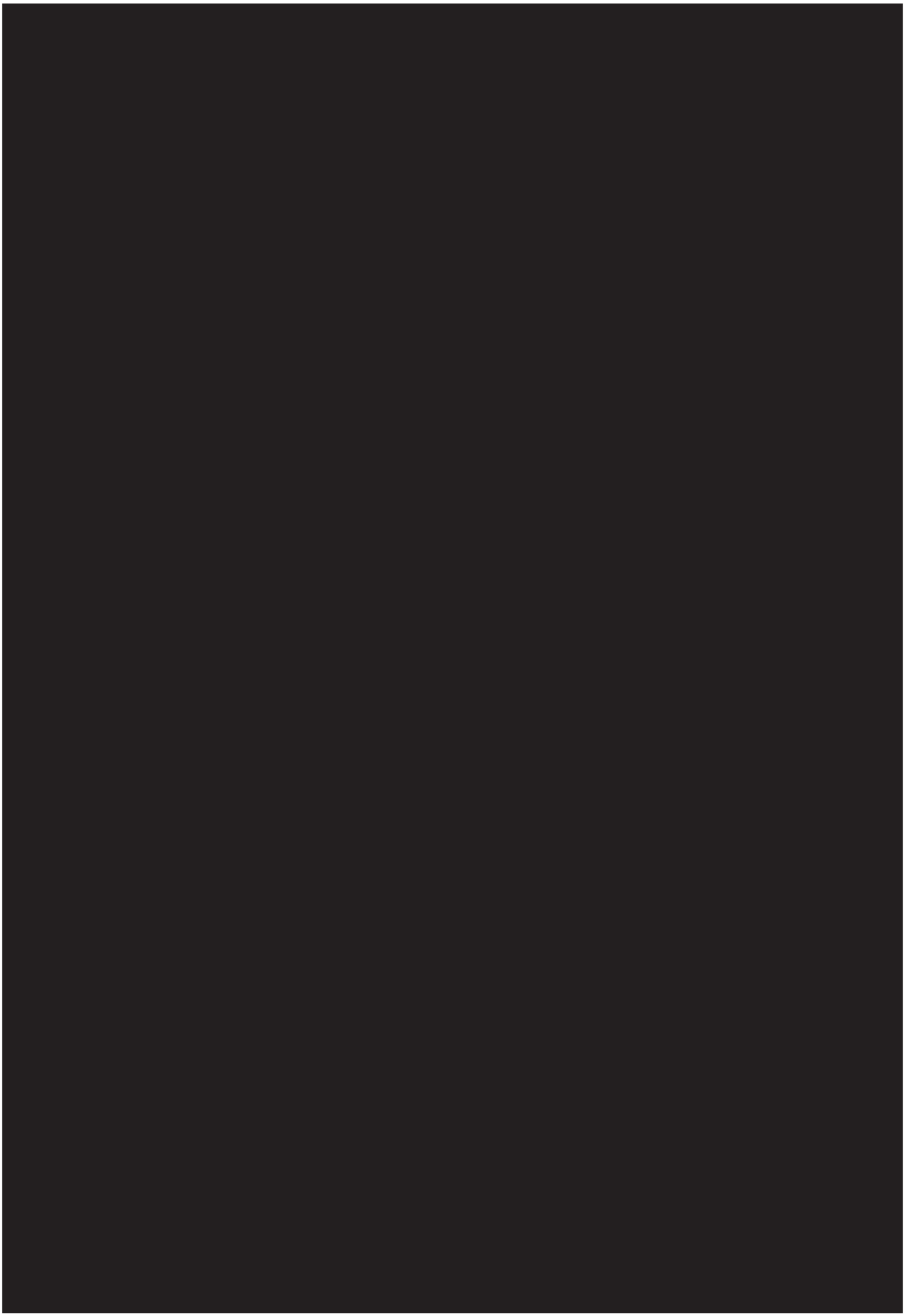


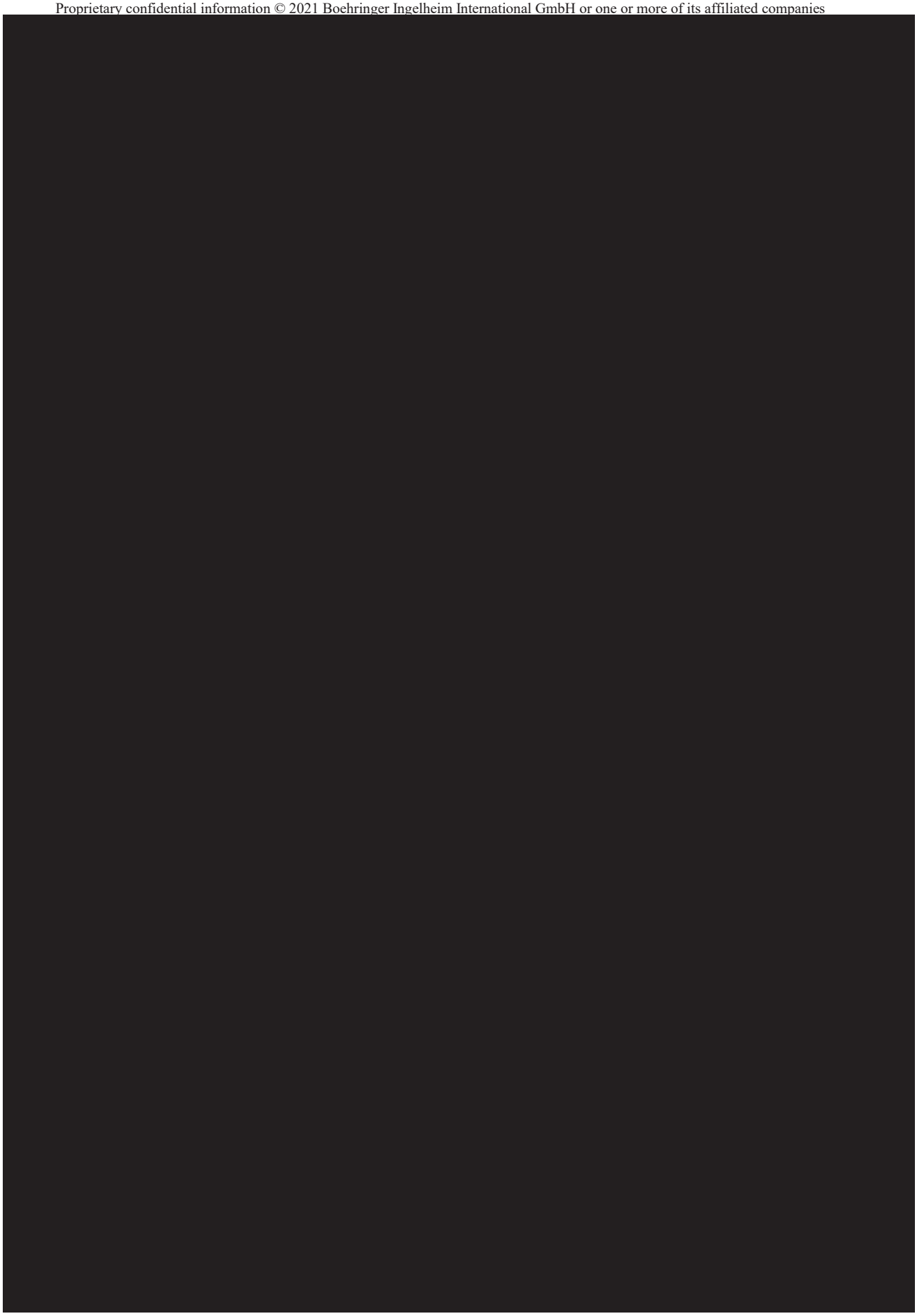


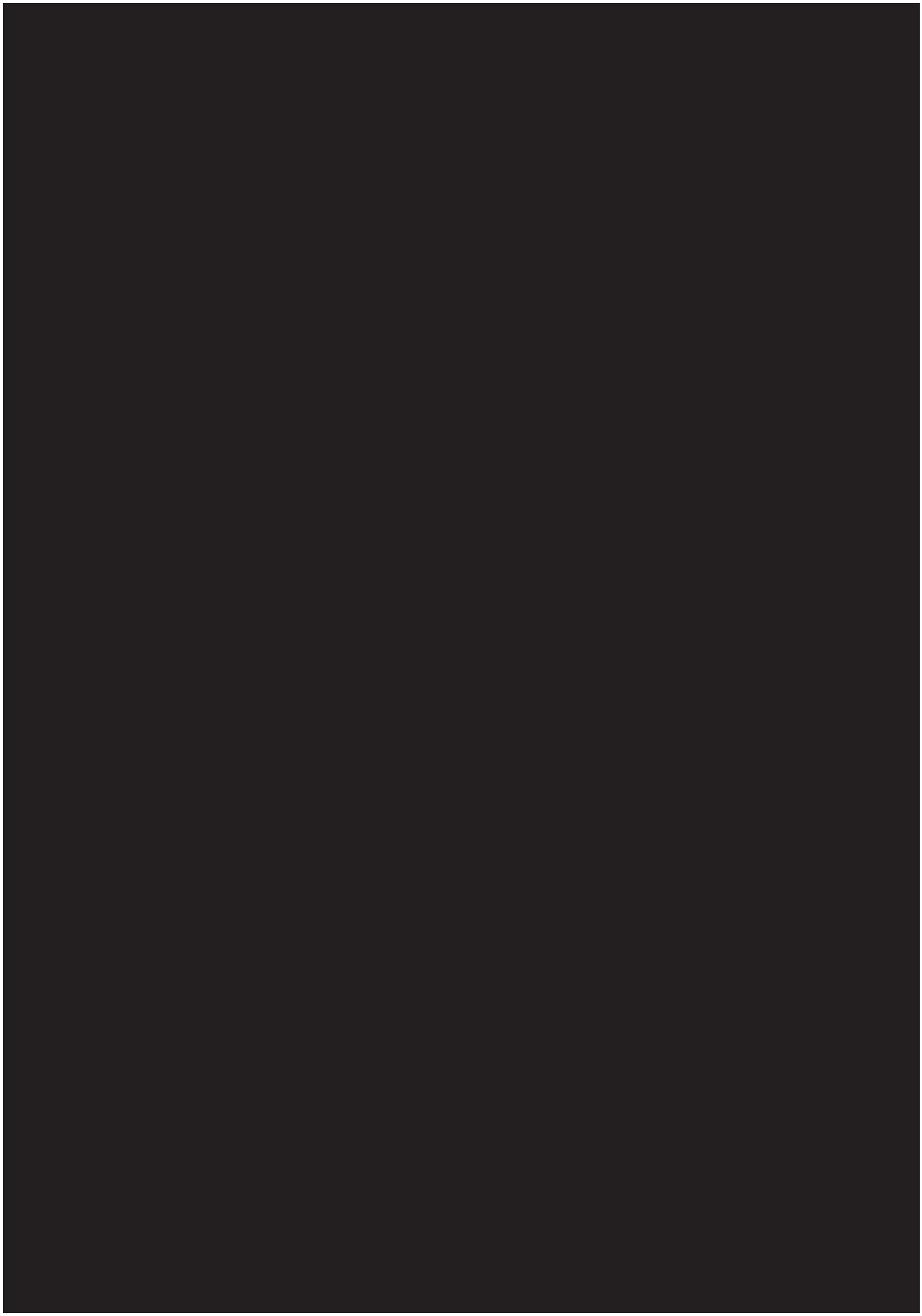


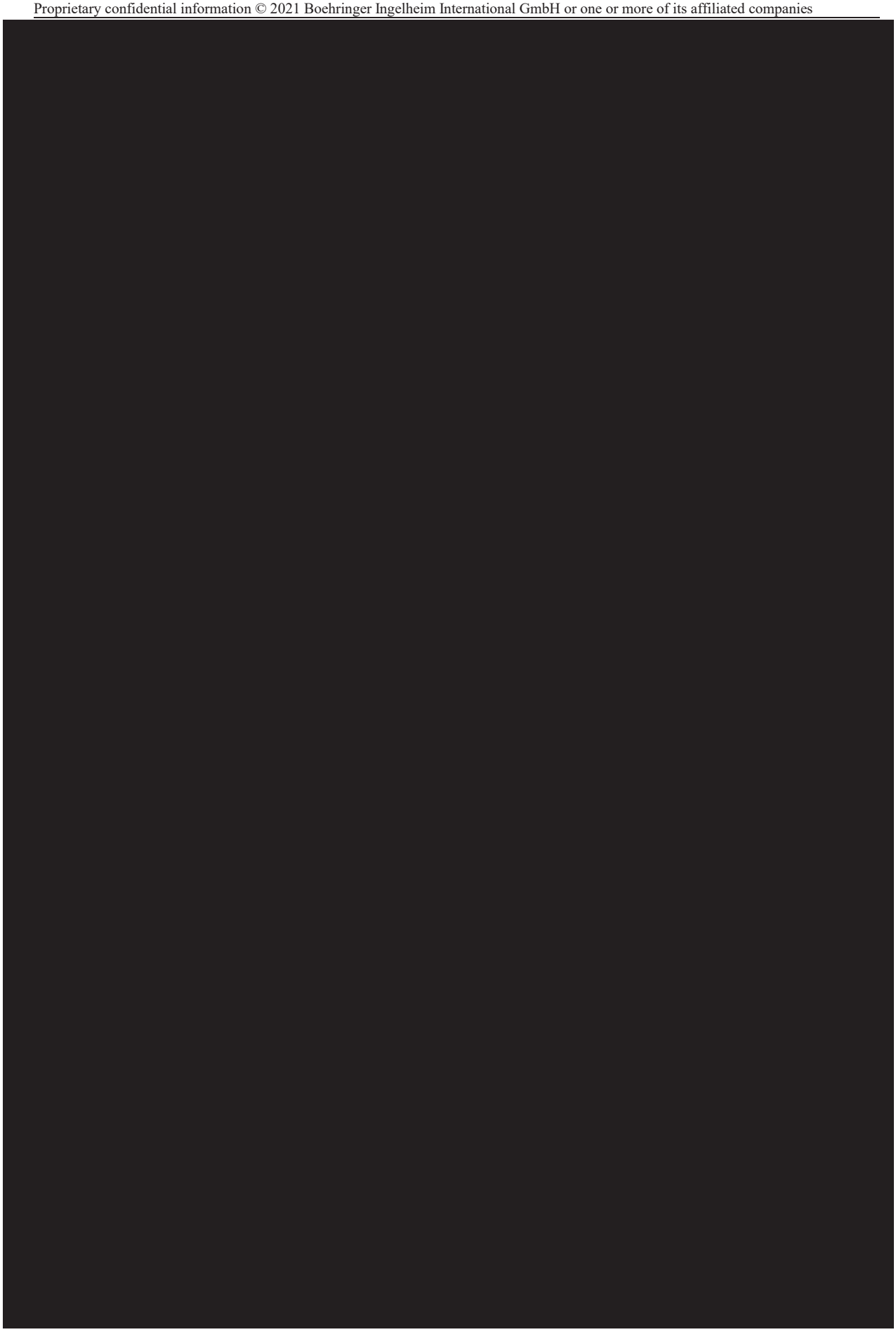


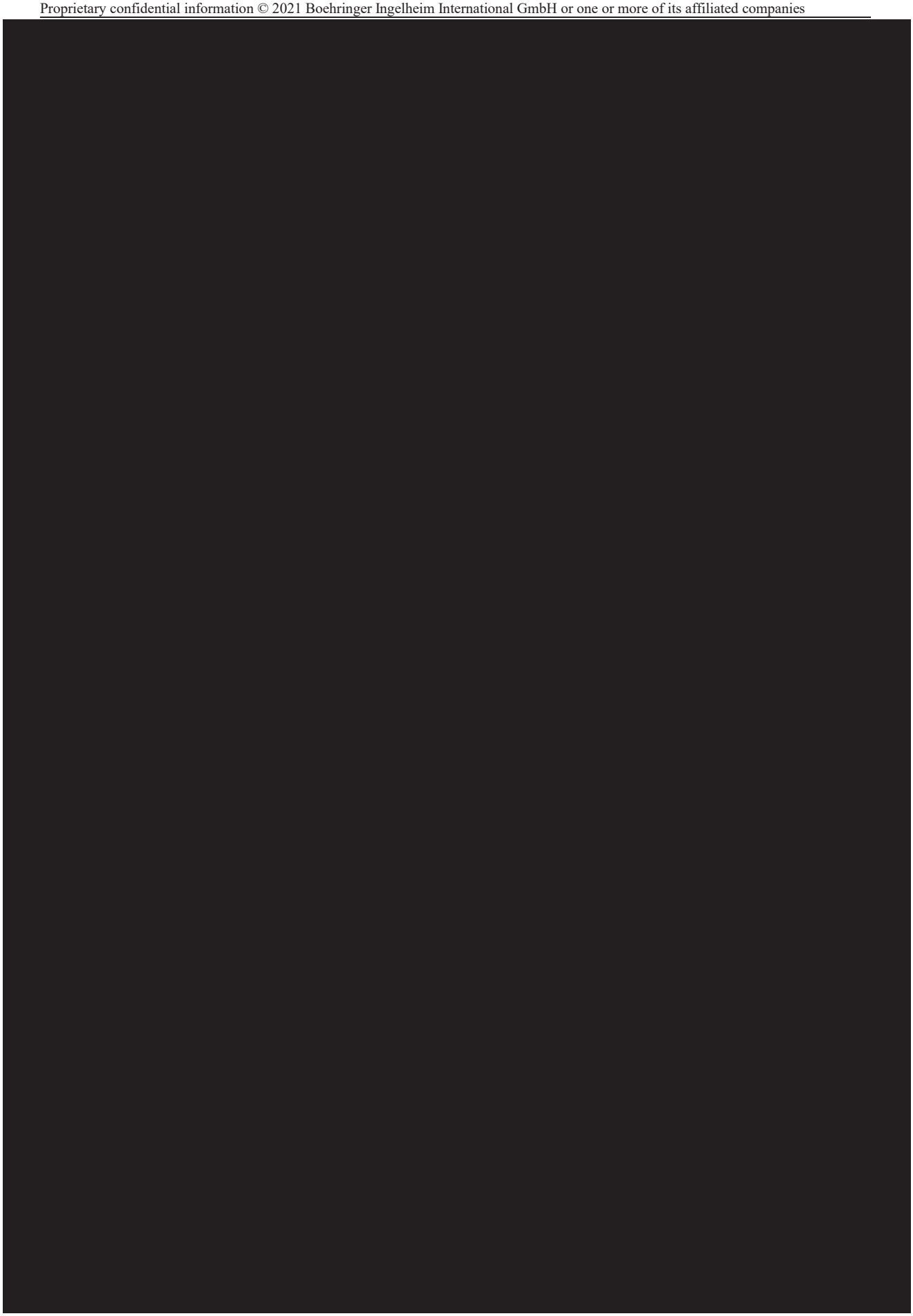












ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

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

Reviewer	NIS involving BI product(s)	NIS not involving BI product(s)	
		Global NIS	Local NIS
NIS Lead	X	X	X
Global TM Epi*	X	X	X
NIS Data Manager	X	X	X
TSTAT (for NISnd only)	X	X	X
RWE CoE	X	X	

** When BI NIS lead is not TM Epi*

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

Study Number: 0135-0348

Protocol Version:1.0

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

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____