14 December 2023
EMA/37096/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Metalyse

International non-proprietary name: Tenecteplase

Procedure No. EMEA/H/C/000306/II/0070/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AcT	Alteplase Compared to Tenecteplase in Patients with Acute Ischemic Stroke Trial
AHA	American Heart Association
AIS	Acute Ischaemic Stroke
ALT	Alteplase
ASA	American Stroke Association
ATTEST	Alteplase versus tenecteplase for thrombolysis after ischaemic stroke trial
BI	Boehringer Ingelheim
CCDS	Company Core Data Sheet
CHO	Chinese hamster ovary
CI	Confidence Interval
CPMP	Committee for Proprietary Medicinal Products
CSBPR	Canadian Stroke Best Practices Recommendations
CSC	Comprehensive stroke centre
CT	Computed tomography
DLP	Data Lock Point
ECASS	The European Cooperative Acute Stroke Study
EEA	European Economic Area
EMA	European Medicines Agency
ESO	European Stroke Organisation
EU	European Union
EXTEND	Extending the Time for Thrombolysis in Emergency Neurological Deficits
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	Intracerebral haemorrhage
ICSR	Individual Case Safety Report
IIS	Investigator Initiated Study
IQR	Interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
i.v	Intravenous
IVT	Intravenous thrombolysis
LVO	Large vessel occlusion

MAH	Marketing Authorisation Holder
MI	Myocardial Infarction
mITT	Modified Intention to treat
MNI	Minor neurological impairment
mPP	Modified per protocol
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders & Stroke (NIH)
NOR-TEST	The Norwegian tenecteplase stroke trial
OR	Odds Ratio
OTT	Onset of symptoms to treatment
PK	Pharmacokinetics
PSC	Primary stroke centre
RCT	Randomised Clinical Trial
RD	Risk Difference
rt-PA	Recombinant tissue plasminogen activator
RWE	Real World Evidence
SD	Standard deviation
sICH	Symptomatic intracerebral haemorrhage
SITS	Safe Implementation of Treatments in Stroke
SITS-MOST	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
SmPC	Summary of product characteristics
STEMI	ST-Elevation Myocardial Infarction
STREAM	STrategic Reperfusion Early After Myocardial Infarction
STTC	Stroke Thrombolysis Treatment (STT) Collaboration database
TASTE	Tenecteplase with alteplase for the early treatment of ischaemic stroke
TNK	Tenecteplase
t-PA	Tissue plasminogen activator
UK	United Kingdom
US	United States
USA	United States of America

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 24 July 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
B.II.b.3.a	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	Type IB	None
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	Type II	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.e.5.c	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	Type II	I, IIIA, IIIB and A

Grouped application consisting of:
C.I.6.a (Type II): To add the new therapeutic indication Acute Ischemic Stroke (AIS) for the new 25 mg presentation. Consequently, a separate SmPC and Package Leaflet are provided for the 25 mg presentation with the new indication. In addition, the MAH took the opportunity to implement editorial changes and minor updates to the PI of Metalyse 40 mg (8,000 U) and 50 mg (10,000 U).
B.II.e.5.c (Type II): To add the new 25 mg presentation for the sterile parenteral biological medicinal product Metalyse (tenecteplase) powder for solution for injection.
B.II.b.3.a (Type IB, by default): Minor changes in the manufacturing process of 25 mg presentation for the sterile parenteral biological medicinal product Metalyse (tenecteplase) powder for solution for injection to add a new DP filling line, to adapt freeze-drying cycle for lyophilization process, to replace unsuitable sterile filter with suitable one in the new filling line, to add three In-Process controls (IPCs), and to increase the batch size.
B.II.e.1.b.2 (Type II): Change in the immediate packaging of 25 mg presentation for the sterile parenteral biological medicinal product Metalyse (tenecteplase) powder for solution for injection to introduce a new rubber stopper.

The group of variations requested amendments to the Summary of Product Characteristics, Labelling, Package Leaflet and Annex A.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 26 January 2023 (EMA/SA/0000117176). The Scientific Advice pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	24 July 2023
Start of procedure:	12 August 2023
CHMP Rapporteur Assessment Report	6 October 2023
CHMP members comments	31 October 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 November 2023
Request for supplementary information (RSI)	9 November 2023
CHMP Rapporteur Assessment Report	29 November 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	8 December 2023
Opinion	14 December 2023

2. Scientific discussion

2.1. Introduction

Disease or condition

Stroke is a disease characterized by brain tissue damage, due to vascular occlusion (ischaemic stroke) or sudden rupture of cerebral blood vessels (haemorrhagic stroke). Stroke is one of the leading causes of death and disability worldwide. Acute ischaemic stroke (AIS) is the most common form of stroke,

accounting for 87% of all cases and is primarily caused by thrombosis or embolism blocking the cerebral arteries.

Alteplase thrombolysis is the only worldwide approved pharmacologic treatment of AIS. The positive individual benefit-risk ratio and the positive population outcome by improving or avoiding a disability status (as defined by mRS at 90 days) has established alteplase as standard of care in AIS within 4.5 h after stroke onset in eligible patients. The impact of time is well established, as the earlier fibrinolytic treatment is started in eligible patients, the greater the clinical outcome benefit. Since thrombolysis has become available, AIS has become a medical emergency because of the ability to provide an etiological treatment allowing reperfusion of blocked cerebral arteries, triggering the adaptation or development of new processes of care, mainly based on reduction of time intervals from onset of symptoms to initiation of thrombolysis in eligible patients.

Based on emerging clinical trial evidence, namely the earlier recanalization rates and better clinical outcome after 3 months with tenecteplase as compared with alteplase in the subset of AIS patients presenting with LVO [P12-03304, P18-03928], several stroke guidelines have been updated to include recommendations for tenecteplase at the dose of 0.25 mg/kg (max 25 mg) [P19-02504]. In patients with large vessel occlusion (LVO)-related ischaemic stroke eligible for intravenous thrombolysis (IVT) before mechanical thrombectomy, tenecteplase (0.25 mg/kg) is suggested over alteplase (0.9 mg/kg) by the ESO/ESMINT Guidelines [P19-02504], and proposed as a reasonable option over intravenous (i.v.) alteplase by the AHA Stroke Guidelines [P19-10385]. IVT followed by mechanical thrombectomy has become the standard of care for patients with LVO [P19-02504]. In LVO patients eligible for both, IVT plus mechanical thrombectomy is recommended as quickly as possible [P19-02504, P19-10385]. Evidence for use of tenecteplase in a large population (i.e. ischaemic stroke patients within 4.5 h of symptom onset), was needed, as has been provided for alteplase, the current standard of care for thrombolytic eligible patients. Several Phase III randomized clinical trials have been initiated to answer this question (AcT [P22-05053], ATTEST 2 (ClinicalTrials.gov Identifier: NCT02814409, [P18-05706]), TASTE (Australian New Zealand Clinical Trials Registry Identifier: ACTRN12613000243718), and NOR-TEST 2 [P22-03558]). The MAH is also conducting a Phase II trial in China; BI 1123-0040 [c33415518], The first completed Phase III trial, the AcT clinical trial [P22-05053], outcome results provide the evidence of tenecteplase non-inferiority to alteplase in the AIS population within 4.5 h of stroke onset eligible for thrombolysis.

With the current variation the Applicant is applying for the following indication for tenecetaplase (TNK):

Metalyse is indicated in adults for the thrombolytic treatment of acute ischaemic stroke (AIS) within 4.5 hours from last known well and after exclusion of intracranial haemorrhage.

2.1.1. About the product

Tenecteplase, a bioengineered variant of alteplase, exhibits improved pharmacological properties and is adapted for a simple administration suited to emergency treatment, as established in the ST elevation myocardial infarction (STEMI) indication. As a result of the modifications, tenecteplase has a greater fibrin specificity, a higher resistance to inactivation by plasminogen activator inhibitor, a longer half-life, and a slower plasma clearance compared with alteplase, enabling a single-bolus administration. Therefore, the clinical community has triggered exploratory studies with tenecteplase for AIS aiming at demonstrating improved outcomes versus alteplase, and also aiming to streamline and shorten care processes.

For the now sought indication a new presentation has been developed, i.e. vials containing 5 000 units (25 mg) tenecteplase. As for the hitherto approved presentations, the reconstituted solution contains 1 000 units (5 mg) tenecteplase per mL.

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

The Applicant received scientific advice of the EMA in January 2023 (Initial Scientific Advice, Tenecteplase. Doc Ref: EMADOC-1700519818-1010744; Case No: EMA/SA/0000117176, [ra01312627]). Issues discussed in the advice regarding the now sought indication mainly concerned:

- shelf-life for the planned new Metalyse presentation containing 25 mg TNK; acceptability of a MAA for Metalyse in AIS based on clinical studies performed with Metalyse or TNKase;

- whether the clinical evidence for TNK in AIS within the 4.5 h treatment window, which is mainly based on the AcT trial serving as pivotal evidence and other investigator initiated studies (IIS) is sufficient for an MAA in the AIS indication;

- acceptability of the weight-band dosing scheme by 10 kg steps

At the time of the EMA Scientific Advice, the relevant studies included in this application had already been completed.

The clinical issues raised in the Scientific advice were taken into consideration in the submitted Clinical overview and/or in the extensive AcT data re-analysis, summarised in a clinical report [c42081819] and discussed in the Ancillary analyses of the main (AcT) study (see Section 2.5.2. of this Report).

2.1.3. General comments on compliance with GCP

The MAH has provided a statement to the effect that the following clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC: AcT trial and the Extend-IA TNK trial.

2.2. Quality aspects

Quality aspects

Introduction

The scope of this variation application is to introduce a new presentation, tenecteplase lyophilisate for solution for injection 25 mg vial, in addition to the already approved presentations of 40 mg tenecteplase/vial and 50 mg tenecteplase/vial. The proposed presentation is intended to be used for a new indication: acute ischaemic stroke (AIS).

Tenecteplase is supplied as lyophilized product containing no preservatives. The finished product, also referred to as drug product (DP), Metalyse is intended for single use and is reconstituted to 5 mg tenecteplase/mL using sterile WFI. The reconstituted product is designed for parenteral administration.

With registration of the additional 25 mg presentation for Metalyse, the tenecteplase availability for treating AIS will be increased. In this context, the DS manufacturing process and product composition is identical as for the approved presentations Metalyse 40 mg and Metalyse 50 mg as well as the materials of the primary container (glass vial, rubber stopper and aluminium crimp cap). The new presentation is provided in a smaller, 10 mL, glass vial. Additional sections are introduced covering primary and secondary packaging, DP development, DP manufacturing process and controls, and related DP stability data.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT (P.1)

Tenecteplase 25 mg/vial is presented in 10 mL clear glass vials, with a rubber stopper and a dark blue crimp cap with a nominal volume of 5.0 mL. The qualitative and quantitative composition of tenecteplase 25 mg/vial has been provided. The finished product contains the following excipients: arginine, phosphoric acid concentrated[2], polysorbate 20, water for injections (WFI).

PHARMACEUTICAL DEVELOPMENT (P.2)

Components of the Finished Product (P.2.1)

Active substance

Tenecteplase is a genetically engineered variant of htPA, which binds to fibrin and converts plasminogen to plasmin.
Tenecteplase active substance, also referred to as drug substance (DS), is formulated in arginine phosphate buffer and polysorbate 20 (PS20)

There is no change to the drug substance compared to the existing presentations.

Excipients

All excipients comply with the current pharmacopoeial and/or compendial standards.

There is no change to selection and amount of excipients compared to the existing presentations.

Finished Product (P.2.2)

Formulation development

The formulation of the 25 mg presentation is identical and unchanged to the formulation developed for the established 40 mg and 50 mg presentations.

MANUFACTURE (P.3)

Batch Formula (P.3.2)

The batch formula for the exemplary production batch is provided.

Description of the Manufacturing Process and Process Controls (P.3.3)

The finished product manufacturing process for tenecteplase lyophilisate for solution for injection 25 mg and the in-process controls (IPCs) applied during manufacturing It includes DS thawing, sterile filtration, filling, lyophilisation, crimping, visual inspection, labelling, and secondary packaging.Sterile filtration and filling are performed under aseptic conditions, with routine monitoring of production areas and personnel. Removable product contacting parts are cleaned and sterilized prior to use.

Justification of Controls at Critical Steps (P.3.4)

For manufacturing of tenecteplase lyophilisate for solution for injection 25 mg, in-process controls (IPCs) are established to ensure process consistency and product quality. The final IPCs are a result of significant process development experience along with manufacturing of the drug product at production scale.

The hold time limits for process intermediates were established through small scale studies and validation activities:

Process validation (P.3.5)

Validation of the drug product manufacturing process for the tenecteplase lyophilisate for solution for injection 25 mg was performed in the commercial drug product sterile manufacturing area During the procedure satisfactory data supporting the successful validation of the relevant aseptic process was provided. The PPQ activity was conducted with three consecutive batches by executing the manufacturing process under proposed commercial conditions according to approved batch records Control of the unit operations was demonstrated by monitoring parameters and material attributes to ensure that the process is maintained in a state of control pre-defined in a validation protocol.

Process parameters evaluated during process validation were based on the outcome of a risk assessment (3.2.P.2 Pharmaceutical Development). All parameters classified as critical and key within the risk assessment were evaluated in detail during PPQ.

Effectiveness of the unit operations was demonstrated by evaluating appropriate quality attributes and performance indicators. All results clearly demonstrate that the aseptic filling and lyophilization process of tenecteplase lyophilisate for solution for injection 25 mg consistently delivers a product meeting pre-defined quality criteria.

CONTROL OF EXCIPIENTS (P.4)

The excipients are controlled to the respective compendial monograph(s).

No excipients of human or animal origin are used in the tenecteplase manufacturing process.
There are no novel excipients in the drug product.

CONTROL OF THE DRUG PRODUCT (P.5)

Release and shelf life specification includes tests for: lyophilizate appearance, reconstitution time, water content (all in-house), uniformity of content of single-dose preparations (Ph. Eur.); appearance and description after reconstitution (clarity and degree of opalescence, degree of colouration, all Ph. Eur.); particulate contamination (sub-visible particles, Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), identity (RP-HPLC), purity (High performance size exclusion chromatography), heterogeneity (imaged capillary isoelectric focusing) , potency (Clot lysis), excipients (arginine and polysorbate 20, in-house), quantity (protein concentration by UV-scan), contaminants (bacterial endotoxins, Ph. Eur.), sterility (Ph. Eur.) container closure integrity (in house).

Analytical Procedures (P.5.2)

All analytical procedures used for the analysis of tenecteplase drug product are identical to the corresponding analytical procedures for drug substance. The adaptation of the additional 25 mg dose presentation led to a different content per vial.

Validation of analytical procedures (P.5.3)

During introduction of the 25 mg DP presentation, existing validation data sets were augmented with additional data specific to the 25 mg presentation. Updated validation data sets are relevant for tenecteplase DP only.

Batch analyses (P.5.4)

Analytical data of tenecteplase DP 25 mg/vial lots used in development and stability studies as well as process performance qualification (PPQ) intended to be used for market supply are provided. All DP batches met the proposed specification as outlined in Section “3.2.P.5.1.

Impurities of the Drug Product (P.5.5)

There are no new impurities introduced during manufacture of tenecteplase lyophilisate for solution for injection 25 mg.

Justification of Specifications (P.5.6)

The drug product specification for the new presentation (25 mg/vial) is the same as the existing specifications for the 40 mg/vial and 50 mg/vial presentations except for the size related parameters (e.g. extractable volume etc.). Since the same bulk drug substance solution is filled, the resulting DP solution after reconstitution being tested is the same composition for all three presentations. Thus, the scope of testing remains unchanged. The acceptance criteria for tenecteplase lyophilisate for solution for injection 25 mg release and stability testing are identical to the registered dose presentations of 40 mg and 50 mg unless otherwise specified. The same drug substance is used for all presentations and analytical comparability was established between the 40 mg and 25 mg presentation.

REFERENCE STANDARDS OR MATERIALS (P.6)

The DP tenecteplase lyophilisate for solution for injection 25 mg is, in regard to formulation and composition of the active pharmaceutical ingredient (API), identical to the tenecteplase DS. Information on the reference standards used for release, in process controls, and stability testing of the tenecteplase drug product and drug substance is provided in Section 3.2.S.5.

CONTAINER CLOSURE SYSTEM (P.7)

The container closure system of tenecteplase lyophilisate for solution for injection 25 mg consists of a clear Type I borosilicate glass vial, closed with a coated rubber stopper, and secured with an aluminium crimp cap. Details on the components of the container closure system are provided.

The container closure system is only changed with respect to dimensions. The same type of glass vials and same type of rubber stopper with the same coating is used but with different dimensions. The suitability of the primary container closure components is assured.

STABILITY (P.8)

The claimed shelf life and recommended long-term storage conditions for tenecteplase lyophilisate for solution for injection 25 mg are based on the experience of the approved 40 mg and 50 mg tenecteplase presentations. Therefore, a shelf life of 36 months at storage conditions is also recommended for the 25 mg/vial presentation.

- Shelf life: 36 months
- Storage conditions: Do not store above 30°C

In-use stability

Under the in-use conditions applied during in-use stability testing, the in-use storage recommendations are as follows:

- Up to 24 hours at 2-8°C or up to 8 hours at 30°C

Post-Approval Stability Protocol and Stability Commitment

Post-approval stability testing will be performed according to the approved regulatory analytical procedures and the corresponding data will be evaluated by the approved specifications for the drug product.

2.2.1. Conclusion on the quality aspects

Considering the above data, the new presentation, tenecteplase lyophilisate for solution for injection 25 mg vial, is considered approvable from a quality standpoint.

2.3. Non-clinical aspects

2.3.1. Ecotoxicity/environmental risk assessment

The applicant provided a justification for not submitting an updated Environmental Risk Assessment in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00.

Tenecteplase is an antithrombotic agent administered intravenously via bolus injection currently approved for patients with acute myocardial infarction. TNK is a non-toxic glycoprotein consisting only of natural amino acids and carbohydrates being readily metabolised and biodegraded.

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 01 June 2006), an ERA is not required for proteins, amino acids, and carbohydrates, as they are considered to be unlikely to result in significant risk to the environment due to the nature of their constituents; they are generally exempted from the requirement to file a complete Phase I & II ERA. Therefore, an environmental risk assessment is not provided of the intended new indication for Metalyse. This is considered acceptable.

Tenecteplase is not expected to pose a risk to the environment.

2.3.2. Conclusion on the non-clinical aspects

Considering the above data, tenecteplase is not expected to pose a risk to the environment.

No new clinical data have been submitted in this application. Since this concerns an extension of indication, this is considered acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. This is relevant for AcT trial (ClinicalTrials.gov NCT03889249) and the Extend-IA TNK (ClinicalTrials.gov NCT02388061) trial.

The clinical studies relevant to the above variation are investigator-initiated trials. For two of these studies (the pivotal AcT trial and the main supporting Extent-IA TNK study), clinical study reports have been submitted, in which it is stated that the trial was carried out in compliance with the clinical trial protocol, in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH GCP, and in accordance with applicable regulatory requirements and standard operating procedures.

After an agreement with the AcT trial sponsor, the Governors of the University of Calgary, BI has conducted an audit of the AcT trial by an external vendor. The external audit included, but was not limited to, study organisation, management, monitoring, study reporting, study compliance, safety reporting, data protection and data management. The audit was conducted as an on-site audit at the University of Calgary from 24th to 26th April 2023 and covered both the Sponsor Investigator activities and the Clinical Site performance.

Furthermore, a study specific audit for the EXTEND-IA TNK studies (Parts 1 & 2) was performed as a

remote audit from 15th to 19th May 2023 2023. The purpose of the audit was to assess whether processes relevant for sponsor (Neuroscience Trials Australia) and clinical conduct (Royal Melbourne Hospital) of the study were adequate to ensure compliance with applicable regulations, applicable SOPs, policies, working instructions, and other reference documents and to ensure the rights, safety and well-being of patients had been protected and the integrity of data had been ensured.

It is stated in the Clinical overview provided within this application that the audits conducted provide assurance that the AcT and EXTEND-IA TNK studies had been conducted in accordance with ethical standards and Good Clinical Practice and that the data and reported results are credible.

An overview of the clinical studies referred to in this applicant is provided in the following table.

- Tabular overview of clinical studies

Table 1. Summary of the clinical studies included in the safety and efficacy evaluations

Study Document no.	No. of study centres/locations Start and completion	Study design	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window
Haley *et al.* (2005) [P05-02918]	- Jul 2000-Apr 2003	Open-label, single-arm, dose-escalation safety trial	Study drug Tenecteplase 0.1/0.2/0.4/0.5 mg/kg	To test whether tenecteplase could be administered safely to patients with AIS within 3 h of onset at doses that may be associated with improvement in clinical neurological outcome.	Non-image selected severe AIS Patients enrolled in safety analysis Total: 88 Tenecteplase 0.1 mg/kg: 25 Tenecteplase 0.2 mg/kg: 25 Tenecteplase 0.4 mg/kg: 25 Tenecteplase 0.5 mg/kg: 13	≤3 h
Molina *et al.* (2008) [P08-04525]	- -	-	Study drug Tenecteplase 0.4 mg/kg Control drug Alteplase 0.9 mg/kg	To compare the effects of tenecteplase and alteplase on MCA recanalization, early clinical course and long-term outcome.	AIS with MCA occlusion and mismatch Patients enrolled in safety analysis Total: 122 Tenecteplase 0.4 mg/kg: 42 Alteplase 0.9 mg/kg: 80	-
Parsons *et al.* (2009) [P09-03649]	- Jan 2006-Jul 2007	Prospective, open-label, non-randomised, pilot study	Study drug Tenecteplase 0.1 mg/kg Control drug Alteplase 0.9 mg/kg	To assess the biologic efficacy of 0.1 mg/kg tenecteplase	Image-selected AIS patients Patients enrolled in safety analysis Total: 50 Tenecteplase 0.1 mg/kg: 15 Alteplase 0.9 mg/kg: 35	3-6 h
Haley *et al.*, (2010) [P10-04112]	Eight in US Mar 2006-Dec 2008	The study was initially designed as a small, multicentre, randomised, double-blind, controlled, Phase IIB, then the	Study drug Tenecteplase 0.1/0.25/0.4 mg/kg Control drug Alteplase 0.9 mg/kg	Phase IIB To choose a best dose of tenecteplase to carry forward To provide evidence for either promise or futility of further testing of tenecteplase vs. alteplase Phase III	Non-imaging selected AIS with severe neurological defect Patients enrolled in safety analysis Total: 112 Tenecteplase 0.1 mg/kg: 31 Tenecteplase 0.25 mg/kg: 31 Tenecteplase 0.4 mg/kg: 19 Alteplase 0.9 mg/kg:31	≤3 h

Study Document no.	No. of study centres/locations Start and completion	Study design	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window
		trial would continue as a Phase III efficacy trial		To compare the selected tenecteplase dose to alteplase		
Parsons *et al.,* (2012) [P12-03304]	Three in Australia 2008-2011	Phase IIB, randomised, open-label, blinded endpoint evaluation study	Study drug Tenecteplase 0.1/0.25 mg/kg Control drug Alteplase 0.9 mg/kg	To compare the standard dose of alteplase with two different doses of tenecteplase	AIS population screened based on CT perfusion imaging Patients enrolled in safety analysis Total: 75 Tenecteplase 0.1 mg/kg: 25 Tenecteplase 0.25 mg/kg: 25 Alteplase 0.9 mg/kg: 25	<6 h
ATTEST [P15-02640]	One in UK Jan 2012-Sept 2013	Single-centre, Phase II, prospective, randomised, open-label, blinded endpoint evaluation study	Study drug Tenecteplase 0.25 mg/kg Control drug Alteplase 0.9 mg/kg	To assess the efficacy and safety of tenecteplase vs. alteplase within 4.5 h of stroke onset in a population not selected on the basis of advanced neuroimaging	Non-imaging selected broad AIS Patients enrolled in safety analysis Total: 103 Tenecteplase 0.25 mg/kg: 52 Alteplase 0.9 mg/kg: 51	≤4.5 h
TEMPO-1 [P15-01653]	Eight in Canada Jul 2012- Jul 2014	Prospective, multicentre, 2-cohort, dose-escalation study	Study drug Tenecteplase 0.1/0.25 mg/kg	To assess in a 2-cohort dose-escalation study whether the treatment of minor stroke with intracranial occlusion with tenecteplase was safe and feasible	Minor stroke with proven occlusion Patients enrolled in safety analysis Total: 50 tenecteplase 0.1 mg/kg: 25 tenecteplase 0.25 mg/kg: 25	≤12 h
NOR-TEST [P17-08885]	13 in Norway Sept 2012-Sept 2016	Phase III, randomised, open-label, blinded endpoint,	Study drug Tenecteplase 0.4 mg/kg Control drug Alteplase	To investigate the safety and efficacy of tenecteplase vs. alteplase in patients with acute stroke who	Non-imaging selected broad AIS Patients enrolled in safety analysis Total: 1100	≤4.5 h of symptom onset or ≤4.5 h after

Study Document no.	No. of study centres/locations Start and completion	Study design	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window
		superiority trial	0.9 mg/kg	were eligible for iv thrombolysis	Tenecteplase 0.4 mg/kg: 549 Alteplase 0.9 mg/kg: 551	awakening with symptoms
EXTEND-IA TNK [P18-03928]	13 in Australia and New Zealand Mar 2015-Oct 2017	Investigator-initiated, multicentre, prospective, randomised open-label, blinded outcome trial	Study drug Tenecteplase 0.25 mg/kg Control drug Alteplase 0.9 mg/kg	To compare tenecteplase with alteplase in establishing reperfusion in patients before endovascular thrombectomy when it was administered within 4.5 h after the onset of symptoms	Patients with LVO ischaemic stroke Patients enrolled in safety analysis Total: 202 Tenecteplase 0.25 mg/kg: 101 Alteplase 0.9 mg/kg: 101	≤4.5 h
EXTEND-IA TNK Part 2 [P20-01928]	28 in Australia and New Zealand Dec 2017-Jul 2019 with follow-up until Oct 2019.	Investigator-initiated, multicentre, randomised, open-label, blinded endpoint trial	Study drug Tenecteplase 0.25/0.4 mg/kg	To determine whether 0.40 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs. 0.25 mg/kg of tenecteplase in patients with LVO ischaemic stroke.	Patients with LVO ischaemic stroke Patients enrolled in safety analysis Total: 300 Tenecteplase 0.25 mg/kg: 150 Tenecteplase 0.4 mg/kg: 150	≤4.5 h
NOR-TEST 2 Part A [P22-03558]	11 in Norway Oct 2019- Sept 2021 with follow-up until Dec 2021	Investigator-initiated, multicentre, randomised, open-label, blinded endpoint non-inferiority trial	Study drug Tenecteplase 0.4 mg/kg Control drug Alteplase 0.9 mg/kg	To determine noninferiority of 0.4 mg/kg tenecteplase compared with a standard dose of 0.9 mg/kg alteplase in patients with moderate or severe ischaemic stroke eligible for intravenous thrombolysis	Clinically suspected AIS screen by MRI imaging Patients enrolled in primary analysis Total: 216 (ITT: 204) Tenecteplase 0.4 mg/kg: 100 Alteplase 0.9 mg/kg: 104	≤4.5 h

Study **Document no.**	**No. of study centres/locations** **Start and completion**	**Study design**	**Study & control drugs** **Dose regimen**	**Study objective**	**Study population** **No. of patients (total and by treatment arm)**	**Time window**
AcT [P22-05053]	22 in Canada Dec 2019-Jan 2022 with follow-up until May 2022	Investigator-initiated, parallel-group, open-label, registry-linked, randomised, controlled trial with blinded outcome assessment	Study drug Tenecteplase 0.25 mg/kg Control drug Alteplase 0.9 mg/kg	To determine if i.v. 0.25 mg/kg tenecteplase is non-inferior to i.v. 0.9 mg/kg alteplase in patients with AIS otherwise eligible for intravenous thrombolysis	Non-imaging selected AIS with disabling neurological deficit Patients enrolled in primary analysis Total: 1600 (ITT: 1577) Tenecteplase 0.25 mg/kg: 806 Alteplase 0.9 mg/kg: 771	≤4.5 h

2.4.2. Pharmacokinetics

There are PK data on tenecteplase available in patients with STEMI. The PK profile in patients with AIS is not expected to be different compared with patients with STEMI, although limited PK data has been generated in patients with AIS [P05 02918].

The applicant referenced an article describing a population PK model for AMI patients (based on the phase II TIMI 10B study, n=103 patients with 785 PK observations). The developed final population PK model was used to simulate the tenecteplase concentrations expected for AIS patients in the N1811s study. These simulations were compared with the observations from the study N1811s (n=75 patients with AIS, one concentration sample at 1 h post-dose). This evaluation is based on several assumptions. Since the raw patient-level PK data from study N1811s were not available, the reported summary statistics were used to derive a weighted dose-normalized mean and approximate weighted SD. To approximate the IIV in study N1811s, expected percentiles were constructed assuming a normal distribution. Because body weight and creatinine clearance, which were significant covariates in the final model, were not reported for the acute ischemic stroke data, weight was assumed to be the same as in the analysis data set; creatinine clearance was estimated using a linear model based on reported median ages in N1811s for each dose group and the relation between creatinine clearance versus age estimated using the analysis data set.

The evaluation revealed that dose-normalized concentration means in the acute ischemic stroke data set (837.0 ng/mL) appeared to be 27% lower compared with the analysis data set (1146 ng/mL). This difference could only in a small part be explained by the higher age in the acute ischemic stroke population, with assumed lower creatinine clearance values.

In conclusion, the comparison of exposure between AMI and AIS patients is based on several assumptions. Therefore, the result indicating lower (dose-normalized) exposure in AIS patients compared to AMI patients should be interpreted with caution.

Absorption, Bioavailability, Distribution, Metabolism, and Elimination

In patients with STEMI, tenecteplase administered as a single bolus exhibited a biphasic disposition from the plasma. Tenecteplase was cleared from the plasma with an initial half-life of 20 to 24 min. The terminal phase half-life of tenecteplase was 90 to 130 min. In 99 of 104 patients treated with tenecteplase, mean plasma clearance ranged from 99 to 119 mL/min. The initial volume of distribution was weight related and approximated plasma volume. Liver metabolism was shown to be the major clearance mechanism for tenecteplase.

Pharmacokinetics of tenecteplase in patients with AIS were assessed in a pilot dose escalation safety study. Eighty-eight eligible patients were treated with an i.v. bolus infusion of tenecteplase within 3 h of stroke onset (0.1 mg/kg [n = 25], 0.2 mg/kg [n = 25], 0.4 mg/kg [n = 25] and 0.5 mg/kg [n = 13]). Tenecteplase blood levels at 1 hour after treatment ranged from a mean of 389 ± 146 ng/mL with a dose of 0.1 mg/kg to 1647 ± 732 ng/mL with 0.5 mg/kg dose [P05 02918].

A specific evaluation of patients with AIS is undertaken in the TIMEKEEPER study, a Phase I study to evaluate the pharmacokinetics, pharmacodynamics, and safety of tenecteplase after single dose administration in 20 adult participants with AIS who present to the research site and can be treated in less than 4.5 h of symptoms onset, sponsored by Roche (USA). The conduct of the study is completed (as per ISRCTN registry No. ISRCTN13376195 [P23 04144], however the results were not available at the time of writing the Clinical overview.

2.4.3. Pharmacodynamics

Mechanism of action

Not specifically discussed in the submitted dossier.

Primary and secondary pharmacology

No data are available yet for the STEMI and AIS indications. The TIMEKEEPER trial has been completed at the time of writing the Clinical Overview [according to the ISRCTN registry, P23 04144], but data were not yet available.

2.4.4. Discussion on clinical pharmacology

The mechanism of action of tenecteplase is not discussed in the current application. However, from the STEMI indication, the mechanism of action of tenecteplase is considered established. Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native t -PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI -1) compared to native t -PA.

PK data of tenecteplase have been established based on data in patients with STEMI. Limited published data based on popPK exercises indicating lower dose-normalised exposure in AIS compared to STEMI patients are based on several assumptions and need to be interpreted with caution. Based on general similarities of the STEMI and AIS populations, it is agreed with the Applicant that the PK characteristics of TNK would not be expected to relevantly differ in patients with AIS compared to patients with STEMI. Of note, for AIS half the dose is proposed than the dose approved for STEMI.

2.4.5. Conclusions on clinical pharmacology

Only limited data on the pharmacokinetics of TNK in AIS is available, however, the PK characteristics of TNK in AIS is not expected to relevantly differ from those established in patients with STEMI. The information proposed for section 5.2 of the SmPC of the AIS TNK presentation is in line with the respective information given in the SmPC for the STEMI presentations. This is agreed, as it is clearly indicated that the information on TNK in patients is derived from the STEMI indication.

2.5. Clinical efficacy

Efficacy of TNK in AIS is mainly based on 8 completed, randomised, investigator-initiated phase II and III studies that clinically investigated TNK in patients with AIS (see

Table 2), and on one meta-analysis (Burgos and Saver, 2019). A total of 3,638 patients were enrolled in the efficacy analysis of these 8 studies with 2,022 receiving tenecteplase (0.1 mg/kg n=56, 0.25 mg/kg n=1144, 0.4 mg/kg n=806) and 1605 receiving alteplase. Additionally, real word data have been submitted.

The phase III non-inferiority AcT trial serves as the pivotal evidence of efficacy for this application, the other studies are supportive.

Table 2: Tabulated summaries of the studies included in the efficacy evaluation

Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
Haley *et al.* (2010) [P10-04112]	8 in US Mar 2006-Dec 2008	The study was initially designed as a small, multicentre, randomised, double-blind, controlled, Phase IIB, then the trial would continue as a phase III efficacy trial.	Study drug Tenecteplase 0.1/0.25/0.4 mg/kg Control drug Alteplase 0.9 mg/kg	Phase IIB To choose a best dose of tenecteplase to carry forward To provide evidence for either promise or futility of further testing of tenecteplase vs alteplase Phase III To compare the selected tenecteplase dose to standard alteplase	Non-imaging selected AIS with severe neurological defect Patients enrolled in primary analysis Total: 112 Tenecteplase 0.1 mg/kg: 31 Tenecteplase 0.25 mg/kg: 31 Tenecteplase 0.4 mg/kg: 19 Alteplase 0.9 mg/kg: 31	≤3 h	The trial was prematurely terminated for slow enrolment during Phase IIB. % (95%CI) of mRS 4-6 at 3 m Tenecteplase 0.1 mg/kg: 22.6 (9.6, 41.1) Tenecteplase 0.25 mg/kg: 35.5 (19.2, 54.6) Tenecteplase 0.4 mg/kg: 31.6 (12.6, 56.6) Alteplase 0.9 mg/kg: 32.3 (16.7, 51.4) % (95%CI) of mRS 0-1 at 3 m Tenecteplase 0.1 mg/kg: 45.2% (27.3, 64.0) Tenecteplase 0.25 mg/kg: 48.4% (30.2, 66.9) Tenecteplase 0.4 mg/kg: 36.8% (16.3, 61.6) Alteplase 0.9 mg/kg: 41.9% (24.6, 60.9)
Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population, No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
Parsons *et al.* (2012) [P12-03304]	3 in Australia 2008-2011	Phase IIB, randomised, open-label, blinded endpoint evaluation	Study drug Tenecteplase 0.1/0.25 mg/kg Control drug Alteplase	To compare the standard dose of alteplase with two different doses of tenecteplase	AIS population screened based on CT perfusion imaging Patients enrolled in primary analysis	<6 h	This study had a co-primary endpoint and was designed to test the pooled dose of tenecteplase against alteplase for superiority.

Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
		study	0.9 mg/kg		Total: 75 Tenecteplase 0.1 mg/kg: 25 tenecteplase 0.25 mg/kg: 25 alteplase 0.9 mg/kg: 25		% of the perfusion lesion that was reperfused 24 h after treatment, mean (SD) Tenecteplase 0.1 mg/kg: 69.3 (31.2) Tenecteplase 0.25 mg/kg: 88.8 (23.1) Tenecteplase pooled: 79.3 (28.8) Alteplase 0.9 mg/kg: 55.4 (38.7) P-value for superiority: 0.004 Extent of clinical improvement at 24 h (ie change on the NIHSS score from before treatment to 24 h after treatment), mean (SD) tenecteplase 0.1 mg/kg: 6.3 (5.1) tenecteplase 0.25 mg/kg: 9.6 (5.5) tenecteplase pooled: 8.0 (5.5) alteplase 0.9 mg/kg: 3.0 (6.3) P-value for superiority: <0.001
Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population, No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
ATTEST (2015) [P15-02640	1 in UK Jan 2012-Sept 2013	Single centre, phase II, prospective, randomised,	Study drug Tenecteplase 0.25 mg/kg	To assess the efficacy and safety of tenecteplase vs	Non-imaging selected broad AIS Patients enrolled in primary analysis	≤4.5 h	The study was designed to test for superiority. % of penumbra salvaged at 24-48 h, mean (SD)

Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
]		open-label, blinded endpoint evaluation study	Control drug Alteplase 0.9 mg/kg	alteplase within 4.5 h of stroke onset in a population not selected on the basis of advanced neuroimaging	Total: 96 Tenecteplase 0.25 mg/kg: 47 Alteplase 0.9 mg/kg: 49		Tenecteplase 0.25 mg/kg: 68% (28) Alteplase 0.9 mg/kg: 68% (23) mean difference 1.3%, 95% CI -9.6, 12.1, p=0.81
NOR-TEST (2017) [P17-08885]	13 in Norway Sept 2012-Sept 2016	Phase III, randomised, open-label, blinded endpoint, superiority trial	Study drug Tenecteplase 0.4 mg/kg Control drug Alteplase 0.9 mg/kg	To investigate the safety and efficacy of tenecteplase vs alteplase in patients with acute stroke who were eligible for iv thrombolysis	Non-imaging selected broad AIS Patients enrolled in primary analysis Total: 1100 Tenecteplase 0.4 mg/kg: 549 Alteplase 0.9 mg/kg: 551	≤4.5 h of symptom onset or ≤4.5 h after wakening with symptoms	The study was designed to test for superiority. % of patients achieved mRS score 0-1 point at 3 months Tenecteplase 0.4 mg/kg: 64% Alteplase 0.9 mg/kg: 63% OR (95% CI): 1.08 (0.84, 1.38), p=0.52
Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
EXTEND-IA TNK (2018) [P18-03928]	13 in Australia and New Zealand Mar 2015-Oct 2017	Investigator-initiated, multicentre, prospective, randomised, open-label, blinded outcome trial.	Study drug Tenecteplase 0.25 mg/kg Control drug Alteplase 0.9 mg/kg	To compare tenecteplase with alteplase in establishing reperfusion in patients before endovascular thrombectomy when it was administered within 4.5 h after the onset of symptoms	Patients with LVO ischaemic stroke. Patients enrolled in primary analysis Total: 202 Tenecteplase 0.25 mg/kg: 101 Alteplase 0.9 mg/kg: 101	≤4.5 h	Noninferiority of tenecteplase was tested with a non-inferiority margin of –2.3%, followed by superiority. % of patients with substantial reperfusion at initial angiographic assessment Tenecteplase 0.25 mg/kg: 22% Alteplase 0.9 mg/kg: 10% RD (95% CI): 12% (2, 21) (p=0.002 for non-inferiority; p=0.03 for

Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
							superiority)
EXTEND-IA TNK Part 2 (2020) [P20-01928]	28 in Australia and New Zealand Dec 2017-Jul 2019 with follow-up until Oct 2019	Investigator-initiated, multicentre, randomised, open-label, blinded endpoint trial.	Study drug Tenecteplase 0.25/0.4 mg/kg	To determine whether 0.4 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs 0.25 mg/kg of tenecteplase in patients with LVO ischaemic stroke.	Patients with LVO ischaemic stroke. Patients enrolled in primary analysis Total: 300 Tenecteplase 0.4 mg/kg: 150 Tenecteplase 0.25 mg/kg: 150	≤4.5 h	Noninferiority of tenecteplase was tested with a RR non-inferiority margin of 0.23 % of patients with substantial reperfusion at initial angiographic assessment Tenecteplase 0.25 mg/kg: 19.3% Tenecteplase 0.4 mg/kg: 19.3% unadjusted risk difference, 0.0% 95% CI -8.9%, -8.9% Adjusted RR, 1.03 95% CI 0.66, 1.61
Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
NOR-TEST 2 Part A (2022) [P22-03558]	11 in Norway Oct 2019-Sept 2021 with follow-up until Dec 2021	Investigator-initiated, multicentre, randomised, open-label, blinded endpoint non-inferiority trial	Study drug Tenecteplase 0.4 mg/kg Control drug Alteplase 0.9 mg/kg	To determine noninferiority of 0.4 mg/kg tenecteplase compared with a standard dose of 0.9 mg/kg alteplase in patients with moderate or severe ischaemic stroke eligible for intravenous	Clinically suspected AIS screen by MRI imaging Patients enrolled in primary analysis Total: 216 Tenecteplase 0.4 mg/kg: 100 Alteplase 0.9 mg/kg: 104	≤4.5 h	Noninferiority of tenecteplase was tested with a non-inferiority margin of −3%. % of patients achieved mRS score 0-1 point at 3 months Tenecteplase 0.4 mg/kg: 32% Alteplase 0.9 mg/kg: 51% OR (95% CI): 0.61 (0.32, 1.14), p=0.0064

Study Document no.	No. of study centres/locations Start and completion	Study design and type of control	Study & control drugs Dose regimen	Study objective	Study population No. of patients (total and by treatment arm)	Time window	Results for primary endpoint
				thrombolysis			RD (95% CI): -19% (-33% to –6%),
AcT (2022) [P22-05053]	22 in Canada Dec 2019-Jan 2022 with follow-up until May 2022	Investigator-initiated, parallel-group, open-label, registry-linked, randomised, controlled trial with blinded outcome assessment	Study drug Tenecteplase 0.25 mg/kg Control drug Alteplase 0.9 mg/kg	To determine if i.v. 0.25 mg/kg tenecteplase is non-inferior to i.v. 0.9 mg/kg alteplase in patients with AIS otherwise eligible for intravenous thrombolysis	Non-imaging selected AIS with disabling neurological deficit Patients enrolled in primary analysis Total: 1577 Tenecteplase 0.25 mg/kg: 806 Alteplase 0.9 mg/kg: 771	≤4.5 h	Noninferiority of tenecteplase was tested with a non-inferiority margin of –5%, followed by superiority. % of patients achieved mRS score 0-1 point at 90-120 days Tenecteplase 0.25 mg/kg: 36.9% Alteplase 0.9 mg/kg: 34.8% unadjusted risk difference 2.1% [95% CI – 2.6 to 6.9]

AIS, acute ischaemia stroke; CI, confidence interval; h, hours; iv, intravenous; LVO, large vessel occlusion; mRS, modified rankin scale; NIHSS, National Institutes of Health Stroke Scale Score; OR, odds ratio; SD, standard deviation; UK, United Kingdom; US, United States; vs versus.

Studies' clinical trials registry no.: Haley et al. (2010), NCT00252239; Parsons et al. (2012), ACTRN12608000466347; ATTEST, NCT01472926; NOR-TEST, NCT01949948; EXTEND-IA TNK, NCT02388061; EXTEND-IA TNK Part 2, NCT03340493; NOR-TEST 2 Part A, NCT03854500; ACT, NCT03889249

2.5.1. Rationale for a dose of 0.25 mg/kg (maximum dose 25 mg) for the intended indication

The Burgos and Saver Meta-analysis [P19 06342] indicated that the 0.25 mg/kg dose is both efficacious and safe, in the same magnitude of alteplase 0.9 mg/kg.

The 0.25 mg/kg dose was selected for the EXTEND-IA TNK trial [P18 03928] while the 0.4 mg/kg dose was selected for the NOR-TEST trial [P17 08885, P19 04021].

While the EXTEND-IA TNK trial [P18 03928] showed a favourable efficacy/safety profile of the 0.25 mg/kg (vs. alteplase 0.9 mg/kg), it was expected that a dose increase could provide even better efficacy. This option was tested in EXTEND-IA TNK Part 2 [P20 01928], comparing, in an LVO population undergoing thrombectomy, the dosage of 0.4 mg/kg vs. 0.25 mg/kg. The outcome of EXTEND-IA TNK Part 2 did not show an improved efficacy of 0.4 mg/kg as compared with 0.25 mg/kg. In addition, the assessment of the safety in the elderly population enrolled in EXTEND-IA Parts 1 and 2 did show that the 0.25 mg/kg was safer in the elderly population.

The NOR-TEST study [P19 04021], conceived as superiority trial, failed its primary endpoint and did not show superiority of tenecteplase 0.4 mg/kg vs. alteplase 0.9 mg/kg, in a mild Stroke population. Two clinical trials have further evaluated the dose of 0.40 mg/kg after the non-conclusive results of the NOR-TEST trial [P19 04021]: these are the EXTEND-IA TNK Part 2 [P20 01928] and the NOR-TEST 2 study Part A [P22 03558], detailed below:

EXTEND-IA TNK Part 2 [P20 01928] objective was to determine whether 0.40 mg/kg tenecteplase (n=150) safely improves reperfusion before endovascular thrombectomy vs. 0.25 mg/kg tenecteplase (n=150) in patients with LVO ischaemic stroke undergoing thrombectomy. Median NIHSS score (IQR) at baseline was 17 (11 21) for the 0.40 mg/kg tenecteplase group and 16 (9 20) for the 0. 25 mg/kg tenecteplase group.

The primary endpoint of substantial reperfusion with the same definition with EXTEND-IA TNK [P18 03928], occurred in 29 patients (19.3%) in both tenecteplase dose groups (difference 0.0%, 95% CI -8.9, 8.9; adjusted risk ratio [RR] 1.03, 95% CI 0.66, 1.61; p = 0.89). There were no significant differences for any of the secondary endpoints. Therefore, among patients with LVO ischaemic stroke, a dose of 0.4 mg/kg compared with 0.25 mg/kg of tenecteplase did not significantly improve cerebral reperfusion prior to endovascular thrombectomy. The authors concluded that the dose of 0.4 mg/kg tenecteplase confers no additional benefit over 0.25 mg/kg in AIS patients with LVO scheduled for thrombectomy.

It is also to be noted that apart from the Haley 2005 and 2010 studies, only the EXTEN-IA TNK part 2 study evaluated 0.25 mg/kg vs. 0.4 mg/kg TNK within the same study. The Haley 2005 study was a pilot dose-escalation safety study of TNK in AIS, no symptomatic ICH were reported within 36 h in the 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg groups. The Haley 2010 study was terminated early due to slow enrolment and does not allow for firm conclusions.

The NOR-TEST 2 Part A study [P22 03558] tested the dose of 0.4 mg/kg in a large Phase III clinical trial, recruiting AIS (NIHSS = 6 or higher) thrombolytic eligible patients as per EU guidelines within 4.5 h of onset of symptoms. The NOR-TEST 2 Part A patients had a higher NIHSS than the patients from the NOR-TEST [P17 08885] study (and therefore more representative of the average AIS population). In this study, tenecteplase at 0.4 mg/kg (maximum dose 40 mg) yielded worse safety than alteplase (significant increase in ICH and Mortality at 3 months), leading to discontinuing of the 0.4 mg dose, which was replaced, as per protocol, by the dose of 0.25 mg/kg. The study Part B has not resumed at the time of this writing, as the approach needs further evaluation in light of the AcT results.

As a consequence, the dose of 0.4 mg/kg in NOR-TEST 2 Part A, has not shown any trend in favor of a better efficacy than the 0.25 mg /kg dose in the AIS studied populations. On the contrary, due to a signal of increase in bleeding in elderly patients and possibility also in severe strokes (NIHSS = 15 or higher) [P19 04021], the 0.4 mg/kg dose has been abandoned and is no longer used in any further clinical trial. Abandonment of the 0.4 mg/kg TNK dose is therefore endorsed.

The results above support the efficacy and safety of the tenecteplase dose of 0.25 mg/kg (maximum dose 25 mg), which has been assessed in comparison with alteplase 0.9 mg/kg in the large AcT trial [P22 05053], which is detailed below. It was expected that superiority could be shown in a more severe population (NIHSS >= 6), leading to the conception of the NOR-TEST 2 trial [P22 03558], a non-inferiority trial evaluating efficacy and safety of tenecteplase 0.4 mg/kg vs. alteplase 0.9 mg/kg. The NOR-TEST 2 trial was interrupted prematurely, after 204 patients were recruited, because of an unexpected excess of sICH and mortality in the tenecteplase 0.4 mg/kg group.

This substantial IIS and RWE data described above is considered sufficient by the Applicant for the current submission, along with the recommendations in internationally renowned guidelines for the use of tenecteplase in AIS (ESO/ESMINT 2019: [P19 02504]; CSBPR [P23-00203]; ESO 2021: [P21 02289]; AHA/ASC: [P19 10385]; Stroke Foundation Australia: [P22 05638]; ESO expedited recommendations on tenecteplase: [P23 01257]).

Based on the above, tenecteplase 0.25 mg/kg (maximum dose 25 mg) is considered to be the optimal dose to be used for treatment of AIS.

Additionally, the combination of the above results indicate that the 0.25 mg/kg is an appropriate dose to be tested in the following ongoing Phase III studies: ATTEST 2 (ClinicalTrials.gov Identifier: NCT02814409), 1123 0040 BI China trial [c33415518], TASTE (Australian New Zealand Clinical Trials Registry Identifier: ACTRN12613000243718), and the local trial in Japan, T-FLAVOR [P22 00589], aiming at comparing tenecteplase 0.25 mg/kg (maximum dose 25 mg) vs. alteplase in an AIS guidelines selected population within 4.5 h from onset of symptoms. The still ongoing ATTEST 2 (ClinicalTrials.gov Identifier: NCT02814409) and BI 1123 0040 trial in China (read out expected by beginning of 2024) use the dosage of 0.25 mg/kg tenecteplase, in comparison with the Standard of Care alteplase 0.9 mg/kg, in general AIS populations, within 4.5 h from onset of stroke.

Applicant's justification for recommended 5-tiers dose regimen

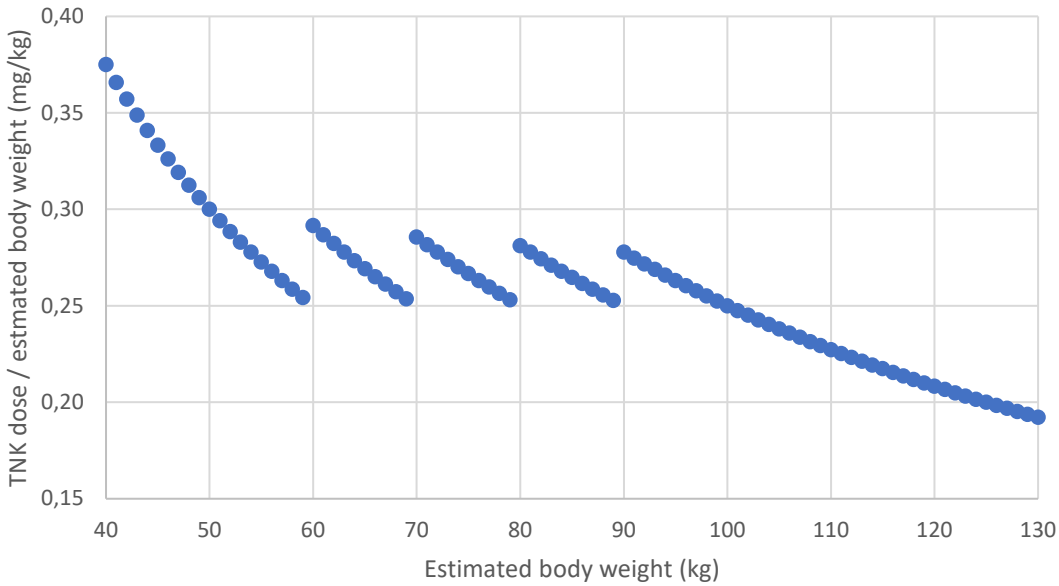
In AcT, the body weight of each patient was estimated, and the drug administered according to the 10 kg step doses (in 5 steps) in the table below.

Table 3: Tenecteplase dosing scheme as used in the AcT trial:

Patient Weight (Kg)	TNK dose (mg) based on 0.25 mg/kg for the maximum weight at each level	Volume of TNK to be administered (ml) of a 5mg/mL solution*
<60	15.0 mg	3.0 ml
≥60 to <70	17.5 mg	3.5 ml
≥70 to <80	20.0 mg	4.0 ml
≥80 to <90	22.5 mg	4.5 ml
≥90	25.0 mg	5.0 ml

Using this stepwise dose regimen, the individual patient dose varies from 0.25 mg/kg to 0.3 mg/kg.

Figure 1 Intravenous tenecteplase (TNK) dosing regimen used in the AcT trial Source: [c42415260, Figure 1.4.3.1.5]



The 5-dose-tiers regimen has proved to be overall safe and efficient in the AcT study. This 5-step body weight-adapted approach is recommended and approved in STEMI. A 5-step dosing regimen will potentially reduce mistakes based on estimated body weight, misestimation being especially more frequent when patients are at the extremes of body weight. In STEMI, in general, the weight misestimation seems to be moderate (about 1 kg) and it is likely that misestimation of body weight is comparable between STEMI and AIS indications. In clinical use of the approved full dose for more than 20 years (double dose as compared to AIS indication) for all STEMI patients, no safety signal has been reported for low weight patients during these 2 decades of use. The Applicant further argues that small variations in dosing as well as small misdosing are unlikely to produce clinically meaningful changes on the clinical outcome as for STEMI. From a process of care and medical perspective, it is not uncommon that both STEMI and AIS patients are initially taken in charge by the same medical emergency personnel, and a common Metalyse 5-step bodyweight adapted dosing has the potential to reduce errors and facilitate medical care.

Overall, the posology proposed for the SmPC, i.e. 0.25 mg/kg dose administered according to a 5-steps bodyweight-adapted dosing with boundaries at < 60 mg and ê 90 kg BW, is in line with the posology used in the AcT trial, which constitutes the pivotal evidence for the submission, and can in general be agreed, taking also into consideration, that in the established STEMI indication TNK is dosed in comparable 10 kg BW steps. Below 50 kg no further dose adaptation is proposed (in line with the AcT trial and the established STEMI posology), which leads to a higher dose per kg BW (up to approx. 0.38 mg/kg) in patients below 50 kg. With regard to this please refer to ancillary analyses of the main study (AcT), below.

2.5.2. Main study (AcT trial, Menon et al. 2022; P22-05053)

Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, noninferiority trial

Methods

The trial was a pragmatic, registry linked, prospective, randomized (1:1) controlled, open-label parallel group clinical non-inferiority trial with blinded endpoint assessment. The intervention group received intravenous tenecteplase as a single bolus over 5-10 seconds as soon as possible after randomization. The control group received intravenous alteplase as 10% bolus and 90% infusion over 60 min as per standard care.

Study participants

Inclusion criteria were pragmatic and informed by the Canadian Stroke Best Practice Recommendations (CSBPR).

• All patients with acute ischemic stroke eligible to receive intravenous alteplase as per standard care were eligible for enrolment in the proposed trial.

• Patients eligible for endovascular thrombectomy in addition to intravenous thrombolysis were eligible for enrolment.

Standard contra-indications to intravenous thrombolysis as in the CSBPR applied. Patients < 18 years of age were excluded. Women with pregnancy known to the investigator by history or examination, without requiring pregnancy testing, could only be enrolled in consultation with an expert stroke physician. Since the benefits of thrombolysis with intravenous alteplase in the paediatric population are unknown, patients < 18 years of age were not enrolled.

In addition, the Applicant's justification of generalisability of this Canadian study to the EU population provided in the Clinical overview can be summarised as follows:

In AcT more than 90% of the studied population was enrolled in Comprehensive Stroke Centers (CSCs). The AcT patient selection criteria are essentially similar with those defined as eligible for thrombolysis in EU guidelines (ESO/ESMINT 2019: [P19-02504]; ESO 2021: [P21-02289]; ESO expedited recommendations on tenecteplase [P23-01257]), as well as US guidelines (AHA/ASA: [P19-10385]) and other main AIS guidelines worldwide, such as Stroke Foundation Australia: [P22-05638]. Thus, the results can be generalized to patients that are recommended to be treated according to guidelines covering most patients worldwide. The AcT enrolled a population presenting similar baseline characteristics (e.g. onset of symptoms to initiation of reperfusion, stroke severity (NIHSS), age, sex, incidence of large vessel occlusion) to that observed in EU-based RCTs (e.g. [P22-10196]) and, importantly, to that observed in registries [P16-10105, P22-04770]. The absence of medically meaningful ethnical disparities between Canada (AcT trial) and Europe or worldwide is assumed. From a patient management perspective, the recommendations are consistent worldwide as reflected in the main AIS guidelines.

Treatments

Investigational product: Tenecteplase (TNKase, marketed by Genentech/Roche)

Table 4: Intravenous tenecteplase (TNK) dosing regimen used in the AcT trial

Patient Weight (Kg)	TNK dose (mg) based on 0.25 mg/kg for the maximum weight at each level	Volume of TNK to be administered (ml) of a 5mg/mL solution*
<60	15.0 mg	3.0 ml
≥60 to <70	17.5 mg	3.5 ml
≥70 to <80	20.0 mg	4.0 ml
≥80 to <90	22.5 mg	4.5 ml
≥90	25.0 mg	5.0 ml

*50 mg TNK, vial diluted with 10 ml sterile water

Comparator product: Alteplase (Activase, marketed by Genentech/Roche)

Dose: 0.9 mg/kg body weight (maximum dose 90 mg)

Mode of administration: Intravenous, 10% bolus and 90% infusion over 60 min

Objectives

The Alteplase compared to Tenecteplase (AcT) trial's primary objective is to seek to demonstrate the non-inferiority of intravenous tenecteplase compared to intravenous alteplase on 90-day functional outcome assessed using the modified Rankin Score. The secondary objective of this study is to compare the safety of intravenous tenecteplase compared to alteplase.

Outcomes/endpoints

The primary outcome measure was Modified Rankin Scale (mRS) 0-1 (freedom from disability) from 90 to 120 days from enrolment. The mRS is a 7-point ordered categorical scale for functional neurological outcome, with 0 meaning no neurological symptoms and 6 meaning death.

Secondary Outcomes

- Actual 90–120-day mRS score
- 90-120 day mRS score of 0-2
- Return to baseline level of functioning at 90-120 days
- EQ-5D-5L at 90-120 days
- EQ-VAS at 90-120 days
- Discharge destination (home, early supported discharge, rehabilitation facility, long term care, death)
- Door to needle time
- Door-in-door-out (DIDO) times at Primary Stroke Centres*
- Recanalization status (mTICI score) at first angiographic acquisition in patients taken to the angiosuite for the purpose of administering endovascular thrombectomy (EVT)

- Proportion of patients administered EVT
- Door-to-groin puncture time in patients undergoing EVT
- CT-to-puncture time in patients undergoing EVT
- Home time (defined as number of days subject spends at home after index stroke event)
- Cognition assessed via a brief, on-line cognitive assessment tool (Feasibility sub-study only)

(*DIDO times were difficult to obtain from primary stroke centres during the COVID-19 pandemic)

Primary clinical outcome data (assessed using the modified Rankin Scale) was determined by the Rankin Focused Assessment (RFA) method [R23-0805] using centralized telephone interviews conducted by central trial personnel blinded to treatment allocation.

The validity of evaluation of the mRS via telephone interview is justified by the Applicant based on the following argumentation:

• Mobile phone-based automatic assessments of mRS performed well in comparison with clinical visit mRS, and could be used as an alternative in stroke follow-up (Cooray, 2015 [R23-2173], Janssen, 2010 [R23-2174]).

• Furthermore, remote evaluation is now developing because of 1) the COVID 19 pandemic situation that has forced it 2) the development of telemedicine in AIS, which may combine the advantages of remote and visual assessment.

Sample size

Sample size was calculated using mRS distributions and non-inferiority margins from previous studies [P14-16838, R23-0804, P20-09086, R23-0807]. 5% was chosen as the non-inferiority margin. This choice means that at least half of the point estimate of effect for intravenous alteplase versus control will be preserved [P14-16838]. Assuming 35% of patients in the alteplase group and 38% of patients in the tenecteplase group have a 90-day mRS score of 0-1, a one-sided non-inferiority margin of 5% and a one-sided significance α of 0.025, a total sample size of 1600 patients would ensure at least 90% power to test noninferiority of tenecteplase versus alteplase with up to 5% withdrawal or loss to follow-up [R23-0804, P20-09086, R23-0807]. Notably, with this sample size, if the rate of excellent functional outcome (i.e., mRS score of 0-1) in the alteplase group at the end of the trial was actually 35%, as postulated, the worst corresponding excellent outcome rate in the tenecteplase group that would meet the non-inferiority test would be 34.7%, for which the lower 95% CI bound on the difference is -4.96%. No interim non-inferiority analyses were done.

Randomisation

Eligible patients were randomly assigned (1:1) to tenecteplase vs. alteplase using a previously validated minimal sufficient balance algorithm to balance allocation by site. Simple randomization occurred until a site had enrolled 5 subjects after which the algorithm became active. The standard distribution for randomization was 50-50, but when an imbalance was detected with a p-value less than 0.3, the distribution was biased to 65-35 in the direction against the imbalance and therefore, all randomization assignments were non-deterministic. In addition, randomization was dynamic, occurring in real-time and therefore allocation was fully concealed. Randomization was operationalized centrally, using a secure real-time web-based server that was accessed via web browser, text messaging or a telephone line.

Of note, changing effects over time may lead to bias if adaptive randomization is applied. For this reason, the applicant evaluated the mechanics of the minimal sufficient balance (MSB) method applied to AcT, which is purely stochastic in nature. This evaluation confirmed that there is a negligible increase (1.4%) in the ability to correctly predict the outcome. According to the detailed analysis of a potential selection bias, a biased evaluation of the study due to adaptive randomization can be excluded.

Blinding (masking)

The trial had allocation concealment and blinded endpoint assessment. Given the time sensitive nature of acute stroke treatment, blinding the enrolling health personnel and patient to treatment allocation was not practical. Primary clinical outcome data (assessed using the modified Rankin Scale) was determined by the Rankin Focused Assessment (RFA) method [R23-0805] using centralized telephone interviews conducted by central trial personnel blinded to treatment allocation.

Statistical methods

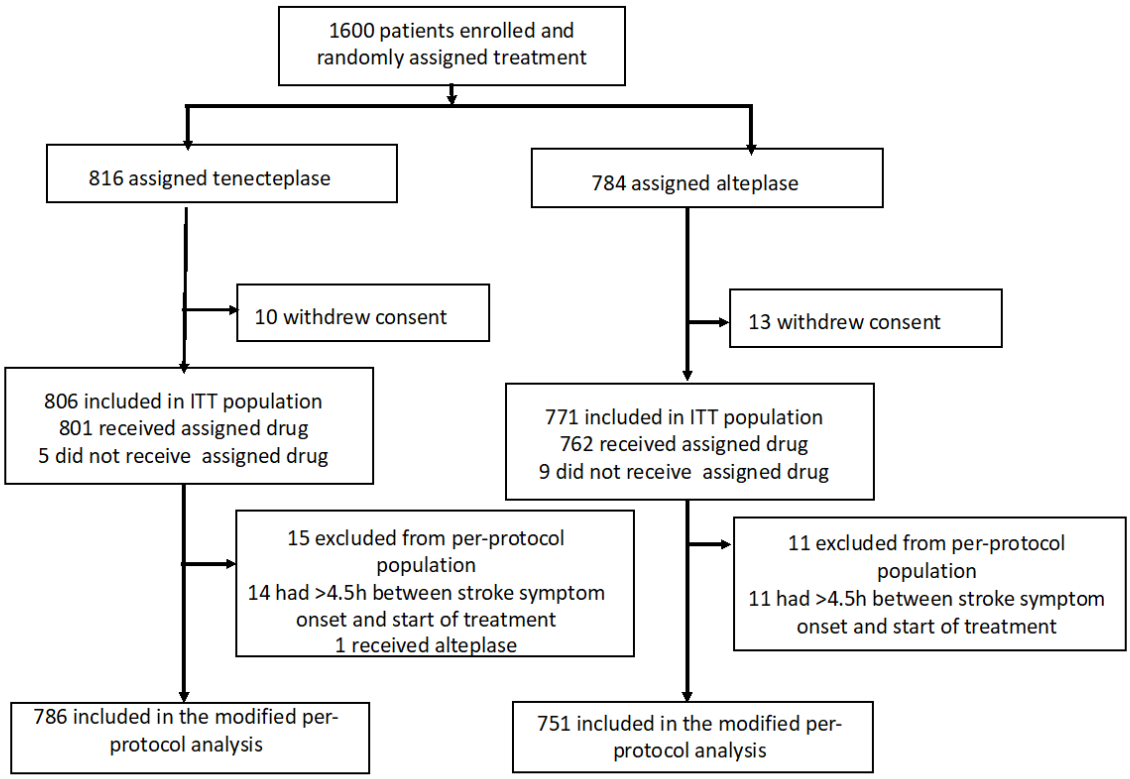
Primary analysis of the trial data to establish non-inferiority will be conducted using risk difference analysis. First, non-inferiority will be established if the lower boundary of the 95% confidence interval of the percentage difference in subjects achieving excellent outcome (mRS 0-1) in the tenecteplase versus the alteplase arm is greater than – 5% (the non-inferiority margin). If non-inferiority is demonstrated, then a test of superiority of tenecteplase vs. alteplase will be performed as part of secondary analysis. ln addition, logistic regression will be used to provide an adjusted estimate of the effectiveness of tenecteplase over alteplase for the primary outcome. The risk ratio of good 90-day outcome (mRS01) associated with the treatment groups will be estimated using a mixed-effects logistic regression model that adjusts for age, sex, baseline stroke severity, and stroke onset-to-needle time as fixed effects, and site, and registry (QuiCR vs. OPTIMISE) as random effects.

Secondary analyses will evaluate key safety (mortality and symptomatic intracerebral hemorrhage as defined in the AcT trial MOP) and secondary outcomes using relevant tests of association. Frequency tables will be used to summarize categorical variables by treatment group. Descriptive statistics will be used to summarize continuous data variables by treatment group.

For the secondary outcomes and the corresponding analyses, both unadjusted and adjusted analyses will be reported. Unadjusted analysis will be tests of difference in proportions, means or medians or regression analysis as appropriate.

Results

Participant flow



There were 14 patients (5 in the TNK group, 9 in the ALT group), who did not receive drug after randomization. The reasons were clinical and to do with patient condition, namely, significant worsening of neurological status, respiratory compromise or another condition that became apparent after randomization that precluded thrombolytic administration.

Recruitment

The trial recruited patients from the emergency departments of the 22 participating primary or comprehensive stroke centers across Canada.

Conduct of the study

The participating stroke centres also participated in either the QuiCR (Quality Improvement and Clinical Research) or OPTIMISE (Optimizing Patient Treatment in Major Ischemic Stroke with EVT) registries. These Canadian quality improvement registries track processes and outcomes for patients who receive intravenous thrombolysis or endovascular thrombectomy. Data from these ongoing registries, including patient baseline characteristics and workflow/processes, were linked to the trial data. The trial had set up processes to ensure completeness and quality of registry data in enrolled subjects.

The emphasis in trial execution was on making sure that the "right" patient receives the appropriate intervention (i.e., correct randomization, treatment assignment) with adequate assessment of primary outcome (i.e., complete, correct, and timely blinded event ascertainment). To align the requirements of good clinical practice with the considerations in a pragmatic randomized clinical trial, a risk-based approach to monitoring was used. Central monitoring was the primary focus with limited on-site risk-

based monitoring (if required) in coordination with the sites and registry coordinators. The AcT trial portal facilitated such monitoring. The following steps were in place and monitored: enrolment and randomization, consent, conduct and reporting of data including regular safety outcome monitoring, maintenance of delegation, training and personnel logs, fidelity, accuracy and quality of intervention, quality of registry data and of data linkages and that of the blinded primary outcome assessments.

Trial data included data on essential baseline demographics, randomization and treatment allocation, consent documents, any protocol deviations, SAEs and SUADRs along with any appropriate source data/information, trial monitoring and communications, blinded 90–120-day outcome assessments, all delegation and training logs and any other documents essential to trial conduct from a regulatory perspective. All imaging data was assessed with standardized case-report forms by trained raters blinded to all clinical data and treatment allocation in a central imaging core lab. This trial data was linked to registry data from either the QuiCR (Quality Improvement and Clinical Research) or OPTIMISE (Optimizing Patient Treatment in Major Ischemic Stroke with EVT) registries. These Canadian quality improvement registries track processes and outcomes for patients who receive intravenous thrombolysis or endovascular thrombectomy.

Data from these ongoing registries, including patient baseline characteristics and workflow/processes, were linked to the trial data. The trial had set up processes to ensure completeness and quality of registry data in enrolled subjects. This combined data was used for the analyses reported in the clinical trial report. Data from a third source, the CIHI (a federal government agency that collects and analyses information on administrative health and health services use in Canada), will inform additional economic analyses but is not included in the CTR.

Between Dec 10, 2019, and Jan 25, 2022, 1600 patients were enrolled and randomly assigned to treatment. According to the study report, data cut-off was on Jan 21, 2022 and '*the statistical analysis plan was finalised before database lock (on April 21, 2022)'*.

Baseline data

The median age was 74 years (IQR 63–83), 755 (47.9%) of 1577 patients were female and 822 (52.1%) were male. Data on race and ethnicity were not collected.

Baseline demographic and clinical characteristics of the patients were similar between the tenecteplase and alteplase groups in the ITT, mITT and mPP populations.

Table 5: Most relevant baseline characteristics, ITT population (derived from Clinical trial report, Table 6)

	Tenecteplase group (N=806)	Alteplase group (N=771)
Age in years	74 (63-83)	73 (62-83)
Female sex	382/806 (47.4)	373/771 (48.4)
Baseline NIHSS score (n=1570) *	9 (6-16)	10 (6-17)
Baseline NIHSS score categories (n=1570) *		
< 8	325/804 (40.4)	294/766 (38.4)
8-15	248/804 (30.9)	256/766 (33.4)
> 15	231/804 (28.7)	216/766 (28.2)
Stroke symptom onset to needle (intravenous thrombolysis start) (n=1563)	128 (93-185)	131 (95-188)

Numbers analysed

Intention-to-Treat (ITT) population: 1577 patients (806 TNK; 771 ALT) who were randomized and did not withdraw consent.

Modified Intention-to-Treat (mITT*) population: 1563 patients (801 TNK; 762 ALT) who were randomized, did not withdraw consent, and received the drug. Fourteen patients who were randomised but did not then receive the drug were excluded.

The modified per Protocol (mPP*) population: 1537 patients (782 TNK; 751 ALT) without important major protocol deviations and who received the drug.

Safety population: 1563 patients who were randomized, and received the drug (tenecteplase or alteplase specifically). The one patient who received alteplase instead of allocated tenecteplase was included in the alteplase group for this analysis.

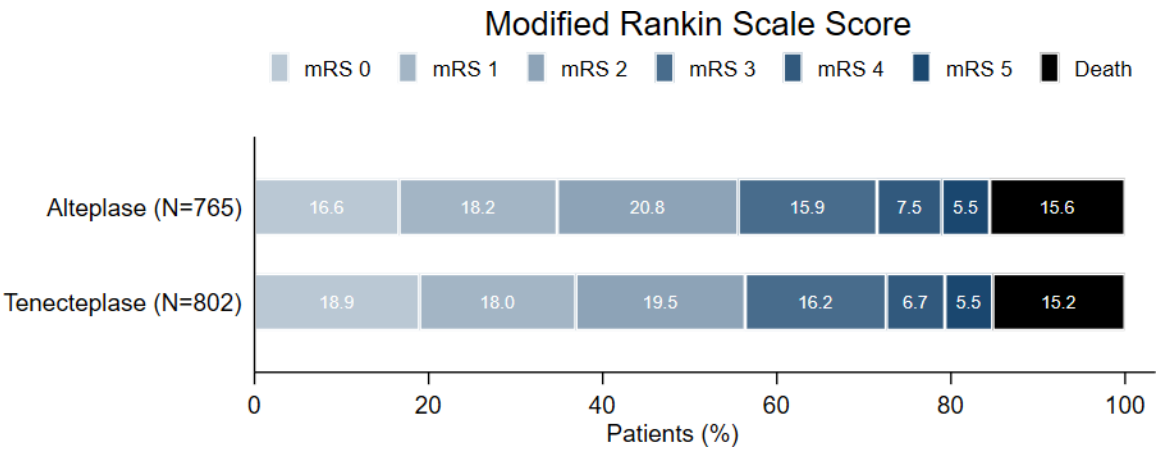
* The mITT and mPP populations were defined for the re-analysis of the study data by the Applicant.

Outcomes and estimation

Primary endpoint

For the primary outcome and all other 90–120-day assessments, the median follow-up was 97 days (IQR 91–111). The primary outcome (90–120-day mRS score of 0-1) occurred in 296 (36.9%) of 802 patients assigned to tenecteplase and 266 (34.8%) of 765 assigned to alteplase with available data (unadjusted risk difference 2.1% [95% CI -2.6 to 6.9]; as reported in the primary manuscript [P22-05053]). The lower bound 95% CI of the difference in primary outcome rate (-2.6%) was greater than -5%, thus meeting the prespecified non-inferiority threshold. The direction of effect favoured tenecteplase, but tenecteplase was not superior to alteplase in secondary analyses (p=0.19) (**Figure 2**).

Figure 2 Distribution of the Modified Rankin Scale at 90 days in the Intention-to-Treat Population.



Shown are the scores on the modified Rankin scale (mRS) for the patients in the tenecteplase group and alteplase group at 90 days. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Numbers indicate rounded percentages. Tenecteplase was noninferior to alteplase in the unadjusted analysis for the primary outcome i.e., mRS 0-1 at 90 days (risk difference 2.1%; 95% Confidence Intervals -2.6 % to 6.9%).

Source: [P22-05053]

The primary and secondary study outcomes in the ITT population analysed as specified in the protocol and later in the SAP are shown in the following Table.

Table 6: Efficacy Outcomes in the ITT population. In any adjusted analysis, "registry" is used as a random effects variable. This analysis was what was specified in the protocol and later in the SAP - AcT study.

	Tenecteplase group (N=806)	**Alteplase group (N=771)**	**Measure of Effect**	**Estimate (95% CI)**
Primary outcome				
modified Rankin Score 0-1 at 90 days (n=1567)	296/802 (36.9)	266/765 (34.8)	Difference in proportion (unadjusted)	2.1 (-2.6, +6.9)
Secondary outcomes*				
modified Rankin Score 0-1 at 90 days (n=1567)	296/802 (36.9)	266/765 (34.8)	Risk ratio (adjusted*)	1.1 (1.0, 1.2)
modified Rankin Score 0-2 at 90 days (n=1567)	452/802 (56.4)	425/765 (55.6)	Difference in proportion (unadjusted)	0.8 (-4.1, +5.7)
			Risk ratio (adjusted*)	1.0 (1.0, 1.1)
modified Rankin Score at 90 days (n=1567)	3 (2 - 5)	3 (2 - 5)	Difference in medians	0
			Common odds ratio† (adjusted*)	0.9 (0.8, 1.1)
Return to baseline function (n=1454)	219/740 (29.6)	199/714 (27.9)	Difference in proportion (unadjusted)	1.7 (-2.9, +6.4)
			Risk ratio (adjusted*)	1.1 (1.1, 1.1)
Euro-QOL Visual Analogue Scale (EQ-VAS) at 90 days (n=1262)	70.5 (21.3)	68.1 (22.6)	Difference in proportion (unadjusted)	2.4 (-0.1, +4.8)
			beta-coefficient (adjusted*)	2.1 (-0.3, +4.5)
Endovascular Thrombectomy Utilisation (n=1577)	258/806 (32.0)	248/771 (32.2)	Difference in proportion (unadjusted)	-0.2 (-4.8, +4.5)
			Risk ratio (adjusted*)	1.0 (0.8, +1.2)
eTICI score ≥ 2b on initial angiography of EVT (n=502)	26/256 (10.2)	26/246 (10.6)	Difference in proportion (unadjusted)	-0.4 (-5.7, +4.9)
			Risk ratio (adjusted*)	1.0 (0.8, +1.3)
rAOL score ≥ 2b on initial angiography of EVT (n=500)	49/254 (19.3)	39/246 (15.9)	Difference in proportion (unadjusted)	3.4 (-3.2, +10.1)
			Risk ratio (adjusted*)	1.2 (0.9, 1.6)
Length of hospital stay# (n=1481)	5 (2 - 11)	5 (3 - 11)	Difference in medians	0
			Risk ratio (adjusted*)	1.0 (0.8, 1.1)

Table 7: The Primary Efficacy Outcomes for the mPP population - AcT study

	Tenecteplase group (N=786)	**Alteplase group (N=751)**	**Measure of Effect**	**Estimate (95% CI)**
Primary outcome				
modified Rankin Score 0-1 at 90 days (n=1529)	292/783 (37.3)	259/746 (34.7)	Difference in proportion (unadjusted)	2.6 (-2.2, +7.4)

Table 8: The Primary Efficacy Outcomes for the mITT population – AcT study

	Tenecteplase group (N=801)	**Alteplase group (N=762)**	**Measure of Effect**	**Estimate (95% CI)**
Primary outcome				
modified Rankin Score 0-1 at 90 days (n=1554)	296/797 (37.1)	264/757 (34.9)	Difference in proportion (unadjusted)	2.3 (-2.5, +7.0)

In the clinical study report, the Applicant provided various additional analyses "to address what was proposed in the initial protocol and any subsequent revisions made in the SAP and from what was reported in the primary paper" (Tables 10-20 of the Clinical trial Report). These analyses included reporting any adjusted analyses using "registry" as a fixed effects variable with "site" as random effects as also reported in the manuscript. In addition, the Applicant also reports any adjusted analyses using "registry" as random effects variable and "registry" as both fixed and "random effects variable". Different analyses were provided for the ITT population (but also for the later defined mITT and mPP population). Finally, an additional table was included presenting all secondary outcomes specified in the SAP and not just those reported in the main paper.

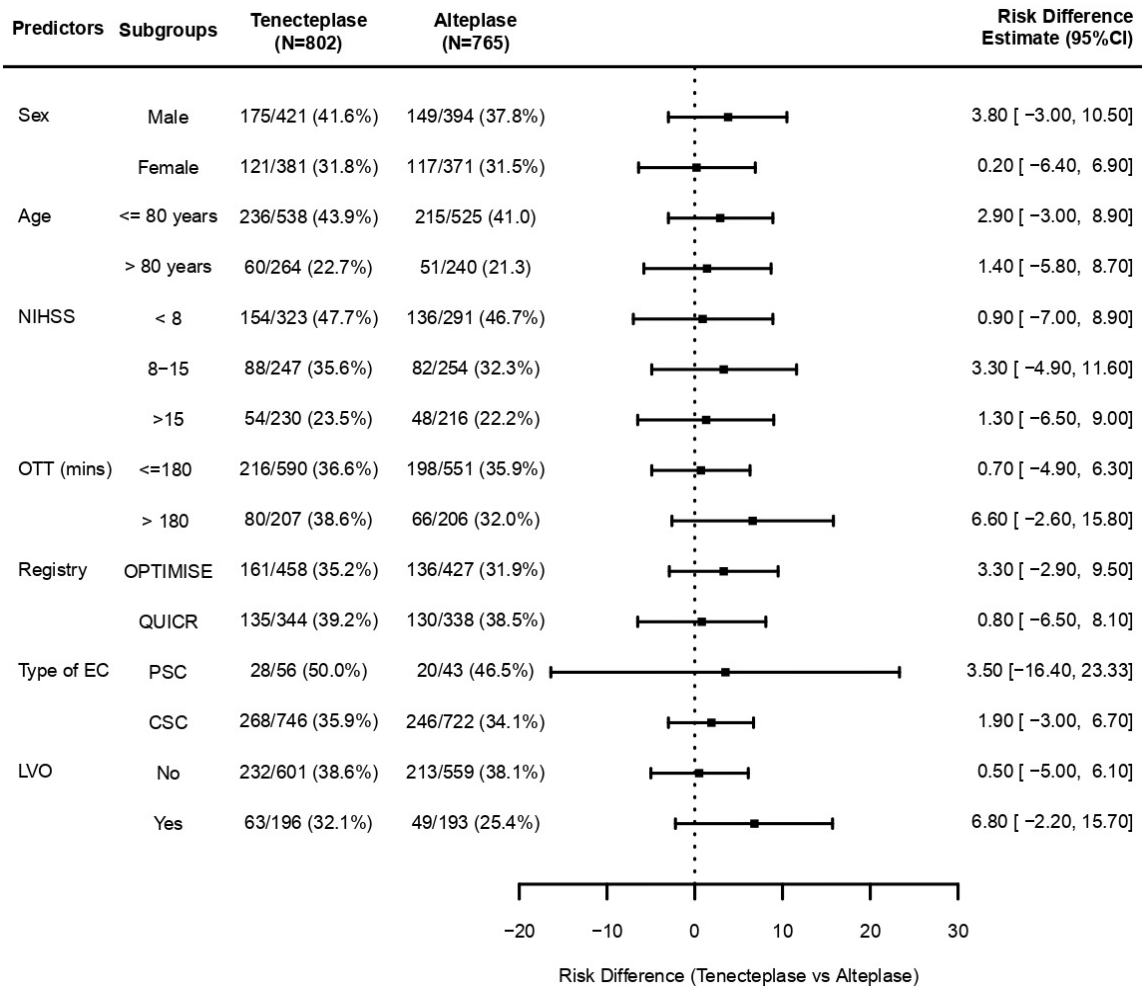
There were no material changes in any results from these various analyses.

Subgroups

No heterogeneity of treatment effect was observed across any prespecified subgroups.

A Forest plot of unadjusted risk difference estimates for the primary outcome (modified Rankin Scale 0-1) stratified by pre-specified sub-groups in the ITT population is provided in the following figure. Positive risk differences favour tenecteplase.

Figure 3 Forest plot of unadjusted risk difference estimates for the primary outcome (modified Rankin Scale 0-1) stratified by pre-specified sub- groups in the ITT population



Ancillary analyses

Reanalysis of AcT Data

The MAH has established a specific data access and exchange agreement with the sponsors of the AcT trial to verify suitability of data and results and to generate additional analyses. The MAH was provided access to the individual patient data of the AcT study [P22 05053] in December 2022 with the aim to re-analyse the data independently [c42081819].

The first objective for the re-analysis was to reproduce the results from the journal publication, and the second objective was to produce new additional analyses, and to comply with the scientific advice (and guidelines) of the EMA.

To these objectives several questions were raised (These clinical questions address Background (B1 - B3), Efficacy (E1 - E4), Safety (S1 - S4) and Efficacy/Safety (ES1 - ES3):

B1• Can the MAH reproduce all basic background data (demographics, baseline characteristics and registry information), as published in Lancet 2022 [P22 05053]?

B2• Are the provided criteria for the intention-to-treat (ITT) population, Safety and Per Protocol Set populations robust enough for regulatory evaluation?

B3• How similar is the population in the AcT study to the historical studies, for the key prognostic factor(s)?

E1• Can the MAH reproduce all efficacy data, as published in Lancet 2022 [P22 05053]?

E2• Are the results of the endpoint modified Rankin Scale (mRS) 0-1 at Day 90-120 robust enough?

E3• Is the effect of tenecteplase over alteplase similar across all levels of severity? Are the assumptions of common odds valid?

E4• Are the alteplase known prognostic factors still important in AcT for both thrombolytics, are they similar for each of the thrombolytics, or is there a treatment by subgroup interaction, are the effects of alteplase according to historical meta-analysis [Emberson, 2013], and in relation to the important prognostic factors, similar with the AcT study? Are these prognostic factors also relevant for tenecteplase?

S1• Can the MAH reproduce all safety data, as published in Lancet 2022 [P22 05053]?

S2• Can other bleeding definitions (intracerebral haemorrhage) be applied to the existing data?

S3• Is the assessment of death robust for the regulators evaluation, with regard to timing of death, within subgroups and in relation to the important prognostic factor(s), including also the reason for death?

S4• Is there still a relationship between sICH within 24 h and the important prognostic factor(s)?

ES1• How do the results for the three main endpoints for tenecteplase and alteplase look in the alteplase EU summary of product characteristics (SmPC) filtered population? (i.e. the mITT set of patients when partially filtered for the SmPC criteria; OTT >4.5h and NIHSS >25 (or unknown). No other filtering is possible due to data collection.)

ES2 • What do the key results look like in the high-risk population?

ES3• What is the impact of weight-based dosing strategy on the pharmacological effect in the patients at extreme ends of the weight spectrum?

The methodology, the statistical methods and the results of these additional analyses are extensively described in the accompanying reports (Analysis plan [c42415120], Reanalysis report [c42081819]). Minor corrections were made to the database since the publication, and this re-analysis was performed on the updated database.

Relevant details and results, respectively of the exploratory analyses presented by the Applicant are given below (for further details see the Clinical report on exploratory analyses of the AcT trial [c42081819] provided in module 5.3.5.4 of the submission; for the ease of reading, exploratory analyses relating to safety or efficacy and safety, respectively are also presented in this section):

• The clinical trial plan (CTP) of the AcT study was summarised in a manuscript published in Stroke 2022 [P22-08756] and was slightly different from the analysis to the CTP provided to the investigators in the study [c42580393]. The results of the study, as published in Lancet, were produced according to the trial statistical analysis plan (TSAP, [c42580422]) that was based on the original protocol version 2.0 and the CTP published in Stroke. The clinical trial report is stated by the Applicant to address possible analysis gaps that might have been caused by discrepancies between two versions of the CTP of the AcT study.

• Regarding Question **B1**: According to the Applicant, all the important numbers in the original manuscript [P22-05053] based upon the Soft Lock were reproducible (Appendix 1) and any minor discrepancies were explainable.

• Regarding Question **B2** (Analyses population):

The patient disposition and baseline characteristics were reproducible, and any minor discrepancies are discussed in the CTR. The originally defined ITT population and PP population included patients what did not received study drug. The Applicant therefore defined new populations based on relevant guidelines for non-inferiority studies.

For the re-analysis, two additional populations (modified ITT [mITT] and modified PPS [mPPS]) were defined, following the removal of the fourteen patients who did not receive the trial medication from the AcT-defined ITT population and PPS. The mITT was then used as the main data set for the analysis of efficacy and the mPPS was used in a sensitivity analysis.

The criteria considered in the definitions of the analysis sets are stated by the Applicant to be in line with ICH E9 Statistical principles for clinical trials (CPMP/ICH/363/96, [P17-11411]), and *Table 9* provides a summary of the analysis sets.

Table 9: Distribution of patients in the analysis sets

Analysis set	Tenecteplase	Alteplase	Total
Randomised set	816	784	1600
ITT set	806	771	1577
mITT set	801	762	1563
PP set	791	760	1551
mPP set	786	751	1537
Safety set	800	763	1563

ITT- intention-to-treat, mITT- modified intention-to-treat, PP- per-protocol, mPP - modified per protocol. Please refer to the definitions above.

Source: Appendix 1, Table 1.1.2.1.

(Further details on the analysis set definitions and an explanation of the patient distribution to the analysis sets are provided in the exploratory analyses report, results of clinical question B2).

• Regarding Question **B3** (comparison of important prognostic factors between historical meta-analysis and AcT): An important difference between the populations in AcT versus meta-analysis concerned the OTT. In the historical metaanalysis, 36% of the patients were treated in the 0-3 h time window, in contrast to 73% of patients in AcT, who were treated in the 0-3 h time window.

• Regarding Question **E1** (Reproducibility of efficacy results in the Lancet 2022 manuscript [AcT trial]:

All the important numbers in the original manuscript [P22-05053] based upon the Soft Lock were reproducible (Appendix 3), and any minor discrepancies were explainable:

1. The Common Odds Ratio in Table 2 in the manuscript presents the unfavourable outcome, so the favourable is the inverse of the numbers, (1/x)

2. The risk ratio-adjusted numbers slightly differ, most likely due to a different software being used (BI use SAS, Calgary use STATA)

All identified changes are documented in a changes log

• Regarding Question **E2** (Robustness of mRS 0-1 score at Day 90-120, including subgroups, population (study) adjusted NI margin, indirect comparison with control):

The primary endpoint in AcT was the proportion of patients who had a score of 0-1 on the mRS at Day 90-120. Because this study was a non-inferiority study comparing tenecteplase to alteplase, it was important to determine a non-inferiority margin. The non-inferiority margin was derived from the historical meta-analysis [P14-11754].

AcT had a pre-defined margin of -5% for the analysis of the risk difference of having a score on mRS 0-1 at Day 90-120, comparing tenecteplase with alteplase.

From *Table 10*, below, the value of 9.81% was used as the M1*, and 50% of this value led to approximately M2**=5%, the inverse being the non-inferiority margin of -5%.

*M1 = the entire effect of the active control assumed to be present in the NI study

**M2 = the largest clinically acceptable difference (degree of inferiority) of the test drug compared with the active control.

Table 10: Proportion of patients with mRS score 0-1 at Day 90 from historical meta-analysis [P14-11754]

Time window	Alteplase	Control	Unadjusted RD (95% CI), %
0-3 h	259/787 (32.9%)	176/762 (23.1%)	9.81% (5.37 to 14.25)
3-4.5 h	485/1375 (35.3%)	432/1437 (30.1%)	5.21% (1.75 to 8.67)
0-4.5 h	744/2162 (34.4%)	608/2199 (27.7%)	6.76% (4.02 to 9.50)
0-4.5 h with a 0.73 weighting for 0-3 h time window			8.57% (5.20 to 11.94)

Source: P14-11754, Figure 2 and Appendix 1, Table 1.2.2.3.1

This pre-defined margin derivation has two limitations in the context of the classical 95-50-95 rule for determining a non-inferiority margin:

1. The derivation was based upon the 0-3 h time window

2. The point estimate of the results was used, rather than the lower bound of the 95% CI

To overcome this limitation, further investigations were performed, to reassess an appropriate margin.

In the determination of the ESO guidelines, an absolute non-inferiority margin was chosen via secret ballot. The panel voted for a margin of -3.0% [P23-01257], which was the most stringent absolute non-inferiority margin among all published randomised clinical trials (RCT)s comparing the safety and efficacy of IVT with tenecteplase to IVT with alteplase in AIS patients. Although this margin was also based upon Lancet 2014 historical meta-analysis [P14-11754], and it was not well defined how the results of the meta-analysis were derived, the final non-inferiority margin was considered by the panel to be of clinical relevance.

The results of the historical meta-analysis [P14-11754] early time window (0-4.5 h) led to an M1 of 4.02% and taking 50% of this led to an M2 of 2.0%, the inverse being the noninferiority margin of -2%.

Therefore, it was clear that an appropriate non-inferiority margin was in the range of -2% to -3%, and that the actual value depended on the contribution of the 0-3 h and 3-4.5 h time windows to the pharmacological effect of alteplase.

Given that the difference in time windows for treatment was the main difference between the two populations (see Table 6: 2 of Report on exploratory analyses, c42081819-01) and given the large impact of this important prognostic factor, it seemed reasonable to adjust for time window in the historical meta-analysis.

Table 6: 2 of Report on exploratory analyses: Distribution of important prognostic factors in the historical meta-analysis and AcT study

Covariate	Historical meta-analysis (STTC database, n=4361)	AcT study mITT (n=1563)
OTT		
0-3 h	1549 (36%)	1147 (73%)
3-4.5 h	2812 (64%)	370 (24%)
>4.5 h		46 (3%)
Age		
≤80y	3089 (71%)	1062 (68%)
>80y	1272 (29%)	501 (32%)
Sex		
Male	2356 (54%)	816 (52%)
Female	2003 (46%)	747 (48%)
NIHSS at baseline		
0-4	377 (9%)	252 (16%)
5-10	1542 (35%)	602 (39%)
11-15	1041 (24%)	265 (17%)
16-21	926 (21%)	279 (18%)
≥22	475 (11%)	165 (11%)

Source: Appendix 1, Table 1.1.3.1

This adjustment was done by attributing a 0.73 weighting to the results of the 0-3 h time window and a 0.27 weighting to the 3-4.5 h time window and applying the same weightings to the standard error of the risk difference results for both time windows. The methodology for this adjustment is similar to the Cochran-Mantel-Haenszel method of pooling subgroups and is explained in Section 5.2.2. "Performing this adjustment resulted in a population adjusted risk difference of 8.57% (95% CI: 5.20 to 11.94), with an M1 of 5.20% and M2 of 2.6%, preserving 50% of the effect of alteplase. The population adjusted non-inferiority margin was then -2.6%, which was compliant with both methods of derivation (e.g. based on clinical expectations and mathematical derivations as specified above).

To compare the results as risk ratios using the 95-50-95 rule, the same non-weighted and weighted approaches were used to derive non-inferiority margins for risk ratios; 0.937 non-weighted (comparable with -2.0% for RD), and 0.915 for the weighted (comparable with the -2.6% for RD). These calculations were performed on the log scale and back transformed.

Table 11: Overview of all non-inferiority margins for the primary endpoint in AcT

NI margin	Description of NI margin
-5.0% for RD	AcT protocol pre-defined margin for mRS 0-1 based upon the 0-3 h time window and Canadian guidelines
-3.0% for RD	ESO recommended clinically relevant NI margin assuming 34% alteplase event rate
-2.6% for RD	Population adjusted margin, weighted 73:27 for 0-3:3-4.5 h time window from historical meta-analysis (Lancet 2014) using 95-50-95 rule
-2.0% for RD	Non population adjusted margin from historical meta-analysis (Lancet 2014) using 95-50-95 rule
0.915 for RR	Population adjusted margin, weighted 73:27 for 0-3:3-4.5 h time window from historical meta-analysis (Lancet 2014) using 95-50-95 rule and determined on the log scale
0.937 for RR	Non population adjusted historical meta-analysis (Lancet 2014) using 95-50-95,

Calculation of non-inferiority margins were performed based on following sources: [P22-05053], [P22-08756], [P23-01257], [P14-11754] and Appendix 1, Table 1.2.2.3.1

The results of all analyses were interpreted in the context of these non-inferiority margins:

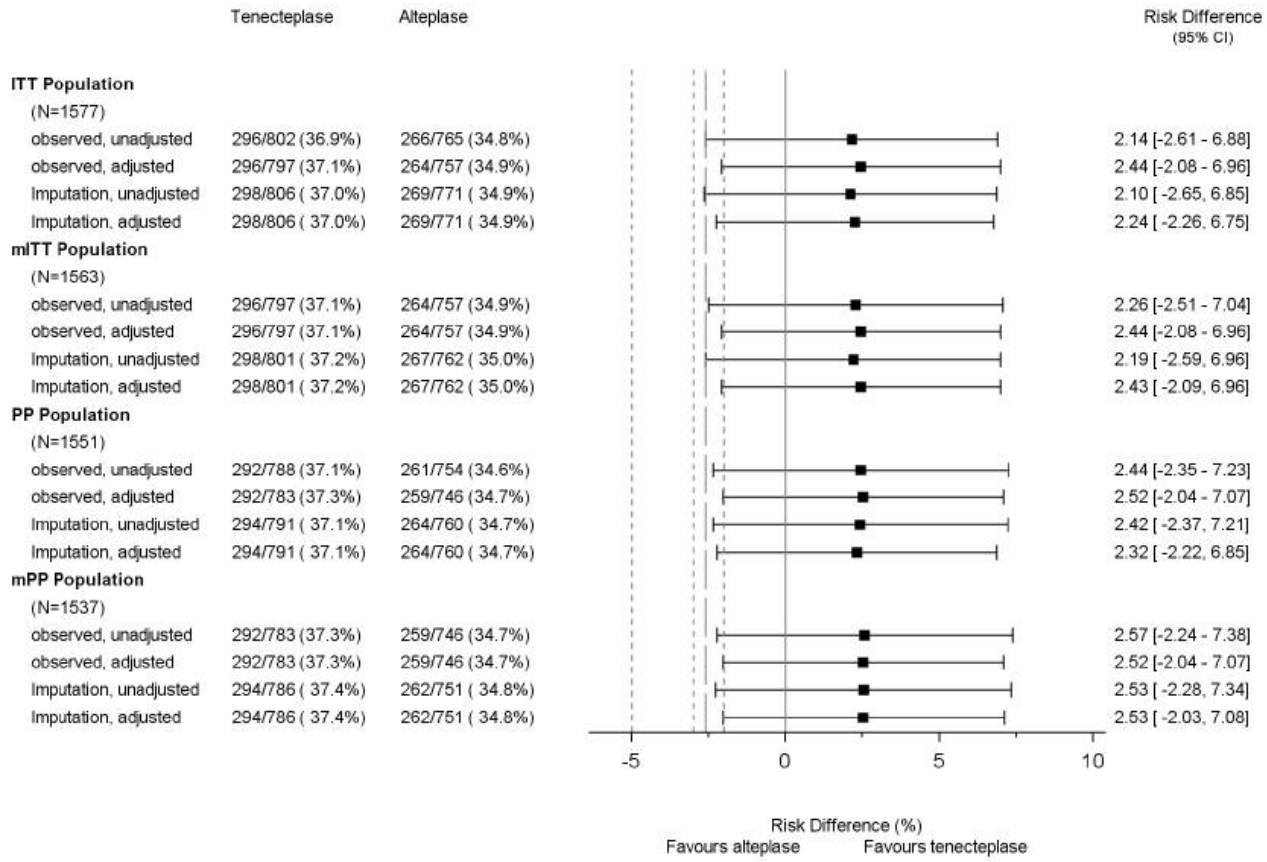
1. The protocol determined that non-inferiority margin was -5.0% and the protocol defined analyses of the primary endpoints were interpreted in the context of this margin.

2. The post hoc and population adjusted non-inferiority margin of -2.6% was used for the interpretation of the non-protocol defined analyses of the primary endpoint.

The protocol-defined analyses in the ITT population were to compare tenecteplase with alteplase using the proportion of patients who had a score of 0 or 1 on the mRS at Day 90-120 via the lower bound of the 95% CI of the unadjusted risk difference. If this value was greater than the pre-defined non-inferiority margin of -5%, then the study was considered to show that tenecteplase was non-inferior to alteplase. These criteria were met.

Whilst the possible narrower non-inferiority margins lie in the range of -2% to -3%, so also do the results of the risk difference analyses of mRS 0 1 at Day 90 120. **Figure 4** presents the risk difference results of the various population, adjusted and unadjusted, and including imputation for the missing data, albeit minimal missing data. The vertical dashed lines for all the non-inferiority margins of relevance (-5%, -3%, -2.6%, -2%, and 0% for superiority).

Figure 4 Forest Plot of the Risk Difference of mRS score 0-1 at Day 90-120 by different approaches and populations.



Reference lines cross at -5%, -3%, -2.6%, -2.0% and 0%

Source: [c42081819] Appendix 1, Figure 1.2.2.4.5.1

1. For all analyses, the risk difference point estimate was in favour of tenecteplase compared with alteplase

2. All analyses on the mITT, PP and mPP sets had the lower bound of 95% CI in the range -2.59% to -2.04%

3. Analyses on the ITT, adjusted for the important prognostic factors had lower bound of 95% CI values of -2.08% to -2.26%, the latter including multiple imputation for missing values. This analysis included the patients that did not receive study drug

4. Analyses on the ITT, unadjusted for the important prognostic factors had lower bound of 95% CI values of -2.61% to -2.65%, the latter including multiple imputation for missing values. This analysis included the patients that did not receive study drug

5. Following the second step in the protocol pre-defined hierarchical testing, the results did not show superiority of tenecteplase to alteplase.

Finally, the results of the indirect comparison, comparing tenecteplase to control, via alteplase, confirm that tenecteplase is indeed superior to control (placebo or standard treatment). Using the population

adjusted meta-analysis the risk difference is 10.7%, (p = 0.0004), or without adjusting for the population differences, risk difference is 8.9% (p = 0.0017), see following table.

Table 12: Results of indirect comparison between tenecteplase and control

ITT, observed	Tenecteplase	Alteplase	Control	unadjusted RD% (95% CI), p
Historical MA		744/2162	608/2199	6.8% (4.0 to 9.5)
Alteplase *vs.* control		(34.4%)	(27.6%)	8.6% (5.2 to 11.9)[1]
AcT (ITT)	296/802	266/765		2.1% (-2.6 to 6.9)
Tenecteplase *vs.* Alteplase	(36.9%)	(34.8%)		
Indirect comparison				8.9% (3.4 to 14.4), p = 0.0015
Tenecteplase *vs.* control				10.7% (4.9 to 16.5)[1], p = 0.0003

[1]Population weighted (OTT)

Source: Appendix 1, Table 1.2.2.3.2

Risk difference calculation over time (changing the estimand component: variable)

Each patient had one mRS assessment, and according to the protocol, they were due to be done between Days 90 and 120. Due to the COVID-19 pandemic, some mRS assessments were performed much later than planned (beyond one year). All efforts were made to get the mRS information as complete as possible, even if mRS values assessed at much later timepoints had to be accepted.

In the mITT population, 35%, 85%, 95% and 98% of the patients had mRS assessments up to Days 90, 120, 150 and 180. A very small percentage of patients was assessed after 180 days, and the data from these patients added variability without affecting the results (the nominal 90-120 days that included data collected beyond 180 days, shifted the point estimate to the left, i.e. less in favour of TNK). Therefore, all the patients with data collected beyond Day 120 are included in nominal Day 90-120.

The point estimates for the risk difference (adjusted) up to day 90, 120, 150 and 180 respectively were always similar, and only the confidence intervals narrowed down as more data was collected. Considering the timing of the mRS assessments that were being performed outside of the planned Day 90-120 window, the effect of tenecteplase on the number of patients with mRS score 0-1 was robust in the context of the -2.6% population adjusted non-inferiority margin, and even the non-population adjusted -2.0% non-inferiority margin.

Summary of the submitted considerations and analyses regarding question E2:

1. The protocol defined NI margin was -5% and the protocol defined results (unadjusted for important prognostic factors) with a lower bound of -2.61% met this margin 2. A clinically relevant NI margin and the mathematically derived NI margin, to preserve at least 50% of effect of alteplase, lie in the range of -2% to -3%

3. A population adjusted NI margin, adjusted for prevalence of OTT, is -2.6%

4. All results obtained from the mITT set (excluding patients who did not receive treatment from the analysis) met the -2.6% margin

5. All results obtained from the mPP set met the -2.6% margin

6. Events assessed post 180 days increase variability, and excluding these, the lower bound of the 95% CI is > -2%

7. Alteplase has a similar effect on the percentage of patients with mRS score 0-1 between historical studies and AcT (approximately 34% in both studies)

8. Indirectly comparing tenecteplase to control shows superiority of tenecteplase (p = 0.0003 if adjusted for population)

• Regarding question **E4** (mRS 0-1 by prognostic factors: OTT, NIHSS, age, sex):

1. The effect of alteplase in the investigated subgroups (Sex, Age group, NIHSS at baseline, OTT) is relatively consistent with the effect seen in the historical metaanalysis

2. The effect of tenecteplase in the investigated subgroups is similar to the effect of alteplase

3. To compare the effect of alteplase in relation to OTT between AcT and historic metaanalysis, it is important to adjust the probability of mRS score 0-1 for the other prognostic factors (age, sex, NIHSS)

• Regarding question **S1**: (Reproducibility of safety results in Lancet 2022 manuscript)

All important safety information presented in the Lancet 2022 manuscript [P22-05053] was reproduced. In the corrected database, one less patient (from alteplase group) had an SAE angioedema after reconciliation, compared with the published results. An in-depth data evaluation resulted in more granularity of the SAEs, in terms of system organ class and preferred terms. The grouping of SAEs was re-defined, adding a separate category of peripheral bleedings not requiring blood transfusion and therefore, there are less SAEs in the 'Other serious adverse events' category.

All identified changes are documented in a changes log.

There are no major imbalances in the SAEs overall or in any subgroup. The occurrence of angioedema, which is a potentially life-threating event mentioned in the SmPC for actilyse ([R23-2033], Special warnings and precautions for use), in tenecteplase is similar to what is reported in the manuscript with 9/800 (1.1%) in tenecteplase and 8/763 (1.0%) in alteplase (Appendix 1, Table 1.3.1.3.1).

• Regarding question **S2**: (Assessment of other intracerebral haemorrhage bleeding definitions)

The definition of symptomatic intracerebral haemorrhage (sICH) used in the AcT trial (any intracerebral haemorrhage that was temporally related to, and directly responsible for, worsening of the patient's neurological condition and in the investigator's opinion was the most important factor for the neurological worsening) was broader than the definition used for sICH in SITS-MOST (because the imaging was not taken into account) and in the Heidelberg definition (because only local haemorrhages were included).The 24 h window of ascertainment in the AcT study was smaller than the time window used in SITS-MOST (AcT used imaging up to 24 h, symptomatic element was covered by SAEs recorded up to 24 h; STTC used 36-48 h and the symptomatic element was covered by a neurological component).

To allow for a proper evaluation of the sICH bleeding risk of tenecteplase compared with alteplase in AIS based on AcT, additional analyses that exclude less severe sICHs were required. In this context, the sICH definition applied in the AcT trial is compared with various definitions used in the historical meta-analysis (published in The Lancet in 2016 [P16-06898], also referred to as the STTC (Stroke Thrombolysis Trialists' Collaboration) data by the Applicant), based on the safety population.

Upon close examination of the individual patient database of the AcT study, the Applicant found, that the definition that could most closely be replicated was SITS-MOST of ICH occurring within time window of 24-36 h from treatment. Two definitions were used in the historical metaanalysis for SITS-MOST, one as defined in all the BI studies mentioned in the meta-analysis, and the other one as defined in the IST-3 study [P16-06898]. The differences between two definitions were mostly due to the symptomatic component and were considered to have a minimal effect on the pooling in the meta-analysis. Both BI-based and IST-3-based versions were applied to the AcT data during re-analysis. Fatal ICH within 7 days was also included in the re-analysis.

In defining a symptomatic intracerebral haemorrhage (sICH) for the re-analysis of AcT data, three main components from SITS-MOST were considered:

1. Imaging identified bleeding type (local or remote)

2. Symptomatic component (neurological deterioration)

3. The time window after treatment start (24-36 h or 7 days)

The following table describes the definitions used for the sICH events according to SITS-MOST in the historical meta-analysis, and the closest possible match in AcT.

Table 13: Definitions used for sICH events according to SITS-MOST and the closes possible match in AcT

Symptomatic ICH (sICH)	Imaging identified bleeding type	Neurological deterioration (symptomatic)	Time window (after treatment start)
SITS-MOST definition (BI-RCTs)	local or remote PH-2 on the imaging scan obtained 24 to 36 h after treatment start	Increase of NIHSS score ≥4 compared with baseline, or death	36 h
SITS-MOST definition (IST-3)	Any PH-2 bleeding (local or remote)	Not available	2 days
AcT study	Any PH-2 bleeding	SAE reported as sICH within the nominal 24 h	24 h CT or MRI scan

RCT- randomised control trial

Note: the endpoint PH-2 from the meta-analysis was not used because, unlike in AcT with time-window of bleeding assessment of the first 24-36 h, it was assessed up to 7 days.

The PH-2 (Heidelberg classification), without the symptomatic component, is comparable with the IST-3 SITS-MOST definition. The symptomatic PH-2 (also Heidelberg classification) is comparable with the BI-RCTs SITS-MOST definition. Since the historical meta-analysis was made up of a combination of the two (BI-RCTs and IST-3), both definitions applied to AcT are considered, to compare like-for-like definitions. It is however the IST-3 SITS-MOST definition that has the most comparable alteplase sICH rate in the AcT study vs. the historical meta-analysis (2.7% for AcT and 3.4% in STTC). Table 14**:** presents the proportion of patients with intracerebral haemorrhages according to various definitions that can be derived from the AcT study database in tenecteplase and alteplase groups.

Table 14: Proportion of patients with ICH and Risk difference in AcT (SAF), according to various definitions of ICH

	Tenecteplase	Alteplase	Risk difference (95% CI)
Symptomatic[1] ICH (without imaging but with symptomatic component)	27 / 800 (3.4%)	24 / 763 (3.2%)	0.23% (−1.53% to 1.99%)
ICH[2] (with imaging but without symptomatic component)	139 / 795 (17.5%)	140 / 754 (18.6%)	−1.08% (−4.91% to 2.75%)
PH-2[2] (local)	21 / 795 (2.6%)	18 / 754 (2.4%)	0.25% (−1.30% to 1.81%)
PH-2[3] (Heidelberg classification, comparable with IST-3 SITS-MOST)	23 / 795 (2.9%)	20 / 754 (2.7%)	0.24% (−1.39% to 1.88%)
symptomatic PH-2 (comparable with BI-RCTs SITS-MOST)	19 / 800 (2.4%)	14 / 763 (1.8%)	0.54% (-0.88% to 1.96%)

[1]Symptomatic means recorded as SAE within nominal 24 h, and this is determined without information from a scan.

[2]Confirmed by scan means any of the nominal 24 h scans (CT/MRI scans)

[3]Confirmed by scan and any location means that all of local and remote are assessed, which is in relation to location of infarct. Bleeding Type PH−2 is according to the Heidelberg definition.

Only one type of bleeding is counted per patient. A patient could have different bleeding types: 1. On the available scans or 2. On the identified locations. PH−2 is the worst bleeding type identified.

Source: Appendix 1, Table 1.3.2.1.3

There is no consistent NI margin to be applied to sICH, but a value of -1% has been quoted in the Burgos and Saver meta-analysis [P19-06342] and would fit with a 95-50-95 rule derivation. If the 95-50-95 rule were applied to the SITS-MOST definition, restricted to the 0-4.5 h time window, [95% CIs is 2.06% to 3.69%], this gives us an M1 = 2.06%, 50% of which is 1% giving a non-inferiority margin of -1%. In that case, the PH-2 definition applied to AcT (IST-3 SITS-MOST definition), with a lower 95% confidence interval of -1.39%, cannot lead to any conclusions with regard to non-inferiority. With the symptomatic PH-2 definition applied to AcT (IST-3 SITS-MOST definition), the lower 95% confidence interval is -0.88%, which would suggest non-inferiority. With two sets of inconsistent results, there can be no consistent conclusion. One or two events can change the direction of the effect.

The rate of fatal ICH events within 7 days in the AcT trial was 2% in the TNK and 1.7% in the ALT group, the respective incidence in the historical metaanalysis (Whiteley, 2016) in the ALT group was 2.6%.

Table 15: Number of patients (N, %) with fatal ICH within 7 days pos-ttreatment (AcT, SAF)

	Tenecteplase	Alteplase
Number of patients (N)	800	763
NIHSS at baseline (N, %)		
≤25	14/775 (1.8%)	13/749 (1.7%)
>25	2/25 (8.0%)	0/14 (0.0%)
SmPC population (N, %)		
Yes	14/756 (1.9%)	13/724 (1.8%)
No	2/44 (4.5%)	0/39 (0.0%)
Weight (N,%)		
<50 kg	1/36 (2.8%)	2/19 (10.5%)
≥50 kg	15/764 (2.0%)	11/744 (1.5%)
Age (N, %)		
≤80 years	8/537 (1.5%)	4/525 (0.8%)
>80 years	8/263 (3.0%)	9/238 (3.8%)

Source: Appendix 1, Table 1.1.2.1, Table 1.3.3.2.7

• Regarding question **S3**: (Assessment of deaths)

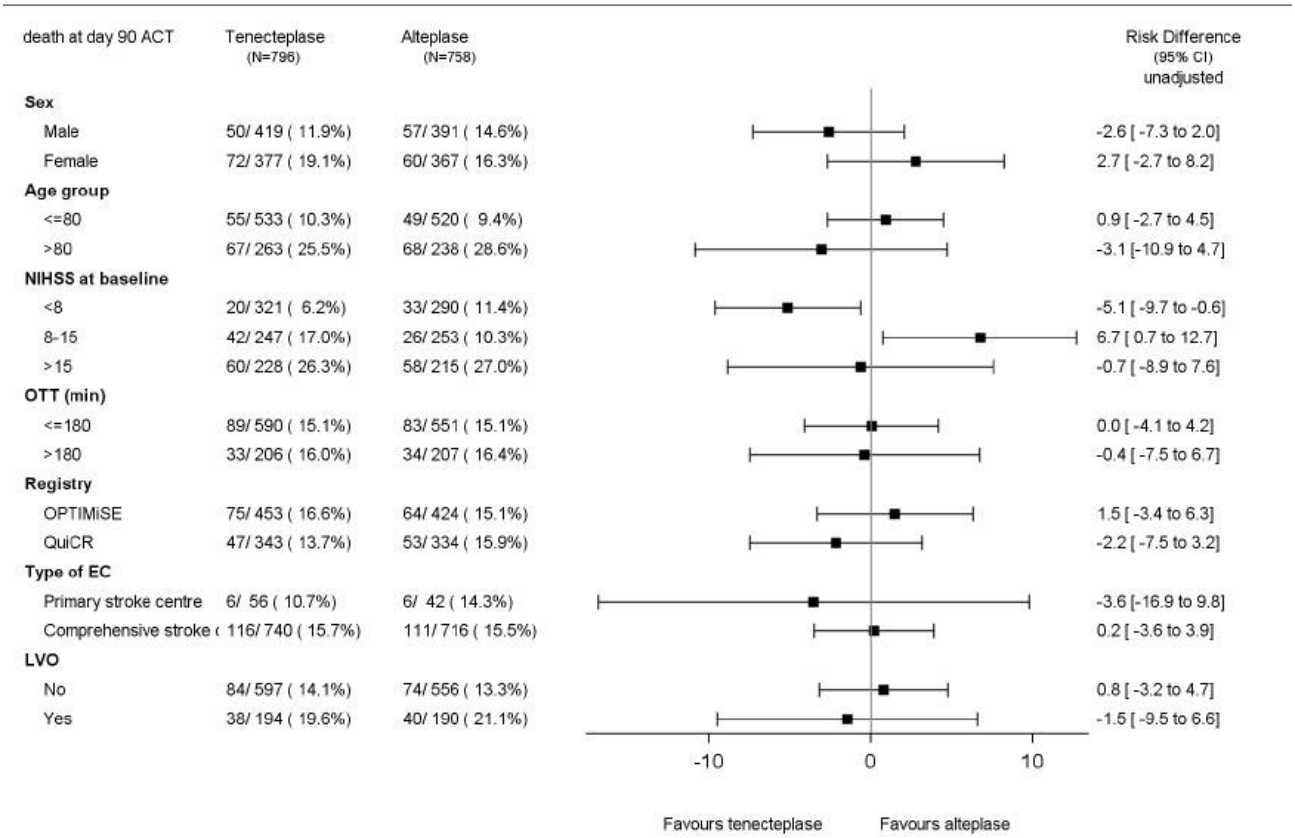
Overall, there is a similar rate of deaths within (nominal) 90 days in tenecteplase (122/796, 15.3%) compared with alteplase (117/758, 15.4%). The death rate in alteplase in AcT (15.4%) is slightly lower than the alteplase death rate in the historical meta-analysis (18.8%). According to an indirect comparison, the risk difference for death is less than 1% (0.75%) in tenecteplase compared with control, and this difference is not statistically significant. A non-inferiority margin for death up to Day 90 provides no added value since the historical meta-analysis did not show superiority (albeit for a non-favourable endpoint).

The deaths in the TNK group did not occur earlier than in the ALT group. The timepoint at which there is the largest apparent difference between the treatment groups, is at about Day 10 when death rate is 6.3% in TNK and 8.0% in ALT, with a RD of -1.7% (95%: -4.3% to 0.8%). This difference quickly disappears and thereafter the curves are the same, up to Day 90 and beyond (see Appendix 1, Table 1.3.3.1.1.2, Figure 6: 12).

From the historical meta-analysis (Lancet 2014), it can be seen that there are significantly more deaths up to Day 7 in alteplase compared with control [please refer to Figure 5 of reference P14-16838, instead of P14-11754 as referred to in the Exploratory analyses report by error].

Death within 90 days in the AcT study for the same subgroups as evaluated for efficacy are given in the following figure.

Figure 5 Forest Plot of death within 90 days (AcT) Risk Difference by subgroups – SAF population (N=1563)



The risk difference point estimates for the subgroups (Sex, Age group, NIHSS at baseline, OTT, Registry, Type of EC and LVO) fluctuate across the zero line, and for NIHSS the fluctuations are more extreme:

- The most severe group of NIHSS >25 have significantly more deaths with tenecteplase (14/25, 56%) than with alteplase (3/14, 21.4%) with a risk difference of 34.6% (95% CI: 5.6% to 63.6%)

Deaths within 90 days by baseline NIHSS was then evaluated with more granularity. Kaplan Meier plots showing the probability of death were produced for NIHSS at baseline in the categories of [0-4, 5-10, 11-15, 16-21, ≧22] and additionally categories in which the highest category is included in the high-risk set [0-4, 5-9, 10-14, 15-19, 20-25, >25] were provided. No consistent pattern may be observed across the NIHSS categories. In the highest NIHSS category (>25), the percentages of death on tenecteplase (14/25, 56%) were much higher than on alteplase (3/14, 21.4%), with a risk difference of 34.6% (95% CI: 5.6% to 63.6%), but there were substantially fewer patients in this category in alteplase group (tenecteplase: 25, alteplase: 14, Appendix 1, Table 1.3.3.1.4.1.2. Nevertheless, most of the deaths were occurring within the first 30 days, and at Day 30 the risk difference was 33.7% (95% CI: 6.9% to 60.5%), statistically significant and not in favour of tenecteplase. Importantly, the SmPC criteria for alteplase exclude these patients with NIHSS >25. These patients possibly had many comorbidities, making it difficult to make a proper assessment of the effect of the drug product.

The evaluation of deaths in relation to the four important prognostic factors (OTT, sex, age, NIHSS), led to the conclusion, that the effect of TNK was generally very similar to that of ALT. In the >80 years group, there was a larger probability of a death on tenecteplase as compared with alteplase. However, the difference was minimal and could be driven by confounding factors since this interaction disappeared after adjustment for baseline NIHSS, sex and OTT.

• Regarding question **S4**: (Investigate relationships of sICH at 24 h for tenecteplase, alteplase and control for important prognostic factors)

Given the low number of sICH events, it is difficult to accurately assess any relationship with the important prognostic factors. The only group with higher death rate in tenecteplase, are the most severe patients with NIHSS >25, which are excluded from alteplase treatment according to SmPC.

• Regarding question **ES1** (see comment on **Applicant's Summary of the main results of the exploratory analyses of the AcT study,** point 14., below).

• Regarding question **ES2** (regarding AcT outcomes in a high risk population)

High risk patients are those who have a high baseline NIHSS severity, aged >80 y, with comorbidities and perhaps with an abnormally low body weight. Not all information was available to fully define a high-risk set, and initial investigations were done for the important prognostic factors, except for OTT, which is not a patient characteristic.

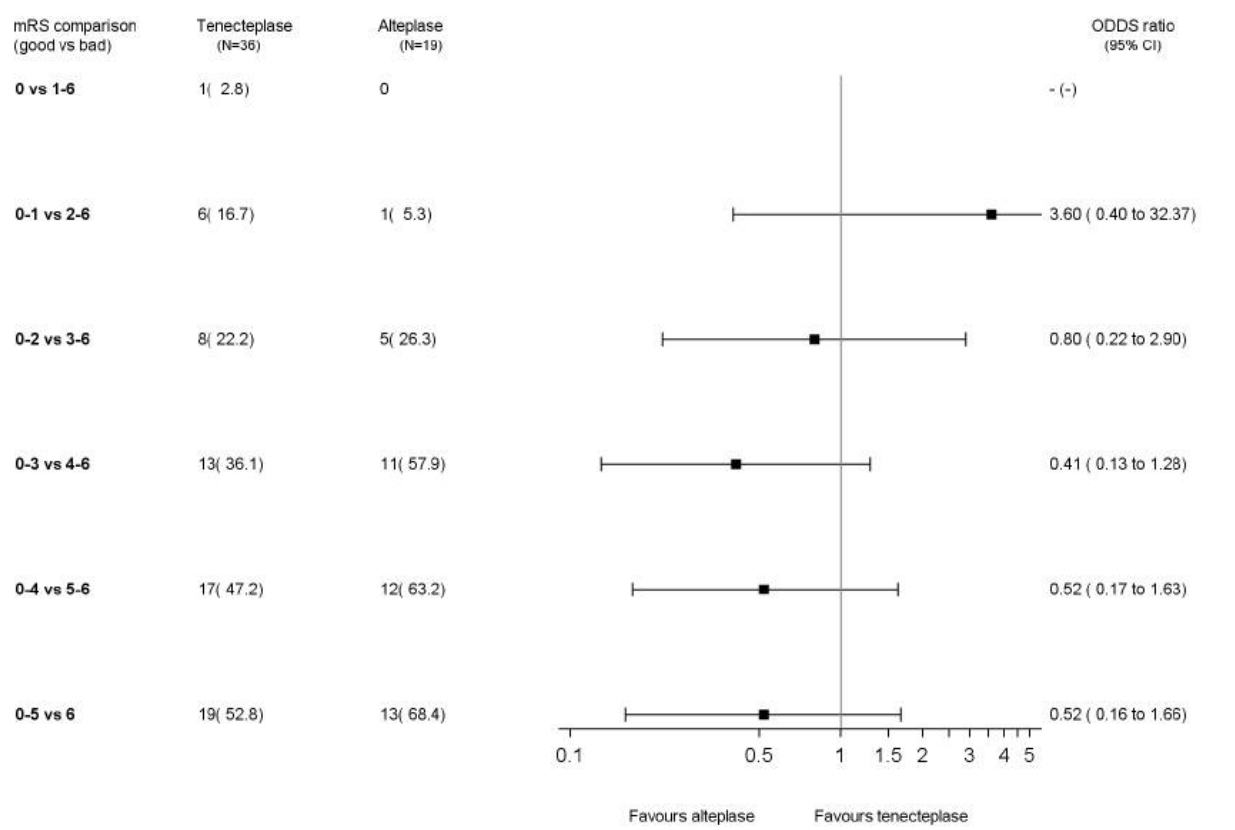
Whilst there is some fluctuation of effect across the various categorisations and endpoints, one consistent finding is in the group of NIHSS >25. For the unfavourable outcomes of death and sICH, there are more events on tenecteplase. It is a small group, so the confidence intervals are wide, as expected.

• Regarding question **ES3** (risk for incorrect dosing for the 5-step dose adjustment):

Within the body weight range of 50-100 kg, the dose/body weight ranges from 0.25 to 0.30 mg/kg. Below 50 kg, the dose ranges from 0.30 to 0.38 mg/kg, approaching the 0.40 mg/kg. Above 100 kg, the dose ranges from 0.25 to 0.20 mg/kg or less. Patients with weight more than 100 kg could be underdosed and patients with weight less than 50 kg, potentially slightly overdosed. There were two patients with estimated body weight between 34 kg-39 kg, and their respective doses would then be 0.44 to 0.38 mg/kg.

Odds rations for cumulative endpoints on the mRS scale for the subgroup of patients < 50 kg are presented in the following figure.

Figure 6 Odds ratios comparing tenecteplase to alteplase for cumulative endpoints on the modified Rankin Scale, for patients with <50 kg (n=55, mITT population)



Applicant's summary derived from re-analyses relating to ES3:

1. For patients with an estimated body weight of 40 to 50 kg the corresponding dose is in the range of 0.30- 0.38 mg/kg, and for patients with an estimated body weight of 35 to 39 kg the corresponding dose is in the range of 0.44 to 0.38 mg/kg.

2. AcT has few patients (n=55, tenecteplase: 36, alteplase: 19) in the <50 kg body weight category, of which two patients are between 34 kg and 39 kg

3. These patients with weight less of <50 kg are mostly female (52/55, 95%) and older than 80 years (36/55, 65%), and the additional risk factors from potential comorbidities cannot be assessed in this low sample size

4. In this group of patients with <50 kg, where is a large imbalance in the treatment groups (tenecteplase: 36, alteplase: 19), efficacy is similar and there appear to be more deaths in tenecteplase (17/36 [47%] than in alteplase (6/19 [32%]) up to Day 90-120. The surplus of deaths in tenecteplase is not due to an increase in number of fatal sICHs (Table 6: 12 of the Exploratory analyses report) compared with alteplase.

5. In the group of patients with >100 kg, the dose ranges from 0.25 to 0.20 mg/kg or less. These patients appear to have similar efficacy, sICH within 24 h and deaths [in the TNK vs. ALT group].

6. The benefit-risk of administering tenecteplase/alteplase together with the 5-step dose adjustment as used in AcT, needs to be gauged against the individual patient risk of complications from the disease vs. potential complications from treatment.

For further details of the exploratory analyses to evaluated the robustness of the outcomes of the AcT trial, see the Clinical report [c42081819] provided in module 5.3.5.4 of the submission.

Applicant's Summary of the main results of the exploratory analyses of the AcT study:

1. The re-analysis of the AcT study data confirms the robustness of the protocol defined results regarding the primary endpoint (proportion of patients with mRS score 0-1 at Day 90-120), with the protocol defined non-inferiority margin of -5%, and with more stringent population adjusted-non inferiority margin of -2.6%. More than 50% of the established effect of alteplase over control is preserved.
2. During the re-analysis, an extensive set of estimands was applied, and sensitivity analyses accounting for missing data were performed.
3. The assumption of the common Odds Ratio was valid, suggesting that the effect of tenecteplase and alteplase on the outcome is proportional to the level of severity of the modified Rankin Scale.
4. Indirect comparison between tenecteplase and control, after confirmation that the pharmacological effect of alteplase is constant across studies, shows statistically significant superiority of tenecteplase over control.
5. The pharmacological effect of tenecteplase in relation to the four prognostic factors (Gender, Age, NIHSS at baseline, OTT) is very similar to the pharmacological effect of alteplase.
6. There are similar event rates of sICH for both tenecteplase and alteplase, regardless of which definition of sICH within 24 h was used.
7. When comparing the alteplase treatment-related rates of sICH between AcT and meta-analysis, the most similar alteplase event rate between STTC (3.4%) and AcT (2.7%) were obtained when the SITS-MOST definition from IST-3 without the symptomatic component was used.
8. For fatal ICH, there are similar event rates between tenecteplase and alteplase in the SmPC filtered population (excluding patients with NIHSS >25).
9. Overall, there is a similar rate of deaths within (nominal) 90 days in tenecteplase group (122/796, 15.3%) compared with alteplase group (117/758, 15.4%).
10. In the early time period (Ţ10 days), there were fewer deaths in the tenecteplase group (50/800, 6.3%) compared with the alteplase group (61/763, 8.0%) with a difference of -1.7% (95% CI: -4.3% to 0.8%).
11. The group with the highest NIHSS >25 has significantly more deaths in the tenecteplase group (14/25, 56%) than in the alteplase group (3/14, 21%) with a risk difference of 34.6% (95% CI: 5.6% to 63.6%).
12. Analysis of the rate of fatal ICH events by Day 7 showed that the rate of events was almost similar in the SmPC partially filtered population (tenecteplase: 1.9%, alteplase: 1.8%). In the high-risk population analysis, there was a difference in rate of sICH for patients with weight under 50 kg (tenecteplase: 2.8%, alteplase: 10.5%) and for patients with age Ţ80 years (tenecteplase: 1.5%, alteplase: 0.8%), although the low number of events precludes from making robust comparisons between two treatments.
13. In the SmPC partially filtered set, for the primary efficacy endpoint, and for rate of sICH within 24 h, the effect of tenecteplase over alteplase is more favourable as compared with non-filtered set. These endpoints have the following event rates on tenecteplase and alteplase, with RD and 95% CI:

- mRS score 0-1 at Day 90-120: 288/753 (38.2%) vs. 255/719 (35.5%), adjusted RD -2.30% (95% CI: -2.38% to 6.97%)
- Death within 90 days: 105/753 (13.94%) vs. 112/719 (15.58%), unadjusted RD 1.63% (95% CI: -5.26% to 1.99%)
- sICH within 24 h (without imaging): 22/756 (2.91%) vs. 23/724 (3.18%), unadjusted RD -0.27% (95% CI-2.02% to 1.48%)
- Fatal ICH within 7 days: 14/756 (1.9%) vs. 13/724 (1.8%)

14. In the group of patients <50 kg (n=55), who are mostly female (52/55, 95%) and >80 y (36/55, 65%), efficacy of tenecteplase and alteplase is similar. It is difficult to compare between sICH event rate in alteplase vs. tenecteplase due to a very low number of events. In this group of patients, there are more total deaths on tenecteplase compared to alteplase, although specifically the number of deaths due to ICH is higher in the alteplase group, with the number of patients who died in tenecteplase: 1/36, (2.8%) and alteplase: 2/19 (10.5%). This assessment should be taken with caution, due to a low number of events in both tenecteplase and alteplase groups.
15. In the patient group of patients with weight below 50 kg, the 5-step dose adjustment as used in AcT could lead to overdose of tenecteplase, which may lead to a higher rate of sICHs. Therefore, the benefit-risk ratio of administering tenecteplase vs. alteplase or vs. no treatment needs to be gauged against the individual patient risk of developing sICH due to treatment.

In patients with weight below 50 kg, the benefit-risk ratio of administering tenecteplase vs. alteplase together with the 5-step dose administration as used in AcT, needs to be gauged against the individual patient risk of disease being treated.

The incidence of fatal ICH within 7 days for the NIHSS >25, the elderly >80 years and <50 kg body weight subgroups are summarised in Table 4.2.1: 1. Sensitivity analysis of fatal ICH events by Day 7 (excluding patients with NIHSS Ê3) confirmed that the rate of fatal ICH was similar between treatment groups (tenecteplase: 14/672, [2.1%], alteplase: 13/667 [1.9%].

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16 Summary of Efficacy for trial: Act

Title: Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, noninferiority trial		
Study identifier	ClinicalTrials.gov NCT03889249	
Design	A pragmatic, registry linked, prospective, randomized (1:1) controlled, open-label parallel group clinical non-inferiority design with blinded endpoint assessment	
	Duration of main phase:	Single dose administration; evaluation of primary endpoint at D90-120.
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority	
Treatments groups	TNK	Tenecteplase, single-dose, i.v. bolus, number randomized: 816

	ALT		Alteplase, single-dose, i.v. infusion, number randomized: 784
Endpoints and definitions	Primary endpoint	mRS 0-1 D90-120	modified Rankin Score 0-1 (freedom of disability) between 90 and 120 days
	Secondary endpoint	mRS at D90-120	Actual modified Rankin at 90 and 120 days
Database lock	April 21st, 2022		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	TNK	ALT
	Number of subjects	N=802	N=765
	% of subjects who reached the primary endpoint	36.9	34.8
	median mRS at Day 90-120	3	3
	interquartile range	(2-5)	(2-5)
Effect estimate per comparison	Primary endpoint	Comparison groups	TNK vs. ALT
		Difference in proportion (unadjusted)	2.1
		95% CI	-2.6, +6.9
	Secondary endpoint (day 90-120 mRS)	Comparison groups	TNK vs. ALT
		Common odds ratio[1] (adjusted[2])	0.9
		95% CI	(0.8, 1.1)
Notes	[1]) Common odds ratio is the odds ratio for a unit increase in the modified Rankin Score for tenecteplase vs. alteplase [2]) Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time with source registry (QuiCR vs. OPTIMISE) and "site" as a random effects variable.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	modified Per protocol (patients who received the drug, without major protocol violations)		
Descriptive statistics and estimate variability	Treatment group	TNK	ALT
	Number of subjects	N=786	N=751
	% of subjects who reached the primary endpoint	37.3	34.7

Effect estimate per comparison	Primary endpoint	Comparison groups	TNK vs. ALT
		Difference in proportion (unadjusted)	2.6
		95% CI	-2.2, +7.4

Analysis performed across trials (pooled analyses and meta-analysis)

Burgos and Saver (2019) [P19 06342] conducted a meta-analysis of 5 randomised clinical trials (RCT (Haley et al. (2010) [P10 04112], Parsons et al. (2012) [P12 03304], ATTEST [P15 02640], NOR-TEST [P17 08885], and EXTEND-IA TNK [P18 03928]) to compare tenecteplase (n=828) with alteplase 0.9 mg/kg (n=757). This meta-analysis was conducted in accordance with preferred reporting items for systemic reviews and meta-analyses and used the search terms tenecteplase AND alteplase AND AIS in PubMed from Jan 2005 to August 2018. Studies were included if they met the following criteria: RCT; patients enrolled with acute cerebral ischaemia, with brain imaging performed before enrolment to exclude haemorrhage; allocation to tenecteplase vs. active comparator alteplase; and treatment initiated acutely, within 6 h after last known well time.

These trials enrolled a total of 1585 patients. The proportions of patients treated with tenecteplase at 0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg were 6.8%, 24.6%, and 68.6%, respectively. The primary efficacy endpoint analysed was disability-free outcome (mRS 0 1) at 3 months post-stroke.

The mean age was 71 years, 59% of patients were male, mean NIHSS score at baseline was 7, and mean time from last known well to treatment start was 148 min. For the primary endpoint, the 3-month mRS 0-1 rate was 57.9% in the pooled tenecteplase groups (0.1, 0.25 and 0.4 mg/kg) and 55.4% in the alteplase group. The risk difference between the tenecteplase group and the alteplase group from an informal, random effects meta-analysis was 4% (95% CI - 1%, 8%, 5 trials, n=1585). The rate of functional independence (mRS 0 2) at 3 months was 71.9% after tenecteplase and 70.5% after alteplase with a risk difference of 8% (95% CI -4%, 20%; 4 trials, n=1473).

The European Stroke Organisation (ESO) Expedited Recommendation on Tenecteplase for Acute Ischaemic Stroke, based on independent efficacy and safety analysis, were published in early 2023 [P23 01257]. The ESO module working group conducted a study-level random-effects meta-analysis of seven RCTs comparing IVT with tenecteplase 0.25 mg/kg versus IVT with alteplase 0.9 mg/kg, comprising a total of 2,197 AIS patients. Included studies: Act [P22-05053], Extend-IA TNK [P18 03928], Haley et al. (2010) [P10 04112], Parsons et al. (2012) [P12 03304], ATTEST [P15 02640], Taste-A (Bivard et al, 2022) [P22 03386], and Trace 2021 [Li S, Pan Y, Wang Z, et al. Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (TRACE): a multicentre, randomised, open label, blinded-endpoint (PROBE) controlled phase II study]. Stroke Vasc Neurol 2022; 7: 47–53.]. Compared to patients randomised to IVT with alteplase the pooled unadjusted OR for excellent functional outcome in patients randomised to IVT with tenecteplase was 1.17 (95% CI: 0.98–1.39; p = 0.08; I2 = 0%). The corresponding risk difference was 3.68% (95% CI: −0.32% to 7.69%; p = 0.07; I2 = 0%). Therefore, non-inferiority was met for the excellent functional outcome based on the ESO module working group's pre-specified 3% margin. Importantly though, non-inferiority was also met based on the minimum clinically important difference of 1.3% proposed by some module working group members. Similar results were obtained when they conducted a sensitivity analysis for excellent functional outcome after additional inclusion of all patients returning to baseline mRS.

Based on the meta-analysis described above and independent academic clinical research data and real-world clinical experience, ESO:

- Recommend tenecteplase as an effective alternative to alteplase with a similar safety profile for AIS treatment, and suggest tenecteplase over alteplase because of its ease of administration
- Recommend tenecteplase over alteplase for patients with Large Vessel Occlusion (LVO) who are eligible for intravenous thrombolysis
- Suggest tenecteplase over alteplase for patients with AIS of <4.5 h duration and are admitted to a center without capability for mechanical thrombectomy, before rapid transfer to a mechanical thrombectomy-capable center, as well as for patients in mobile stroke units
- Suggest, for wake-up stroke and stroke from unknown onset, tenecteplase 0.25 mg/kg as a reasonable alternative to alteplase only when advanced imaging is available, and recommend against IVT when imaging is by plain computerized tomography (CT) only (following the non-conclusive results of the TWIST study [P22 10196].

Supportive study(ies)

For a brief summary of the main features of the supportive studies see

Table 2,above.

The Extend-IA TNK studies (Part 1 and Part 2), respectively are considered the most relevant supportive studies and are therefore presented first.

EXTEND-IA TNK (Campbell et al., 2018); Reference of publication: [P18 03928];

Title of the study: Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial Using Intravenous Tenecteplase

Objective: The study objective was to test the hypothesis that tenecteplase is non-inferior to alteplase in achieving reperfusion at initial angiogram when administered within 4.5 h of ischemic stroke onset in patients planned to undergo endovascular therapy.

Methods: This was a prospective, randomised, open-label, blinded endpoint (PROBE) design trial involving patients with ischemic stroke within 4.5 hours after onset who had large-vessel occlusion of the internal arotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy.

Study Participants

Main diagnosis for trial entry: Ischaemic stroke with large vessel occlusion

Main criteria for inclusion:

- Patients presenting with acute ischemic stroke eligible using standard criteria to receive IV thrombolysis within 4.5 hours of stroke onset
- Patient's age is ê18 years
- Intra-arterial clot retrieval treatment can commence (arterial puncture) within 6 hours of stroke onset.
- Arterial occlusion on CTA or MRA of the ICA, M1, M2 or basilar artery.

Treatments

Investigational product: Tenecteplase at a dose of 0.25 mg/kg; i.v. bolus over 10 seconds

Comparator product: Alteplase at a dose of 0.9 mg/kg; 10% as i.v. bolus and 90% infusion over 1 hour

Primary outcome:

Proportion of patients with substantial angiographic reperfusion (mTICI) score of 2b/3 (restoration of blood flow to >50% of the affected arterial territory) or absence of retrievable thrombus at initial angiogram. (Time Frame: Initial angiogram [day 0])

Secondary outcomes:

- Proportion of patients with ê8 point reduction in NIHSS or reaching 0-1 at 3 days (favourable clinical response) adjusted for baseline NIHSS and age. (Time Frame: Initial angiogram [day 0])
- Modified Rankin Scale (mRS) at 3 months post stroke, ordinal analysis
- mRS 0-1 or no change from baseline at 3 months post stroke
- mRS 0-2 or no change from baseline at 3 months post stroke
- Proportion of patients with angiographic reperfusion adjusted for hyperdense clot length on non-contrast CT and time from thrombolysis to initial angiogram (up to 24 hours post treatment)
- CT perfusion imaging was performed, but the requirement for mismatch and an ischemic-core volume

of less than 70 ml was removed in a protocol amendment when approximately 80 patients were enrolled.

Safety criteria for evaluation

- Symptomatic intracranial hemorrhage (SICH) within 36 hours post treatment
- Death due to any cause up to 3 months post stroke

Sample size/Numbers analysed

Planned: 120-276; blinded adaptive sample size re-estimation was performed after 100 patients were randomised, final calculated sample size: 202.

Based on recent external information from the most complete meta-analysis available at the time of compiling Version 3 of the study protocol [Goyal ett al., 2016], the estimated angiographic reperfusion following alteplase is 7.5% (95%CI: 4.6%-11.5%). Following this, blinded analysis of trial operational characteristics based on the first 75 patients was performed and the observed proportion of patients with angiographic reperfusion in the total cohort was 16%. The minimum sample size was subsequently re-set to 120 patients (assuming 8% angiographic reperfusion in alteplase arm and 24% angiographic reperfusion in tenecteplase arm and absolute non-inferiority margin of 2.3% that corresponds to preserving at least half of the effect of the conservative lower 95%CI limit for alteplase effect).

Actual study numbers: screened: 204, entered: 202;

TNK - entered/treated/analysed (for primary endpoint): 101 each;

ALT - entered/treated/analysed (for primary endpoint): 101 each.

Randomisation

Patients were randomised to receive either the investigational drug (tenecteplase) or standard care (alteplase) according to a centralised web-based procedure coordinated via the Florey Institute of Neuroscience and Mental Health. The randomization system for investigational product was based on computer generated randomisation code lists (permuted blocks), with stratification for site of baseline arterial occlusion.

Blinding

An open-label treatment, blinded endpoint assessment (PROBE) design was applied

According to the study protocol, all those involved in the subsequent clinical and imaging assessment of outcomes will be blinded to treatment allocation. The Data Safety Monitoring Board (DSMB) will have access to unblinded grouped data. The primary outcome of angiographic reperfusion will be centrally adjudicated by consensus of blinded assessors using the modified Treatment in Cerebral Ischemia (mTICI) scale with mTICI 2b/3 (>50% reperfusion of the affected territory) classified as successful reperfusion due to intravenous thrombolysis. Also, the assessors of the neurological impairment and functional scores were blinded to the treatment group.

Statistical methods

The noninferiority boundary was defined to preserve at least 50% of the most conservative estimate of the reperfusion efficacy of alteplase from the meta-analysis (that estimate being 4.6%). Noninferiority would be established if the lower boundary of the two-sided 95% confidence interval of the difference in the

percentages of patients with substantial reperfusion at the initial angiographic assessment in the tenecteplase group versus the alteplase group was greater than -2.3 percentage points.

The two-sided 95% confidence interval of the incidence difference was estimated by generating incidence differences with corresponding 95% confidence intervals for each of the four strata of patients (those with occlusion of the internal carotid artery, basilar artery, the first segment of the middle cerebral artery, or the second segment of the middle cerebral artery) with subsequent pooling across strata with the use of the Mantel–Haenszel method. If noninferiority was established, superiority of tenecteplase was tested with the use of binary logistic regression, with adjustment for the site of vessel occlusion. Incidence ratios were estimated with the use of modified Poisson regression with robust error estimation, with adjustment for the site of vessel occlusion.
The analysis of the secondary outcome of the modified Rankin scale score was performed with the use of ordinal logistic regression if proportional-odds assumptions were satisfied or, otherwise, with the use of assumption-free ordinal analysis on the full range (0 to 6) of the modified Rankin scale.

The differences in the distributions of the NIHSS scores between the tenecteplase group and the alteplase group at 24 hours and at 72 hours were analyzed with the use of Wilcoxon–Mann–Whitney generalized odds ratios, with stratification according to baseline NIHSS score.

Trial subjects:

From March 2015 through October 2017, 204 patients were enrolled. A total of 101 patients were assigned to receive tenecteplase, 101 were assigned to receive alteplase, and 2 were excluded owing to withdrawal of consent (1 patient) and to withdrawal by the enrolling physician before treatment was commenced because of an error in assessing patient eligibility (1 patient). There were no significant differences in characteristics between the two groups at baseline. The mean age (SD) was 70.4 (15.1) in the tenecteplase group and 71.9 (13.7) in the alteplase group. In the tenecteplase group 57% of patients were male, and in the alteplase group 51% of patients were male. The median NIHSS score (interquartile range, IQR) at baseline was 17 (12-22) in both treatment groups. Median time from stroke onset to initiation of intravenous thrombolysis (IQR) was 125 (102-156) min in the TNK vs. 134 (104-176) min in the ALT group.

Outcomes and estimation

Efficacy results: The primary outcome occurred in 22% of the patients treated with tenecteplase vs 10% of those treated with alteplase (incidence difference, 12%; 95% CI 2, 21; incidence ratio, 2.2; 95% CI 1.1, 4.4; p = 0.002 for non-inferiority; p = 0.03 for superiority). The proportion of mRS 0-1 at 90 d was 51% for tenecteplase group vs 43% for alteplase group (p = 0.23).

Table 17: Ouctomes – Extend-IA TNK trial

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis‡	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06
Excellent outcome — no. (%)§	52 (51)	43 (43)		
Adjusted incidence ratio			1.2 (0.9–1.6)	0.20
Adjusted odds ratio			1.4 (0.8–2.6)	0.23
Early neurologic improvement — no. (%)§¶	72 (71)	69 (68)		
Adjusted incidence ratio			1.0 (0.9–1.2)	0.70
Adjusted odds ratio			1.1 (0.6–2.1)	0.70
Safety outcomes				
Death — no. (%)§	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)§‖	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99
Parenchymal hematoma — no. (%)§**	6 (6)	5 (5)		
Risk ratio			1.2 (0.4–3.8)	0.76
Odds ratio			1.2 (0.4–4.1)	0.76

* Substantial reperfusion was defined as the restoration of blood flow to greater than 50% of the involved territory or no retrievable thrombus at the time of the initial angiographic assessment. The analysis was adjusted for the site-of-vessel occlusion strata. The P value for the difference is for noninferiority, and the P values for the incidence ratio and odds ratio are for superiority.

† Scores on the modified Rankin scale range from 0 (no neurologic deficit) to 6 (death). A functionally independent outcome was defined as a modified Rankin scale score of 0 to 2 or no change from baseline. An excellent outcome was defined as a modified Rankin scale score of 0 or 1 or no change from baseline.

‡ The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed with a common odds ratio from ordinal logistic regression.

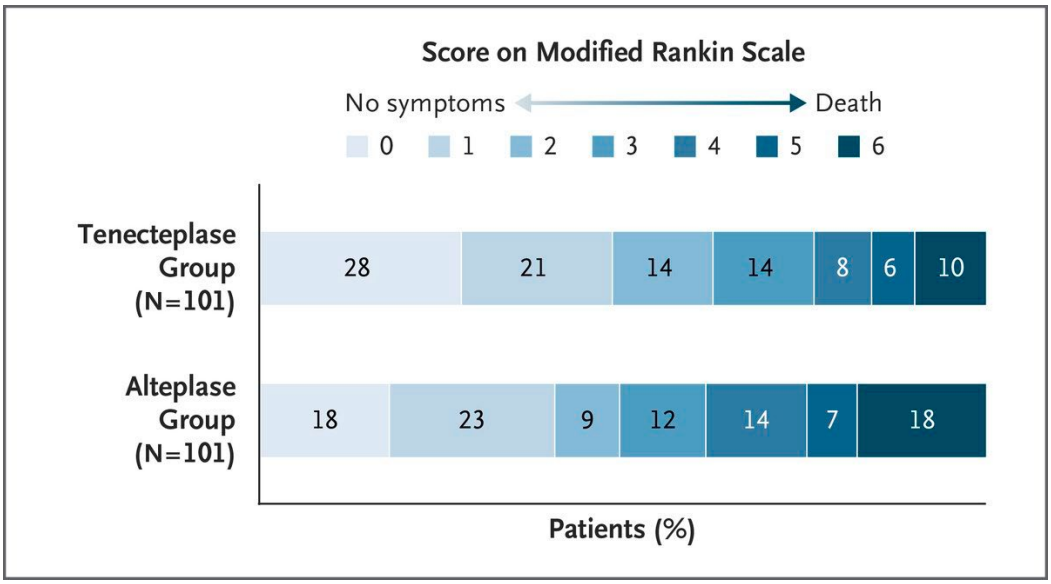
§ The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed as an incidence or risk ratio from Poisson regression and as an odds ratio from logistic regression.

¶ Early neurologic improvement was defined as a reduction of 8 points in the NIHSS score between baseline and 72 hours or as a score of 0 or 1 at 72 hours. An 8-point reduction is considered to be highly clinically significant.

‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of the infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.

** Parenchymal hematoma was defined as intraparenchymal blood clot with mass effect.

Figure 7: Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population – EXTEND-IA TNK



EXTEND-IA TNK Part 2 (Campbell et al., 2020); Reference: [P20 01928]

Title: Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischaemic stroke: the EXTEND-IA TNK part 2 randomised clinical trial

Objective: To determine whether 0.4 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs. 0.25 mg/kg of tenecteplase in patients with large vessel occlusion (LVO) ischaemic stroke.

Methods: Adult patients with ischaemic stroke due to occlusion of the intracranial internal carotid, basilar, or middle cerebral artery were included less than 4.5 h after symptom onset using standard iv thrombolysis eligibility criteria. Patients were randomly assigned (1:1) to receive the tenecteplase 0.25 mg/kg or 0.4 mg/kg. The primary outcome was reperfusion of greater than 50% of the involved ischaemic territory prior to thrombectomy, assessed by consensus of 2 blinded neuroradiologists.

Disposition and demographics: All 300 patients who were randomised (mean age, 72.7 years; 159 [53%] men) completed the trial. Median NIHSS score (IQR) at baseline was 17 (11 21) for tenecteplase0.4 mg/kg group and 16 (9 20) for tenecteplase 0.25mg/kg group.

Efficacy results: The number of participants with more than 50% reperfusion of the previously occluded vascular territory was 29 of 150 (19.3%) in the 0.4 mg/kg group vs 29 of 150 (19.3%) in the 0.25 mg/kg group (unadjusted risk difference, 0.0%[95% CI 8.9%, 8.9%]; adjusted risk ratio (RR), 1.03 [95% CI 0.66, 1.61]; p=0.89). Among the 6 secondary outcomes, there were no significant differences in any of the 4 functional outcomes between the 0.4 mg/kg and 0.25 mg/kg groups nor in all-cause deaths (26 [17%] vs 22 [15%], unadjusted risk difference, 2.7% [95% CI -5.6%, 11.0%]).

Efficacy conclusion: Among patients with LVO ischaemic stroke, a dose of 0.4 mg/kg compared with 0.25 mg/kg of tenecteplase did not significantly improve cerebral reperfusion prior to endovascular thrombectomy.

Other supportive studies:

Haley et al., (2010), Reference: [P10 04112]

Title: Phase IIB/III trial of tenecteplase in AIS: results of a prematurely terminated randomised clinical trial.

Objective: This trial adopted an adaptive sequential design. Phase IIB was to determine a best dose of tenecteplase among 3 doses (0.1, 0.25 and 0.4 mg/kg) and provide evidence for therapeutic potential of tenecteplase vs. alteplase. Phase III was to compare the selected tenecteplase dose to alteplase.

Methods: The trial began as a small, multicentre, randomised, double-blind, controlled clinical trial comparing 0.1, 0.25, and 0.4 mg/kg tenecteplase with standard 0.9 mg/kg alteplase in patients with acute stroke within 3 h of onset. An adaptive sequential design used an early (24 h) assessment of major neurological improvement (MNI, reduction of ê8 in National Institutes of Health Stroke Scale Score [NIHSS] score from baseline or NIHSS=0) balanced against occurrence of symptomatic intracranial haemorrhage (sICH) to choose a "best" dose of tenecteplase to carry forward. Once a "best" dose was established, the trial was to continue until at least 100 pairs of the selected tenecteplase dose vs alteplase patients could be compared by 3 month outcome using the modified Rankin Scale (mRS) in an interim analysis. Decision rules were devised to yield a clear recommendation to either stop for futility or to continue into Phase III. The primary outcome measures for Phase III were the proportion of good outcomes (mRS 0 1) and poor outcomes (mRS 4 6) at the selected dose.

Disposition and demographics: The study was prematurely terminated due to slow enrolment whereas a sample size of 600 patients for the Phase IIB portion was pre-established. A total of 112 patients were enrolled at the time of termination and 110 patients received the assigned medication and dose. According to pre-defined criteria (MNI at 24 h and sICH), the 0.4 mg/kg dose of tenecteplase was discarded as inferior to the leading dose of 0.25 mg/kg when the cumulative score for the 0.4 mg/kg dose fell 6 points behind that for 0.25 mg/kg.

The patients randomised to alteplase were older and had more severe stroke deficits at baseline than patients in the tenecteplase groups. The median (interquartile range [IQR]) of NIHSS score at baseline were 8 (5 11) for 0.1 mg/kg, 10 (6 15) for 0.25 mg/kg, and 9 (5 17) for 0.4 mg/kg of tenecteplase, and 13 (5 17) for alteplase 0.9 mg/kg.

Efficacy results: In terms of good outcome (mRS 0 1), the 0.25 mg/kg tenecteplase group had the highest proportion (15 of 31 [48.4%]), but the 0.1 mg/kg tenecteplase group was similar (14 of 31 [45.2%]). By comparison, the alteplase group had 13 of 31 (41.9%) good outcomes (*Table 18*). In terms of poor outcome (mRS 4 6), the 0.1 mg/kg tenecteplase group had the lowest proportion (7 of 31 [22.6%]), but the alteplase group had 10 of 31 (32.3%) poor outcomes.

Table 18: Comparison of efficacy between different doses of tenecteplase and alteplase

	Tenecteplase 0.1 mg/kg (n=31)	Tenecteplase 0.25 mg/kg (n=31)	Tenecteplase 0.4 mg/kg (n=19)	Alteplase 0.9 mg/kg (n=31)
mRS 0-1 n (%) (95% CI)	14 (45.2) (27.3, 64.0)	15 (48.4) (30.2, 66.9)	7 (36.8) (16.3, 61.6)	13 (41.9) (24.6, 60.9)
mRS 4-6 n (%) (95% CI)	7 (22.6) (9.6, 41.1)	11 (35.5) (19.2, 54.6)	6 (31.6) (12.6, 56.6)	10 (32.3) (16.7, 51.4)

Source: Haley et al. (2010) [P10-04112]

Efficacy conclusion: This prematurely terminated trial demonstrated the potential efficiency of a novel design in selecting a propitious dose for future study of a new thrombolytic agent for acute stroke. Considering the study was not completed, no convincing conclusions can be made about the promise of future study of tenecteplase in acute stroke.

Parsons et al., (2012), Reference: [P12 03304]

Title: A randomised trial of tenecteplase versus alteplase for AIS

Objective: To compare the standard dose of alteplase (0.9 mg/kg) with two different doses (0.1 mg/kg and 0.25 mg/kg) of tenecteplase to plan the design and dose of a proceeding Phase III clinical trial.

Methods: This trial randomly assigned 75 patients to receive alteplase (0.9 mg/kg) or tenecteplase (0.1 or 0.25 mg/kg) less than 6 h after the onset of ischaemic stroke. The eligibility criteria were a perfusion lesion at least 20% greater than the infarct core on computed tomographic (CT) perfusion imaging at baseline and an associated vessel occlusion on CT angiography. The co-primary endpoints were the proportion of the perfusion lesion that was reperfused at 24 h on perfusion-weighted magnetic resonance imaging and the extent of clinical improvement at 24 h as assessed on the NIHSS. Secondary imaging efficacy outcomes were the extent of infarct growth at 24 h and at 90 days (d) and vessel recanalization at 24 h. Secondary clinical efficacy outcomes were MNI at 24 h (reduction of ệ8 in NIHSS score from baseline), excellent recovery at 90 d (mRS 0-1), and excellent or good recovery at 90 d (mRS 0 2).

Disposition and demographics: The three treatment groups each comprised 25 patients. The mean (standard deviation [SD]) NIHSS score at baseline for all patients was 14.4 (2.6), and the time to treatment was 2.9 (0.8) h.

Efficacy results: Compared with the alteplase group (n=25), the two tenecteplase groups (n=50) had greater proportion (%) of reperfusion lesion at 24 h (tenecteplase 79.3 ± 28.8 vs. alteplase 55.4 ± 38.7; p=0.004) and greater clinical improvement in NIHSS score between baseline and 24 h (8.0 ± 5.5 vs 3.0 ± 6.3; P<0.001). A higher proportion of patients had an excellent or good recovery (mRS score 0 2) at 90 d in the two tenecteplase groups than in the alteplase group (72% vs. 44%, p = 0.02). The 0.25 mg/kg tenecteplase was superior to the 0.1 mg/kg tenecteplase and to alteplase (p<0.05) for all efficacy outcomes.

Efficacy conclusion: Tenecteplase was associated with significantly better reperfusion and clinical outcomes than alteplase in patients with stroke who were selected on the basis of CT perfusion imaging. The higher dose of tenecteplase (0.25 mg/kg) was superior to the lower dose (0.1 mg/kg) and to alteplase for all efficacy outcomes. The differences on all efficacy outcomes between the 0.25 mg/kg tenecteplase group and the alteplase group were statistically significant.

ATTEST (Huang et al., 2015), Reference: [P15 02640]

Title: Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study

Objective: To assess the efficacy and safety of tenecteplase vs. alteplase within 4.5 h of stroke onset in a population not selected on the basis of advanced neuroimaging, and to use imaging biomarkers to help design Phase III clinical trial.

Methods: Adults with supratentorial ischaemic stroke eligible for iv thrombolysis within 4.5 h of onset were recruited in the study. Patients were randomly assigned (1:1) to receive tenecteplase 0.25 mg/kg or alteplase 0.9 mg/kg. Imaging comprised baseline CT, CT perfusion, and CT angiography; and CT plus CT angiography at 24 48 h. The primary endpoint was percentage of penumbra salvaged (CT perfusion-defined penumbra volume at baseline minus CT infarct volume at 24 48 h).

Disposition and demographics: A total of 104 patients were enrolled, of which 52 were assigned to the alteplase group and 52 to tenecteplase group. The data of 71 patients (35 assigned tenecteplase and 36 assigned alteplase) contributed to the analysis of the primary endpoint. Groups were well-balanced for clinical baseline characteristics and comorbidities, had moderate stroke severity (median NIHSS 11 12), and had similar onset-to-treatment time at slightly longer than 3 h. Participants randomly assigned to tenecteplase had a larger median core volume, and a higher proportion within this group had large artery occlusion (defined as complete absence of flow; internal carotid artery or proximal middle cerebral artery

occlusion in 26 [75%] of 35 patients given tenecteplase vs. 23 [61%] of 38 patients given alteplase) on baseline CT angiography, although these potential differences were not statistically significant.

Efficacy results: No significant difference between the two treatment groups was noted for percentage of penumbral salvaged (68% [SD 28] for the tenecteplase group vs 68% [SD 23] for the alteplase group; mean difference (95% confidence interval [CI]) 1.3% (-9.6, 12.1); p = 0.81). No statistically significant differences were noted for any secondary endpoints, either for imaging or for clinical outcomes. *Table 19* provides the efficacy outcomes of the tenecteplase and alteplase group.

Table 19: Efficacy outcomes of the tenecteplase and alteplase groups in the perprotocol analysis

	Tenecteplase 0.25 mg/kg (n=47)	Alteplase 0.9 mg/kg (n=49)	p-value[1]	Mean difference (95% CI)	OR (95% CI)
Primary outcome					
Percentage penumbral salvaged at 24-48 h, mean (SD)	68 (28)	68 (23)	0.81	1.3 (-9.6, 12.1)	-
Secondary imaging outcomes					
Co-registered final infarct volume at 24-48 h (mL)[2], mean (SD)	50 (62)	47 (62)	1.00	0.1 (-19.4, 19.6)	-
Total infarct volume at 24-48 h (mL)[3], mean (SD)	75 (101)	66 (91)	0.75	5.0 (-25.6, 35.4)	-
Recanalization at 24-48 h[4], n/N (%)	21/32 (66)	26/35 (74)	0.38	-	0.6 (0.2, 1.8)
Secondary clinical outcomes					
Early neurological improvement at 24 h[5], n (%)	19 (40)	12 (24)	0.10	-	2.1 (0.9, 5.2)
Improvement in NIHSS between baseline and 24 h mRS at 30 d, n (%)	3 (6)	2 (6)	0.74	-0.4 (-3.1, 2.2)	-
0 – 1	7 (15)	7 (15)	0.89	-	1.1 (0.3, 3.5)
2 – 3	20 (43)	21 (44)	-	-	-
4 – 5	15 (32)	14 (29)	-	-	-
6	5 (11)	6 (13)	-	-	-
mRS 0-1 at 90 d, n (%)	13 (28)	10 (20)	0.28	-	1.8 (0.6, 5.5)
D at home by 90 d, mean (SD)	45 (39)	50 (36)	0.64	-3.1 (-15.8, 9.7)	-
Mortality at 90 d, n (%)	8 (17)	6 (12)	0.51	-	1.3 (0.4, -3.7)

[1]Calculated from linear or logistic regression models that adjust for stratification variables and are a test for difference between groups.

[2]Infarct volume measured on 24-48 h CT slices co-registered to baseline CT perfusion.

[3]Total infarct volume measured on follow-up CT at 24-48 h.

[4]Thrombolysis in myocardial infarction grade 2-3. Percentages were derived from the number of participants with an occlusion.

[5]NIHSS reduction ≥8 points or 24-48 h NIHSS 0-1.

Source: ATTEST [P15-02640]

Efficacy conclusion: Neurological and radiological outcomes did not differ between the tenecteplase and alteplase groups.

NOR-TEST (Logallo et al., 2017); Reference: [P17 08885]

Title: Tenecteplase versus alteplase for management of AIS (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial

Objective: To investigate the safety and efficacy of tenecteplase vs. alteplase in patients with acute stroke who were eligible for iv thrombolysis.

Methods: This trial enrolled adults with suspected AIS who were eligible for thrombolysis and admitted within 4.5 h of symptom onset or within 4.5 h of awakening with symptoms, or who were eligible for bridging therapy before thrombectomy. Patients were randomly assigned (1:1) to receive tenecteplase 0.4 mg/kg or alteplase 0.9 mg/kg. The primary outcome was excellent functional outcome defined as mRS

score 0 1 at 3 months. The secondary efficacy outcomes were MNI at 24 h measured with NIHSS, ordinal shift analysis of mRS at 3 months.

Disposition and demographics: 1100 patients were randomly assigned to the tenecteplase (n=549) or alteplase (n=551) groups. The median age of participants was 77 years (IQR 64 79) and the median NIHSS score at baseline was 4 points (IQR 2 8). A final diagnosis other than ischaemic stroke or transient ischaemic attack was found in 99 (18%) patients in the tenecteplase group and 91 (17%) patients in the alteplase group.

Efficacy results: In this population presenting with mild stroke (median NIHSS =4) within 4.5 h from onset, in the intention-to-treat (ITT) analysis, 354 (64%) of 549 patients in the tenecteplase group and 345 (63%) of 551 patients in the alteplase group achieved the primary outcome of mRS score 0-1 points at 3 months (odds ratio [OR] 1.08; 95% CI 0.84, 1.38; p=0.52). There was no difference in MNI at 24 h or ordinal shift analysis at 3 months. The per-protocol analysis results are consistent with ITT analysis results in primary and all secondary efficacy endpoints, including MNI at 24 h and ordinal shift analysis of mRS at 3 months.

Efficacy conclusion: Tenecteplase was not superior to alteplase in the treatment of AIS.

NOR-TEST 2 Part A (Kvistad et al., 2022); Reference: [P22 03558]

Title: Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial

Objective: The aim of NOR-TEST 2 was to establish the non-inferiority of tenecteplase 0.4 mg/kg to alteplase 0.9 mg/kg for patients with moderate or severe ischaemic stroke.

Methods: This Phase III, randomised, open-label, blinded endpoint, non-inferiority trial was performed at 11 hospitals with stroke units in Norway. Patients with suspected acute ischaemic stroke with a National Institutes of Health Stroke Scale score of 6 or more who were eligible for thrombolysis and admitted within 4.5 h of symptom onset were consecutively included. Random assignment, done by a computer with a block size of 4 and with allocations placed into opaque envelopes to be opened consecutively, was 1:1 between intravenous tenecteplase (0.4 mg/kg) or standard dose alteplase (0.9 mg/kg). Doctors and nurses providing acute care were not masked to treatment, but primary outcome assessment at 3 months was masked. The primary outcome was favourable functional outcome defined as a modified Rankin Scale score of 0–1 at 3 months, assessed in the modified intention-to-treat analysis (excluding patients who did not qualify for thrombolysis after randomisation or who withdrew informed consent). The noninferiority margin was 3%. This trial (NOR-TEST 2) is registered with EudraCT (number 2018–003090–95) and ClinicalTrials.gov (NCT03854500). The trial was stopped early for safety reasons and is designated part A for analysis. Part B is ongoing with a lower dose of tenecteplase (0.25 mg/kg).

Disposition and demographics: Between Oct 28, 2019, and Sept 26, 2021, 216 patients were enrolled. Patient enrolment was stopped after a per-protocol safety review showed an imbalance in the rates of symptomatic intracranial haemorrhage between the treatment groups, which surpassed the prespecified criteria for stopping the trial. After analysis, the independent data safety monitoring committee could not identify specific subgroups with a marked increased bleeding risk within the study population. Therefore, the first part of the trial was ended as part A. Of 204 patients entering the modified intention-to-treat analysis, 100 were randomly allocated tenecteplase and 104 were allocated alteplase. All patients were followed up within 14 days of the end of the 3 months' follow-up period. On univariate analysis, patients in the tenecteplase group were noted to be older than patients in the alteplase group, and less frequently had an mRS score of 0 on admission. Moreover, a higher proportion of patients in the tenecteplase group ended up with a final diagnosis of ischaemic stroke, whereas a lower proportion were diagnosed with stroke mimics compared with the alteplase group. Other baseline characteristics did not differ significantly between the treatment groups on univariate analysis, including rates of stroke risk factors, intracranial occlusions, endovascular treatment, admission stroke severity, and stroke causes using Trial of ORG

10172 in Acute Stroke Treatment classifications, except for a higher rate of large vessel disease in patients receiving tenecteplase.

Efficacy results: A favourable functional outcome was reported less frequently in patients receiving tenecteplase (31 [32%] of 96 patients) compared with alteplase (52 [51%] of 101 patients; unadjusted OR 0.45 [95% CI 0.25–0.80]; p = 0.0064). Major neurological improvement at 24 h was noted in 53 (58%) of 91 patients in the tenecteplase group compared with 73 (74%) of 98 patients in the alteplase group (unadjusted OR 0.48 [95% CI 0.26 0.88]; p = 0.018). At 3 months, a poor functional outcome was noted in 17 (18%) of 96 patients in the tenecteplase group compared with six (6%) of 101 patients in the alteplase group (unadjusted OR 3.41 [95% CI 1.28–9.05]; p = 0.010). When adjusted for differences in age, pre-stroke mRS score, and proportion of stroke mimics, the ordinal shift analysis of mRS score showed a poorer functional outcome for tenecteplase at 3 months compared with alteplase (adjusted OR 2.01 [95% CI 1.20–3.38]; p = 0.0081).

Efficacy conclusion: This study did not show non-inferiority of 0.4 mg/kg tenecteplase to a standard dose of alteplase in moderate or severe ischaemic stroke. In the modified intention-to-treat population, favourable functional outcome at 3 months occurred less frequently in patients allocated tenecteplase compared with those allocated alteplase. In the per-protocol analysis, fewer patients administered tenecteplase had a favourable outcome and major neurological improvement, compared with those who received alteplase. The findings of NOR-TEST 2 part A (0.4 mg/kg tenecteplase) and those of EXTEND-IA TNK part 2 (0.25 mg/kg vs 0.4 mg/kg tenecteplase) suggest that 0.25 mg/kg could be the dose of choice for tenecteplase in ischaemic stroke.

Additional supportive data from real word evidence (RWE) studies

The findings from RCT and the available recommendations have generated a tenecteplase off-label use in AIS, and have been reported and published in several prospective and retrospective cohorts (listed below), showing a similar or favourable safety and effectiveness profile of tenecteplase in comparison with intravenous alteplase. Studies comparing tenecteplase (0.25 mg/kg) versus alteplase (0.9 mg/kg) within 4.5 h that included at least 100 patients treated with tenecteplase, and reported adjusted (or propensity score matched) estimates are: Tsivgoulis et al. [P22-04770], Warach et al. [P22-07546], Gerschenfeld et al. [P22-05938], and Zhong et al. [P21-01816] (*Table 20*).

Table 20: Key observational studies on treatment of AIS (within 4.5 h of stroke onset) with adjusted analyses comparing tenecteplase (0.25 mg/kg) versus alteplase (0.9 mg/kg) with at least 100 tenecteplase patients

Study (Journal)	Patients (Country, n) / product type	Safety outcomes**	Functional outcomes**	Limitations
Tsivgoulis *et al.*, 2022 *(Annals of Neurology)* [P22-04770]	Several SITS-ISTR countries* 331 TNK/797 ALT BI Metalyse/Actilyse (apart from 44 patients from India who used a local tenecteplase bio-copy)	•**sICH**: OR 0.72 95% CI = 0.20–2.64 •**All-cause mortality at 3 months**: OR 0.43 95% CI = 0.27–0.67	•**mRS distribution (3-mon functional outcomes)**: OR 1.54, 95% CI = 1.18–2.00 •**Good functional outcomes (3-month mRS ⩽ 2)**: OR 2.00, 95% CI = 1.45–2.77 •**Excellent functional outcomes (3-month mRS ⩽ 1)**: OR 1.31, 95% CI = 0.96–1.78	•Potential slight imbalance in patient characteristics between tenecteplase and alteplase patient groups after propensity score matching.
Warach *et al.*, 2022 *(Stroke)* [P22-07546]	US 234 TNK/354 ALT Genentech's TNKase/Activase	•**Unfavourable Outcome** (sICH, in-hospital mortality, or discharge to hospice): adjusted OR 0.77 (0.42-1.37)	•**Favourable Outcome** (discharge to home with independent ambulation): adjusted OR 1.26 (0.89–1.80) **Management times:** •**door-to-needle time within 45 min**: adjusted OR 1.85 (1.27–2.71); P=0.001 (favourable for TNK) Among transferred patients •**door-in-door-out time within 1.5h (%)**: adjusted OR 3.62 (1.30–10.74); P=0.02 (favourable for TNK)	•The study investigated short term outcomes, and no 3-month outcomes were explored.
Gerschenfeld *et al.*, 2022 *(European Stroke Journal)* [P22-05938]	France 408 TNK/387 ALT BI Metalyse/Actilyse	•**PH rate**: adjusted OR 0.68, 95% CI 0.41–1.12, (p= 0.13)	•**3-month functional independence**: adjusted OR 1.68, 95% CI 1.15–2.48; p<0.01).	•The study compared process times, sICH rate, and 3-month mortality between tenecteplase patients and alteplase patients; however, no statistical adjustment was performed.

Zhong *et al*., 2021 *(Stroke)* [P21-01816]	New Zealand 165 TNK/254 ALT BI Metalyse/Actilyse	•**sCIH**: adjusted OR 0.62 (95% CI, 0.14–2.80) p = 0.53	•**90-day functional Independence**: adjusted OR 1.20 [95% CI, 0.74–1.95] p=0.46	•Tenecteplase patients and alteplase patients were treated at different centres. •The study compared process times and angioedema between tenecteplase patients and alteplase patients; however, no statistical adjustment was performed. •The analysis was not adjusted for sex, baseline mRS, and baseline glucose.

Additional RWE studies [P19-10136, P19-09894, P21-00428, P21-07525, P21-10587, P22-08570, P21-08380, P21-00844, P22-10215, P22-07879, P22-07542, P22-09324, P22- 02530, P22-07530, P22-06759, P23-00846, P23-01373, P22-09871, P23-02629, P23-03741, P23-04061] have been conducted, six of which have been included in a systematic review and meta-analysis [Katsanos et al., 2022; P22-02530]. The authors conclude that this meta-analysis provides supporting evidence from nonrandomized studies with 0.25 mg/kg tenecteplase that treatment for AIS is at least as safe and effective as alteplase under actual use conditions.

The observational studies mentioned above included several thousands of AIS patients and reported an overall consistent similar or favourable safety and effectiveness profile of tenecteplase in comparison with intravenous alteplase. The listed RWE studies have not evaluated elderly subgroups separately.

2.5.3. Discussion on clinical efficacy

The evidence of efficacy of 0.25 mg/kg TNK for i.v. thrombolysis in AIS within an onset to treatment time of 4.5 h is mainly based on 8 investigator initiated trials, one of which, the AcT trial serves as the main study. The MAH has established a specific data access and exchange agreement with the sponsors of the AcT trial and has reanalysed the data independently and provided additional exploratory analyses which overall support the robustness of the protocol defined study results. The Applicant has stated to have received and analysed the data from the EXTEND trials and that the numbers in the manuscript were reproducible. Clinical study reports have been submitted for the AcT trial as well as for the main supportive trial, the Extend-IA TNK trial. Further, the Applicant has performed an onsite audit of the AcT trial (as well as a remote audit of the Extend-IA TNK trial) providing additional reassurance of credibility of the study data.

The AcT trial was a pragmatic, registry linked, prospective, randomized (1:1) controlled, open-label parallel group non-inferiority clinical trial with blinded endpoint assessment. The PROBE (Prospective randomized open blinded endpoint) design in the AcT trial is considered acceptable, taking the time-sensitive indication and infusion over one hour in the comparator group compared to bolus i.v. injection of TNK into consideration. Further, expedient measures were taken in the AcT study in order to ascertain blinding of the outcome assessors. The AcT trial was performed in 22 study sites in Canada and included AIS patients as per the Canadian Stroke Best Practice Recommendations, i.e. all patients with AIS eligible to receive the approved thrombolysis with ALT as per standard of care (with or without additional mechanical thrombectomy [MT]) were eligible for treatment. The Applicant has provided sufficient justification for the generalisability of the study data to a European population based on similarity of the Canadian and European treatment guidelines for stroke, supported by additional exploratory analyses based on an EU-SmPC filtered population, i.e. excluding patients with NIHSS > 25 and OTT > 4.5 h in line with the SmPC of Actilyse. The posology used in the AcT trial (i.e. 25 mg/kg in 5 dose tiers) was fully in line with the TNK posology proposed in the SmPC for the AIS indication, ALT was dosed according to the approved standard dose. Moreover, patients below 18 years have not been included in the AcT trial and the proposed indication of Metalyse in AIS patients is restricted to adult patients, which is endorsed. Baseline characteristics were generally balanced across treatment groups. In the primary analysis of the primary endpoint 36.9% (296/802) TNK patients and 34.8% (266/765) ALT patients had an mRS of 0-1 at day 90–120. However, the primary analysis was not pre-specified with respect to the confidence interval to be used for difference in proportion. A number of different methods to derive a confidence interval for a difference in proportion are available. Hence, post-hoc selection of the method is not considered to be a valid procedure. Due to the large sample size, however, results of the different methods may be similar. The Applicant should specify the method that was actually used and provide confidence intervals according to the different possible options. As a guide to which options are to be used the Applicant should refer to Newcombe RG (1998): Interval estimation for the difference between

independent proportions: comparison of eleven methods. StatMed 17, 873-890. The estimate for the unadjusted difference in proportion was 2.1 (95% CI: -2.6, +6.9) (ITT population). The pre-specified non-inferiority margin of 5% was met. However, as discussed in detail in the Ancillary analyses of the main study, exploratory analyses of the AcT trial, question E2, a smaller non-inferiority margin within the range of 2-3% is considered more appropriate. The Applicant's argumentation for applying a population adjusted non-inferiority margin based on the large imbalance of the AcT study compared to the Emberson meta-analysis population regarding treatment within the early time window (0-3 hr) could be accepted, resulting in a NI-margin of 2.6%, as this is still below the NI-margin of 3% recommended by the ESO experts. In the exploratory analyses based on a modified PP population as well as a modified ITT population (i.e. the respective population that actually received study treatment), the lower bound of the 95% CI was even more favourable (mPP: -2.2; mITT: -2.5). None of the secondary outcomes raises concerns regarding a worse efficacy of TNK vs. ALT. Overall, the results of the AcT trial indicate non-inferiority of 25 mg/kg TNK compared to ALT within 4.5 h in patients eligible for i.v. thrombolysis. Of note that the timelines of the AcT study could not clearly be followed. However, the Applicant has clarified the correct data cutoff date and provided an overview of relevant trial events for the AcT trial. Therefore, the issue is considered resolved.

The Extend-IA TNK and the Extend-IA TNK Part 2 study evaluated TNK in a subset of AIS patients eligible for thrombolysis, i.e. patients with large vessel occlusion (LVO) scheduled for mechanical thrombectomy. As the investigators expected the effect of mechanical thrombectomy on the clinical outcome to obscure any potential difference between TNK and ALT, the primary endpoint was based on early reperfusion (before mechanical thrombectomy) in these studies. In the Extend-IA TNK study, 0.25 mg/kg TNK was non-inferior to a standard dose of ALT within 4.5 hours of AIS in patients scheduled for mechanical thrombectomy in restoring perfusion (reperfusion of > 50% or absence of retrievable thrombus) in the involved ischaemic territory with 22% TNK vs. 10% ALT patients reaching the primary outcome (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI 1.1, 4.4). In this non-inferiority study, sequential testing of superiority after testing of non-inferiority was planned and superiority was declared, as the lower end of the 95% CI was > 0. Patients in the TNK group had nominally statistically significantly better functional outcomes than those in the ALT group in an ordinal analysis of the modified Rankin scale scores at day 90, but there was no significant difference in the incidence of recovery to independent function (modified Rankin scale score of 0 to 2 or no change from baseline function) at day 90, which occurred in 64% TNK patients vs. 51% ALT patients (adjusted incidence ratio, 1.2; 95% CI, 1.0 to 1.5; P=0.06; adjusted odds ratio, 1.8; 95% CI, 1.0 to 3.4; P=0.06). There were also no significant differences in the incidence of early neurologic improvement at 72 hours. Baseline demographics and disease characteristics were generally balanced across groups. However, the median onset-to-thrombolysis-treatment time was 9 min shorter in the TNK vs. ALT group. In addition, the somewhat lower proportion of females and slightly lower age might have favoured the TNK group compared to the ALT group.

The EXTEND-IA TNK study is considered to provide relevant evidence of at least non-inferior efficacy of 0.25 mg/kg TNK vs. ALT within 4.5 h in AIS patients eligible to mechanical thrombectomy.

In the Extend-IA TNK Part 2 study (Campbell, 2020), 0.4 mg/kg TNK did not show any relevant improvement in efficacy vs. 0.25 mg/kg TNK, with very similar results regarding the primary endpoint.

From the 5 other supportive studies, in particular the study published by Parsons 2012 provides some supportive evidence of efficacy of 0.25 mg/kg. The study results are indicative of an improved efficacy of 0.25 mg/kg TNK vs. 0.1 mg/kg TNK (with no additional bleeding risk) as well as of an improved efficacy of 0.25 mg TNK vs. ALT. However, this was a small study (including 25 patients per treatment group), the patient population was selected to most likely benefit from thrombolytic therapy (based on CT perfusion imaging) limiting generalisability of results, and the Co-primary endpoint addressed early re-

perfusion as well as early clinical improvement (based on change in NIHSS at 24 hrs). Nevertheless, at three months 72% of patients in the 0.25 mg/kg TNK group had an excellent recovery (mRS 0-1 according to the submitted online supplement to this publication), as compared with 40% of those in the ALT group (P = 0.02).

The Nor-Test study (Logallo et al, 2017) evaluated only the 0.4 mg/kg dose of TNK vs. 0.9 mg/kg ALT within 4.5 h of AIS onset in patients eligible for thrombolysis. The study included 1100 patients with mild stroke (median baseline NIHSS: 4, IQR 2-8). The study was designed as a superiority study, which however was not shown for the higher than now proposed TNK dose, rather similar efficacy and safety results in the evaluated population. Nor-Test 2 Part A study (Kvistad, 2022) designed as a non-inferiority trial evaluating only 0.4 mg/kg TNK vs. a standard dose of ALT in moderate to severe AIS was stopped early for safety reasons. Also, the contribution of the other studies is rather limited due to methodological issues (Attest study, Huang et al. 2015) and early termination due to recruitment problems (Haley, 2010), respectively.

The meta-analysis of 5 supporting RCTs by Burgos and Saver (2019) generally supports non-inferiority of TNK vs. the standard dose of ALT for i.v. thrombolysis in AIS with regard to D90 mRS of 0-1, even if a very strict NI-margin of 1.3% was applied to the primary endpoint (mRS 0-1 at Day90). However, there were methodological issues, in particular inclusion of different TNK doses in this meta-analysis with 68.6% TNK patients receiving a higher than now intended dose (exceeding the intended 0.25 mg/kg dose). Nevertheless, the recent meta-analysis of seven available RCTs performed by ESO (Alamowitch, 2023) supports non-inferiority of 0.25 mg/kg dose of TNK vs. ALT with regard to Day 90 mRS 0-1 based on the pre-specified 3% NI margin (and with regard to the primary analysis also based on the very stringent 1.3% NI-margin). It is noted that one of the studies (TRACE, 2021), included in the meta-analysis performed by the ESO (Alamowitch, 2023) was performed with a medicinal product that has not been proven to be biosimilar with Metalyse. Excluding this study, the pooled risk difference for mRS 0-1 at 90 days in patients with AIS of <4.5 h duration treated with TNK 0.25 mg/kg vs. a standard dose of ALT was 4.72% with a lower bound of the 95% CI of – 0.64, still meeting the NI criteria applied to the ESO meta-analyses. These data are not verifiable, as they are based on unpublished data. Nevertheless, taking into consideration that the results of the TRACE trial were not more favourable than the results of the original meta-analysis, it is plausible, that exclusion of the TRACE study did not negatively impact the results.

The findings from RCT and the available recommendations have led to tenecteplase off-label use in AIS, and have been reported and published in several prospective and retrospective observational cohorts. The informational value of these studies are clearly limited with regard to evidence of efficacy, nevertheless, taken together, the reported results are generally compatible with at least comparable efficacy of TNK vs. ALT under actual use conditions.

Dose:

The TNK posology proposed for AIS is fully in line with the regimen used in the pivotal AcT trial, i.e. 0.25 mg/kg given in 5 dose tiers and is endorsed. There is no substantial evidence of an increased efficacy of the 0.4 mg/kg compared to the 0.25 mg/kg dose, whereas the Parsons study (2012) indicated superior efficacy of the 0.25 mg/kg vs. 0.1 mg/kg dose of TNK.

Subgroups:

In the pivotal study, the results of the primary outcome were generally consistent across subgoups. Nevertheless, the favourable results of the Extend-IA TNK including patients with large vessel occlusion (LVO) was well as of the small Parsons (2012) study (evaluating patients with penumbra) may indicate, that imaging selected AIS patients are highly responsive to TNK.

2.5.4. Conclusions on the clinical efficacy

The provided clinical studies and exploratory analyses seem to support, that TNK at the 0.25 mg dose has a non-inferior efficacy within the 4.5 time window in AIS patients eligible for thrombolysis compared to the approved ALT treatment (0.9 mg/kg).

2.6. Clinical safety

Introduction

Tenecteplase (TNK) is approved in the EU since February 2001 in adults for the thrombolytic treatment of suspected myocardial infarction with persistent ST elevation or recent left Bundle Branch Block within 6 hours after the onset of acute myocardial infarction (AMI) symptoms.

In the established STEMI indication, the most frequent adverse reaction of TNK is haemorrhage, which occurs very commonly. The type of haemorrhage is predominantly superficial at the injection site. However, serious bleeding episodes may occur (including intracranial bleeding), that can lead to permanent disability or death. Anaphylactoid reaction has also been associated with TNK and rarely been reported. TNK is applied as a single intravenous bolus dose, however the dose established for STEMI is twice as high as the dose proposed for the now sought AIS indication.

The submitted Summary of Clinical Safety (SCS) of TNK for the treatment of AIS is mainly based on data from 12 completed, investigator-initiated studies (IIS) and two meta-analyses (Burgos and Saver, 2019 [P19-06342] and Rose et al., 2023 [P23-02260]).

Patient exposure

A total of 2,244 patients with AIS were exposed to a single intravenous dose of TNK across all 12 IIS, with 1,184 patients with AIS exposed to TNK 0.25 mg/kg, the intended dose.

Table 21: Exposure to TNK in AIS

Study	Tenecteplase single iv bolus dose (mg/kg)				
	0.1	0.2	0.25	0.4	0.5
Haley *et al.* (2005) [P05-02918]	25	25	-	25	13
Molina *et al.* (2008) [P08-04525]	-	-	-	42	-
Parsons *et al.* (2009) [P09-03649]	15	-	-	-	-
Haley *et al.* (2010) [P10-04112]	31	-	31	19	-
Parsons *et al.* (2012) [P12-03304]	25	-	25	-	-
TEMPO-1 [P15-01653]	25	-	25	-	-
ATTEST [P15-02640]	-	-	52	-	-
NOR-TEST [P17-08885]	-	-	-	549	-
EXTEND-IA TNK [P18-03928]	-	-	101	-	-
EXTEND-IA TNK Part 2 [P20-01928]	-	-	150	150	-
NOR-TEST 2 Part A [P22-03558]	-	-	-	100	-
AcT [P22-05053]	-	-	800	-	-
Sum	121	25	1184	885	13

For a tabulated summary of the 12 IIS included in the safety evaluation see **Error! Reference source not found.** of this Report.

Safety findings from individual studies

Main study: AcT (Menon et al., 2022), Reference: [P22-05053]:

The AcT study serves as the main study for this Application, and evaluated 25 mg/kg TNK in 5 dose given as i.v. bolus injection vs. 0.9 mg/kg ALT in AIS patients eligible for i.v. thrombolysis within 4.5 h OTT.

Safety criteria for evaluation

• All-cause mortality (Death) after 90 days [evaluated between day 90-120; median follow-up was 97 days]

• Number of Patients Diagnosed with a Symptomatic intracranial haemorrhage (sICH) post-acute stroke treatment by CT/MRI;

AcT defines sICH as intracerebral hemorrhage that in the opinion of the investigator is temporally related to and directly responsible for worsening of the neurological condition.

Time Frame: 24 hours days from Baseline-[Randomization]);

According to the study report, all imaging was assessed with standardized case-report forms by trained raters blinded to all clinical data and treatment allocation in a central imaging core lab at the University of Calgary. Available 24-hour imaging, acquired as per standard of care, was assessed for any intracranial hemorrhage, and classified using the Heidelberg classification.

Symptomatic ICH was defined as any intracerebral hemorrhage that was temporally related to, and directly responsible for, worsening of the patient's neurological condition and in the investigator's opinion was the most important factor for the neurological worsening.

Applicant's position regarding the validity of the Heidelberg classification for imaging identified ICH in the AcT trial:

• The Heidelberg classification for imaging identified ICH has been developed to improve the evaluation of this important safety endpoint in AIS clinical trials [P15-09432][P23-04145].

• The Heidelberg classification is currently commonly used in AIS clinical trials in addition to other ICH classifications (e.g. ECASS-3, SITS-MOST) and has helped to achieve a more meaningful evaluation of bleeds on imaging.

These classifications may be seen as complementary to assess the bleedings on stroke imaging in AIS trials of fibrinolysis and/or mechanical thrombectomy. The AcT trial used a pragmatic definition of sICH similar to the one used in the NINDS trials [P95-4908]. The consistency of the results of the AcT re-analyses performed using 3 different definitions associated with the Heidelberg definition support the validity of sICH results of the AcT study.

Adverse events of special interest were symptomatic intracerebral hemorrhage (sICH), any orolingual angioedema, and any extracranial bleeding requiring blood transfusion all occurring within 24 hours of thrombolysis administration.

The Safety population of the AcT study included 1563 patients who were randomized and received tenecteplase (n=800) or alteplase (n=763).

There were no meaningful differences in the rate of 24-hour symptomatic intracerebral hemorrhage or mortality (90-day and overall). Orolingual angioedema and peripheral bleeding requiring blood transfusion were rare and not different between groups. No significant differences were noted for any intracranial hemorrhage types on follow-up imaging.

The Safety outcomes of the AcT trial are summarised in the following (as presented in the submitted Clincial study report).

Table 22 Safety outcomes in patients who received at least some dose of either thrombolytic agent and reported "as treated".

	Tenecteplase group (N=800)	Alteplase group (N=763)	Risk Difference (95% C
Death - All (n=1554)	122/796 (15.3)	117/758 (15.4)	-0.1 (-3.7, +3.5)
Death within 90 days (n=1554)	112/796 (14.1)	110/758 (14.5)	0.0 (-3.9, +3.0)
Symptomatic intracerebral haemorrhage	27/800 (3.4)	24/763 (3.2)	0.2 (-1.5, +2.0)
Extracranial bleeding requiring blood transfusions	6/800 (0.8)	6/763 (0.8)	0.0 (-0.9, +0.8)
Orolingual angioedema	9/800 (1.1)	8/763 (1.1)	-0.1 (-1.1, +1.0)
Other SAEs	81/800 (10.1)	69/763 (9.0)	1.1 (-1.8, +4.0)
Imaging identified intracranial haemorrhage	154/795 (19.4)	157/754j (20.8)	-1.5 (-5.4, +2.5)
Subarachnoid haemorrhage (SAH)	53/795 (6.7)	52/754 (6.9)	-0.2 (-2.7, +2.3)
Subdural haemorrhage (SDH)	2/795 (0.3)	5/754 (0.7)	-0.4 (-1.1, +0.3)
Intraventricular haemorrhage (IVH)	24/795 (3.0)	17/754 (2.3)	0.8 (-0.8, +2.4)
HI1 (scattered small petechiae)	18/795 (2.3)	24/754 (3.2)	-0.9 (-2.5, +0.7)
HI2 (confluent petechiae)	62/795 (7.8)	67/754 (8.8)	-1.0 (-3.8, +1.7)
PH1 (haematoma occupying <30% of infarct with no substantive mass effect)	28/795 (3.5)	20/754 (2.6)	0.9 (-0.8, +2.6)
PH2 (haematoma occupying ≥30% of infarct with obvious mass effect)	21/795 (2.6)	18/754 (2.4)	0.3 (-1.3, +1.8)
remote PH-1†	6/795 (0.8)	9/754 (1.2)	-0.4 (-1.4, +0.5)
remote PH-2†	2/795 (0.3)	3/754 (0.4)	-0.1 (-0.7, +0.4)

Data are n/N (%) or risk difference with 95% CI in parentheses. Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification.

†Remote parenchymal haematoma type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect.
‡Remote parenchymal haematoma type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.

Supportive studies (in order of their publication):

Haley et al., (2005), Reference: [P05-02918]

Eligible patients were treated with an intravenous (iv) bolus infusion of tenecteplase within 3 h of stroke onset. The dose escalation was conducted in tiers of 25 patients, starting at 0.1 mg/kg, to a planned maximum of 0.6 mg/kg.

Enrolment into the fourth tier at 0.5 mg/kg was closed after 2 of 13 patients (15%) had sICH and 3 (23%) had asymptomatic intracranial haemorrhages (aICH). No sICH were observed within 36 h of treatment in tenecteplase 0.1 mg/kg, 0.2 mg/kg, or 0.4 mg/kg (Table 23). Fifteen patients (17%) died during the 3-month follow-up period of the study. The rate of aICH in 4 escalating dosage tiers at 48 h ranged from 8% to 32%. Except for the 2 patients in tier 4 who died after sICH, none of the deaths was attributable to tenecteplase administration. Serious adverse events (SAEs) were reported at rates similar to those of other ischemic stroke populations. Except for two fatal cases of sICH, one additional SAE was related to tenecteplase (serious orolingual angioedema within 1 h after 0.5 mg/kg).

Table 23: Haemorrhages in Haley et al., 2005

	Tenecteplase dose			
	0.1 mg/kg (n=25)	0.2 mg/kg (n=25)	0.4 mg/kg (n=25)	0.5 mg/kg (n=13)
sICH <36 h, n (%)	0 (0)	0 (0)	0 (0)	2 (15)
aICH <48 h, n (%)	2 (8)	8 (32)	7 (28)	3 (23)
All intracranial haemorrhages <48 h, n (%)	2 (8)	8 (32)	7 (28)	5 (38)
Minor bleeding <36 h, n (%)	4 (16)	10 (40)	9 (36)	3 (23)

Source: [P05-02918]

Molina et al., (2008), Reference: [P08-04525]

A total of 122 consecutive stroke patients with middle cerebral artery occlusion were allocated to tenecteplase 0.4 mg/kg iv bolus (n=42) or alteplase 0.9 mg/kg (n=80). sICH and aICH were assessed.

sICH occurred in one (2.3%) and three patients (3.7%) treated with tenecteplase and alteplase, respectively. aICH was observed in 28% and 21% of the patients (p = 0.089).

Parsons et al., (2009), Reference: [P09-03649]:

A non-randomised pilot study comparing tenecteplase 0.1 mg/kg in image-selected AIS patients treated 3-6 h after ischaemic stroke onset with patients contemporaneously treated with 0.9 mg/kg of alteplase within 3 h using standard selection criteria. The parenchymal haematoma at 24 h were assessed. Four of the 35 alteplase patients and none of the 15 tenecteplase patients had parenchymal haematoma at 24 h. Five of the tenecteplase patients and eight of the alteplase patients had haemorrhagic infarction.

Haley et al., (2010), Reference: [P10-04112]:

The trial was to compare 0.1, 0.25, and 0.4 mg/kg tenecteplase with 0.9 mg/kg alteplase in patients with acute stroke within 3 h of onset. The sICH and aICH, death and major systemic bleeding were collected and measured.

The study was terminated due to slow enrolment, safety results are presented in the following table.

Table 24 Selected safety outcome by treatment group

	Tenecteplase 0.1 mg/kg (n=31)	Tenecteplase 0.25 mg/kg (n=31)	Tenecteplase 0.4 mg/kg (n=19)	Alteplase 0.9 mg/kg (n=31)
sICH, n (%)	0 (0)	2 (6.5)	3 (15.8)	1 (3.2)
aICH, n (%)	3 (9.7)	2 (6.5)	2 (10.5)	4 (12.9)
All intracranial haemorrhages, n (%)	3 (9.7)	4 (12.9)	5 (26.3)	5 (16.1)
Major systemic bleeding, n (%)	0 (0)	1 (3.2)	0 (0)	0 (0)
All-cause mortality within 3 months, n (%)	2 (6.5)	7 (22.6)	3 (15.8)	8 (25.8)

Source: [P10-04112]

The 0.4 mg/kg dose of tenecteplase was discarded as inferior to the leading dose of 0.25 mg/kg regarding pre-defined criteria (including sICH). Safety of tenecteplase 0.1 and 0.25 mg/kg was comparable with alteplase 0.9 mg/kg. Tenecteplase 0.4 mg/kg showed higher incidence of bleeding events compared to lower doses.

Parsons et al., (2012), Reference: [P12-03304]:

This trial randomly assigned 75 patients to receive alteplase or tenecteplase (0.1 or 0.25 mg/kg) less than 6 h after the onset of ischaemic stroke. Secondary imaging safety outcomes were the occurrence of large parenchymal haematoma (>30% of the infarct volume), parenchymal haematoma of any size, and sICH. Secondary clinical safety outcomes were poor outcome (ie severe disability) or death at 90 days, defined as a score of 5 or 6, respectively, on the modified Rankin scale (mRS). Safety results are displayed in the following table.

Table 25 Safety outcomes by treatment group

	Tenecteplase			Alteplase
	Tenecteplase 0.1 mg/kg n=25	Tenecteplase 0.25 mg/kg n=25	Total n=50	n=25
Large parenchymal haematoma, n (%)	1 (4)	1 (4)	2 (4)	4 (16)
Any parenchymal haematoma, n (%)	2 (8)	1 (4)	3 (6)	5 (20)
sICH, n (%)	1 (4)	1 (4)	2 (4)	3 (12)
Poor outcome at 90 days, n (%)	3 (12)	2 (8)	5 (10)	7 (28)
Death, n (%)	3 (12)	1 (4)	4 (8)	3 (12)

Source: [P12-03304]

Table 26 Frequency of patients with SAEs other than ICH

	Tenecteplase 0.1 mg/kg N=25	Tenecteplase 0.25 mg/kg N=25	Alteplase 0.9 mg/kg N=25
Total number of patients with SAE[1]	6 (24)	5 (20)	7 (28)
Neurologic deterioration	4 (16)	3 (12)	6 (24)
Infectious	1 (4)	1 (4)	1 (4)
Respiratory	2 (8)	1 (4)	1 (4)
Cardiac	1 (4)	1 (4)	0 (0)
Renal	0 (0)	1 (4)	1 (4)
Gastrointestinal	0 (0)	1 (4)	1 (4)

[1] Some patients had more than one Serious Adverse Event (SAE).
Source: [P12-03304]

ATTEST (Huang et al., 2015), Reference: [P15-02640]:

Patients were randomly assigned (1:1) to receive tenecteplase 0.25 mg/kg or alteplase 0.9 mg/kg. ICH related safety outcomes were: the proportion of patients with sICH at 24-48 h post treatment defined by as the SITS-MOST, the proportion of patients with sICH as defined in the ECASS II, and the proportion of patients with any intracerebral haemorrhage.

The safety population included 52 patients given tenecteplase 0.25 mg/kg and 51 given alteplase 0.9 mg/kg. Any intracranial haemorrhages numerically were less numerically after iv thrombolysis with tenecteplase than alteplase (15% vs. 27%; OR 0.4, 95% CI 0.2, 1.2; p = 0.09). Only one patient (2%) in the tenecteplase group had a parenchymal haemorrhage compared with five (10%) in the alteplase group. Incidence of sICH with either ECASS II definition (6% vs. 8%, p = 0.59) or SITS-MOST definition (2% vs. 4%, p = 0.50), did not differ between tenecteplase and alteplase. Up to Day 90, 32 (62%) SAE were noted in 22 (42%) patients given tenecteplase and 16 (31%) patients given alteplase. SAEs probably or definitely related to study drug were reported in 6% TNK vs. 10% ALT patients. Up to Day 7, SAEs were reported in 15% TNK vs. 18% ALT patients. Mortality at 90 days was 17% in the tenecteplase and 12% in the alteplase group (p = 0.51). AT 30 days, 11% TNK vs. 13% ALT patients had died (mRS score of 6).

Table 27 Safety outcomes by treatment group

	Tenecteplase 0.25 mg/kg (n=52)	Alteplase 0.9 mg/kg (n=51)	p-value	OR (95% CI)
Any intracranial haemorrhages, n (%)	8 (15)	14 (27)	0.09	0.4 (0.2, 1.2)
Any parenchymal haemorrhage, n (%)	1 (2)	5 (10)	0.12	-
Parenchymal haemorrhage type 2, n (%)	0 (0)	3 (6)	0.94	-
sICH (ECASS II), n (%)	3 (6)	4 (8)	0.59	0.6 (0.1, 3.2)
sICH (SITS-MOST), n (%)	1 (2)	2 (4)	0.50	0.4 (0.04, 5.1)

Source: [P15-02640]

TEMPO-1 (Coutts et al., 2015), Reference: [P15-01653]:

TEMPO-1 was a multicentre, prospective, uncontrolled, dose-escalation, safety, and feasibility trial. Primary outcome was the rate of drug-related SAE. Safety was assessed by the rate of expected SAE associated with study drug. Expected study drug-related SAE included sICH with associated neurological worsening, symptomatic extracranial haemorrhage, severe orolingual angioedema, or thrombolysis-associated hypotension.

25 patients each were enrolled in the 0.1 mg/kg and 0.25 mg/kg dose groups. Patients were treated early with a median time to treatment of 3.5 h. Median baseline NIHSS was 2.5 (interquartile range [IQR] 1), and median age was 71 (IQR 22) years.

There were no drug-related SAE in the 0.1 mg/kg tenecteplase group. In the 0.25 mg/kg tenecteplase group, there was one sICH (4%; 95% CI 0.01, 20.0) that fulfilled the NINDS criteria or the ECASS II critieria, but not the SITS-MOST criteria. Stroke progression occurred in 3 (6%) of 50 patients. There were no other drug-related SAE in either dose tier.

NOR-TEST (Logallo et al., 2017), Reference: [P17-08885]:

Patients were randomly assigned (1:1) to receive tenecteplase 0.4 mg/kg or alteplase 0.9 mg/kg. Intracranial haemorrhages after thrombolysis was described according to the European Cooperative Acute Stroke Study (ECASS) morphological definition and sICH was defined on the basis of ECASS III criteria. The patients included in the safety analysis were from the intention-to-treat (ITT) population.

1100 patients were randomly assigned to the tenecteplase (n=549) or alteplase (n=551) groups. The median age was 77 years (IQR 64-79) and the median NIHSS score at baseline was 4 points (IQR 2-8).

During the first 24-48 h after thrombolytic treatment, any intracranial haemorrhages (ECASS I criteria) occurred in 47 (9%) patients in the tenecteplase group and 50 (9%) patients in the alteplase group (OR 0.94 [95% CI 0.60, 1.45]; p = 0.82) and sICH (ECASS III criteria) in 15 (3%) and 13 (2%) patients, respectively (OR 1.16 [95% CI 0.51, 2.68]; p = 0.70).

By 3 months, 29 (5%) of 549 patients had died in the tenecteplase group compared with 26 (5%) of 551 in the alteplase group (odds ratio [OR]=1.12, 95% CI [0.63, 2.02]; p = 0.68). A similar frequency of SAE was reported in the tenecteplase and alteplase groups (145 [26%] vs. 141 [26%], respectively; p = 0.74). The most frequent SAE up to Day 7 was any type of intracranial haemorrhages, which occurred in 47 (9%) patients in the tenecteplase group and 50 (9%) patients in the alteplase group (OR=0.94, 95% CI [0.60, 1.45]; p = 0.82).

EXTEND-IA TNK (Campbell et al., 2018), Reference: [P18-03928]:

Adult patients with LVO ischaemic stroke planned to undergo thrombectomy were treated with either a single dose 0.25 mg/kg tenecteplase or with 0.9 mg/kg ALT within 4.5 h of onset of stroke.

Safety criteria for evaluation were symptomatic intracerebral haemorrhage (sICH) within 36 hours and mortality within 90 days. SICH was defined as "Intracerebral hemorrhage (parenchymal hematoma type 2 - PH2 within 36 hours of treatment) combined with neurological deterioration leading to an increase of ę 4 points on the NIHSS from baseline, or the lowest NIHSS value between baseline and 24 hours" and included any sub-arachnoid bleeding associated with clinical symptoms and sICH. The Investigator and designated study personnel monitored each subject for adverse events for the acute phase of the study up to day 3.

sICH occurred in 1% of the patients in each group. There were 10 deaths in the tenecteplase group and 18 in the alteplase group, but the difference was not significant in the pre-specified logistic-regression analysis (Table 28). Most of the deaths were related to progression of major stroke (9 in tenecteplase group and 14 in alteplase group). See also Table 29 for a detailed list of SAEs.

Table 28 Safety of Tenecteplase and Alteplase in the EXTEND-IA TNK

	Tenecteplase 0.25 mg/kg (n=101)	Alteplase 0.9 mg/kg (n=101)	Effect Size (95% CI)	p-value
Death[1], n (%)	10 (10)	18 (18)		
Adjusted RR			0.5 (0.3-1.0)	0.049
Adjusted OR			0.4 (0.2-1.1)	0.08
sICH, n (%)	1 (1)	1 (1)		
RR			1.0 (0.1-15.9)	0.99
OR			1.0 (0.1-16.2)	0.99
Parenchymal haematoma, n (%)	6 (6)	5 (5)		
RR			1.2 (0.4-3.8)	0.76
OR			1.2 (0.4-4.1)	0.76

RR risk ratio; OR, odds ratio.

[1] The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed as an incidence or risk ratio from Poisson regression and as an odds ratio from logistic regression.

Source: [P18-03928]

Table 29 SAEs in the EXTEND-IA TNK study*

	Alteplase	Tenecteplase
Deaths	18	10
Progression of major stroke	14	9
Cardiac events	3	0
Symptomatic haemorrhage	1	0
Metastatic cancer diagnosed after presentation	0	1
sICH	1	1
Groin haematoma	3	1
Femoral artery pseudoaneurysm	1	0
Post-procedure leg ischaemia distal to puncture site	0	1

Source data: [P18-03928, Table S3]

* The number of SAEs is given; ALT and TNK groups both included 101 patients; in the upper half of the table, fatal SAEs are listed.;

EXTEND-IA TNK Part 2 (Campbell et al., 2020), Reference: [P20-01928]:

Adult patients with LVO ischaemic stroke planned to undergo thrombectomy were treated with single iv bolus doses of either 0.25 or 0.4 mg/kg of tenecteplase within 4.5 h of onset of stroke.

Symptomatic ICH occurred in 7 patients (4.7%) in the 0.40 mg/kg group and 2 patients (1.3%) in the 0.25 mg/kg group (unadjusted risk difference, 3.3% [95% CI, -0.5, 7.2]; risk ratio [RR], 3.50 [95% CI

0.74, 16.62]; P=0.12). There were 26 deaths (17%) in the 0.40 mg/kg tenecteplase group and 22 deaths (15%) in the 0.25 mg/kg tenecteplase group (adjusted RR, 1.27 [95% CI 0.77, 2.11]; P=0.35).

Table 30 . Safety outcomes in the EXTEND-IA TNK Part 2 study

	Tenecteplase 0.25 mg/kg (n=150)	Tenecteplase 0.4 mg/kg (n=150)	Unadjusted Risk Difference (95% CI), %	RR[1] (95% CI), p-value
Deaths, n (%)	22 (15)	26 (17)	2.7 (-5.6, 11.0)	1.27 (0.77, 2.11), 0.35
sICH, n (%)	2 (1.3)	7 (4.7)	3.3 (-0.5, 7.2)	3.50 (0.74, 16.62), 0.12
Parenchymal haematoma, n (%)	6 (4.0)	4 (2.7)	-1.3 (-5.4, 2.7)	0.67 (0.19, 2.32), 0.52

[1] Adjusted RR for the death endpoint.
Source: [P20-01928, Table 2]

NOR-TEST 2, Part A (Kvistad et al, 2022), Reference: [P22-03558]:

The aim of NOR-TEST 2 was to establish the non-inferiority of tenecteplase 0.4 mg/kg to alteplase 0.9 mg/kg for patients with moderate or severe ischaemic stroke. Patients with suspected AIS with a NIHSS score of 6 or more who were eligible for thrombolysis and admitted within 4.5 h of symptom onset were included. 216 patients were enrolled; patient enrolment was stopped after a per-protocol safety review showed an imbalance in the rates of symptomatic intracranial haemorrhage between the treatment groups, which surpassed the prespecified criteria for stopping the trial. After analysis, the independent data safety monitoring committee could not identify specific subgroups with a marked increased bleeding risk within the study population.

Any intracranial haemorrhage was reported in 21 (21%) of 100 patients allocated tenecteplase and seven (7%) of 104 patients allocated alteplase (unadjusted OR 3.68 [95% CI 1.49–9.11]; p=0.003, Table 31). Numerically more cases of symptomatic intracranial haemorrhage were reported with tenecteplase (six [6%] of 100 patients) than with alteplase (one [1%] of 104 patients; unadjusted OR 6.57 [95% CI 0.78–55.62]; p=0.061). The distribution of morphological subtypes was similar between the treatment groups, except more cases of parenchymal haemorrhage type 2 were reported in patients allocated tenecteplase (eight [8%] of 100 patients) than in those allocated alteplase (one [1%] of 104 patients; p=0.017). Mortality at 3 months was higher in the tenecteplase group (15 [16%] of 96 patients) than in the alteplase group (five [5%] of 101 patients; unadjusted OR 3.56 [95% CI 1.24–10.21]; p=0.013, Table 31). More patients in the tenecteplase group had at least one SAE at Day 90, compared with the alteplase group (45 [45%] of 100 patients vs. 22 [21%] of 104 patients, p=0.0003). Compared with patients allocated alteplase, more patients allocated tenecteplase had cerebral haemorrhage (four [4%] vs. 16 [16%]; p=0.0042), recurrent ischaemic stroke (none vs. 5 [5%]; p=0.027), and other complications (four [4%] vs. 15 [15%]; p=0.0074).

Table 31 Safety of tenecteplase 0.4 mg/kg and alteplase 0.9 mg/kg in the NORTEST 2 Part A trial

	Tenecteplase 0.4 mg/kg (n=100)	Alteplase 0.9 mg/kg (n=104)	OR/Risk difference (95% CI), p-value
Death, n (%)	15 (16)	5 (5)	
Adjusted OR (95% CI)			2.94 (0.97-8.89), 0.013
Unadjusted risk difference (95% CI)			0.11 (0.02-0.19)
sICH, n (%)	6 (6)	1 (1)	
Adjusted OR (95% CI)			5.91 (0.69-50.68), 0.061
Unadjusted risk difference (95% CI)			0.05 (0.00-0.10)
Any intracranial haemorrhage, n (%)	21 (21)	7 (7)	
Adjusted OR (95% CI)			3.54 (1.40-8.99), 0.0031
Unadjusted risk difference (95% CI)			0.14 (0.05-0.23)

Source: [P22-03558, Table 2]

SAEs

Relevant findings regarding haemorrhage and death are discussed in the context of the individual studies.

TNK as well as ALT are also associated with the risk of hypersensitivity. Angioedema is the most common hypersensitivity reaction reported with alteplase. The incidence of angioedema was almost identical in tenecteplase and alteplase groups (<1%), as shown from the published randomised controlled trials, and matched the expected known incidence for alteplase in AIS.

Table 32 Incidence of angioedema reported in published randomised controlled trials

	Tenecteplase 0.25 mg/kg or 0.40 mg/kg	Alteplase 0.9 mg/kg
AcT, n/N (%)	9/800 (1.1)	9/763 (1.2)
EXTEND-IA TNK, n/N (%)	2/401 (< 1)	0/101 (0)
NOR-TEST, n/N (%)	1/549 (< 1)	2/551 (< 1)
ATTEST, n/N (%)	1/52 (1.9)	0/51 (0)
Overall Incidence, n/N (%)	13/1802 (< 1)	11/1466 (< 1)

Sources: AcT [P22-05053], EXTEND-IA TNK [P18-03928], EXTEND-IA TNK Part 2 [P20-01928], NOR-TEST [P17-08885], ATTEST [P15-02640]

Meta-analyses:

Burgos and Saver, 2019 performed a formal meta-analysis of 5 RCTs enrolling 1,585 patients (828 tenecteplase, 757 alteplase, [P19-06342]). RCTs included: Haley et al. (2010) [P10 04112], Parsons et al. (2012) [P12 03304], ATTEST [P15 02640], NOR-TEST [P17 08885], and EXTEND-IA TNK [P18 03928].

Across all trials, mean age was 70.8, 58.5% of patients were male, baseline NIHSS mean was 7.0, and time from last known well to treatment start mean was 148 min. All alteplase patients received standard 0.9 mg/kg dosing, while tenecteplase dosing was 0.1 mg/kg in 6.8%, 0.25 mg/kg in 24.6%, and 0.4 mg/kg in 68.6% of patients. For safety endpoints, lower event rates reduced power, but point estimates were also consistent with noninferiority.

According to the publication, crude summary sICH rates were TNK 3% versus ALT 3%, risk difference 0% (95% CI, –1% to 2%); the lower 95% CI bound of -1% fell on the NI-margin. For death, crude mortality rates at 3 months were TNK 7.6% versus ALT 8.1%, risk difference 0% (95% CI, –3% to 2%). The lower 95% CI bound of -3% fell did not fall within the stringent margin of -1%.

The SCS also refers to the meta-analysis made for the European Stroke Organisation Guidelines [P23-01257], published in February 2023. The meta-analysis included the following studies: Act (2022), Attest

(2015), Taais (Parsons, 2012), Extend-IA TNK (2018), Taste-A (Bivard, 2022), TNK-S2B (Haley, 2019) and Trace (LI, 2021). Amongst others, the following results were presented: The rates of sICH according to individual study definition in patients AIS of < 4.5 h duration did not differ between treatment groups of 0.25 mg/kg tenecteplase and 0.9 mg/kg alteplase (OR=0.98; 95% CI: 0.59–1.62; p = 0.93; I2=0%). A sensitivity analysis including the studies that reported sICH by the SITS-MOST definition (which was the most common available definition across all trials) yielded similar results.

Real word evidence (RWE):

In key RWE studies (Tsivgoulis et al. [P22-04770], Warach et al. [P22-07546], Gerschenfeld et al. [P22-05938], and Zhong et al. [P21-01816]), comparing tenecteplase 0.25 mg/kg vs. alteplase 0.9 mg/kg (within 4.5 h of stroke onset with adjusted and at least 100 tenecteplase patients), there were no significant differences in the safety profiles of the drugs.

The safety and efficacy of tenecteplase versus alteplase (tenecteplase at a dose of 0.25 mg/kg or alteplase at a dose of 0.9 mg/kg) in AIS patients were compared by analysing propensity score matched data from 20 centres participating in the Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Register [P22-04770]. No difference was found in the likelihood of 24-hour sICH (1.0% vs. 1.3%, OR = 0.72, 95% CI = 0.20–2.64).

A 10-hospital regional network in the United States transitioned to tenecteplase as the standard of care stroke thrombolytic in September 2019 because of potential workflow advantages and reported noninferior clinical outcomes relative to alteplase in meta-analyses of randomised trials. To assess whether tenecteplase use in routine clinical practice reduced thrombolytic workflow times with noninferior clinical outcomes, a prospective registry-based observational, sequential cohort comparison of tenecteplase- (n=234) to alteplase-treated (n=354) stroke patients was conducted [P22-07546]. Unfavourable outcome was less for tenecteplase, 7.3% versus 11.9%, adjusted odds ratio, 0.77 (95% CI, 0.42–1.37) but did not fall within the prespecified 1% noninferior boundary.

Due to practical advantages, increasing trial safety data, recent Australian Guideline endorsement and local population needs, a regional stroke network in New Zealand switched to tenecteplase for stroke thrombolysis from alteplase. RWE included mixed methods including stakeholder engagement, pre-implementation and post-implementation surveys, and assessment of patient treatment rates, metrics, and clinical outcomes pre-implementation and post-implementation adjusting regression analyses for age, sex, National Institutes of Health Stroke Scale, premorbid modified Rankin Scale score, and thrombectomy using New Zealand National Stroke Registry data. Between January 2018 and February 2021, 555 patients were treated with alteplase and 283 with tenecteplase. Symptomatic intracranial haemorrhage rates (tenecteplase 1.8% versus alteplase 3.4%; adjusted odds ratio, 0.46 [95% CI, 0.13–1.64]) and death by Day 7 (tenecteplase 7.5% versus 11.8%; adjusted odds ratio, 0.46 [95% CI, 0.21–0.99]) did not significantly differ for the 42 transferred regional patients (tenecteplase 155 [113–248] versus 200 [158–266]; P=0.27).

Post marketing experience

Evaluation of the safety profile of tenecteplase in the labelled indication of Myocardial Infarction (MI) versus the off-label use in AIS, together with a comparison with alteplase in AIS use, based on post-marketing data was performed by BI with a DLP of 30 Sep 2022 by BI.

A search in the BI global safety database for all tenecteplase Individual Case Safety Reports (ICSRs, further referred to as "cases") with indications of MI and AIS, as well as all alteplase ICSRs with indication of AIS was performed, with a data lock point (DLP) of 30 Sep 2022. BI clinical trial cases were excluded.

A detailed evaluation of ICSRs was preformed for TNK in the AIS vs. the MI indication, which included analyses by event types; case seriousness; most frequently reported AEs, patients' age and gender, most common concurrent conditions and concomitant medications, and detailed evaluation of haemorrhagic events and hypersensitivity events.

Tenecteplase use pattern according to age group and gender (by order of frequency of reporting of specific age group or gender) was found to be similar in both AIS and MI indications. However, case seriousness was lower in AIS group.

Patients with both AIS and MI were found to widely use antithrombotics, which are usually part of chronic therapy in people having risk factors for cardiovascular diseases. Most frequent concomitant conditions in both groups were vascular hypertensive disorders and glucose and lipid metabolic disorders. Several concomitant conditions were reported more frequently in AIS patients compared with MI patients, including vascular hypertensive disorders and central nervous system vascular disorders, Cardiac arrhythmias, renal disorders. Also pre-existent allergic conditions were reported more frequently in AIS patients (10.1% vs. 1.9%), although the reason and the significance of the latter it is unclear.

The proportion of cardiac arrhythmias among the total reported cases was clearly higher for patients with MI compared to AIS (10.2% vs. 0.7%). Cardiac arrhythmias in MI patients are most likely not related to the drug, since it is well known that about 90% of patients who have an acute MI develop some form of cardiac arrhythmia during or immediately after the event. All other HLGTs were reported with a generally comparable proportion of total reported cases.

Regarding Haemorrhage related events (by PT), in the AIS vs. the MI indication, a higher proportion of reported cases concerned haemorrhagic transformation stroke (10.1% vs. 0%), haemorrhagic infarction (7.2% vs. 0.1%), and cerebral haematoma (6.5% vs. 1.5%), whereas haemorrhagic stroke (0% vs. 7.5%) was reported only in MI. All other haemorrhages had a comparable proportion among the total number of cases with haemorrhagic events.

Apart from this, no marked differences in the safety profile of TNK across both indications were derived from this analysis.

Comparison of all AEs (MedDRA PTs) with frequency >0.5% between TNK and ALT in AIS and respective listedness based on the Company Core Data Sheets (CCDS) showed generally similar results between both substances. Overall, a lower proportion of reported cases of TNK compared with ALT concerned intracranial haemorrhages, but these results need to be interpreted with caution.

2.6.1. Discussion on clinical safety

The safety profile of tenecteplase (TNK) is established for the approved STEMI indication and is predominantly characterised by bleeding events and angioedema. The safety profile of TNK in the now claimed AIS indication is mainly derived from data of 12 completed, investigator-initiated studies (IIS). A total of 2,244 patients with AIS were exposed to a single intravenous dose of TNK across all 12 IIS, with 1,184 patients with AIS exposed to TNK 0.25 mg/kg, the intended dose. The majority of AIS patients treated with TNK were evaluated in the AcT study, which serves as the main study for the AIS indication and in which the efficacy and safety of 0.25 mg/kg TNK in patients eligible for i.v. thrombolysis within 4.5 h of AIS was compared to an approved standard dose of alteplase (ALT). No clinically relevant differences in the overall safety profile of TNK vs. ALT are discernible from the AcT study. The incidence of sICH within 24 hours using the pre-specified definition (a pragmatic definition similar to the NINDS definition) as well as the incidence of death was similar between the TNK and the ALT group (sICH: 3.4% vs. 3.2%; all death: 15.3% vs. 15.4%). Within the AcT study, orolingual angioedema was reported in 1.1% patients of both treatment groups.

As the definition of sICH originally applied to the AcT study potentially included also less severe symptomatic ICHs, the Applicant has re-analysed the sICH rates of the AcT trial according to various definitions. No NI margin regarding any safety endpoint was pre-specified in the AcT trial. There is no consistent NI margin to be applied to sICH, but the Applicant has discussed sICH results regarding a margin of -1% that has been quoted in the Burgos and Saver meta-analysis (2019) and would fit with a 95-50-95 rule derivation. The lower bound of the 95% CI for the 'IST-3-SITS-MOST' definition crossed the -1% NI margin, whereas results regarding the 'BI-RCT-SITS-MOST' definition were above -1% indicating non-inferiority. While the latter results, which evaluated the most severe sICHs (apart from fatal sICH), could be considered reassuring, non-inferiority with regard to sICH cannot be clearly concluded for TNK vs. ALT in AIS based on these conflicting results. However, overall the incidence of sICH in TNK the AcT study did not lead to a deleterious effect on functional outcome or to an increased incidence of death in the TNK compared to the ALT group.

In the AcT study, the incidence of fatal ICH within 7 days was minimally higher in TNK (2%) vs. ALT (1.7%) patients; however the overall incidence of death of any cause up to day 90 was minimally lower in TNK vs. ALT treated patients (15.3% vs. 15.4%). Further, the incidence of fatal ICH was almost identical between treatment groups in the SmPC filtered population (1.9% vs. 1.8%). However, although numbers were low, it is striking, that fatal ICH was reported in 8% (2/25) TNK vs. 0% (0/14) ALT patients with NIHSS>25 at baseline, i.e. with severe stroke. Based on the significantly higher incidence of fatal ICH (up to 7 days) in the TNK vs. the ALT group, but also based on an overall higher death rate in this subgroup with TNK compared to ALT of 56% vs. 21.4%, TNK for thrombolysis in AIS has been contraindicated in patients with severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques, in line with the respective contraindication of Alteplase.

The results of the AcT trial are supported by the Extend-IA TNK (2020) study, which resulted in a similar safety profile of 0.25 mg TNK administered within 4.5 h of AIS in patients with large vessel occlusion (LVO) scheduled for mechanical thrombectomy compared to a standard dose of ALT. In both study groups, 1 out of 101 subjects reported a sICH within 36 hours of treatment that was associated with a deterioration of ≥4 points on the NIHSS within 36 hours of treatment. The overall incidence of death was numerically in favour of TNK vs. ALT (10% vs. 18%). Also, the overall incidence of SAEs or the evaluation of SAEs by reported term (up to day 3) did not raise any unexpected safety concerns.
Other supportive evidence of safety of the intended 0.25 mg/kg dose of TNK in AIS is provided by the small study of Parsons (2012) and in the Attest (2015) study, with a numerically lower incidence of sICH in TNK compared to ALT treated patients in both studies.

Overall, no unexpected safety concerns with regard to safety of the intended 0.25 mg/kg TNK dose for thrombolysis in AIS within 4.5 h, can be derived from the 12 investigator initiated trials or from the meta-analyses of published studies referenced by the Applicant. In contrast, the 0.4 mg/kg TNK dose led to an excess in sICH and mortality at least in elderly patients and in patients with more severe stroke (in the Nor-Test 2, Part A study) whereupon further evaluation of the higher TNK dose was abandoned.

In meta-analyses published by the European Stroke organisation (Alamowitch, 2023 [P23-01257]), the rates of sICH (according to the individual study definition as well as according to the SITS-MOST definition) did not differ between AIS patients treated within 4.5 h with 0.25 mg/kg TNK vs. 0.9 mg/kg ALT. This could further corroborate safety of TNK in the sought indication. Of note, the TRACE study (2021) included in the ESO meta-analysis (Alamowitch, 2023) used a biocopy, that has not been proven to be biosimilar with Metalyse. Nevertheless, Alamowitch et al. also performed a sensitivity analysis of sICH according to the SITS-MOST definition, using the studies that reported these events (i.e., Attest, TAAIS, Extend-IA TNK and TASTE-A, which all used medicinal products, that can be regarded as similar with Metalyse), which does not raise any safety concerns (unadjusted pooled OR, random-effects meta-analysis; OR=0.49; 95% CI: 0.12-2.08). In addition, a sensitivity analysis for any intracranial

haemorrhage after excluding TRACE was provided in the published ESO meta-analysis and yielded similar results than the meta-analysis including this study (favouring TNK over ALT; unadjusted pooled OR, random-effects meta-analysis).

Available RWE appears to support the safe use of 0.25 mg/kg TNK in AIS, however, these data need to be interpreted cautiously.

Two differences regarding safety of TNK in the approved STEMI vs. the intended AIS indication were identified:

• The frequency of intracranial haemorrhage (ICH) in the AIS indication is higher (very common) than in the STEMI indication (uncommon). This would be expected because of the generally increased risk of ICH in AIS patients and is generally in line with Actilyse, for which ICH is also very commonly reported in the treatment of AIS but with a lower frequency in the treatment of acute myocardial infarction.

• Undesirable Effects of reperfusion arrhythmias are the only undesirable effects applicable only to patients with acute myocardial infarction. By its nature, reperfusion arrhythmias are indication-specific AEs. Cumulative search in BI´s global safety database with DLP of 26 Apr 2023, of spontaneous cases in AIS, with reported AEs from "HLGT Cardiac arrhythmias" was performed. Four cases were identified, but reported events were not indicative of reperfusion arrhythmias.

Apart from this, no general differences in the safety profile of TNK in the AIS vs. the established STEMI indication were identified by the Applicant, which is in general plausible, taking the large overlap of both study populations into consideration. It is further reassuring, that the proposed dose for AIS (0.25 mg/kg) is only half of the dose established for STEMI, while the proposed dosing scheme in 5 dose tiers by 10 kg steps (with <60 kg and ≥ 90 kg as upper and lower boundaries) is the same.

It could therefore be agreed, that apart from both above differences, the ADRs listed in Table 1 of SmPC section 4.8 generally correspond across both indications. Of note, in line with the established safety profile of Actilyse the Applicant has also proposed to add transfusion (frequency: not known) to SmPC section 4.8 of the TNK AIS presentation, which is accepted.

2.6.2. Conclusions on clinical safety

The safety profile of 0.25mg/kg TNK given within 4.5h in AIS patients eligible for i.v. thrombolysis can be considered similar to the established safety profile of 0.9 mg/kg ALT. However, TNK for thrombolysis in AIS has been contraindicated in patients with severe stroke as assessed clinically (e.g. NIHSS > 25) and/or by appropriate imaging techniques, in line with the respective contraindication of Alteplase. Differences of the safety profile of TNK established for the STEMI indication compared to the AIS indication concern the expected higher frequency of sICH in the AIS indication while the occurrence of reperfusion arrhythmia is applicable only to patients with acute myocardial infarction.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Update of the Product information

As a result of this grouped variation, a separate SmPC and Package Leaflet are provided for the 25 mg

presentation with the new indication. In addition, the MAH took the opportunity to implement editorial changes and minor updates to the PI of Metalyse 40 mg (8,000 U) and 50 mg (10,000 U). Please refer to the Product information as adopted by CHMP in Attachment 1 for further details.

The MAH submitted a request for a deviation from the QRD recommendation on the expression of strength for the new and existing indication, to express the strength as follows:

- Metalyse 25 mg (5 000 U), 40 mg (8 000 U) and 50 mg (10 000 U)

The QRD group concluded via written consultation that the request for the expression of strength in "units (mg)" was found acceptable by the majority of the Group, with the exception of Belgium and France.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

For all marketing authorisations granted after 30 October 2005, all the requirements set out in Directive 2001/83/EC as amended apply. Since Metalyse was registered prior to this date, a user consultation was not required for this product in the past.

Nevertheless, Metalyse has been on the market in EU for more than 20 years so the package leaflet is well known by the healthcare professionals and users. The Applicant is not aware that issues with the readability of the package leaflet have been reported in the past. In addition, Metalyse is a hospital use only product that should only be used with the involvement of physicians experienced in neurovascular care and the use of thrombolytic treatment, so healthcare professionals are expected to be available for consultation in case of doubts from the patients about any information included in the package leaflet.

The proposed package leaflet for Metalyse 5 000 U (25 mg) has the same structure as the currently registered package leaflets for Metalyse 8 000 U (40 mg) and 10 000 U (50 mg) and the information included for several sections is common between the 3 presentations.

Furthermore, additional information related only to the new Metalyse 5 000 U (25 mg) presentation and the acute ischaemic stroke (AIS) indication is in line with the product information of Actilyse (alteplase), which is also a very well-established product that has been in the EU market for more than 30 years with the AIS indication approved for more than 20 years. Therefore, BI considers that a consultation with target patient groups would not be required for the upcoming submission intended to register Metalyse 5 000 U for AIS indication.

In addition, the Applicant has provided a bridging report making reference of the new Metalyse (25 mg) presentation to the current to Metalyse 8 000 U (40 mg) and 10 000 U (50 mg) presentations with regard to key safety messages, design/layout as well as to the Actilyse 10, 20and 50 mg presentations with regard to information specific to the now sought AIS indication of Metalyse. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Stroke is a disease characterized by brain tissue damage, due to vascular occlusion (ischaemic stroke) or sudden rupture of cerebral blood vessels (haemorrhagic stroke). Stroke is one of the leading causes of death and disability worldwide. Acute ischaemic stroke (AIS) is the most common form of stroke, accounting for 87% of all cases and is primarily caused by thrombosis or embolism blocking the cerebral arteries.

3.1.2. Available therapies and unmet medical need

Intravenous thrombolysis with alteplase within 4.5 h of stroke onset is the only approved pharmacologic treatment for AIS.

The European Stroke Organisation has recently published an expedited recommendation, that for patients with AIS of <4.5 h duration who are eligible for IVT, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg (Alamowitch, 2023). In these recommendations as well as in the ESO/ESMINT Guidelines on Mechanical Thrombectomy in AIS, tenecteplase is favoured over alteplase in patients with large vessel occlusion AIS, who are eligible for intravenous thrombolysis before mechanical thrombectomy (Turc, 2019).

After implementation of tenecteplase (0.25 mg/kg) in relevant treatment guidelines increasing off-label use of tenecteplase in the AIS indication must be assumed. However, there are currently extensive shortages in the supply chain with alteplase and tenecteplase in Europe. The Applicant has developed a new Metalyse presentation for the AIS indication, containing only 5 000 units (25 mg) of TNK compared to the currently available Metalyse presentations approved for the STEMI indication, which contain 8 000 units (40 mg) and 10 000 units (50 mg), respectively per vial. Therefore, approval of the new presentation is expected to mitigate the supply shortage of alteplase and tenecteplase to some extent.

3.1.3. Main clinical studies

The Act study is the most relevant of the individual studies submitted for this application and evaluated the efficacy and safety of 0.25 mg/kg TNK vs. a standard dose of ALT (0.9 mg/kg) for intravenous thrombolysis in AIS patients within a 4.5 h time window. The AcT trial was a pragmatic, registry linked, prospective, randomized (1:1) controlled, open-label parallel group non-inferiority clinical trial with blinded endpoint assessment. The PROBE (Prospective randomized open blinded endpoint) design in the AcT trial is considered acceptable, taking the emergency indication and infusion over one hour in the comparator group compared to bolus i.v. injection of TNK into consideration. Further, expedient measures were taken in the AcT study in order to ascertain blinding of the outcome assessors. The AcT trial was performed in 22 study sites in Canada and included AIS patients as per the Canadian Stroke Best Practice Recommendations, i.e. all patients with AIS eligible to receive the approved thrombolysis with ALT as per standard of care (with or without additional mechanical thrombectomy [MT]) were eligible for treatment. The Applicant has provided sufficient justification for the generalisability of the study data to a European population based on similarity of the Canadian and European treatment guidelines for stroke supported by additional exploratory analyses based on an EU-SmPC filtered population. The posology used in the AcT trial (i.e. 25 mg/kg in 5 dose tiers) was fully in line with the TNK posology proposed in the SmPC for

the AIS indication, ALT was dosed according to the approved standard dose. The primary efficacy endpoint was based on a dichotomised analysis of the mRS at day 90-120 (measured as close as possible to day 90) with favourable outcome defined as mRS 0-1 which can be endorsed. The study enrolled 1577 patients and baseline characteristics were generally balanced across treatment groups. The relevant timelines of the AcT trial have been clarified.

The Extend IA-TNK study evaluated efficacy and safety of 0.25 mg/kg TNK compared to the approved standard dose of ALT within 4.5 hours in a subset of AIS patients eligible for i.v. thrombolysis, i.e. in patients with large vessel occlusion (LVO) scheduled for mechanical thrombectomy and constitutes the main supportive evidence of TNK in the AIS indication. The study had a prospective, randomised, open-label, blinded endpoint (PROBE), non-inferiority design. As the investigators expected the effect of mechanical thrombectomy on the clinical outcome to obscure any potential difference between TNK and ALT, the primary endpoint was based on early reperfusion (before mechanical thrombectomy). Functional outcomes (including an ordinal analysis of the median mRS, proportion of subjects with mRS 0-1 and 0-2, respectively at 90 days) were secondary endpoints endpoints. The study enrolled 202 patients.

3.2. Favourable effects

Results derived from the main (AcT) study:

In the primary analysis of the primary endpoint, 36.9% (296/802) TNK patients and 34.8% (266/765) ALT patients had an mRS of 0-1 at day 90–120. The estimate for the unadjusted difference in proportion was 2.1 (95% CI: -2.6, +6.9) (ITT population). The pre-specified non-inferiority margin of 5% was met.

In the mPP population, the point estimate was also somewhat more favourable regarding TNK, with a more favourable lower bound of the 95% CI compared to the ITT analysis; the estimate for the unadjusted difference in proportion was 2.6 (95% CI: -2.2, +7.4). Also the results regarding the mITT tended to be slightly more favourable regarding TNK compared to the ITT analysis with a lower bound of the 95% CI of -2.5.

mRS of 0-2 at day 90–120 was reported in 56.4% TNK vs. 55.6% ALT patients; the estimate for the unadjusted difference in proportion was 0.8 (95% CI: -4.1, +5.7). None of the other secondary outcomes indicates raises concerns regarding a worse efficacy of TNK vs. ALT.

In the pivotal study, the results of the primary outcome were generally consistent across subgroups. Nevertheless, the favourable results of the Extend-IA TNK including patients with large vessel occlusion (LVO) as well as of the small Parsons (2012) study (evaluating patients with penumbra) may indicate, that imaging selected AIS patients are highly responsive to TNK.

Results of the EXTEND-IA TNK study:

0.25 mg/kg TNK was non-inferior to a standard dose of ALT within 4.5 hours of AIS in patients scheduled for mechanical thrombectomy in restoring perfusion (reperfusion of > 50% or absence of retrievable thrombus) in the involved ischaemic territory with 22% TNK vs. 10% ALT patients reaching the primary outcome (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI 1.1, 4.4). Superiority was declared, as the lower end of the 95% CI was > 0.

Patients in the TNK group had nominally statistically significantly better functional outcomes than those in the ALT group in an ordinal analysis of the modified Rankin scale scores at day 90, but there was no significant difference in the incidence of recovery to independent function (modified Rankin scale score of 0 to 2 or no change from baseline function) at day 90, which occurred in 64% TNK patients vs. 51% ALT patients (adjusted incidence ratio, 1.2; 95% CI, 1.0 to 1.5; P=0.06; adjusted odds ratio, 1.8; 95% CI,

1.0 to 3.4; P=0.06). There were also no significant differences in the incidence of early neurologic improvement at 72 hours.

In the Extend-IA TNK Part 2 study (Campbell, 2020), 0.4 mg/kg TNK did not show any relevant improvement in efficacy vs. 0.25 mg/kg TNK, with very similar results for both groups regarding the primary endpoint.

Of the 5 other supportive studies, in particular the study published by Parsons 2012 provides some supportive evidence of efficacy of 0.25 mg/kg of TNK. The study results are indicative of an improved efficacy of 0.25 mg/kg TNK vs. 0.1 mg/kg TNK (with no additional bleeding risk) as well as of an improved efficacy of 0.25 mg TNK vs. ALT. However, this was a small study (including 25 patients per treatment group), the patient population was selected to most likely benefit from thrombolytic therapy (based on CT perfusion imaging) limiting generalisability of results, and the Co-primary endpoint addressed early re-perfusion as well as early clinical improvement (based on change in NIHSS at 24 hrs). Nevertheless, at three months 72% of patients in the 0.25 mg/kg TNK group had an excellent recovery (mRS 0-1 according to the submitted online supplement to this publication), as compared with 40% of those in the ALT group (P = 0.02).

The meta-analysis of 5 supporting RCTs by Burgos and Saver (2019) generally supports non-inferiority of TNK vs. the standard dose of ALT for i.v. thrombolysis in AIS with regard to D90 mRS of 0-1, even if a very strict NI-margin of 1.3% was applied to the primary endpoint (mRS 0-1 at Day90). However, there were methodological issues, amongst others, inclusion of different TNK doses in this meta-analysis with 68.6% TNK patients receiving a higher than now intended dose (exceeding the intended 0.25 mg/kg dose).

The recent meta-analysis of seven available RCTs performed by the European Stroke Organisation (ESO) (Alamowitch, 2023) concluded non-inferiority of 0.25 mg/kg dose of TNK vs. ALT with regard to Day 90 mRS 0-1 based on the pre-specified 3% NI margin (and with regard to the primary analysis also based on the very stringent 1.3% NI-margin). The pooled risk difference for mRS 0-1 at 90 days in patients with AIS of <4.5 h duration treated with TNK 0.25 mg/kg vs. a standard dose of ALT was 3.68% with a lower bound of the 95% CI of – 0.32. It is noted however that a non-inferiority proof by a meta-analysis of known studies is of less confirmatory value.

3.3. Uncertainties and limitations about favourable effects

The evidence of efficacy of TNK in AIS is not based on own studies performed by the Applicant but on investigator initiated trials, of which the AcT trial serves as the main study. The MAH has established a specific data access and exchange agreement with the sponsors of the AcT trial and has reanalysed the data independently and provided additional exploratory analyses which overall support the robustness of the protocol defined study results. The Applicant has further stated to have received and analysed the data from the EXTEND trials (i.e., the most relevant supporting studies) and that the numbers in the manuscript were reproducible. Further, the Applicant has performed an onsite audit of the AcT trial (as well as a remote audit of the Extend-IA TNK trial) providing additional reassurance of credibility of the study data. It is further considered reassuring, that results for the ITT, mITT and mPP populations, as well as for the various additional analyses according to the initial protocol and subsequent revisions, the SAP and the criteria used for the publication were generally similar.

The originally planned derivation of the non-inferiority margin to be used for the AcT study was not appropriate for regulatory decision making. The pre-specified non-inferiority (NI) margin of 5% derived from the meta-analysis of Emberson et al. (2014) was based on approx. 50% of a point estimate and an onset-to-treatment time (OTT) of 0-3 hours and is therefore considered to lack methodological rigour,

potentially overestimating the ALT effect due to restriction to the 0-3 time window and since it was not based on a confidence interval that would have taken the uncertainty in the effect estimate into account.

Based on a 0 - 4.5 hr time window, a 2% NI margin would result from this meta-analysis using 50% of the lower limit of the 95% confidence interval. However, there were substantially more subjects in the AcT trial treated within the 0-3 hour window as compared to the population included in the meta-analysis by Emberson (73% vs. 36%). Under the assumption that the difference in OTT was the main difference between the study populations and given the large impact of this important prognostic factor, a population adjusted NI margin was calculated to be 2.6% and could be considered appropriate under this assumption. However, there are remaining uncertainties due to the post-hoc determination of an appropriate NI margin, and as a potential deviation from the constancy assumption due to potential further effect modifiers, that may have been different between the populations, cannot be fully excluded. As the Applicant stated, there have been significant changes to the standard of care since the historical meta-analysis was conducted in 2014 and the patient population has changed. The arguments that the alteplase response rate for mRS0-1 at Day 90 in both the historical meta-analysis and in AcT was 34% and is perfectly constant overall, and that the risk ratio results for the primary endpoint also demonstrate non-inferiority generally support but do not provide clear evidence for the constancy assumption. The Applicant also provided a comparison of the distributions of prognostic factors between the historical meta-analysis and the AcT study. While the differences in OTT may point to a change in standard of care with regard to beginning of treatment, the demographic characteristics (age, gender, stroke severity) did not show a change in the patient population. In addition, the alteplase response rates for mRS0-1 at Day 90 for studies conducted between 1992 and 2014 did not show a time trend and the alteplase response rate in AcT falls within the range observed in historical studies, which is not strong evidence for the absence of changes in standard of care but does at least not show relevant changes in treatment outcomes over time.

The primary analysis of the AcT study was not pre-specified with respect to the confidence interval to be used for difference in proportion. A number of different methods to derive a confidence interval for a difference in proportion are available. Hence, post-hoc selection of the method is not considered to be a valid procedure. However, the Applicant provided on request the results from methods proposed by Newcombe RG (1998), Interval estimation for the difference between independent proportions: comparison of eleven methods. StatMed 17, 873-890, that were reassuring on the consistency of potential methods to be used.

While baseline demographics and disease characteristics in the Extend-IA TNK trial were generally balanced across groups, the median onset-to-thrombolysis-treatment time was 9 min shorter in the TNK vs. the ALT group and the TNK group had a somewhat lower proportion of females and slightly lower age. However, as in the provided subgroup analyses, the risk difference for the primary endpoint favoured TNK over ALT for all subgroups regarding age, OTT and gender, respectively, it is considered unlikely, that these slight imbalances had a relevant impact on the overall study results.

One of the studies (TRACE, 2021), included in the meta-analysis performed by the ESO (Alamowitch, 2023) was performed with a medicinal product that has not been proven to be biosimilar with Metalyse. Excluding this study, the pooled risk difference for mRS 0-1 at 90 days in patients with AIS of <4.5 h duration treated with TNK 0.25 mg/kg vs. a standard dose of ALT was 4.72% with a lower bound of the 95% CI of – 0.64, still meeting the NI criteria applied to the ESO meta-analyses. These data are not verifiable, as they are based on unpublished data. Nevertheless, taking into consideration that the results of the TRACE trial were not more favourable than the results of the original meta-analysis, it is plausible, that exclusion of the TRACE study did not negatively impact the results.

3.4. Unfavourable effects

Results derived from the main (AcT) study:

In the AcT trial, symptomatic intracranial haemorrhage (sICH) according to the pre-specified definition (any ICH being the main reason for neurological worsening; within 24 hours) was reported in 3.4% 27/800 TNK vs. 3.2% ALT patients.

The Applicant performed exploratory analyses of sICH replicating the SITS-MOST criteria as close as possible. Using the SITS-MOST criteria as defined in the IST-3 study (IST-3-SITS-MOST criteria), sICH occurred in 2.9% TNK vs. 2.7% ALT patients in the AcT study; the risk difference (95% CI) was 0.24% (-1.39% to 1.88%). Using the SITS-MOST criteria as defined in the randomised controlled studies by the Applicant (BI-RCTs-SITS-MOST criteria), sICH occurred in 2.4% TNK vs. 1.8% ALT patients in the AcT study; the risk difference (95% CI) was 0.54% (-0.88% to 1.96%).

Exploratory analyses of fatal sICH (i.e. sICH within 24 hours leading to death within 7 days); fatal ICH occurred in 2.0% TNK and 1.7% ALT patients; in the SmPC filtered population, fatal ICH occurred in 1.9% TNK and 1.8% ALT patients.

In the AcT study, up to day 90-120, overall 15.3% TNK and 15.4% ALT patients died, and up to day 90, overall 14.1% TNK and 14.5% ALT patients died.

Extracranial bleeding requiring blood transfusion occurred in 0.8% patients of both AcT study groups.

The incidence of angioedema in the AcT trial was 1.1% in both treatment groups and was almost identical (<1% each) in AIS patients receiving TNK (evaluated for 0.25mg/kg and 0.4 mg/mg combined) compared to patients receiving a standard dose of ALT.

In exploratory analyses of the AcT study, the incidence of fatal ICH in the overall group of patients thrombolysed in accordance with ALT SmPC inclusion criteria (i.e. excluding patients treated after 4.5 h and patients with baselind NIHSS> 25) was almost identical across study groups (1.9% TNK and 1.8% ALT patients, SmPC filtered population). However, in the subgroup of patients with severe stroke, i.e., NIHSS >25, fatal ICH occurred in 2 out of 25 TNK patients vs. none out of 14 ALT patients and the rate of death by any cause was also higher with TNK in this subgroup, i.e. 14/25 TNK vs. 3/14 ALT patients. These data are difficult to interpret as subject numbers with baseline NIHSS score > 25 was low. Nevertheless, as requested TNK for thrombolysis in AIS has been contraindicated in patients with severe stroke in line with the respective contraindication established for Actilyse.

Exploratory analyses of the AcT trial did not identify any clear imbalances of SAEs reported within 24 hours within the evaluated SAE categories (symptomatic intracerebral bleeding, peripheral bleeding with blood transfusion, peripheral bleeding, angioedema, and other SAE, respectively) by SOC or PT, respectively.

Results from the EXTEND-IA TNK study:

The safety profile of 0.25 mg TNK administered within 4.5 h of AIS in patients with LVO scheduled for mechanical thrombectomy was similar to that of a standard dose of ALT. In each group, 1 out of 101 subjects reported a sICH within 36 hours of treatment that was associated with a deterioration of ê4 points on the NIHSS within 36 hours of treatment. The overall incidence of death was numerically in favour of TNK vs. ALT (10% vs. 18%). Also, the overall incidence of SAEs or the evaluation of SAEs by reported term (up to day 3) did not raise any unexpected safety concerns.

Overall, no unexpected safety concerns with regard to safety of the intended 0.25 mg/kg TNK dose for thrombolysis in AIS within 4.5 h, were derived from the 12 investigator initiated trials or from the meta-analyses of published studies referenced by the Applicant.

In meta-analyses published by the European Stroke organisation (Alamowitch, 2023), the rates of sICH according to the individual study definition did not differ between AIS patients treated within 4.5 h with 0.25 mg/kg TNK vs. 0.9 mg/kg ALT.

3.5. Uncertainties and limitations about unfavourable effects

In principle the uncertainties identified for efficacy in investigator initiated trials also apply to safety. Specific to safety, only serious adverse events (SAEs) that started within 24 h of treatment were recorded in the AcT study. However, death was evaluated up to at least Day 90 and the mRS score, which was assessed after three months, can be considered a measure of the net-benefit-risk (at least with regard to critical AEs). The extent of uncertainties resulting from the 24 hour window for reporting SAEs is nevertheless considered limited, due to the short half-life of both thrombolytic agents (for TNK, the initial, dominant half-life is 24 ± 5.5 [mean ± SD] min), which are applied as a single dose and the established safety profile of TNK in STEMI and of ALT in both, the AIS as well as the STEMI indication.

The TRACE study (2021) included in the ESO meta-analysis (Alamowitch, 2023) used a biocopy, that has not been proven to be biosimilar with Metalyse. Neverthelss, Alamowitch et al. also performed a sensitivity analysis of sICH according to the SITS-MOST definition, using the studies that reported these events (i.e., Attest, TAAIS, Extend-IA TNK and TASTE-A, which all used medicinal products, that can be regarded as similar with Metalyse), which does not raise any safety concerns (unadjusted pooled OR, random-effects meta-analysis; OR=0.49; 95% CI: 0.12-2.08). In addition, a sensitivity analysis for any intracranial haemorrhage after excluding TRACE was provided in the published ESO meta-analysis and yielded similar results than the meta-analysis including this study (favouring TNK over ALT; unadjusted pooled OR, random-effects meta-analysis).

3.6. Effects Table

Table 33 Effects Table for Metalyse 5000 units powder for solution for injection. Proposed indication: in adults for the thrombolytic treatment of AIS within 4.5 hours from last known well and after exclusion of intracranial haemorrhage]

Effect	Short description	Unit	TNK	ALT	Uncertainties / Strength of evidence	References
Favourable Effects						
mRS 0-1 at day 90-120 (primary efficacy outcome)	• ITT; primary analysis; Pre-specified NI-margin: 5%	%	• 36.9	• 34.8	• Difference in proportion, unadjusted (95% CI): 2.1 (-2.6, +6.9)	AcT study
	• mITT • mPP (modified population: subset actually receiving IMP)		• 36.7 • 37.3	• 34.9 • 34.7	• 2.3 (-2.5, +7.0) • 2.6 (-2,2, +7.4)	AcT study, Exploratory analyses
mRS 0-2 at day 90-120	ITT analysis (functionally indepen-	%	56.4	55.6%	Difference in proportion, unadjusted (95% CI):	AcT study

Effect	Short description	Unit	TNK	ALT	Uncertainties / Strength of evidence	References
	dent)				0.8 (-4.1, +5.7)	
Substantial re-perfusion at initial angio-graphic assess-ment (primary effiacy outcome)	Reperfusion >50% of affected territory or absence of retrievable thrombus	%	22	10	Incidence difference (95% CI): 12% (2-21); Incidence ratio (95% CI): 2.2 (1.1-4.4); p=0.002 for non-inferioirty; p=0.03 for superiority)	EXTEND-IA TNK study
mRS 0-1 (secondary efficacy outcome)	excellent functional outcome	%	51	43	Incidence ratio, adjusted (95% CI): 1.2 (0.9 - 1.6), p=0.20; Odd ratio, adjusted (95% CI): 1.4 (0.8 – 2.6), p=0.23	EXTEND-IA TNK study
Unfavourable Effects						
sICH	Pre-specified definition (any ICH being main reason for neurological worsening; within 24 h)	%	3.4	3.2	Definition includes also less severe symptomatic ICH	AcT study
sICH	Replicating SITS-MOST criteria as close as possible; • IST3-SITS-MOST • BI-RCTs-SITS-MOST	%	 • 2.9 • 2.4	 • 2.7 • 1.8	Risk difference (95%CI): • 0.24% (-1.39% to 1.88%) • 0.54% (-0.88% to 1.96%)	AcT study, exploratory analyses
Fatal ICH	sICH within 24 h, leading to death within 7 days	%	2.0	1.7		AcT study, exploratory analyses
Extra-cranial bleeding requiring blood trans-fusion		%	0.8	0.8		AcT study
death	within 90 days of randomisation	%	15.3	15.4		AcT study
Angioedema		%	1.1	1.1		AcT study
sICH	Parenchymal	%	1	1		EXTEND-IA

Effect	Short description	Unit	TNK	ALT	Uncertainties / Strength of evidence	References
	hematoma type 2 leading to ⩾ 4 point increase in NIHSS score; within 36 hours					TNK study
death	any cause; up to 3 months	%	10	18		EXTEND-IA TNK study

Abbreviations: ALT: alteplase; IMP: investigational medicinal product; NI: non-inferiority; sICH: symptomatic intracranial haemorrhage; TNK: tenecteplase;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Stroke is one of the leading causes of death and disability worldwide. Acute ischaemic stroke (AIS) accounts for 87% of all cases of stroke and is primarily caused by thrombosis or embolism blocking the cerebral arteries. The only approved pharmacologic treatment of AIS is alteplase (ALT), which is used for intravenous thrombolysis within 4.5 hours after onset of stroke in eligible patients (i.e. in the absence of contraindications).

With the Act trial, the Applicant has provided data indicative of non-inferiority of beneficial effects of 0.25 mg/kg TNK vs. the approved dose of 0.9 mg/kg ALT in AIS patients eligible for intravenous thrombolysis within the established 4.5 h onset to treatment time based on the proportion of patients with an excellent functional outcome after three months. I.e., in the primary analysis of the primary endpoint 36.9% TNK patients and 34.8% ALT patients had an mRS of 0-1 at day 90–120 (ITT population), with a lower bound of the 95% CI of -2.6, meeting the pre-specified non-inferiority (NI) margin of -5%. The 5% margin was derived from the meta-analysis of Emberson et al. (2014), however, it was based on 50% of the point estimate and an onset-to-treatment time of 0-3 hours and is therefore considered to potentially overestimate the ALT effect. Based on a 4.5 hr time window a 2% NI margin (following the 95/50/95 method, i.e. using 50% of the lower limit of the 95% confidence interval from the meta-analysis) would result from this meta-analysis. However, there were substantially more subjects in the AcT trial treated within the 0-3 hour window as compared to the population included in the meta-analysis by Emberson (73% vs. 36%). Assuming that the difference in time windows for treatment was the main difference between the study populations and given the large impact of this important prognostic factor, a population adjusted NI margin was calculated to be 2.6% (also following the 95/50/95 method) and could be considered appropriate under this assumption. However, some uncertainties remain due to the post-hoc determination of an appropriate NI margin, and as a potential deviation from the constancy assumption due to potential further effect modifiers that may have been different between the populations cannot be finally excluded.

Of note, the 2.6% margin is still lower than the -3% NI-margin that was suggested by the European Stroke Organisation for the thrombolysis indication in AIS (Alamowitch, 2023). While the lower bound of the 95% CI of the primary analysis of the primary endpoint fell exactly upon this stricter NI margin of -2.6%, the analyses using the modified PP (-2.2%) as well as the modified ITT population (-2-5%) remained above this margin. The provided results of the re-analysis performed by the Applicant of the

investigator initiated AcT trial data were generally in line with the published results supporting credibility of results.

The impossibility of a conventional conclusion on effectiveness based on the AcT study is outweighed by additional arguments and data. Tenecteplase and alteplase are closely related molecules that share the same mechanism of action. They are both well-established standard options for the thrombolysis of acute myocardial infarction, where Tenecteplase is at least as effective as alteplase. Alteplase is, in addition, approved for the thromobolytic treatment of AIS within 4.5 hours after symptom onset, the indication now sought for tenecteplase.

TNK has a well-known MoA as thrombolytic agent and a well-established efficacy and safety profile in the treatment of acute myocardial infarction. Effective lysis of thrombi in other arteries of the body, e.g. in the brain, can therefore principally be expected. The Extend-IA TNK study was designed for non-inferiority which was shown and additionally showed that the thrombolytic ability of the intended 0.25 mg/kg TNK dose may even be superior to that of the established ALT dose without a higher risk for sICH. While the restoration of perfusion is a physiological rather than clinical endpoint, it is the manifestation of the direct mechanistic effect of tenecteplase, which does not exert efficacy in any other way. Therefore, the results of the EXTEND-IA TNK strongly support that tenecteplase is at least equally effective as alteplase, in the treatment of AIS.

The provided meta-analyses of published studies show consistency with the results of the Act study and none of the individual studies contradicts the results of the AcT study. Based on published data and own meta-analyses, the medical community concluded that TNK and ALT are similar in efficacy and safety also for the AIS indication, as reflected by the inclusion of tenecteplase in clinical treatment guidelines. Although, all of the studies referred to for demonstration of efficacy of TNK in AIS have some limitations, the totality of the evidence indicates comparable efficacy and safety of TNK and ALT for thrombolysis in AIS patients within the 4.5 hour treatment window.

No clinically relevant differences in the overall safety profile of TNK vs. ALT are discernible from the AcT study based on the provided data, including the incidence of death. In the AcT trial, the incidence of sICH within 24 hours of treatment using the pre-specified definition as well as re-analyses of sICH excluding less severe events was numerically slightly higher in the TNK vs. ALT group. Nevertheless, this did not lead to a deleterious effect on functional outcome or to an increased incidence of death, as the proportion of TNK subjects with excellent or functional independent outcome (mRS 0-1 and mRS 0-2), respectively, was numerically somewhat higher whereas the death rate was somewhat lower in TNK vs. ALT treated subjects.

Based on a slightly higher incidence of fatal ICH (2 vs. 0 cases) and a higher overall death rate with TNK (14/25) compared to ALT (3/14) in the subgroup of patients with severe stroke, i.e. NIHSS> 25, TNK has been contraindicated in patients with severe stroke in line with the respective contraindication of Alteplase.

In the Extend-IA TNK study in patients with large vessel occlusion (LVO) scheduled for mechanical thrombectomy, a similar safety profile of 0.25 mg TNK vs. standard dose of ALT was observed, with a 1% sICH rate in both groups while the overall incidence of death was numerically in favour of TNK.

The meta-analyses published by the European Stroke organisation (Alamowitch, 2023) further supports efficacy and safety of TNK in the sought AIS indication, acknowledging that a non-inferiority proof by a meta-analysis of known studies is considered to have less confirmatory value. One of the studies (TRACE, 2021) included in this meta-analysis used a medicinal product, that has not been proven to be biosimlar with Metalyse. However, as the results of this rather small individual study were not more favourable than the overall meta-analyses results, it is plausible that exclusion of the TRACE study does not negatively impact the published results of the meta-analysis in line with unpublished data.

The TNK posology proposed for AIS is fully in line with the regimen used in the AcT and EXTEND-IA TNK trials, i.e. 0.25 mg/kg given in 5 dose tiers and is endorsed.

There is no clear evidence of an increased efficacy of the 0.4 mg/kg compared to the 0.25 mg/kg dose (as evaluated in the Extend-IA TNK part 2 study). However, the 0.4 mg/kg TK dose led to an excess in sICH and mortality, at least in elderly patients and in patients with more severe stroke (in the Nor-Test 2, Part A study).

3.7.2. Balance of benefits and risks

The benefits of TNK in AIS patients eligible for intravenous thrombolysis within 4.5 hours of stroke onset on functional outcome needs to be weighed against the risk of symptomatic intracranial haemorrhage (sICH), which constitutes the main safety concern of thrombolysis in AIS. Overall, the provided data indicate that the thrombolytic effect and the effect on excellent functional outcome (mRS 0-1) of 0.25 mg/kg TNK in AIS is non-inferior to the effect of the approved standard dose of ALT and also suggest an overall similar safety profile (including the risk of symptomatic ICH).

3.7.3. Additional considerations on the benefit-risk balance

The Applicant has developed an AIS only formulation containing 25 mg TNK, i.e. the maximum intended dose in this indication, in addition to the 40 mg and 50 mg strengths approved for STEMI. This is appreciated as the new presentation may potentially mitigate the risk of overdosing in AIS and is expected to reduce waste, the latter being particularly important in the context of the current supply shortage of Metalyse.

In contrast to the STEMI indication, the Applicant applies for a vial presentation of the intended TNK strength without a syringe, that is appropriately graded according to the intended BW adjusted dose tiers. A combined kit may be valuable for the AIS population as well and a respective development is recommended to the Applicant.

TNK (given as a bolus injection) can be administered more rapidly than ALT (which is infused over one hour). While advantages of TNK due to ease of the single bolus administration are claimed over ALT (including reduction of time-intervals and potential misdosing), it has not been proven through adequate studies, that these advantages would translate into an improved outcome with TNK vs. ALT.

However, bolus administration of TNK is faster than the one hour infusion of ALT and it is acknowledged, that the administration of TNK is generally more easy to use than ALT which is advantageous regarding patient management and may potentially lead to an improved benefit.

3.8. Conclusions

The overall B/R of Metalyse 25 mg (5 000 U) powder for solution of injection is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.e.5.c	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	Type II	I, IIIA, IIIB and A
B.II.e.1.b.2	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	Type II	None
B.II.b.3.a	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	Type IB	None

Grouped application consisting of:
C.I.6.a (Type II): To add the new therapeutic indication Acute Ischemic Stroke (AIS) for the new 25 mg (5,000 mg) presentation. Consequently, a separate SmPC and Package Leaflet are provided for the 25 mg presentation with the new indication. In addition, the MAH took the opportunity to implement editorial changes and minor updates to the PI of Metalyse 40 mg (8,000 U) and 50 mg (10,000 U).
B.II.e.5.c (Type II): To add the new 25 mg (5,000 mg) presentation for the sterile parenteral biological medicinal product Metalyse (tenecteplase) powder for solution for injection.
B.II.b.3.a (Type IB, by default): Minor changes in the manufacturing process of 25 mg (5,000 mg) presentation for the sterile parenteral biological medicinal product Metalyse (tenecteplase) powder for solution for injection to add a new DP filling line, to adapt freeze-drying cycle for lyophilization process, to replace unsuitable sterile filter with suitable one in the new filling line, to add three In-Process controls (IPCs), and to increase the batch size.
B.II.e.1.b.2 (Type II): Change in the immediate packaging of 25 mg presentation for the sterile parenteral biological medicinal product Metalyse (tenecteplase) powder for solution for injection to introduce a new rubber stopper.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIA, IIIB and A are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Metalyse-H-C-000306-II-0070-G’