NICE National Institute for Health and Care Excellence

# Cost Comparison Appraisal

# Tenecteplase for treating acute ischaemic stroke [ID6306]

# Committee Papers

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## COST COMPARISON APPRAISAL

## Tenecteplase for treating acute ischaemic stroke [ID6306]

**Contents:**

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Boehringer Ingelheim:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Clarification response appendix

3. **Professional group submissions** from:
   a. Association of British Neurologists (ABN)
   b. British and Irish Association of Stroke Physicians (BIASP)
   c. St George's University Hospital (part of Royal College of Physicians)

4. **Expert personal perspectives** from:
   a. Dr. Ajay Bhalla – clinical expert, nominated by BIASP
   b. Prof. Keith Muir – clinical expert, nominated by ABN

5. **External Assessment Report** prepared by Peninsula Technology Assessment Group

6. **External Assessment Group response to factual accuracy check of EAR**

*Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.*

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Single technology appraisal: cost-comparison

# Tenecteplase for thrombolytic treatment of acute ischaemic stroke [ID6306]

# Document B

# Company evidence submission

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID6306 Tenecteplase Document B redacted | Redacted | No - redacted | 14 March, 2024 |



 

# Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) when a cost-comparison case is made as part of the single technology appraisal process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 100 pages, excluding appendices and the pages covered by this template. If it is too long it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE health technology evaluation guidance development manual.

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# Tables and figures





# Abbreviations

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AIS | Acute ischaemic stroke |
| AMI | Acute myocardial infarction |
| CI | Confidence interval |
| CT | Computed tomography |
| CTA | Computed tomographic angiography |
| DSA | Deterministic sensitivity analyses |
| DTN | Door-to-needle |
| EPAR | European Public Assessment Report |
| ESO | European Stroke Organisation |
| EVT | Endovascular thrombectomy |
| HCRU | Healthcare resource use |
| HRQL | Health-related quality of life |
| ICH | Intracerebral haemorrhage |
| IQR | Interquartile range |
| ITT | Intention-to-treat |
| IV | Intravenous |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| mRS | Modified Rankin scale |
| MRI | Magnetic resonance imaging |
| NHS | National Health Service |
| NIHSS | National Institutes of Health Stroke Scale |
| OPTIMISE | Optimizing Patient Treatment in Major Ischemic Stroke With EVT |
| PROBE | Prospective, multicentre, randomized, open-label, blinded-endpoint |
| QuiCR | Quality Improvement and Clinical Research registry |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SE | Standard error |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| VAS | Visual analogue scale |



# B.1. Decision problem, description of the technology and clinical care pathway

## *B.1.1. Decision problem*

The submission covers the technology's full marketing authorization for this indication. A summary of how the decision problem is addressed by this submission is presented in Table 1.



**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | People with acute ischaemic stroke who can have thrombolytic treatment | Adults for the thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well and after exclusion of intracranial haemorrhage | As per marketing authorization |
| **Intervention** | Tenecteplase | As per final scope | N/A |
| **Comparator(s)** | Other established clinical management without tenecteplase including:<br>• Alteplase | As per final scope | N/A |
| **Outcomes** | The outcome measures to be considered include:<br>• Disability or change in daily activities status<br>• Functional recovery<br>• Neurological deficit<br>• Mortality<br>• Length of hospital stay<br>• Adverse effects of treatment, including bleeding events<br>• Health-related quality of life | As per final scope | N/A |



| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Economic analysis** | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.<br>Costs will be considered from an NHS and Personal Social Services perspective. | Tenecteplase has demonstrated similar clinical efficacy to alteplase at lower costs. Hence, a cost-comparison model has been developed. | Compared with alteplase, tenecteplase is associated with non-inferior efficacy and equivalent safety outcomes. Tenecteplase is also associated with treatment cost savings and time saved in administration.<br>The evidence on efficacy and safety for this submission is based on two clinical trials, AcT[1, 2] and EXTEND-IA TNK Part 1.[3, 4]<br><br>**AcT**<br>• In patients with AIS presenting within 4.5 hours of stroke symptom onset, tenecteplase demonstrated a clinically relevant non-inferiority to alteplase for the primary outcome of excellent functional outcome (measured as mRS score 0–1) at 90–120 days.[1, 2] The direction of the effect favoured tenecteplase; however, this was not statistically significant.<br>• These results were consistent across all pre-specified subgroups, including: age (< 80 vs ≥ 80 years), sex, baseline stroke severity, symptom onset-to-needle time, large vessel occlusion, type of enrolling centre, and source registry for both ITT and per-protocol populations.<br>• There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage, extracranial bleeding, or 90-day mortality. |



| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| | | | **EXTEND-IA TNK Part 1**<br>• In patients with AIS presenting within 4.5 hours of stroke symptom onset, tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome (measured as mRS score at 90 days) compared with alteplase.[3, 4]<br>• There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage or 90-day mortality. |
| **Subgroups to be considered** | If the evidence allows, the following subgroup will be considered:<br>• Subgroups by time to treatment (0 to 3 hours and 3 to 4.5 hours) | Clinical evidence presented for this subgroup, but not cost-effectiveness evidence | Evidence from two large, well-conducted randomized controlled trials demonstrate that the results of tenecteplase treatment versus alteplase are applicable to the whole AIS target population (Subgroup Analysis, Appendix E).[2, 3] Hence, subgroup analyses including the one suggested in the final scope are not justified. |
| **Special considerations including issues related to equity or equality** | Guidance will only be issued in accordance with the marketing authorization. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorization granted by the regulator. | N/A | N/A |
| **Key:** AIS, acute ischaemic stroke; ITT, intention-to-treat; mRS, modified Rankin scale; N/A, not applicable; NHS, National Health Service. | | | |



## *B.1.2. Description of the technology being evaluated*

The draft Summary of Product Characteristics (SmPC) and the draft European Public Assessment Report (EPAR) are presented in Appendix C.

Table 2 provides a summary of the technology being appraised.

**Table 2: Technology being evaluated**

| | |
|---|---|
| **UK approved name and brand name** | Tenecteplase (Metalyse®) |
| **Mechanism of action** | Tenecteplase is a recombinant fibrin-specific plasminogen activator that is derived from native tissue-type plasminogen activator 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 (plasminogen activator inhibitor-1) compared with native tissue-type plasminogen activator. |
| **Marketing authorization/CE mark status** | MHRA International Recognition Procedure using EU as the reference regulator, with a best-case marketing authorization date of [redacted]. |
| **Indications and any restriction(s) as described in the summary of product characteristics (SmPC)** | Tenecteplase is indicated in adults for the thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well and after exclusion of intracranial haemorrhage.<br>Tenecteplase must be prescribed by physicians experienced in neurovascular care and the use of thrombolytic treatment, with the facilities to monitor that use.<br>Treatment with tenecteplase must be initiated as early as possible and no later than 4.5 hours after last known well and after exclusion of intracranial haemorrhage by appropriate imaging techniques. The treatment effect is time-dependent; therefore, earlier treatment increases the probability of a favourable outcome.<br>The appropriate presentation of tenecteplase product should be chosen carefully and in line with the indication. The product licence states any unused tenecteplase in the vial should be disposed of once the required dose is prepared. The recommended dose of tenecteplase in AIS is up to 25 mg. In order to minimize product wastage, the 25 mg presentation of tenecteplase is only intended for use in AIS. |
| **Method of administration and dosage** | Tenecteplase for AIS is supplied as 25 mg vials, which contain the maximum dose for this indication. |



| | |
|---|---|
| | The reconstituted solution should be administered intravenously and is for immediate use. Any unused reconstituted solution should be discarded.<br>The reconstituted solution is a clear and colourless to slightly yellow solution.<br>Tenecteplase should be administered on the basis of body weight. The recommended dose is 0.25 mg/kg (up to 25 mg) as a single intravenous bolus over approximately 10 seconds. |
| **Additional tests or investigations** | Intracranial haemorrhage must be excluded by appropriate imaging techniques. |
| **List price and average cost of a course of treatment** | [redacted] for a 25 mg vial, which is the maximum dose. |
| **Patient access scheme/commercial arrangement (if applicable)** | Not applicable. |
| **Key:** AIS, acute ischaemic stroke; MHRA, Medicines and Healthcare products Regulatory Agency; SmPC, Summary of Product Characteristics.<br>**Source:** Tenecteplase SmPC.[5] | |

## *B.1.3. Health condition and position of the technology in the treatment pathway*

### B.1.3.1. Disease overview

Stroke is the fifth leading cause of disability, the fourth leading cause of death and the third leading cause of premature mortality in the UK.[6-8] Stroke is a neurological disorder characterized by impaired perfusion in the brain, which can lead to death of brain cells and cerebral damage.[9] In the UK, approximately 100,000 people have a stroke each year.[10, 11] In 2021/2022, there were 1,187,756 stroke survivors in England and Wales, giving a prevalence rate of approximately 1.89%.[12] The median age of patients presenting with stroke in the UK is 73 years in males and 79 years in females.[13] Mortality statistics in England and Wales from 2022 indicate that 29,265 people died from cerebrovascular diseases (including strokes).[8]

Acute ischaemic stroke (AIS) is the most common type of stroke, accounting for 85% of total stroke cases.[10] AIS is caused by a clot obstructing blood flow, resulting in deficient blood and oxygen supply to the brain.[9] This leads to progressive



inflammation, brain tissue death and neuronal damage.[9, 14-19] If blood flow is not restored in a timely manner, further damage and tissue loss occurs, mainly due to inflammation and cytokine-mediated cytotoxicity.[15-19] It is estimated that for every minute of AIS-related large vessel occlusion, 1.9 million neurons are lost, which is equivalent to 3.6 years of age-related neuronal loss per hour.[20] Therefore, timely restoration of blood flow is crucial for positive patient outcomes.

### B.1.3.2. Disease burden

AIS leads to physical and cognitive symptoms. The effects of AIS depend on the location of the infarct and the extent of the damaged area. Common physical impairments include paralysis or weakness of the affected side of the body, pain, dysarthria (difficulty speaking), dysphagia (difficulty swallowing) and fatigue.[21] While physical symptoms can improve over time, many patients experience problems beyond 6 months, which can cause serious distress.[22-24] Cognitive impairment can also cause significant burden to patients independently of physical symptoms.[25] Mild-to-severe cognitive impairment is reported by approximately 60% of patients in the first year post-stroke, affecting memory, language, attention, executive function and perceptual motor domains. Much like physical symptoms, cognitive impairment can improve over time; though it is unlikely to return to pre-AIS levels of ability and can lead to mental health decline and depression.[26-28,]

Given the range of physical and cognitive symptoms, each with their associated burden, AIS can substantially impact patient health-related quality of life (HRQL) including functional independence and activities of daily living. Patients report significant decreases in EQ-5D™ index scores post-stroke compared with healthy controls, indicating reduced HRQL.[29-31] Across studies, usual activity was the most impacted dimension, with anxiety/depression, pain/discomfort and mobility dimensions moderately affected. Studies also report sex differences in HRQL post-stroke, with women often reporting lower EQ-5D-5L index scores and higher number of problems in mobility, usual activities, pain/discomfort and anxiety/depression than men.[32]



Caregivers of AIS patients also experience substantial burden. The role of informal caregivers in AIS varies depending on the severity of the initial stroke and related comorbidities.[33] It has been reported that reduction in physical function and quality of life in patients with stroke increases caregiver burden.[34-37] The main drivers of caregiver burden include high numbers of hours spent caregiving and disturbed sleep, leading to both anxiety and depression in the informal caregiver. Aggregate annual cost of unpaid care provided by family and other unpaid carers is £15.8 billion.[38]

### B.1.3.3. Current pathway of care

Treatment options for AIS are limited; in the hyperacute phase (the initial hours following the onset of a stroke, typically within the first six hours), intravenous (IV) thrombolysis is the standard of care for restoration of blood flow, along with mechanical thrombectomy in patients with large vessel occlusion.[39-41] Alteplase is the approved standard of care for thrombolysis in AIS in the UK. Clinical guidelines recommend that thrombolysis with alteplase is initiated as soon as possible, and within 4.5 hours of symptom onset, in line with the licensed indication.[39-43]

However, current guidelines also recommend the off-label use of alteplase and tenecteplase (Table 3). Clinical guidelines recommend that thrombolysis with off-label alteplase can be considered between 4.5 and 9 hours post symptom onset, provided there is imaging evidence (computed tomography [CT]/magnetic resonance imaging [MRI]) of salvageable brain tissue.[41] Clinical guidelines also recommend the off-label use of AMI-licensed tenecteplase for patients with AIS in whom treatment can be started within 4.5 hours of known onset and who are eligible for IV thrombolysis.[39, 41]

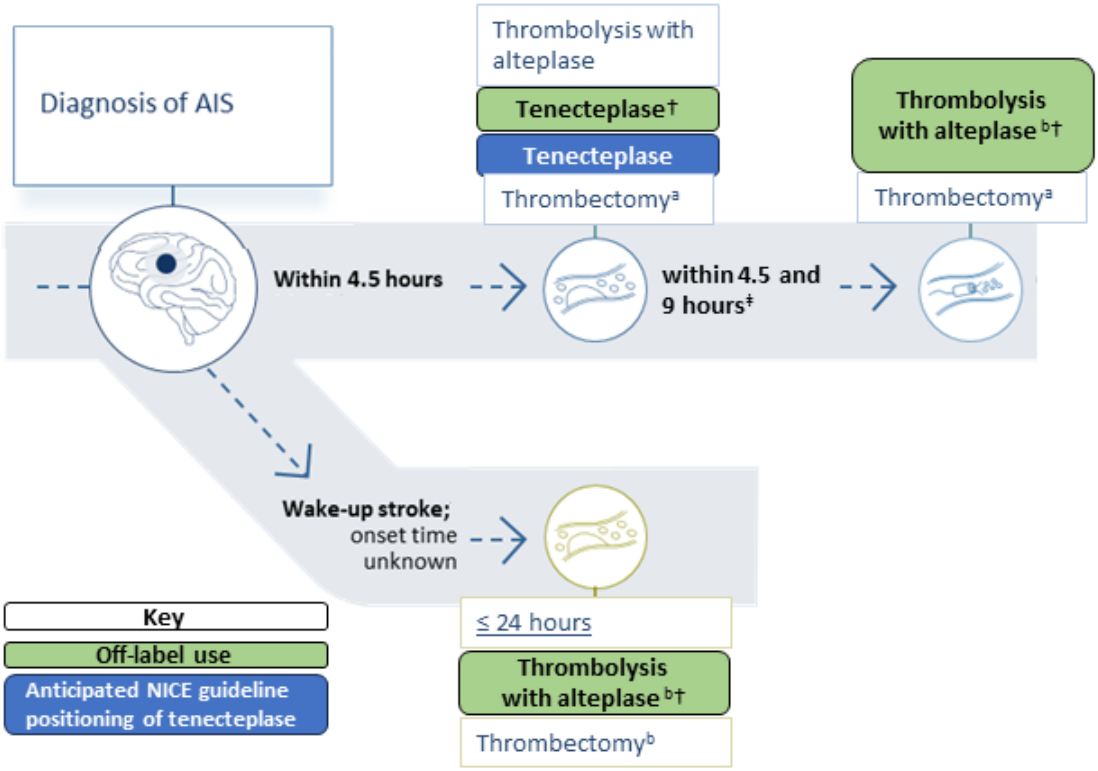
In patients with large vessel occlusion, mechanical thrombectomy following thrombolysis is recommended within 6 hours of symptom onset, where possible.[39-41] Mechanical thrombectomy is also recommended as a standalone procedure in patients who are not eligible for thrombolysis or for whom thrombolysis is contraindicated.



Figure 1 presents the current clinical pathway of care for AIS in the UK including the proposed positioning of tenecteplase. Tenecteplase supplied as 25 mg vials is indicated in adults for the thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well and after exclusion of intracranial haemorrhage.[5] Therefore, as described in Section B.1.1, alteplase is the only relevant comparator in this submission.

**Figure 1: Clinical pathway of care for patients with AIS and anticipated positioning of Tenecteplase**




**Key**: AIS, acute ischaemic stroke; CT, computed tomography; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.
**Notes**: †Denotes off-label use within the National Clinical Guideline for Stroke for the UK and Ireland. ‡ National Clinical Guideline for Stroke for the UK and Ireland. [a] Confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA. [b] Confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA and if there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume.
**Sources**: National Clinical Guideline for Stroke for the UK and Ireland.[41]



Guidance on the treatment of AIS is available in the:

- 2019 NICE Guideline on the treatment of stroke and transient ischaemic attack (NG 128)[40];
- 2023 National Clinical Guideline for Stroke for the UK and Ireland[41]; and
- 2023 and 2021 European Stroke Organisation (ESO) guidelines[39, 42].

Alteplase is the approved standard of care for AIS, but the 2023 National Clinical Guideline for Stroke for the UK and Ireland and 2023 ESO guidelines also recommend the off-label use of tenecteplase in patients with AIS.[39, 41] A summary of the key recommendations from the guidelines is provided in Table 3.



**Table 3: Key recommendations from relevant clinical guidelines**

| Organization | Recommendations |
|---|---|
| NICE, 2019[40] | • Alteplase is recommend within its marketing authorization for treating AIS in adults if:<br>– Treatment is started as soon as possible within 4.5 hours of onset of stroke symptoms **and**<br>– Intracranial haemorrhage has been excluded by appropriate imaging techniques<br>• Offer thrombectomy as soon as possible and within 6 hours of symptom onset, together with IV thrombolysis (if not contraindicated and within the licensed time window), to people who have:<br>– AIS **and**<br>– Confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA, taking into account the factors in Appendix J<br>• Offer thrombectomy as soon as possible to people who were last known to be well between 6 hours and 24 hours previously (including wake-up strokes):<br>– Who have AIS and confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA **and**<br>– If there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume taking into account the factors in Appendix J<br>• Consider thrombectomy together with IV thrombolysis (where not contraindicated and within the licensed time window) as soon as possible for people last known to be well up to 24 hours previously (including wake-up strokes):<br>– Who have AIS and confirmed occlusion of the proximal posterior circulation (that is, basilar or posterior cerebral artery) demonstrated by CTA or MRA **and**<br>– If there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume taking into account the factors in Appendix J |
| National Clinical Guideline for Stroke for the UK and Ireland, 2023[41] | • Patients with AIS, regardless of age or stroke severity, in whom treatment can be started within 4.5 hours of known onset, should be considered for thrombolysis with alteplase or tenecteplase<br>• Patients with AIS, regardless of age or stroke severity, who were last known to be well more than 4.5 hours earlier, should be considered for thrombolysis with alteplase if:<br>– Treatment can be started between 4.5 and 9 hours of known onset, or within 9 hours of the midpoint of sleep when they have woken with symptoms **and** |



| Organization | Recommendations |
|---|---|
| | – They have evidence from CT/MR perfusion or MRI of the potential to salvage brain tissue (see Appendix J)<br>• Patients with AIS eligible for mechanical thrombectomy should receive prior IV thrombolysis (unless contraindicated) irrespective of whether they have presented to an acute stroke centre or a thrombectomy centre. Every effort should be made to minimize process times throughout the treatment pathway, and thrombolysis should not delay urgent transfer to a thrombectomy centre<br>• Patients with acute anterior circulation ischaemic stroke, who were previously independent (mRS score 0–2), should be considered for combination IV thrombolysis and intra-arterial clot extraction (using a stent retriever and/or aspiration techniques) if they have a proximal intracranial large artery occlusion causing a disabling neurological deficit (NIHSS score of 6 or more) and the procedure can begin within 6 hours of known onset<br>• Patients with acute anterior circulation ischaemic stroke and a contraindication to IV thrombolysis but not to thrombectomy, who were previously independent (mRS score 0–2), should be considered for intra-arterial clot extraction (using a stent retriever and/or aspiration techniques) if they have a proximal intracranial large artery occlusion causing a disabling neurological deficit (NIHSS score of 6 or more) and the procedure can begin within 6 hours of known onset<br>• Patients with acute anterior circulation ischaemic stroke and a proximal intracranial large artery occlusion (ICA and/or M1) causing a disabling neurological deficit (NIHSS score of 6 or more) of onset between 6 and 24 hours ago, including wake-up stroke, and with no previous disability (mRS score 0 or 1) should be considered for intra-arterial clot extraction (using a stent retriever and/or aspiration techniques, combined with thrombolysis if eligible) providing the following imaging criteria are met:<br>– Between 6 and 12 hours: an ASPECTS score of 3 or more, irrespective of the core infarct size<br>– Between 12 and 24 hours: an ASPECTS score of 3 or more and CT or MRI perfusion mismatch of greater than 15 mL, irrespective of the core infarct size<br>• Patients with AIS in the posterior circulation within 12 hours of onset should be considered for mechanical thrombectomy (combined with thrombolysis if eligible) if they have a confirmed intracranial vertebral or basilar artery occlusion and their NIHSS score is 10 or more, combined with a favourable PC-ASPECTS score and Pons-Midbrain Index. Caution should be exercised when considering mechanical thrombectomy for patients presenting between 12 and 24 hours of onset and/or over the age of 80 owing to the paucity of data in these groups |



| Organization | Recommendations |
|---|---|
| ESO, 2021[42] | • For patients with AIS of < 4.5-hour duration, the guideline recommends IV thrombolysis with alteplase<br>• For patients with AIS of 4.5–9-hour duration (known onset time), and with no brain imaging other than plain CT, the guideline recommends no IV thrombolysis<br>• For patients with ischaemic stroke of 4.5–9-hour duration (known onset time) and with CT or MRI core/perfusion mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, the guideline recommends IV thrombolysis with alteplase<br>• For patients with ischaemic stroke of 4.5–9-hour duration (known onset), and with no CT or MRI core/perfusion mismatch, nine of nine group members suggest against IV thrombolysis with alteplase<br>• For patients with AIS on awakening from sleep, who were last seen well more than 4.5 hours earlier, who have MRI DWI-FLAIR mismatch, and for whom mechanical thrombectomy is either not indicated or not planned, the guideline recommends IV thrombolysis with alteplase<br>• For patients with AIS on awakening from sleep, who have CT or MRI core/perfusion mismatch within 9 hours from the midpoint of sleep, and for whom mechanical thrombectomy is either not indicated or not planned, the guideline recommends IV thrombolysis with alteplase<br>• For patients with AIS of < 4.5-hour duration and not eligible for thrombectomy, the guideline suggests IV thrombolysis with alteplase over IV thrombolysis with tenecteplase*<br>• For patients with AIS of < 4.5-hour duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom IV thrombolysis is considered before thrombectomy, the guideline suggests IV thrombolysis with tenecteplase 0.25 mg/kg over IV thrombolysis with alteplase 0.9 mg/kg |
| ESO, 2023[39] | • For patients with AIS of < 4.5-hour duration who are eligible for IV thrombolysis, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg<br>• For patients with AIS of < 4.5-hour duration who are eligible for IV thrombolysis, we recommend against using tenecteplase at a dose of 0.40 mg/kg<br>• For patients with AIS of < 4.5-hour duration with prehospital management with a mobile stroke unit who are eligible for IV thrombolysis, we suggest tenecteplase 0.25 mg/kg over alteplase 0.90 mg/kg to increase the rate of early reperfusion and to shorten the time from imaging to treatment initiation |



| Organization | Recommendations |
|---|---|
| | • For patients with large vessel occlusion AIS of < 4.5-hour duration who are eligible for IV thrombolysis, we recommend tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg. IV thrombolysis should not delay mechanical thrombectomy<br>• For patients with AIS on awakening from sleep or AIS of unknown onset who are selected with no brain imaging other than plain CT, we recommend against IV thrombolysis with tenecteplase 0.25 mg/kg outside the context of a clinical trial<br>• For patients with AIS on awakening from sleep or AIS of unknown onset and who are eligible for IV thrombolysis, there is continued uncertainty over the potential benefits and harms of tenecteplase compared with alteplase |

**Key:** AIS, acute ischaemic stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; CTA, computed tomographic angiography; DWI-FLAIR, diffusion-weighted MRI and fluid-attenuated inversion recovery MRI; ESO, European Stroke Organisation; ICA, internal carotid artery; IV, intravenous; M1, first segment; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PC-ASPECTS; posterior circulation – Alberta Stroke Program Early Computed Tomography Score.
**Notes:** * 2023 EMO guidelines have superseded this guideline.
**Sources:** Alamowitch et al. 2023[39], Berge et al. 2021[42]; NG123[40], National Clinical Guideline for Stroke for the UK and Ireland, 2023.[41]



### B.1.3.4. Unmet need

Treatment options for AIS are limited and are aimed at optimizing time to reperfusion (See Section B.1.3.3). In eligible patients, reperfusion through thrombolysis or mechanical thrombectomy can enhance prognosis and functional outcomes.[44] However, thrombolytic treatment has a narrow therapeutic time window, with both prognosis and functional outcomes declining as time to treatment increases. As shorter door-to-needle (DTN) times have been associated with better recovery in patients with AIS[44-46], improving speed of administration of thrombolytics has the potential to greatly improve patient outcomes.

Alteplase was originally granted UK marketing authorization for use in AIS within 3 hours of the onset of symptoms in September 2002.[47] In March 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) approved the use of alteplase within 4.5 hours of the onset of symptoms, and alteplase was subsequently recommended by NICE for the updated indication in September 2012 (TA264).[47] Alteplase remains the only approved thrombolytic treatment for patients with AIS.[40]

Despite remaining the standard of care, treatment with alteplase has been associated with several limitations. The complex administration regimen of alteplase (with 10% of the total dose administered as an initial IV bolus, immediately followed by the remainder of the total dose infused intravenously over 60 minutes) has been associated with treatment delay and potential complications, with a subsequent impact on patients' overall health outcome.[48-53] Alteplase requires patient-specific weight-based dosing (0.9 mg/kg to a maximum of 90 mg) and is administered as an initial bolus followed by an IV infusion for 60 minutes.[54] This means that a long time is needed for dosing to be completed. Monitoring is also required throughout the 1-hour infusion, further increasing treatment delay for those eligible for subsequent mechanical thrombectomy and complicating inter-hospital transfer for patients presenting at an acute stroke centre who require transport to a comprehensive stroke centre for mechanical thrombectomy.[54, 55] Even when patients arrive at a comprehensive stroke centre that provides mechanical thrombectomy, the administration of alteplase has been associated with a delay in the initiation of



mechanical thrombectomy.[56, 57] Delays in treatment administration may cause a drop in plasma concentration of alteplase, potentially making thrombolysis less effective.[48] Additionally, increased DTN times have been associated with increased all-cause mortality and all-cause readmission at 1 year, suggesting that the complex administration regimen necessitated by alteplase may be a barrier to achieving optimal outcomes in patients with AIS.[50]

As described in Section B.1.3.3, due to easier/faster administration versus alteplase, clinical guidelines also recommend the off-label use of tenecteplase 0.25 mg/kg for the treatment of AIS.[39, 41] This has led to the off-label use of commercialized AMI-specific tenecteplase supplied in 50 mg vials, resulting in excess use of healthcare resources due to wastage of unused drug.

Overall, the complex and time-consuming administration of alteplase, and the off-label use of AMI-licensed tenecteplase highlights the unmet need for a quick, easy-to-administer, and AIS-dedicated thrombolytic that improves patient management and reduces associated costs while providing equivalent efficacy and safety to alteplase.

### *B.1.4. Equality considerations*

No equality issues are anticipated.



## B.2. Key drivers of the cost-effectiveness of the comparator(s)

### *B.2.1. Clinical outcomes and measures*

For the NICE appraisal of alteplase (TA264) a cost–utility approach was undertaken, assuming that alteplase offered a survival benefit over the standard care at the time (standard medical and supportive management that does not include alteplase). This survival benefit was maintained for up to 6 months; the Committee noted that there was uncertainty in the long-term relative effectiveness of alteplase versus standard care given the lack of both long-term data and any statistically significant effect of alteplase on mortality when compared to placebo. As results from the two pivotal trials, AcT and EXTEND-IA TNK Part 1 demonstrate that tenecteplase has a similar efficacy and safety profile to alteplase, equal clinical outcomes are assumed. The committee also noted that the lack of adjustment to utility values over-time was a limitation, but acknowledged that results were unlikely to be sensitive to this. For this submission, as differences in effectiveness are not modelled this limitation will not be applicable.

### *B.2.2. Resource use assumptions*

Resource use assumptions used in this analysis are informed by the NICE appraisal TA264 for the comparator alteplase. These assumptions are outlined in Table 4 and were deemed reasonable by both the Committee and the independent evidence review group.

**Table 4: Comparator resource use assumptions**

| Comparator evaluation | Key resource costs associated with comparator(s) | Committee's preferred assumptions in NICE evaluation of comparator(s) |
|---|---|---|
| TA264[47] | The main resource use to the NHS associated with alteplase was the cost of additional staffing requirements for an extended administration window (i.e. treatment administration costs). | Input parameters such as resource use informing treatment administration costs were concluded as reasonable. |



| Comparator evaluation | Key resource costs associated with comparator(s) | Committee's preferred assumptions in NICE evaluation of comparator(s) |
|---|---|---|
| TA264[47] | AE costs included intracranial haemorrhage, captured in the model as a one-off cost relating to the CT scan needed when this AE is experienced. | The Committee concluded that this approach was reasonable. |
| **Key**: AE, adverse event; CT, computed tomography; NHS, National Health Service. | | |



# B.3. Clinical effectiveness

## *B.3.1. Identification and selection of relevant studies*

See Appendix D for full details of the systematic literature review (SLR) process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

The SLR identified 27 unique trials reported by 39 publications in the full data synthesis, and six trial registry records reporting six ongoing trials were included in a summary data synthesis as results of these trials were not yet published at time of review. Of these studies, only two (AcT and EXTEND-IA TNK) were considered relevant to the decision problem specified in the final scope (Table 1); both are head-to-head, randomized controlled studies of tenecteplase versus the comparator of interest in this submission, alteplase.

## *B.3.2. List of relevant clinical effectiveness evidence*

A summary of the most relevant clinical effectiveness evidence for tenecteplase is presented in Table 5.

The two pivotal trials for tenecteplase in patients with AIS are the Phase III trial AcT and the Phase II trial EXTEND-IA TNK Part 1. These two studies have been used to support the application for marketing authorization and are the largest, most robust, Phase II and III randomized, controlled, non-inferiority trials directly comparing the relevant dose of tenecteplase to the comparator of interest in this submission, alteplase. Full details of the pivotal trials are provided in Sections B.3.3 to B.3.5 of this submission. Reasons for the exclusions of other trials including tenecteplase are detailed in Appendix D.1.2.

**Table 5: Clinical effectiveness evidence**

| **Study** | **AcT (NCT03889249)** | **EXTEND-IA TNK Part 1 (NCT02388061)** |
|---|---|---|
| **Study design** | Phase III, investigator-initiated, multicentre, open-label, parallel-group, registry- | Phase II, investigator-initiated, prospective, multicentre, |



| Study | AcT (NCT03889249) | EXTEND-IA TNK Part 1 (NCT02388061) |
|---|---|---|
| | linked, randomized, controlled trial | randomized, open-label, blinded-endpoint (PROBE) trial |
| **Population** | • Adults with a diagnosis of ischaemic stroke causing disabling neurological deficit<br>• Presenting within 4.5 hours of symptom onset<br>• Eligible for thrombolysis as per Canadian guidelines | • Adults presenting with AIS within 4.5 hours of onset<br>• With large vessel occlusion of the internal carotid, middle cerebral or basilar artery<br>• Eligible to undergo intravenous thrombolysis and endovascular thrombectomy |
| **Intervention(s)** | Tenecteplase (n = 816) | Tenecteplase (n = 101) |
| **Comparator(s)** | Alteplase (n = 784) | Alteplase (n = 101) |
| **Indicate if study supports application for marketing authorization (yes/no)** | Yes | Yes |
| **Indicate if study used in the economic model** | Yes | Yes |
| **Rationale if not included in model** | N/A | N/A |
| **Reported outcomes specified in the decision problem** | • Disability or change in daily activities status<br>• Functional recovery<br>• Neurological deficit<br>• Mortality<br>• Length of hospital stay<br>• Adverse effects of treatment, including bleeding events<br>• Health-related quality of life | • Disability or change in daily activities status<br>• Functional recovery<br>• Mortality<br>• Adverse effects of treatment, including bleeding events |
| **All other reported outcomes** | • Recanalization status<br>• Baseline CT to arterial puncture time | • Angiographic reperfusion |

**Key**: AIS, acute ischaemic stroke; CSR, clinical study report; CT, computed tomography; N/A, not applicable.
**Source**: Clinicaltrials.gov (NCT02388061)[58]; EXTEND-IA TNK Part 1 CSR[3]; Campbell et al. 2018[4]; Menon et al. 2022[1]; AcT CSR Revision 1[2]; Clinicaltrials.gov (NCT03889249).[59]



## *B.3.3. Summary of methodology of the relevant clinical effectiveness evidence*

### B.3.3.1. AcT

#### *B.3.3.1.1. Study design*

AcT was a Phase III, investigator-initiated, multicentre, open-label, parallel-group, registry-linked, randomized, controlled trial designed to determine whether IV tenecteplase was non-inferior to IV alteplase in patients with AIS.[1] In total, 1,600 patients were enrolled across 22 stroke centres in Canada between December 2019 and January 2022.[1] Primary completion occurred in April 2022, with study completion in April 2023.[59]

Eligible patients were randomized at a 1:1 ratio to receive IV tenecteplase (0.25 mg/kg body weight up to 25 mg) or IV alteplase (0.9 mg/kg body weight up to 90 mg) using a previously validated minimal sufficient balance algorithm to balance allocation by site.[1] Tenecteplase was given as a single 0.25 mg/kg bolus, whereas alteplase was given as a 0.09 mg/kg bolus followed immediately by a 60-minute infusion of the remaining 0.81 mg/kg. Patients were evaluated up to 120 days after administration, aiming for assessment as close to 90 days post-stroke as possible.[1] A summary of the trial methodology is provided in Appendix K.

Key inclusion criteria were adults (≥ 18 years) presenting with AIS causing disabling neurological deficit eligible for IV thrombolysis within 4.5 hours of symptom onset. Patients eligible for endovascular thrombectomy in addition to IV thrombolysis were eligible for enrolment. Exclusion criteria included patients with contraindications to IV thrombolysis such as active haemorrhage or condition that risked haemorrhage with alteplase.[1]

The primary outcome was the proportion of patients who had a modified Rankin scale (mRS) score of 0–1 at 90–120 days after randomization assessed by blinded review.[1] Key secondary outcomes included 90–120-day mRS score, 90–120-day mRS score of 0–2, return to baseline function at 90 days, 90–120-day EQ-VAS



(visual analogue scale), and 90–120-day EQ-5D-5L, and DTN time. Key safety outcomes were symptomatic intracerebral haemorrhage (ICH), orolingual angio-oedema, and 90-day all-cause mortality. Further details on outcomes are provided in Appendix K.

#### *B.3.3.1.2. Baseline demographics and disease characteristics*

The baseline characteristics for patients in AcT are presented in Table 6. There were no statistically significant differences between the two groups at baseline. The median age of patients was 74 years in the tenecteplase arm and 73 years in the alteplase arm. In the tenecteplase arm, 52.6% were male, while 51.6% were male in the alteplase arm. Median baseline National Institutes of Health Stroke Scale (NIHSS) score was 9 in the tenecteplase arm and 10 in the alteplase arm. Median time from stroke symptom onset to IV thrombolysis was 128 minutes in the tenecteplase arm and 131 minutes in the alteplase arm.

**Table 6: Baseline characteristics and disease characteristics for AcT**

| **Characteristic** | **Tenecteplase arm (n = 806)** | **Alteplase arm (n = 771)** |
|---|---|---|
| **Age, years (%)** | 74 (63–83) | 73 (62–83) |
| **Sex, n (%)** | | |
| Female | 382 (47.4%) | 373 (48.4%) |
| Male | 424 (52.6%) | 398 (51.6%) |
| **Baseline NIHSS score (n = 1,569), median (IQR)** | 9 (6–16) | 10 (6–17) |
| **Baseline NIHSS score categories, n (%)** | | |
| < 8 | 325/803 (40.5%) | 294/766 (38.4%) |
| 8–15 | 247/803 (30.8%) | 256/766 (33.4%) |
| > 15 | 231/803 (28.8%) | 216/766 (28.2%) |
| **Occlusion site on baseline CT angiography (n = 1,558)*, n (%)** | | |
| Intracranial internal carotid artery | 69/801 (8.6%) | 66/757 (8.7%) |
| M1 segment MCA | 118/801 (14.7%) | 119/757 (15.7%) |
| M2 segment MCA | 174/801 (21.7%) | 141/757 (18.6%) |
| Other distal occlusions† | 130/801 (16.2%) | 138/757 (18.2%) |
| Vertebrobasilar arterial system | 26/801 (3.2%) | 38/757 (5.0%) |
| Cervical internal carotid artery | 17/801 (2.1%) | 9/757 (1.2%) |
| No visible occlusions | 267/801 (33.3%) | 246/757 (32.5%) |



| Characteristic | Tenecteplase arm (n = 806) | Alteplase arm (n = 771) |
|---|---|---|
| **Presence of large vessel occlusion on baseline CT angiography (n = 1,558), n (%)** | 196/801 (24.5%) | 193/757 (25.5%) |
| **Type of enrolling centre, n (%)** | | |
| Primary stroke centre | 56/806 (6.9%) | 43/771 (5.6%) |
| Comprehensive stroke centre | 750/806 (93.1%) | 728/771 (94.4%) |
| **Source registry, n (%)** | | |
| QuiCR | 346/806 (42.9%) | 342/771 (44.4%) |
| OPTIMISE | 460/806 (57.1%) | 429/771 (55.6%) |
| **Median workflow times, min (IQR)** | | |
| Stroke symptom onset to hospital arrival (n = 1,560) | 82 (54–140) | 83 (55–138) |
| Stroke symptom onset to randomization (n = 1,570) | 121 (85–179) | 123 (88–179) |
| Door (hospital arrival) to baseline CT (n = 1,561) | 15 (12–21) | 16 (12–22) |
| Stroke symptom onset to needle (IV thrombolysis start; n = 1,562) | 128 (93–186) | 131 (95–188) |
| Door (hospital arrival) to needle (IV thrombolysis start; n = 1,556) | 36 (27–49) | 37 (29–52) |
| Baseline CT to arterial puncture (in patients undergoing EVT; n = 505) | 60 (43–88) | 58 (41–85) |
| Arterial puncture to successful reperfusion (in patients undergoing EVT; n = 445) | 31 (19–47) | 27 (17–45) |

**Key**: CSR, clinical study report; CT, computed tomography; EVT, endovascular thrombectomy; IQR, interquartile range; IV, intravenous; M1, first segment; M2, second segment; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; OPTIMISE, Optimizing Patient Treatment in Major Ischemic Stroke With EVT; QuiCR; Quality Improvement and Clinical Research registry.
**Notes**: Large vessel occlusion is defined as large vessel occlusion of the internal carotid artery, M1 segment MCA, or functional M1 segment MCA occlusion – i.e. all M2 segments MCA occluded on baseline CT angiography scan. If patients had more than one occlusion site, the most proximal occlusion is listed. *19 patients had baseline non-contrast CT but did not have a baseline CT angiography; these patients' characteristics were not different from those who had a baseline CT angiography. †Middle cerebral artery, anterior cerebral artery, or posterior cerebral artery.
**Source**: Menon et al. 2022[1]; AcT CSR Revision 1.[2]



### B.3.3.2. EXTEND-IA TNK Part 1

#### *B.3.3.2.1. Study design*

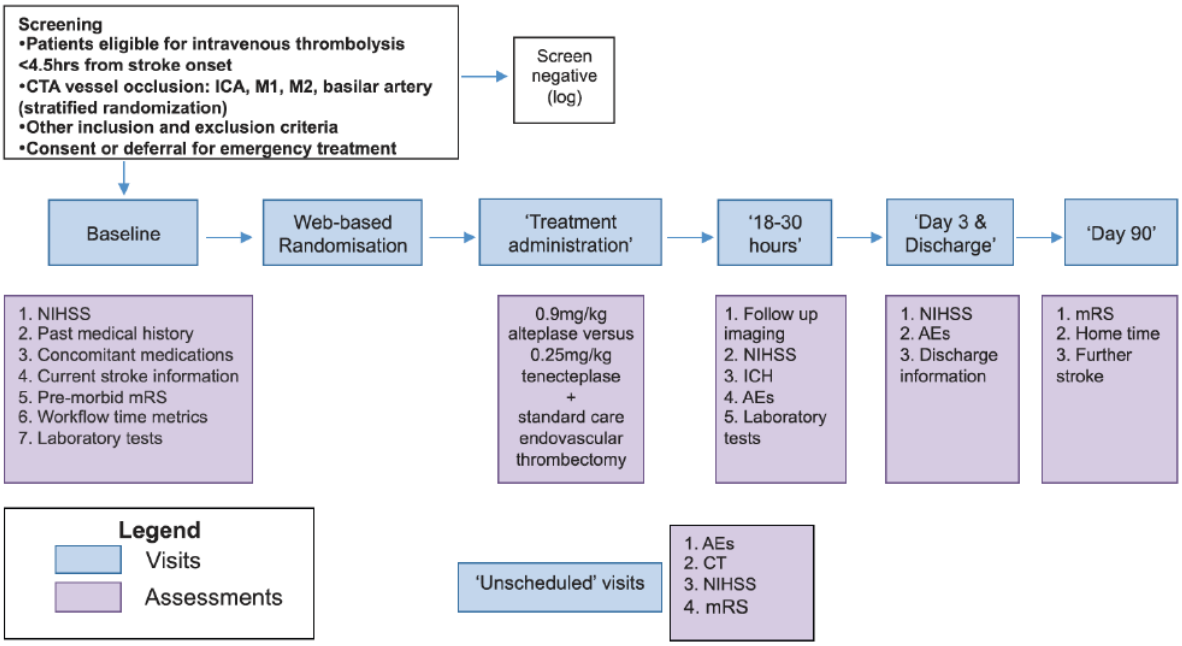
EXTEND-IA TNK Part 1 was a Phase II, investigator-initiated, prospective, multicentre, randomized, open-label, blinded-endpoint (PROBE) trial, designed to determine the efficacy and safety of thrombolysis with tenecteplase versus alteplase before endovascular thrombectomy for the treatment of AIS.[3, 4] In total, 204 patients were enrolled from March 2015 to October 2017 across 12 centres in Australia and one in New Zealand. The trial completed in February 2018, and results are available for all endpoints.

Eligible patients were randomized at a 1:1 ratio to receive IV tenecteplase (0.25 mg/kg of body weight up to 25 mg) or IV alteplase (0.9 mg/kg of body weight up to 90 mg).[3, 4] Randomization was performed according to a centralized web-based procedure coordinated via the Florey Institute of Neuroscience and Mental Health and was stratified based on site of baseline arterial occlusion.[3] Tenecteplase was given as a single 0.25 mg/kg bolus, whereas alteplase was given as a 0.09 mg/kg bolus, followed immediately by a 60-minute infusion of the remaining 0.81 mg/kg. Patients were evaluated up to 90 days after admission. Figure 2 shows the study design and schedule of assessments for EXTEND-IA TK Part 1, and a summary of the trial methodology is provided in Appendix K.



**Figure 2: Study design of EXTEND-IA TNK Part 1**




**Key**: AE, adverse event; CT, computed tomography; CTA, computed tomographic angiography; ICA, internal carotid artery; ICH, intracerebral haemorrhage; M1, first segment; M2, second segment; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.
**Notes**: Unscheduled visits were possible and assessed AEs, CT, NIHSS and mRS.
**Sources**: Campbell et al. 2018.[3, 4]

Key inclusion criteria were adults (≥ 18 years) presenting with AIS with large vessel occlusion of the internal carotid, middle cerebral or basilar artery, and eligible for IV thrombolysis within 4.5 hours of symptom onset and thrombectomy within 6 hours of symptom onset.[3, 4] Exclusion criteria included intracranial haemorrhage confirmed by imaging; an mRS score of ≥ 4 or rapidly improving symptoms confirmed by the investigator; contradiction to imaging; pregnancy; and terminal illness.

The primary endpoint was proportion of patients with angiographic reperfusion of ≥ 50% or absence of retrievable thrombus at initial angiographic assessment.[4] Key secondary endpoints were proportion of patients with > 8-point reduction in NIHSS 3 days post-stroke, mRS score (from 0 [no neurological impairment] to 6 [death]) at 90 days, symptomatic intracranial haemorrhage, and all-cause mortality.[3, 4] Further details on outcomes are provided in Appendix K.



#### *B.3.3.2.2. Baseline demographics and disease characteristics*

The baseline characteristics for patients in EXTEND-IA TNK Part 1 are listed in Table 7. There were no significant differences between the two groups at baseline.[3, 4] The mean age of patients was 70.4 years in the tenecteplase arm and 71.9 years in the alteplase arm. In the tenecteplase arm, 57% of patients were male, compared with 51% in the alteplase arm. Median NIHSS score was 17 in both arms, and the majority of patients in both arms had a pre-morbid mRS score of < 1 (90% tenecteplase vs 86% alteplase). Median time from stroke onset to IV thrombolysis was 125 minutes in the tenecteplase arm, compared with 134 minutes in the alteplase arm.[4]

**Table 7: Baseline characteristics and disease characteristics for EXTEND-IA TNK Part 1**

| **Characteristic** | **Tenecteplase arm (n= 101)** | **Alteplase arm (n = 101)** |
|---|---|---|
| **Age, years (SD)** | 70.4 (15.1) | 71.9 (13.7) |
| **Male, no. (%)** | 58 (57%) | 52 (51%) |
| **Median NIHSS score (IQR)** † | 17 (12–22) | 17 (12–22) |
| **Cause of stroke, no. (%)** | | |
| Cardioembolic occlusion | 46 (46%) | 54 (53%) |
| Large artery occlusion | 21 (21%) | 18 (18%) |
| Undetermined or other | 34 (34%) | 29 (29%) |
| **Median time from stroke onset to hospital arrival, mins (IQR)** | 60 (44–89) | 72 (53–104) |
| **Median time from stroke onset to initiation of IV thrombolysis, min (IQR)** | 125 (102–156) | 134 (104–176) |
| **Median time from initiation of IV thrombolysis to initial angiographic assessment, min (IQR)** | 54 (34-67) | 56 (40-77) |
| **Median time from initiation of IV thrombolysis to arterial puncture, min (IQR)** | 43 (25–57) | 42 (30–63) |
| **Inter-hospital transfer for thrombectomy, no. (%)** | 27 (27%) | 23 (23%) |
| **Site-of-vessel occlusion, no (%)** | | |
| Internal carotid artery | 24 (24%) | 24 (24%) |
| Basilar artery | 3 (3%) | 3 (3%) |
| Middle cerebral artery | | |



| Characteristic | Tenecteplase arm (n= 101) | Alteplase arm (n = 101) |
|---|---|---|
| First segment | 59 (58%) | 60 (59%) |
| Second segment | 15 (15%) | 14 (14%) |
| **Median volume at initial imaging, mL (IQR)‡** | | |
| Ischaemic core | 14 (0–33) | 11 (0–24) |
| Perfusion lesion | 145 (105–175) | 134 (103–170) |
| **Previously diagnosed atrial fibrillation, no. (%)** | 27 (27%) | 40 (40%) |
| **History of hypertension, no. (%)** | 64 (63%) | 63 (62%) |
| **History of diabetes, no. (%)** | 10 (10%) | 18 (18%) |
| **History of current smoking, no. (%)** | 18 (18%) | 11 (11%) |
| **Mean serum glucose, mmol/L, (SD)** | 7.3 (2.6%) | 7.1 (2.3%) |
| **Pre-morbid modified Rankin scale** | | |
| 0, no. (%) | 76 (75%) | 81 (80%) |
| 1, no. (%) | 15 (15%) | 6 (6%) |
| 2, no. (%) | 3 (3%) | 2 (2%) |
| 3, no. (%) | 7 (7%) | 12 (12%) |

**Key**: CSR, clinical study report; CT, computed tomography; IQR, interquartile range; IV, intravenous; NIHSS, the National Institutes of Health Stroke Scale; SD, standard deviation.
**Notes**: There were no significant differences between the two groups. Percentages may not total 100 because of rounding. IQR denotes interquartile range. Scores on NIHSS, a standardized neurological examination, range from 0 (normal function) to 42 (death), with lower scores indicating less severe stroke. ‡ Values for the ischaemic-core volume were calculated with the use of a threshold of relative cerebral blood volume less than 30% of that in a normal brain. The perfusion lesion was defined as the volume of brain with a time to maximum perfusion of more than 6 seconds. CT perfusion imaging was performed, but the requirement for mismatch and an ischaemic-core volume of less than 70 mL was removed in a protocol amendment when approximately 80 patients were enrolled.
**Source**: EXTEND-IA TNK Part 1 CSR[3]; Campbell et al. 2018.[4]

## *B.3.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

### B.3.4.1. AcT

#### *B.3.4.1.1. Statistical analysis*

A summary of the statistical analysis performed during the AcT trial is summarized in Table 8.



The primary outcome was analysed for non-inferiority in the intention-to-treat (ITT) population, which included the 1,577 patients who were randomized and did not withdraw consent (806 received tenecteplase; 771 received alteplase).[1] In line with the statistical analysis plan, as non-inferiority was met, superiority was tested using the Z-test. The primary outcome was also assessed in the per-protocol population as a secondary exploratory analysis. The per-protocol population excluded patients who received thrombolysis 4.5 hours or more after symptom onset and who received any treatment crossovers. Safety was assessed in the safety population, which included 1,563 patients who were randomized, did not withdraw consent, and received the drug tenecteplase or alteplase specifically (800 received tenecteplase, 763 received alteplase).[1]

No interim non-inferiority analyses were completed. Interim safety analyses were completed after 533 and 1,066 patients were enrolled and no unexpected safety signals were noted.[1]

**Table 8: Summary of statistical analyses of the AcT trial**

| | |
|---|---|
| **Hypothesis objective** | Tenecteplase given as a single bolus may increase reperfusion compared with alteplase standard of care in AIS. |
| **Statistical analysis** | Non-inferiority of the primary outcome was established if the lower boundary of the 95% CI of the unadjusted percentage difference in patients obtaining the primary outcome (mRS score of 0–1) in the tenecteplase versus alteplase groups was greater than -5%.<br>The superiority of tenecteplase versus alteplase was to be tested as a secondary analysis using the Z-test only if non-inferiority was met.<br>Adjusted risk difference was estimated between the two treatment arms using logistic regression.<br>Adjusted risk ratios were obtained for these analyses by fitting a generalized linear mixed-effects regression with quasi-Poisson distribution to the data. |
| **Sample size, power calculation** | Sample size was calculated using mRS distributions and non-inferiority margins from previous studies. 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 1,600[b] patients would ensure at least 90% power to test non-inferiority of tenecteplase versus alteplase, with up to 5% withdrawal or loss to follow-up. |



| | |
|---|---|
| **Data management, patient withdrawals** | Patients could withdraw consent from the trial entirely after they were randomized and received study drug or control. In such situations, all patient data had to be deleted.<br>In sensitivity analyses, the effect of any missing data on study conclusions was examined by comparing study results on the basis of complete-case analysis and multiple imputation. |
| **Key:** AIS, acute ischaemic stroke; CI, confidence interval; CSR, clinical study report; mRS, modified Rankin scale.<br>**Source:** Menon et al. 2022[1]; AcT CSR Revision 1.[2] | |

#### *B.3.4.1.2. Patient disposition*

While 1,600 patients were enrolled and underwent randomization, 23 patients withdrew consent, leading to 1,577 forming the ITT population.[1] This meant that 806 were assigned to the tenecteplase arm and 771 were assigned to the alteplase arm. Ten patients were lost to follow-up at 90 days.[1] A patient flow diagram for the AcT trial is provided in Appendix D.2.1.

### B.3.4.2. EXTEND-IA TNK Part 1

#### *B.3.4.2.1. Statistical analysis*

A summary of the statistical analysis performed during EXTEND-IA TNK Part 1 is presented in Table 9.

The primary endpoint was analysed for non-inferiority using both ITT and per-protocol principles, as recommended for non-inferiority trials.[3, 4] Superiority analysis for the primary outcome (if non-inferiority for the primary outcome was established), and all secondary efficacy and safety outcome analyses were conducted on an ITT basis, so that all patients were analysed in the group to which they were randomized irrespective of whether or not they received the allocated treatment.

No interim analyses for efficacy, safety or futility were performed.[3, 4]

**Table 9: Summary of statistical analyses of EXTEND-IA TNK Part 1**

| | |
|---|---|
| **Hypothesis objective** | Primary hypothesis: tenecteplase was non-inferior to alteplase in achieving reperfusion at initial angiogram when administered within 4.5 hours of ischaemic stroke onset in patients due to undergo endovascular therapy. |



| | |
|---|---|
| **Statistical analysis** | **Primary outcome**<br>Non-inferiority was established if the lower boundary of the two-sided 95% CI 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%.<br>Two-sided 95% CI of the incidence difference was estimated by generating incidence differences with corresponding 95% CI 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.<br>If non-inferiority 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.<br>**Secondary outcomes**<br>The analysis of the mRS score was performed using 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 mRS.<br>The proportions of patients with an mRS score of 0 or 1 (excellent function) and with a score of 0 to 2 (functional independence) at 90 days were compared between the tenecteplase group and the alteplase group of the trial, with adjustment for age and baseline NIHSS score with the use of a logistic-regression model.<br>The proportions of patients with early neurological improvement were compared between the two groups, with adjustment for age and baseline NIHSS score, with the use of logistic regression. 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 analysed with the use of Wilcoxon–Mann–Whitney generalized odds ratios, with stratification according to baseline NIHSS score. |
| **Sample size, power calculation** | The minimum sample size was 120; the maximum was 276. A blinded adaptive sample size re-estimation was performed after 100 patients had been enrolled. This re-estimation determined a final sample size of 202 patients for the determination of non-inferiority.<br>Sequential testing of superiority after testing of non-inferiority was planned for the intention-to-treat and per-protocol analyses, but no patients were excluded from the per-protocol analysis of the primary outcome. Only one set of analyses is presented. |



| | |
|---|---|
| **Data management, patient withdrawals** | There were no patients with missing data for the primary or secondary outcomes. |
| **Key:** CI, confidence interval; CSR, clinical study report; mRS, modified Rankin score; NIHSS, National Institutes of Health Stroke Score.<br>**Source:** Campbell et al. 2018[4]; EXTEND-IA TNK Part 1 CSR.[3] | |

#### *B.3.4.2.2. Patient disposition*

Two hundred and four patients entered EXTEND-IA TNK Part 1.[3, 4] Two patients were excluded before treatment due to withdrawal of consent and enrolling physicians' decision, respectively. Therefore, each treatment arm contained 101 patients. Due to nursing error, two patients received a cardiac dose of 0.5 mg/kg of drug, but no adverse consequences were observed. No patients in either arm were lost during follow-up to 90 days post-AIS. A patient flow diagram is provided in Appendix D.2.2.

## *B.3.5. Critical appraisal of the relevant clinical effectiveness evidence*

AcT and EXTEND-IA TNK Part 1 were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies. A complete quality assessment in accordance with the Cochrane risk-of-bias tool is presented in Appendix D.3. The overall risk of bias for both studies is considered to be low.

## *B.3.6. Clinical effectiveness results of the relevant studies*

### B.3.6.1. AcT

In this section, efficacy results are presented from AcT for the ITT population, which included 1,577 patients who were randomized and did not withdraw consent (806 received tenecteplase, 771 received alteplase).[1]

#### *B.3.6.1.1. Primary endpoint: mRS score 0–1 at 90–120 days*

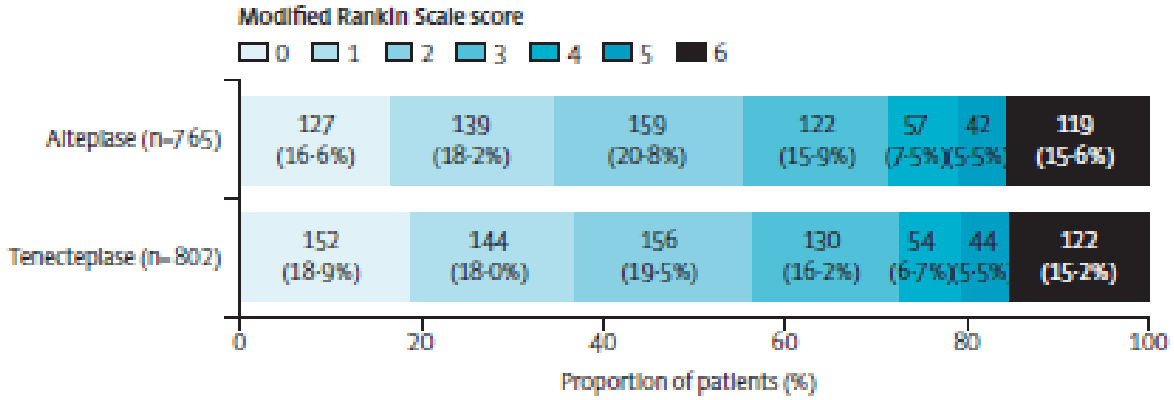
The primary outcome (90–120-day mRS score of 0–1) occurred in 296 (36.9%) of 802 patients assigned to tenecteplase and 266 (34.8%) of 765 assigned to alteplase



with available data (unadjusted risk difference: 2.1% [95% confidence interval (CI): -2.6, 6.9]; Table 10). The lower bound 95% CI of the difference in primary outcome rate (-2.6%) was greater than -5%, thus meeting the pre-specified non-inferiority threshold. The direction of effect favoured tenecteplase, but tenecteplase was not superior to alteplase in secondary analyses (unadjusted risk ratio [RR]: 1.0 [95% CI: 1.0, 1.1]; p = 0.19; Figure 3).[1]

**Figure 3: Distribution of the modified Rankin scale scores at 90–120 days, intention-to-treat population**




**Notes:** 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.
**Source:** Menon et al. 2022.[1]

### *B.3.6.1.2. Secondary endpoints*

A summary of the secondary efficacy endpoints specific to the decision problem (Section B.1.1) from the AcT are presented in Table 10. All other secondary endpoints are presented in Appendix K.2. Overall, secondary outcomes were comparable between the two treatment arms, with point-estimates generally favouring tenecteplase.[1]



**Table 10: Summary of secondary efficacy endpoints specific to the decision problem from the AcT trial**

| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of effect | Estimate (95% CI) |
|---|---|---|---|---|
| mRS score 0–1 at 90–120 days (n = 1,567), n (%) | 296/802 (36.9) | 266/765 (34.8) | Risk ratio (adjusted*) | 1.1 (1.0, 1.2) |
| mRS score 0–2 at 90–120 days (n = 1,567), n (%) | 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) |
| Actual mRS score at 90–120 days (n = 1,567), median (IQR) | 2 (1–4) | 2 (1–4) | Difference in medians | 0 |
| | | | Common odds ratio† (adjusted*) | 0.9 (0.8, 1.1) |
| Return to baseline function (n = 1,454), n (%) | 219/740 (29.6) | 199/714 (27.9) | Difference in proportion (unadjusted) | 1.7 (-2.9, 6.4) |
| | | | Risk ratio (adjusted*) | 1.1 (0.9, 1.2) |
| Length of hospital stay (n = 1,479; post hoc), mean (95% CI) | 5 (2–11) | 5 (3–11) | Difference in proportion (unadjusted) | 0 |
| | | | Risk ratio (adjusted*) | 1.0 (0.9, 1.1) |

**Key**: CI, confidence interval; CSR, clinical study report; IQR, interquartile range; mRS, modified Rankin scale.
**Notes**: *Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time, and source registry as fixed-effects variables, and site as a random-effects variable.
**Source**: Menon et al. 2022[1]; AcT CSR Revision 1.[2]

#### *B.3.6.1.2.1 mRS score 0–2 at 90–120 days*

The incidence of mRS scores between 0–2 at 90–120 days were comparable between treatment arms, occurring in 56.4% (n = 452) of patients in the tenecteplase group and 55.6% (n = 765) of patients in the alteplase group (adjusted RR: 1.0 [95% CI: 1.0, 1.1]; Table 10).[1]



#### *B.3.6.1.2.2 Actual mRS score at 90–120 days*

Both patients in the tenecteplase and alteplase groups had median mRS scores of 2 (interquartile range [IQR]: 1–4) at 90–120 days, indicating comparable function (adjusted common odds ratio, 0.9 [95% CI: 0.8, 1.1]; Table 10).[1]

#### *B.3.6.1.2.3 Return to baseline function*

Return to baseline function was observed in 1,454 patients (tenecteplase: n = 740; alteplase n = 714) and was comparable between treatment arms, occurring in 29.6% (n = 219) of patients in the tenecteplase arm and 27.9% (n = 199) of patients in the alteplase arm (adjusted RR: 1.1 [95% CI: 0.9, 1.2]; Table 10).[1]

#### *B.3.6.1.2.4 Length of hospital stay*

Length of hospital stay was recorded in 1,481 patients and was comparable between treatment arms. Median length of stay was 5 days (IQR: 2–11) in the tenecteplase arm and 5 days (IQR: 3–11) in the alteplase arm (adjusted RR: 1.0 [95% CI: 0.9, 1.1]; Table 10).[1]

### *B.3.6.1.3. HRQL outcomes*

A summary of the HRQL outcomes from the AcT trial are presented in Table 11. HRQL outcomes were measured at 90 days using both the EQ-VAS (n = 1,262) and EQ-5D-5L (n = 1,289) scales. Overall, there no differences observed between treatment arms for the EQ-VAS or EQ-5D-5L domains.

**Table 11: HRQL outcomes measured in the ITT population of the AcT trial**

| **Outcomes** | **Tenecteplase group (n = 806)** | **Alteplase group (n = 771)** | **Measure of effect** | **Estimate (95% CI)** |
|---|---|---|---|---|
| EQ-VAS at 90 days (n = 1,262), mean (SD) | 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) |
| EQ-5D – mobility at 90 days (n = [redacted]) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Common odds ratio† (adjusted*) | [redacted] |



| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of effect | Estimate (95% CI) |
|---|---|---|---|---|
| EQ-5D – self care at 90 days (n = [redacted]) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Common odds ratio† (adjusted*) | [redacted] |
| EQ-5D – usual task at 90 days (n = [redacted]) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Common odds ratio† (adjusted*) | [redacted] |
| EQ-5D – pain at 90 days (n = [redacted]) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Common odds ratio† (adjusted*) | [redacted] |
| EQ-5D - anxiety at 90 days (n = [redacted]) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Common odds ratio† (adjusted*) | [redacted] |

**Key**: CI, confidence interval; CSR, clinical study report; EVT, endovascular thrombectomy; HRQL, health-related quality of life; ITT, intention-to-treat; OPTIMISE, Optimizing Patient Treatment in Major Ischemic Stroke With EVT; QuiCR, Quality Improvement and Clinical Research registry; VAS, visual analogue scale.
**Notes**: * Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time with source registry (QuiCR versus OPTIMISE) and 'site' as a random-effects variable. † Common odds ratio is the odds ratio for a unit increase in the modified Rankin score for tenecteplase versus alteplase.
**Source**: Menon et al. 2022[1]; AcT CSR Revision 1.[2]

### B.3.6.2. EXTEND-IA TNK Part 1

In this section, efficacy results are presented for the ITT population, which included 202 patients who were randomized (101 received tenecteplase, 101 received alteplase).[4]

#### *B.3.6.2.1. Primary endpoint: Reperfusion of greater than 50% at initial angiographic assessment*

Reperfusion of greater than 50% of the involved territory or an absence of retrievable thrombus at the time of the initial angiographic assessment was observed in 22 patients in the tenecteplase arm, compared with 10 patients in the alteplase arm (incidence difference: 12 percentage points [p = 0.002 for non-inferiority]; adjusted



incidence ratio: 2.2 [p = 0.03 for superiority]; and adjusted odds ratio: 2.6 [p = 0.02 for superiority]; Table 12).[4]

**Table 12: Primary endpoint outcomes for EXTEND-IA TNK Part 1**

| Outcome | Tenecteplase arm (n = 101) | Alteplase arm (n = 101) | Effect size (95% CI) | P value |
|---|---|---|---|---|
| **Primary efficacy outcome** | | | | |
| Greater than 50% reperfusion at initial angiographic assessment, no. (%) * | 22 (22%) | 10 (10%) | | |
| Percentage difference | | | 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 |

**Key**: CI, confidence interval; CSR, clinical study report; mRS, modified Rankin scale; IQR, interquartile range; no., number.
**Notes**: * Reperfusion > 50% to the involved territory or no retrievable thrombus. The analysis was adjusted for the site-of-vessel occlusion strata. The P value for the difference is for non-inferiority, and the P values for the incidence ratio and odds ratio are for superiority.
**Source**: EXTEND-IA TNK Part 1 CSR[3]; Campbell et al. 2018.[4]

Patients who met the primary endpoint did not undergo thrombectomy, except for one patient in the tenecteplase group who had substantial reperfusion but residual thrombus that was treated with thrombectomy.[4] Of the patients with reperfusion at the initial angiographic assessment, 20 out of 22 patients in the tenecteplase group and six out of 10 in the alteplase group had initial occlusion of the middle cerebral artery. Procedural characteristics and the incidence of reperfusion according to the site-of-vessel occlusion are shown in Appendix K.1.

#### *B.3.6.2.2. Secondary endpoints*

A summary of the secondary efficacy endpoints of EXTEND-IA TNK Part 1 is presented in Table 13. Overall, secondary outcomes were comparable between the two treatment arms, with point-estimates generally favouring tenecteplase.[3, 4]



**Table 13: Summary of secondary endpoints for mRS score in EXTEND-IA TNK Part 1**

| Outcome | Tenecteplase arm (N = 101) | Alteplase arm (N = 101) | Effect size (95% CI) | P value |
|---|---|---|---|---|
| **Score on the mRS score at 90 days†** | | | | |
| Median score on ordinal analysis (IQR) ‡ | 2 (0–3) | 3 (1–4) | 1.7 (1.0, 2.8) | 0.04 |
| mRS of 0 to 2 or no change from baseline at Day 90, no. (%) § | 65 (64%) | 52 (51%) | | |
| Adjusted incidence ratio | | | 1.2 (1.0, 1.5) | 0.06 |
| Adjusted ratio | | | 1.8 (1.8, 3.4) | 0.06 |
| mRS of 0 or 1 or no change from baseline at Day 90, 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 neurological 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 |

**Key**: CI, confidence interval; CSR, clinical study report; IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Score.
**Notes**: The P value for the difference is for non-inferiority, and the P values for the incidence ratio and odds ratio are for superiority. † Scores on the mRS range from 0 (no neurological deficit) to 6 (death). ‡ 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 neurological 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.
**Source**: EXTEND-IA TNK Part 1 CSR[3]; Campbell et al. 2018.[4]

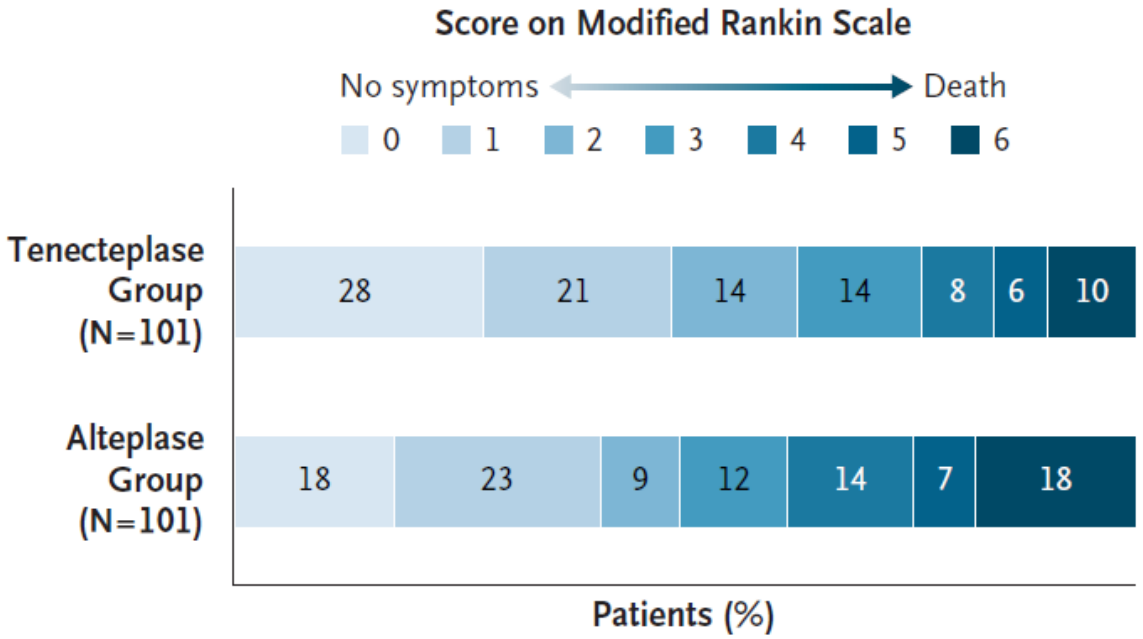
#### *B.3.6.2.2.1 Median mRS score at 90 days*

In an ordinal analysis of the mRS at 90 days, patients in the tenecteplase group had a median score of 2 (IQR: 0–3), which indicated significantly better function than the median score of 3 (IQR: 1–5) among patients in the alteplase group (common odds ratio, 1.7 [95% CI: 1.0, 2.8]; p = 0.04; Table 13 and Figure 4).[4]



**Figure 4: Ordinal analysis of mRS at 90 days in the ITT population of EXTEND-IA TNK Part 1**




**Key**: CSR, clinical study report; mRS, modified Rankin scale; ITT, intention-to-treat.
**Notes**: Scores range from 0 to 6, with 0 indicating no neurological deficit, 1 no clinically significant disability, 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (e.g. with shopping, cleaning, and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention), and 6 death.
**Source**: EXTEND-IA TNK Part 1 CSR[3], Campbell et al. 2018.[4]

#### *B.3.6.2.2.2 mRS score of 0–2 or no change from baseline function at Day 90*

There was no significant difference in the incidence of mRS score of 0–2 or no change from baseline function at Day 90, which occurred in 64% of patients in the tenecteplase group and 51% of patients in the alteplase group (adjusted incidence ratio: 1.2 [95% CI: 1.0, 1.5]; p = 0.06; adjusted odds ratio: 1.8 [95% CI: 1.0, 3.4]; p = 0.06; Table 13).[4]

#### *B.3.6.2.2.3 mRS score of 0–1 or no change from baseline function at Day 90*

There was also no significant difference in the incidence of mRS score of 0–1 or no change from baseline function at 90 days, which occurred in 51% of patients in the tenecteplase group and 43% of patients in the alteplase group (adjusted incidence



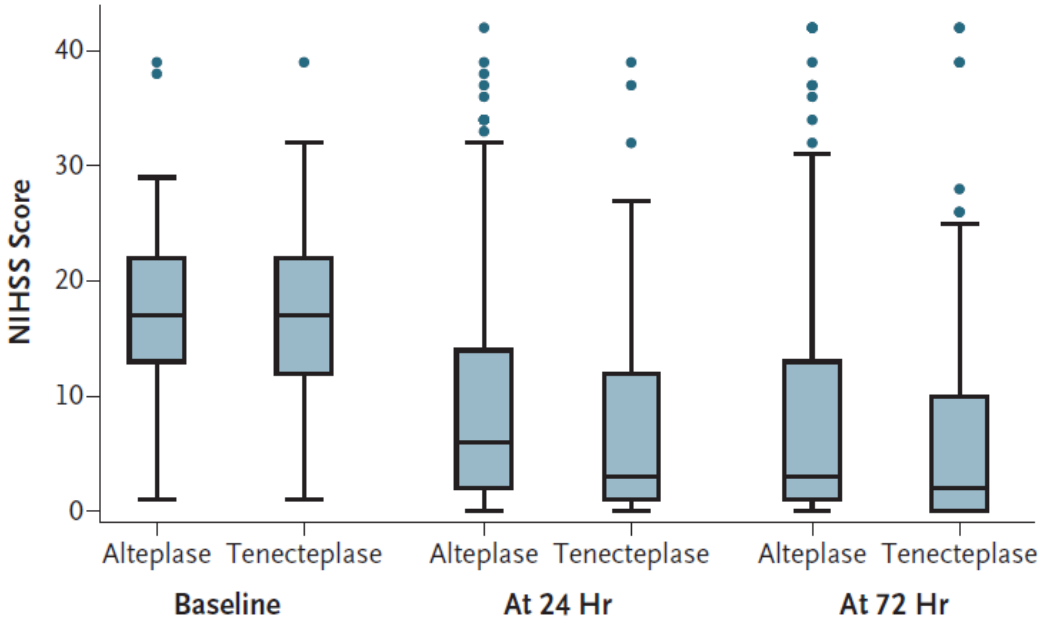
 

ratio: 1.2 [95% CI: 0.9, 1.6]; p = 0.20; adjusted odds ratio: 1.4 [95% CI: 0.8, 2.6]; p = 0.23; Table 13).[4]

#### *B.3.6.2.2.4 Early neurological improvement and NIHSS score at 24 hours and 72 hours*

There were also no significant differences in the incidence of early neurological improvement at 72 hours (Table 13).[4] The median NIHSS score at 24 hours was 3 (IQR: 1–12) among patients in the tenecteplase group and 6 (IQR: 2–14) among those in the alteplase group (odds ratio: 1.4 [95% CI: 1.0, 1.9]; p = 0.06 with adjustment for baseline NIHSS score; Figure 5). At 72 hours, the median NIHSS score was 2 (IQR: 0–10) among patients in the tenecteplase group and 3 (IQR: 1–13) among those in the alteplase group (odds ratio: 1.4 [95% CI: 1.0, 1.9]; p = 0.053, with adjustment for baseline NIHSS score; Figure 5).

**Figure 5: Distribution of NIHSS score at baseline, 24 hours and 72 hours in EXTEND-IA TNK Part 1**




**Key:** CSR, clinical study report; NIHSS, National Institutes of Health Stroke Scale.
**Notes:** Scores on the NIHSS, a standardized neurological examination, range from 0 (normal function) to 42 (death), with lower scores indicating less severe stroke. The horizontal line in each box represents the median, and the top and bottom of the boxes the interquartile range. II bars indicate 1.5 times the interquartile range, and the dots outliers.
**Source**: EXTEND-IA TNK Part 1 CSR[3], Campbell et al. 2018.[4]



## *B.3.7. Subgroup analysis*

### B.3.7.1. AcT

In AcT, pre-specified subgroup analyses were conducted for the primary outcomes and key safety outcomes based on:

- Age (< 80 years versus ≥ 80 years)
- Sex (male versus female)
- Baseline stroke severity as measured by the NIHSS (< 8, 8–15 versus > 15)
- Presence of large vessel occlusion on baseline computed tomographic angiography (CTA)
- Stroke onset-to-needle time
- Registry (Quality Improvement and Clinical Research registry [QuiCR] versus Optimizing Patient Treatment in Major Ischemic Stroke With EVT [endovascular thrombectomy] [OPTIMISE])
- Type of enrolling hospital (primary stroke centres versus comprehensive stroke centres)

All subgroup analyses were exploratory. No heterogeneity of treatment effect was observed across any pre-specified subgroups. Further details on subgroup analyses are presented in Appendix E.

## *B.3.8. Meta-analysis*

Formal meta-analyses have not been conducted. A qualitative overview of key efficacy and safety outcomes from both trials is provided in Table 14.

**Table 14: Key outcomes from AcT and EXTEND-IA TNK Part 1**

| Outcomes | AcT | | EXTEND-IA TNK Part 1 | |
|---|---|---|---|---|
| | Tenecteplase arm (n = 806) | Alteplase arm (n = 771) | Tenecteplase arm (n = 101) | Alteplase arm (n = 101) |
| **Efficacy** | | | | |
| mRS score 0–1, n (%) | 296/802 (36.9%) | 266/765 (34.8%) | 52 (51%) | 43 (43%) |



| Outcomes | AcT | | EXTEND-IA TNK Part 1 | |
|---|---|---|---|---|
| | Tenecteplase arm (n = 806) | Alteplase arm (n = 771) | Tenecteplase arm (n = 101) | Alteplase arm (n = 101) |
| mRS score 0–2, n (%) | 452/802 (56.4%) | 425/765 (55.6%) | 65 (64%) | 52 (51%) |
| Actual mRS score, median (IQR) | 2 (1–4) | 2 (1–4) | 2 (0–3) | 3 (1–4) |
| **Safety** | | | | |
| Death n (%) | [redacted] | [redacted] | 10 (10) | 18 (18) |
| Symptomatic intracerebral haemorrhage n (%) | 27/800 (3.4%) | 24/763 (3.2%) | 1 (1) | 1 (1) |
| Parenchymal haematoma, n. (%) | 57/800 (7.1%) | 50/763 (6.6%) | 6 (6) | 5 (5) |

**Key:** CSR, clinical study report; IQR, interquartile range; mRS, modified Rankin scale.
**Notes:** AcT recorded mRS score endpoints as close to 90 days post-stroke as possible; when 90-day assessment was not possible, 120 days post-stroke was the latest assessment. EXTEND-IA TNK Part 1 recorded all mRS score endpoints 90 days post-stroke**.** These are considered as comparable endpoints.
**Source:** Menon et al. 2022[1]; AcT CSR Revision 1[2]; EXTEND-IA TNK Part 1 CSR[3]; Campbell et al. 2018.[4]

## *B.3.9. Indirect and mixed treatment comparisons*

Indirect treatment comparisons have not been conducted as AcT and EXTEND-IA TNK Part 1 provide head-to-head evidence of tenecteplase and alteplase.

## *B.3.10. Adverse reactions*

### B.3.10.1. AcT

In this section, safety outcomes are presented for the safety population from AcT that included 1,563 patients who were randomized, did not withdraw consent, and received the drug tenecteplase or alteplase specifically (800 received tenecteplase, 763 received alteplase).[1]

A summary of the safety outcomes from AcT are presented in Table 15. There were no meaningful differences in the rate of 24-hour symptomatic ICH or mortality (90-



day and overall) between the two treatment arms.[1, 2] Orolingual angio-oedema (1.1% for tenecteplase vs 1.2% for alteplase) and extracranial bleeding requiring blood transfusion (0.8% in both groups) were rare and had similar occurrences in both groups. Any intracranial haemorrhage on follow-up imaging was present in 19.3% of patients in the tenecteplase group versus 20.6% of patients in the alteplase group.

**Table 15: Summary of safety outcomes and AEs in the AcT trial**

| Outcomes, N (%) | Tenecteplase group (n = 800) | Alteplase group (n = 763) | Risk difference (95% CI) |
|---|---|---|---|
| Death - overall (n = 1,554) | [redacted] | [redacted] | [redacted] |
| Death within 90 days (n = 1,554) | [redacted] | [redacted] | [redacted] |
| 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) | 9/763 (1.2) | -0.1 (-1.1, +1.0) |
| Other SAEs | [redacted] | [redacted] | [redacted] |
| Imaging-identified intracranial haemorrhage | [redacted] | [redacted] | [redacted] |
| Subarachnoid haemorrhage | [redacted] | [redacted] | [redacted] |
| Subdural haemorrhage | [redacted] | [redacted] | [redacted] |
| Intraventricular haemorrhage | [redacted] | [redacted] | [redacted] |
| HI1 (scattered small petechiae) | [redacted] | [redacted] | [redacted] |
| HI2 (confluent petechiae) | [redacted] | [redacted] | [redacted] |
| PH1 (haematoma occupying < 30% of infarct with no substantive mass effect) | [redacted] | [redacted] | [redacted] |
| PH2 (haematoma occupying ≥ 30% of infarct with obvious mass effect) | [redacted] | [redacted] | [redacted] |
| Remote PH-1† | [redacted] | [redacted] | [redacted] |
| Remote PH-2† | [redacted] | [redacted] | [redacted] |

**Key**: AE, adverse event; CI, confidence interval; HI, haemorrhagic infarction; PH, parenchymal haematoma; SAE, serious adverse event.
**Notes**: Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification. † Remote PH type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect. ‡ Remote PH type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.
**Source**: Menon et al. 2022[1]; AcT CSR Revision 1.[2]



### B.3.10.2. EXTEND-IA TNK Part 1

In this section, safety outcomes are presented for the ITT population from EXTEND-IA TNK Part 1, which included 202 patients who were randomized (101 received tenecteplase, 101 received alteplase).[4]

A summary of the safety outcomes from EXTEND-IA TNK Part 1 are presented in Table 16. One patient treated with tenecteplase and one patient treated with alteplase had a symptomatic ICH.[4] The patient treated with tenecteplase had also received IV heparin during a carotid endarterectomy. The patient treated with alteplase had not received a thrombectomy due to reperfusion at initial assessment, but parenchymal haematoma contralateral to the infarction developed, resulting in death.[4]

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 16). In the tenecteplase group, nine patients died due to progression of major stroke, and one patient died due to metastatic cancer diagnosed after presentation of ischaemic stroke symptoms. In the alteplase group, 14 patients died due to progression of major stroke, three died due to cardiac events and one died due to systemic haemorrhage. Full details of serious adverse events (SAEs) are available in Appendix K.

**Table 16: Summary of safety outcomes of EXTEND-IA TNK Part 1**

| **Safety outcome** | **Tenecteplase group (N = 101)** | **Alteplase group (N = 101)** | **Effect size (95% CI)** | **P value** |
|---|---|---|---|---|
| **Deaths, 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 haemorrhage, 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 |



| Safety outcome | Tenecteplase group (N = 101) | Alteplase group (N = 101) | Effect size (95% CI) | P value |
|---|---|---|---|---|
| **Parenchymal haematoma, 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 |

**Key**: CI, confidence interval, CSR, clinical study report; NIHSS, National Institutes of Health Stroke Scale.
**Notes**: § 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. ‖ Symptomatic intracerebral haemorrhage was defined as a large parenchymal haematoma (blood clot occupying > 30% of the infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score. ** Parenchymal haematoma was defined as intraparenchymal blood clot with mass effect.
**Source:** EXTEND-IA TNK Part 1 CSR[3],Campbell et al. 2018.[4]

## *B.3.11. Conclusions about comparable health benefits and safety*

Tenecteplase is indicated in adults for the thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well and after exclusion of intracranial haemorrhage.[5] In current clinical practice, alteplase is recommended by NICE for use in these patients.[40] In comparison with alteplase, administration of tenecteplase is both faster and easier. Tenecteplase is given as a single IV bolus over 5 seconds, reducing administration time and improving patient management.[4] Therefore, introducing tenecteplase supplied as 25 mg vials to the NICE clinical pathway addresses the unmet need for a quick and easily administered thrombolytic.

Tenecteplase has a similar efficacy and safety profile to alteplase, which has been demonstrated in AcT and EXTEND-IA TNK Part 1.[1-4]

AcT was a Phase III, multicentre, open-label, parallel-group, registry-linked, randomized, controlled trial designed to determine whether IV tenecteplase was non-inferior to IV alteplase in patients with AIS.[1] The trial was conducted in 22 stroke centres in Canada and thus enrolled no UK patients. However, the median age of patients treated with tenecteplase was 74 years, which is similar to the median age of patients with stroke in the UK (73 years in males and 79 years in females).[13] In addition, given that the inclusion and exclusion criteria as well as treatments



received, as per the Canadian Stroke Best Practices Recommendations for Acute Stroke Management[1, 3], were in line with current NICE guidelines for AIS and the National Clinical Guideline for Stroke for the UK and Ireland, the trial can be considered representative of UK routine clinical practice.[40]

In AcT, tenecteplase demonstrated clinically relevant non-inferiority to alteplase for the primary outcome of excellent functional outcome (measured as mRS score 0–1) at 90–120 days (unadjusted risk difference: 2.1%).[1, 3] The direction of effect favoured tenecteplase; however, this was not statistically significant (p = 0.19). Results were consistent across all pre-specified subgroups including: age (< 80 vs ≥ 80 years), sex, baseline stroke severity, DTN, large vessel occlusion, type of enrolling centre, and source registry for both the ITT and per-protocol populations (See Section B.3.7). There were no differences between tenecteplase and alteplase across secondary functional or quality-of-life outcomes. Furthermore, there were no differences between tenecteplase and alteplase for safety outcomes, which included symptomatic ICH, orolingual angio-oedema, and extracranial bleeding requiring blood transfusion (all occurring within 24 hours of thrombolytic administration); and 90-day all-cause mortality.[1, 3]

EXTEND-IA TNK Part 1 was a Phase II, prospective, multicentre, randomized, open-label, blinded-endpoint trial, which was designed to determine the efficacy and safety of thrombolysis with tenecteplase versus alteplase before endovascular thrombectomy for the treatment of AIS.[3, 4] The trial was conducted in 12 centres in Australia and one site in New Zealand; as a result, no UK patients were enrolled in the study. However, the mean age of patients treated with tenecteplase was 70.4 years, which is similar to the median age of patients with stroke in the UK (73 years in males and 79 years in females).[10] In addition, the trial is thought to be representative of routine clinical practice in the UK, as the inclusion and exclusion criteria and treatments received, as per the Australian and New Zealand Clinical Guidelines for Stroke Management[3, 4], were in line with current NICE guidelines for the treatment of AIS and the National Clinical Guideline for Stroke for the UK and Ireland.[40, 41]



In EXTEND-IA TNK Part 1, tenecteplase before thrombectomy was associated with a higher incidence of reperfusion (adjusted odds ratio: 2.6; p = 0.02 for superiority) and better functional outcome (measured as mRS score at 90 days [common odds ratio: 1.7; p = 0.04]) compared with alteplase.[3, 4] There were no differences between tenecteplase and alteplase for safety outcomes, which included symptomatic ICH and 90-day mortality.

The findings observed in both AcT and EXTEND-IA TNK Part 1 are further confirmed by earlier studies, which demonstrated similar efficacy of tenecteplase versus alteplase.[60, 61] In the ATTEST study,104 patients in Glasgow, Scotland were randomized to tenecteplase 0.25 mg/kg or alteplase 0.9mg/kg within 4.5 hours of stroke onset. There were no significant differences for the primary outcome (percentage of penumbra salvaged at 24–48 hours, defined as CT perfusion-defined penumbra volume at baseline minus plain CT infarct volume at 24–48 hours) or for the secondary outcome measures of mRS scores 0–1 at 90 days (OR 1.1 [95% CI: 0.3, 3.5]) or symptomatic ICH between the tenecteplase and alteplase groups.[62] See Appendix E for a summary of the safety outcomes. In an SLR and meta-analysis of 14 studies (n = 3,547), there was no statistical difference in the rates of 90-day good outcome (RR: 1.01 [95% CI: 0.91, 1.13]; p = 0.79) and 90-day excellent outcome (RR: 1.04 [95% CI: 0.92, 1.19]; p = 0.50) in patients receiving tenecteplase or alteplase.[60] In another SLR and meta-analysis of nine randomized controlled trials (n = 3,707), tenecteplase led to significantly higher levels of complete recanalization (RR: 1.27 [95% CI: 1.02, 1.57]; p = 0.03).[61] Results were comparable for tenecteplase versus alteplase for early neurological improvement (RR: 1.07 [95% CI: 0.94, 1.21]; p = 0.33), excellent neurological recovery (RR: 1.03 [95% CI: 0.96, 1.10]; p = 0.42), mortality (RR: 0.99 [95% CI: 0.82, 1.18], p = 0.88), intracranial haemorrhage (RR: 1.00 [95% CI: 0.85, 1.18]; p = 0.99), and parenchymal haematoma (RR: 1.13 [95% CI: 0.83, 1.54]; p = 0.44).

Overall, the findings of AcT, EXTEND-IA TNK Part 1, and the earlier studies demonstrate that tenecteplase has comparable health benefits versus the comparator of interest, alteplase.[1, 4, 60, 61] Combined with the quick and easy administration process, the comparable efficacy and safety outcomes make



tenecteplase supplied as 25 mg vials a valuable addition to the NICE clinical pathway for AIS.

### *B.3.12. Ongoing studies*

ATTEST-2 (NCT02814409) is an ongoing Phase III, investigator-initiated, prospective, multicentre, randomized, controlled trial to investigate the superiority of IV tenecteplase compared with alteplase for thrombolysis within 4.5 hours of the onset of AIS in adults.[63] The primary outcome is assessment of mRS distribution at 90 days post-stroke. Recruitment began in 2016 with the aim to recruit 1,870 participants in the UK. The trial is ongoing, with expected publication of data in 2024.[63]



# B.4. Cost-comparison analysis

As summarized in Section B.3.11, tenecteplase has a similar efficacy and safety profile to alteplase in the treatment of AIS.

As the efficacy and safety outcomes for the two treatments are likely to be equal, a cost-comparison analysis was considered appropriate. This analysis considered the drug acquisition and administration costs, treatment and resource use costs, and adverse event (AE) costs.

## *B.4.1. Changes in service provision and management*

AIS is a medical emergency that requires timely restoration of blood flow to maximize patient outcomes in terms of survival, and to reduce the impact of long-term physical and cognitive impairments in stroke survivors.

While alteplase is the current approved standard of care for thrombolysis in AIS, it is associated with several limitations, as discussed in Section B.1.3.4. In comparison with alteplase, administration of tenecteplase is both faster and easier. Tenecteplase is given as a single IV bolus over 5 seconds, reducing administration time and improving patient management.[4] This is demonstrated by the off-label use of AMI-licensed tenecteplase, which is now recommended in UK and European clinical guidelines (See section B.1.3.3).[41, 64]

Results from AcT and EXTEND-IA TNK Part 1 demonstrated that IV thrombolysis with tenecteplase (0.25 mg/kg) has a similar efficacy and safety profile to alteplase in patients with AIS presenting within 4.5 hours of stroke symptom onset.[1-4] There is currently no evidence available to quantify the anticipated reductions in resource use associated with tenecteplase.

## *B.4.2. Cost-comparison analysis inputs and assumptions*

### B.4.2.1. Features of the cost-comparison analysis

As per the equal efficacy assumptions discussed in Section B.3.11, a simple cost-comparison analysis was carried out to estimate the cost to the National Health



Service (NHS) associated with the use of tenecteplase versus alteplase for the treatment of adults with AIS.

As per NICE guidelines, a model time horizon of 72 hours (from the onset of AIS) was chosen to fully reflect any differences in costs and outcomes between the two technologies being compared. Tenecteplase has a similar efficacy and safety profile to alteplase (See Section B.3.6). As such any differences in cost and resource use related to the initial acute treatment period, with no anticipated difference in costs beyond the first 72 hours.

Where possible, evidence was taken from the England, Wales and Northern Ireland Sentinel Stroke National Audit Programme (SSNAP).[1, 10, 59] The SSNAP is a national register covering over 90% of all admitted stroke patients in England, Wales and Northern Ireland. As such, it represents an important source of real-world evidence for stroke care reflective of current clinical practice. Patients entered the model at age 76; this reflects the median age of UK patients with stroke, as per the SSNAP. Input costs were inflated to 2022 when reported for other cost years using the Personal Social Services Research Unit (PSSRU) inflation indices.[65]

To capture the nature of disease onset and early management, a 72-hour cost calculator was constructed. This impact calculator covers the first 72 hours following stroke onset and thrombolysis.

#### *B.4.2.1.1. Cost calculations for first 72 hours after AIS onset*

The cost calculator takes a micro-costing approach and has two main components: timing and outcomes, and resource use and costs. The calculator for the first 72 hours uses data for AIS outcomes under alteplase; given the assumption of equal efficacy, the two treatments have identical efficacy outcomes. The cost calculation considers the following:

- Time from symptom onset to thrombolysis in minutes
- Time from clock start to thrombolysis in minutes
- NIHSS score distribution post thrombolysis
- mRS score distribution at discharge from inpatient care



- The frequency of AEs (ICH)

Data from the 2023 SSNAP were used to inform the distributions of NIHSS scores and mRS scores.[10] Table 17 and Table 18 present the starting mRS and NIHSS distributions applied in the micro-costing part of the analysis, respectively.

There was no difference in either NIHSS score or mRS score by treatment. It was also assumed that time from clock start to thrombolysis would be the same.[1, 59]

**Table 17: Starting mRS score distribution**

| | mRS category | Mean | SE* | Source |
|---|---|---|---|---|
| mRS score at discharge from inpatient care: | 0 (no symptoms) | 0.095 | 0.0096 | SSNAP 2023[10] |
| | 1 (no significant disability) | 0.178 | 0.0174 | |
| | 2 (slight disability) | 0.178 | 0.0172 | |
| | 3 (moderate disability) | 0.189 | 0.0191 | |
| | 4 (moderately severe disability) | 0.16 | 0.016 | |
| | 5 (severe disability) | 0.068 | 0.0069 | |
| | 6 (dead) | 0.132 | 0.0138 | |
| **Key**: mRS, modified Rankin scale; SE; standard error; SSNAP, Sentinel Stroke National Audit Programme. | | | | |

**Table 18: Starting NIHSS score distribution**

| | NIHSS category | Mean | SE* | Source |
|---|---|---|---|---|
| NIHSS score post thrombolysis | 0 | 0.168 | 0.0168 | SSNAP 2023[10] |
| | 1–4 | 0.356 | 0.0356 | |
| | 5–15 | 0.323 | 0.0323 | |
| | 16–20 | 0.071 | 0.0071 | |
| | 21–42 | 0.082 | 0.0082 | |
| **Key**: NIHSS, National Institutes of Health Stroke Scale; SE, standard error; SSNAP, Sentinel Stroke National Audit Programme. | | | | |

Resource utilization categories considered in the impact calculator to determine costs within the first 72 hours following stroke are as follows:



- Transportation (ground ambulance)
- CT scan
- Nurse trained in stroke management
- Stroke specialist consultant physician
- Occupational therapy
- Physiotherapy
- Speech and language therapy
- Thrombolysis (procedure)
- Thrombectomy
- Stroke unit stay
- ICH costs (AEs)

Data from SSNAP 2023 were also used to inform the proportion of patients requiring each of these resources and are presented in Table 19.[10] The healthcare resource use (HCRU) associated with treatment administration for alteplase was aligned to that reported in SSNAP 2022–2023.[13] The percentage of patients using resources within the first 72 hours was conservatively assumed equal across treatment arms. To calculate the costs over the first 72 hours, the percentage of patients using the resource (for 24- and 72-hour intervals) was multiplied by the cost of the resource.

**Table 19: Baseline percentage of patients using resources within the first 72-hour period**

| Resource category | Time period: | Resource use (% of AIS patients) | SE* | Source |
|---|---|---|---|---|
| CT scan | 24 hours from onset | 99.6% | 10.0% | SSNAP 2023[10] |
| | 25–72 hours from onset | 0.0% | 0.0% | |
| Nurse trained in stroke management | 24 hours from onset | 89.1% | 8.9% | |
| | 25–72 hours from onset | 4.9% | 0.5% | |
| Stroke specialist consultant physician | 24 hours from onset | 83.1% | 8.3% | |



| Resource category | Time period: | Resource use (% of AIS patients) | SE* | Source |
|---|---|---|---|---|
| | 25–72 hours from onset | 10.8% | 1.1% | |
| Occupational therapy | 24 hours from onset | 46.3% | 4.6% | |
| | 25–72 hours from onset | 31.3% | 3.1% | |
| Physiotherapy | 24 hours from onset | 51.3% | 5.1% | |
| | 25–72 hours from onset | 30.7% | 3.1% | |
| Speech and language therapy | 24 hours from onset | 24.8% | 2.5% | |
| | 25–72 hours from onset | 21.8% | 2.2% | |
| Thrombolysis | 24 hours from onset | 100.0% | 10.0% | |
| | 25–72 hours from onset | 0.0% | 0.0% | |
| Thrombectomy | 24 hours from onset | 3.6% | 0.4% | SSNAP 2023[10] – assumed first 24 hours only |
| Stroke unit stay | 24 hours from onset | 91.9% | 9.2% | |
| Transportation (ground ambulance) | 24 hours from onset | 72.6% | 7.3% | |
| **Key**: AIS, acute ischaemic stroke; CT, computed tomography; SE, standard error; SSNAP, Sentinel Stroke National Audit Programme. | | | | |

### B.4.2.2. Intervention and comparators' acquisition costs

Table 20 and Table 21 outline the total acquisition costs for tenecteplase and alteplase, respectively. Acquisition costs apply when treatment is administered, and in line with clinical practice and the previous NICE TA264[47]**,** no vial sharing was assumed in the model base case. Therefore, the acquisition cost was based on the number of vials used per administration. For tenecteplase, the mean required dose per patient is 19.7 mg, requiring one vial of tenecteplase at a cost of [redacted]. For alteplase, it requires an initial administration of 0.09 mg/kg and a subsequent administration of 0.81 mg/kg. For initial bolus injection, a 10 mg vial was assumed to always be used. Therefore, for the remaining infusion, the maximum dose was



80 mg. The number of vials required was based on the patient's weight, assuming a normal distribution. This gives a combined total cost of £867.72 for alteplase. Further details on treatment with multiple options, such as alteplase, is provided in Appendix H.



**Table 20: Tenecteplase acquisition costs**

| Name | Form | Vial size (mg) | Acquisition price | Dose (mg/kg) | Mean dose (mg) | Number of vials | Cost | Source |
|---|---|---|---|---|---|---|---|---|
| Tenecteplase | Injection | 25 | [redacted] | 0.25 | 19.73 | 1 | [redacted] | List price |

**Table 21: Alteplase acquisition costs**

| Name | Form | Vial size (mg) | Acquisition price | Dose (mg/kg) | Mean dose (mg) | Cost | Source |
|---|---|---|---|---|---|---|---|
| Alteplase (used in initial injection) | Injection | 10 | £172.80 | 0.9 | 7.10 | £172.80 | BNF[66] |
| Alteplase (remainder of dosage over 1 hour) | Injection | 10 | £172.80 | 0.81 | 63.93 | £694.92 | BNF[66] |
| | Injection | 20 | £259.20 | | | | BNF[66] |
| | Infusion | 50 | £432.00 | | | | BNF[66] |
| **Total cost** | | | | | | £867.72 | |
| **Key:** BNF, British National Formulary. | | | | | | | |



### B.4.2.3. Intervention and comparators' healthcare resource use and associated costs

The resource use associated with treatment administration for alteplase is aligned to that reported in SSNAP 2022–2023.[13] Compared to alteplase, tenecteplase requires fewer resources, including less staff time, to prepare and administer treatment. Currently, there are no data available to quantify the resource efficiencies and associated cost savings. However, these factors contribute to potential extra benefits for the NHS. Therefore, results are likely to under-estimate the cost-savings associated with use of tenecteplase. These benefits are explored in sensitivity and scenario analysis.

Resource use costs used in the cost calculations are presented in Table 22; these values were combined with the percentage of patients who required each resource as presented in Table 19. Total costs for each treatment are presented in Table 23. These values represent the costs accumulated during the first 72 hours after stroke onset.

**Table 22: Healthcare resource unit costs and hours utilized**

| Parameter | Resource item | Mean cost (£) / hours | SE* | Source |
|---|---|---|---|---|
| One-off cost per use | CT scan | £126.21 | £12.29 | NHS Unit costs 21–22[67] |
| | Thrombolysis | £7682.95 | £747.95 | NHS Unit costs 21–22[67] |
| | Thrombectomy | £3983.01 | £398.30 | Grunwald et.al 2022[68] |
| | Stroke unit stay cost-per-bed stay | £314.87 | £31.49 | Grunwald et.al 2022[68] |
| | Transportation (ground ambulance) | £283.51 | £27.60 | PSSRU 2022[65] |
| Cost per working hour | Nurse trained in stroke management | £64.71 | £6.30 | PSSRU 2022[65] |
| | Stroke specialist consultant physician | £148.94 | £14.50 | PSSRU 2022[65] |
| | Occupational therapy | £121.21 | £11.80 | PSSRU 2022[65] |
| | Physiotherapy | £147.92 | £14.40 | PSSRU 2022[65] |



| Parameter | Resource item | Mean cost (£) / hours | SE* | Source |
|---|---|---|---|---|
| | Speech and language therapy | £133.54 | £13.00 | PSSRU 2022[65] |
| Hours used per patient (hours) | Nurse trained in stroke management | 7.569 | 0.757 | De Wit et al. 2005[69] |
| | Stroke specialist consultant physician | 0.473 | 0.0473 | De Wit et al. 2005[69] |
| | Occupational therapy | 0.473 | 0.0473 | Assumed the same as Stroke specialist consultant physician |
| | Physiotherapy | 0.473 | 0.0473 | Assumed the same as Stroke specialist consultant physician |
| | Speech and language therapy | 0.473 | 0.0473 | Assumed the same as Stroke specialist consultant physician |

**Key:** CT, computed tomography; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SE; standard error.

**Table 23: Total resource use costs**

| Total resource use costs | Tenecteplase | Alteplase |
|---|---|---|
| | **£8,899.03** | **£8,899.03** |
| CT scan | £125.71 | £125.71 |
| Nurse trained in stroke management | £461.41 | £461.41 |
| Stroke specialist consultant physician | £66.14 | £66.14 |
| Occupational therapy | £44.48 | £44.48 |
| Physiotherapy | £57.36 | £57.36 |
| Speech and language therapy | £29.43 | £29.43 |
| Thrombolysis | £7,682.95 | £7,682.95 |
| Thrombectomy | £142.20 | £142.20 |
| Stroke unit stay | £289.36 | £289.36 |

**Key:** CT, computed tomography.

### B.4.2.4. Adverse reaction unit costs and resource use

Table 24 shows that the mean cost of an ICH event is £131.52, which comprises the cost of a CT scan and phlebotomy, as per NHS reference costs 21/22[67], and a full blood test.[70] Table 25 presents how the ICH event cost is applied within the 72-hour



micro-costing to the proportion of patients on each arm who are estimated to experience the ICH AE. Evidence of ICH frequency per treatment arm was sourced from SSNAP[10], with no difference in rates by treatment.

**Table 24: ICH event cost**

| ICH cost components | Cost | Year | Source/Note |
|---|---|---|---|
| CT scan cost | £117.50 | 2022 | NHS reference costs 21/22[67] |
| Phlebotomy cost | £3.67 | 2022 | NHS reference costs 21/22[67] |
| Full blood test panel cost | £6.00 | 2015 | NICE NG45[70] |
| **Total cost** | **£131.52** | **2023** | **Sum of above three rows** |
| **Key:** ICH, intracerebral haemorrhage; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.<br>**Note:** The costs of ICH components were inflated to 2023 and summed up to determine the ICH event cost. | | | |

**Table 25: Adverse event costs calculation**

| Mean ICH event cost (NHS resource costs) | Proportion of patients experiencing (%) (SSNAP 2023) | | Total | |
|---|---|---|---|---|
| | Tenecteplase | Alteplase | Tenecteplase | Alteplase |
| £131.52 | 9.7 | 9.7 | £12.76 | £12.76 |
| **Key**: ICH, intracerebral haemorrhage; NHS, National Health Service; SSNAP, Sentinel Stroke National Audit Programme. | | | | |

### B.4.2.5. Clinical expert validation

Many of the assumptions in the cost-comparison model were identified from the previous NICE technology appraisal for alteplase for treating AIS (TA264). The submitted model was deemed suitable for decision making by NICE, and therefore it is appropriate to adopt a similar approach for this submission.

Clinical experts with a background in stroke medicine were consulted by Boehringer Ingelheim during the model conceptualization process, collaborating with health economists on the approach, structure and inputs used in the submitted model.



### B.4.2.6. Uncertainties in the inputs and assumptions

A summary of the inputs used in the cost-comparison analysis is provided in Table 26, and the key assumptions are presented in Table 27. Given the simple nature of the cost-comparison model structure, the majority of inputs were sourced from standard UK sources and are not subject to uncertainty.

**Table 26: Key inputs of the cost-comparison analysis**

| Input name | Base case value | Reference |
|---|---|---|
| **Acquisition costs per pack** | | |
| Tenecteplase 25 mg (list price) | [redacted] | List price |
| Alteplase 10 mg (list price) | £172.80 | BNF[66] |
| Alteplase 20 mg (list price) | £259.20 | BNF[66] |
| Alteplase 50 mg (list price) | £432.00 | BNF[66] |
| **Key:** BNF, British National Formulary. | | |

**Table 27: Key assumptions of the cost-comparison analysis**

| Assumption | Rationale for assumption | Relevant sensitivity analysis |
|---|---|---|
| Vial wastage | Not included in analysis, as per clinical practice – also aligns with TA264 | N/A |
| No costs discount applied | According to NICE cost-comparison appraisal guidelines | N/A |
| Post-hospitalization costs are not included in the analysis | Post-hospitalization costs are assumed to be equal across both treatment arms | N/A |
| No difference in AE incidence rates | No statistically significant difference in trial outcomes | Differing AE rates explored |
| Unit costs per AE are equivalent for tenecteplase and alteplase | Patients in the same treatment pathway are assumed to show similar characteristics. Both treatments have the same mechanism of action. Hence, the costs accrued for AEs are expected to be identical. | N/A |



| Assumption | Rationale for assumption | Relevant sensitivity analysis |
|---|---|---|
| HCRU inputs are equivalent for tenecteplase and alteplase | No quantitative data available; a conservative assumption was applied in the base case | Tenecteplase is faster and easier to administer than alteplase. The potential impact of reductions in HCRU are explored. |
| **Key:** AE; adverse event, HCRU; healthcare resource use, N/A; not applicable. | | |

### *B.4.3. Base case results*

Results of the base case analysis are presented in Table 28 and Table 29. The cost-comparison analysis demonstrates that tenecteplase is a cost-saving treatment option for patients with AIS. Given the assumptions around similar efficacy and resource use, results show that the resource use costs for each treatment are identical. All of the cost savings associated with tenecteplase stem from lower drug acquisition costs.

**Table 28: Base case cost-comparison results**

| Component | Tenecteplase | Alteplase | Incremental (TNK vs ALT) |
|---|---|---|---|
| Thrombolysis (drug costs) | [redacted] | £867.72 | [redacted] |
| 72-hour period AIS resource use costs | £8,899.03 | £8,899.03 | £0.00 |
| Adverse event costs (ICH) | £12.76 | £12.76 | £0.00 |
| **Total** | [redacted] | [redacted] | [redacted] |
| **Key**: AIS, acute ischaemic stroke; ALT, alteplase; ICH, intracerebral haemorrhage; TNK, tenecteplase. | | | |

**Table 29: Base case cost-comparison results – resource use costs breakdown**

| Resource | Tenecteplase | Alteplase | Incremental (TNK vs ALT) |
|---|---|---|---|
| CT scan | £125.71 | £125.71 | £0.00 |
| Nurse trained in stroke management | £461.41 | £461.41 | £0.00 |
| Stroke specialist consultant physician | £66.14 | £66.14 | £0.00 |
| Occupational therapy | £44.48 | £44.48 | £0.00 |



| Resource | Tenecteplase | Alteplase | Incremental (TNK vs ALT) |
|---|---|---|---|
| Physiotherapy | £57.36 | £57.36 | £0.00 |
| Speech and language therapy | £29.43 | £29.43 | £0.00 |
| Thrombolysis | £7,682.95 | £7,682.95 | £0.00 |
| Thrombectomy | £142.20 | £142.20 | £0.00 |
| Stroke unit stay | £289.36 | £289.36 | £0.00 |
| **Total** | **£8,899.03** | **£8,899.03** | **£0.00** |
| **Key:** AIS, acute ischaemic stroke; ALT, alteplase; CT, computed tomography; TNK, tenecteplase. | | | |

### *B.4.4. Sensitivity and scenario analyses*

Deterministic sensitivity analyses (DSAs) and scenario analyses were conducted to demonstrate the impact of varying individual input values.

For the DSA, the proportion of the population that is male was varied above and below the base case value. Alternative demographic data and any potential difference in either intracerebral or intracranial haemorrhage rates were also explored. In addition, three sensitivity analyses considered the impact of tenecteplase's shorter administration on HCRU. As tenecteplase is not anticipated to increase HCRU, parameters were only varied in one direction.

An overview of the sensitivity and scenario analyses considered is provided in Table 30.



**Table 30: Sensitivity and scenario analyses**

| Analysis | Base case | Alternatives | Justification |
|---|---|---|---|
| **Sensitivity analysis** | | | |
| Proportion male | 53.6% from SSNAP | Lower = 48.2%<br>Upper = 59.0% | Vary by ± 10% |
| Mean weight | Weighted average of male (85.1 kg) and female (71.78 kg) weights | Male weight (85.1 kg)<br>Female weight (71.78 kg) | Extreme value testing to assess the impact of higher or lower weights |
| Nurse trained in stroke management (hours) | Multiplier of 1, reflecting no difference | Lower = 0.9<br>Upper = 1 (no change) | Assess the impact of shorter administration on HCRU |
| Stroke specialist consultant physician (hours) | Multiplier of 1, reflecting no difference | Lower = 0.9<br>Upper = 1 (no change) | Assess the impact of shorter administration on HCRU |
| Stroke unit length of stay | Multiplier of 1, reflecting no difference | Lower = 0.9<br>Upper = 1 (no change) | Assess the impact of shorter administration on HCRU |
| **Scenario analysis** | | | |
| Demographic data | SSNAP (age = 76, proportion male = 54%) | AcT (age = 74, proportion male = 52%) | Assess the impact of alternative sources |
| Demographic data | SSNAP (age = 76, proportion male = 54%) | EXTEND-IA TNK Part 1 (age = 72, proportion male = 51%) | Assess the impact of alternative sources |
| AcT difference in intracranial haemorrhage rates | No difference by treatments | Multiplier of 0.936 for tenecteplase | Assess the impact of a difference in adverse events |
| AcT difference in intracerebral haemorrhage rates | No difference by treatments | Multiplier of 1.073 for tenecteplase | Assess the impact of a difference in adverse events |
| **Key:** HCRU, healthcare resource use; SSNAP, Sentinel Stroke National Audit Programme. | | | |

Table 31 presents the key cost drivers of the analysis, ranked by impact on costs. For the sensitivity analyses that considered reduced HCRU with tenecteplase, only one value is provided. Similarly, only one result is provided per scenario. Figure 6 presents a tornado diagram of these results; the use of different average weights and the exploratory scenarios where use of tenecteplase was associated with reduced HCRU had the largest impact.



**Table 31: Results of scenario and sensitivity analyses**

| Parameter | | | Change to costs | |
|---|---|---|---|---|
| **Group** | **Name** | **Applicable arm** | **Lower** | **Upper** |
| Baseline demographics | Use female mean weight | All | N/A | [redacted] |
| Baseline demographics | Use male mean weight | All | [redacted] | N/A |
| Resource use | Nurse trained in stroke management (hours) | Tenecteplase | [redacted] | N/A |
| Resource use | Stroke unit LoS; tenecteplase improvement | Tenecteplase | [redacted] | N/A |
| Baseline demographics | Proportion male | All | [redacted] | [redacted] |
| Resource use | Stroke specialist consultant physician (hours) | Tenecteplase | [redacted] | N/A |
| Scenario | EXTEND-IA TNK Part 1 demographic data | All | [redacted] | |
| Scenario | AcT demographic data | All | [redacted] | |
| Scenario | AcT difference in intracerebral haemorrhage rates | All | [redacted] | |
| Scenario | AcT difference in intracranial haemorrhage rates | All | [redacted] | |

**Key:** LoS, length of stay; N/A, not applicable.



**Figure 6: Tornado diagram of most influential parameters**

**Key:** LoS, length of stay.



### *B.4.5. Subgroup analysis*

In line with the decision problem, no subgroup analyses were considered as part of the cost comparison.

### *B.4.6. Interpretation and conclusions of economic evidence*

Clinical trial data show that tenecteplase has a similar efficacy and safety profile to alteplase in the population under consideration; this is further supported by the current guideline-recommended off-label use of AMI-licensed tenecteplase (See section B.1.3.3).[41, 64] Currently, only a 50 mg vial of tenecteplase is available in the UK. However, a 25 mg vial better matches the recommended dosing requirements in AIS.

Tenecteplase is cost-saving compared with alteplase, the comparator in the current NICE-recommended treatment pathway (NG128).[40] The cost-comparison analysis demonstrates potential cost savings of £[redacted] per patient from reduced drug acquisition costs. Scenario analysis indicated that cost savings of £[redacted] are possible when considering the potential for reduced time requirements for specialist stroke management nurses, as treatment with tenecteplase requires less time to administer and no specialist equipment.



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## B.6. Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Price details of treatment included in the submission

Appendix I: Checklist of confidential information

Appendix J: Further information on clinical guidelines

Appendix K: Further presentation of information from AcT and EXTEND-IA TNK Part 1



# Summary of Information for Patients (SIP):

### The pharmaceutical company perspective

**What is the SIP?**

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

However, any text preceded by the words '**Notes for authors**' simply contains additional prompts for the company to advise them on the type of information that may be most relevant, and the level of detail they need to include. **You may delete this text where indicated.**

# Section 1: submission summary

## 1a) Name of the medicine

Both generic and brand name.

| |
|---|
| Tenecteplase (Metalyse®). |

## 1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

| |
|---|
| People with acute ischaemic stroke (AIS) who can have thrombolytic treatment. |

## 1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state

this, and reference the section of the company submission with the anticipated dates for approval.

| |
|---|
| Marketing authorisation is pending – please see Document B, Section B.1.2 for anticipated dates. |

### 1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

| |
|---|
| Not applicable - no relevant disclosures to report. |

## Section 2: current landscape

### 2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

| |
|---|
| Stroke is the fifth leading cause of disability, the fourth leading cause of death and the third leading cause of premature mortality in the UK.[1-3] Stroke is a disorder that affects the brain. In the UK, approximately 100,000 people have a stroke each year.[4, 5] In 2021/2022, there were 1,187,756 stroke survivors in England and Wales, giving a prevalence rate of approximately 1.89%.[6] The median age of people presenting with stroke in the UK is 73 years in males and 79 years in females.[7] In 2022, 29,265 people died from cerebrovascular diseases (including strokes) in England and Wales.[3]<br><br>AIS is the most common type of stroke, accounting for 85% of total stroke cases.[8] AIS is caused by a clot stopping blood flow to the brain, resulting in the brain not receiving any oxygen and leading to brain tissue damage.[8] If the blockage is not removed quickly, further damage and loss of brain tissue occurs, increasing the |

risk of disability and death.[9-13] Therefore, rapidly removing the blockage and allowing blood flow to resume is crucial.

AIS can result in physical and cognitive (intellectual) disability, both of which can cause significant changes to quality of life. In some cases, people will require additional care for the rest of their lives. Common physical impairments include paralysis or weakness of the affected side of the body, pain, changes to speech, difficulty swallowing and fatigue.[14] Cognitive impairment can also cause significant burden.[15] Around 60% of people report mild-to-severe cognitive impairment in their first year after stroke, affecting their memory, language, attention span, executive function and perceptual motor abilities. The main drivers of caregiver burden include high numbers of hours spent caregiving and disturbed sleep, leading to both anxiety and depression in the informal caregiver. Aggregate annual cost of unpaid care provided by family and other unpaid carers is £15.8 billion.[16]

## 2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

In the UK, NICE guidelines and the NHS website recommend that a stroke is first diagnosed based on the FAST criteria outside a hospital setting. These four common symptoms are[17, 18]:

- **F**ace – the face may have dropped on one side, the person may not be able to smile, or their mouth or eye may have drooped
- **A**rms – the person may not be able to lift both arms and keep them there because of weakness or numbness in one arm
- **S**peech – their speech may be slurred or garbled, or the person may not be able to talk at all despite appearing to be awake; they may also have problems understanding what you're saying to them
- **T**ime – it's time to dial 999 immediately if you notice any of these signs or symptoms

Once a patient is at a hospital, tests are carried out to confirm what type of stroke a person is having.[17, 18] Physical tests, blood tests and brain scans will be performed. NICE recommends using the Recognition of Stroke in the Emergency Room (ROSIER) test if a patient presents at an emergency room with suspected stroke. If a stroke is suspected, patients should be referred to a specialist stroke unit and sent for a brain scan in the form of either a computed tomography (CT) scan or a magnetic resonance imaging (MRI) scan. This will produce images of the

brain to confirm if the stroke is caused by a burst blood vessel or a blood clot. It will also show the severity of the stroke and the area of the brain affected. If the scan shows that a blood clot has caused the stroke, treatment for AIS will be carried out accordingly.[17, 18]

## 2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There are limited treatment options for people with AIS. The main method currently used for clot removal is thrombolysis (a procedure to dissolve or break up a blood clot), along with mechanical thrombectomy (surgical removal) if the clot is in a large blood vessel.[18-20]

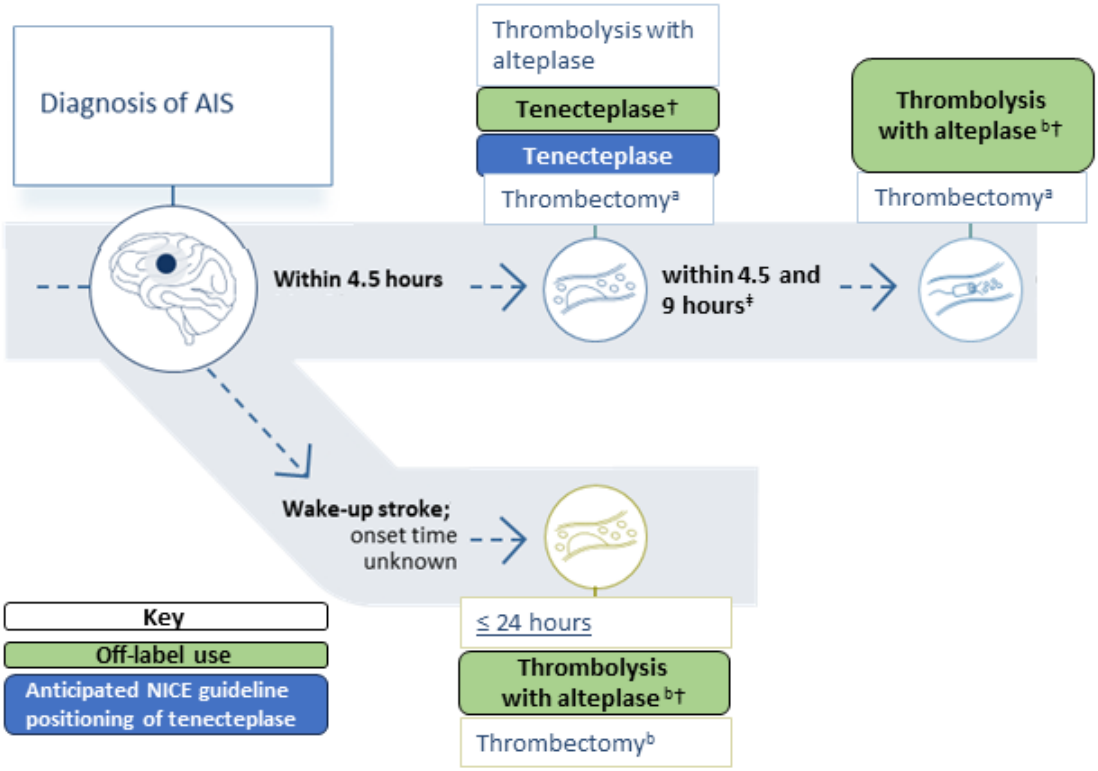
The approved standard of care in the UK is alteplase, a thrombolytic drug (meaning it breaks down blood clots). Generally, clinical guidelines recommend that thrombolysis with alteplase is initiated as soon as possible, and within 4.5 hours of symptom onset, in line with the licensed indication.[18-20] Clinical guidelines also recommend the off-label use of tenecteplase (which is currently licensed for use in acute myocardial infarction [AMI; or heart attack]) for adults with AIS in whom treatment can be started within 4.5 hours of known onset and who are eligible for thrombolysis.[19, 20]

Mechanical thrombectomy is also recommended in patients with a clot in a large blood vessel, either following thrombolysis and within 6 hours of symptom onset or as a standalone procedure.

Tenecteplase – which is supplied as 25 mg vials – is indicated in adults for the thrombolytic treatment of AIS within 4.5 hours from when the patient was last known to be well.[21]

Figure 1 presents the current clinical pathway of care for people with AIS.[18-20, 22] This includes the proposed positioning of tenecteplase in the UK.

**Figure 1: Clinical pathway of care for patients with AIS and anticipated positioning of tenecteplase**




**Key**: AIS, acute ischaemic stroke; CT, computed tomography; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.
**Notes:** †Denotes off-label use within the National Clinical Guideline for Stroke for the UK and Ireland. ‡ National Clinical Guideline for Stroke for the UK and Ireland.[a] Confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA. [b] Confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA and if there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume.
**Sources**: National Clinical Guideline for Stroke for the UK and Ireland.[20]

## 2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might

also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

| |
|---|
| Not applicable - no PBE to report. |

# Section 3: the treatment

## 3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body.

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

| |
|---|
| Tenecteplase is a type of drug called a fibrin-specific plasminogen activator.[21] Fibrin is a string-like protein which creates a net that forms the basis of a blood clot. Blood clots normally form to prevent excessive bleeding, such as when a person gets a cut. However, they are harmful when they block blood vessels and stop blood flow to a person's vital organs.<br><br>Tenecteplase attaches to the fibrin net of the clot and makes a change to another protein called plasminogen.[21] Tenecteplase converts plasminogen into its active form, called plasmin. Plasmin then breaks up the fibrin net and consequently the blood clot, which resumes the flow of blood to the brain.<br><br>The drug alteplase also acts this way.[21] However, compared with alteplase, tenecteplase can form stronger attachments to fibrin. Tenecteplase is also more |

resistant to the body's natural mechanism of stopping plasmin from forming (called plasminogen activator inhibitor-1).

## 3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

No.

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

**If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**

Not applicable.

## 3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Tenecteplase for AIS is supplied as 25 mg vials and is given in a hospital at a recommended dose of 0.25 mg/kg of body weight (up to a maximum of 25 mg) as a single intravenous (IV) bolus (into the vein) over approximately 5–10 seconds.[21]

Alteplase is also administered in a hospital. It is first given as an IV bolus injection of 0.09 mg/kg, followed by a 60-minute IV infusion of 0.81 mg/kg totalling a dose of 0.9 mg/kg (up to a maximum of 90 mg).[23]

Both treatments are administered in a hospital setting.[21, 23] Alteplase is given over the course of 60 minutes. This means that a long time is needed for dosing to be completed. Monitoring is also required throughout the 60-minute infusion. As

tenecteplase is given as a single dose over 5–10 seconds, it has a shorter treatment time compared with alteplase and the drug is delivered into the patient's system faster. This also removes the need for one hour of monitoring. Therefore, treatment with tenecteplase means patients can be treated faster and easier than with alteplase.

## 3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Two randomized clinical trials were used in this NICE submission to present evidence for the efficacy and safety of tenecteplase relative to alteplase in AIS.

**AcT**

AcT was a Phase III, multicentre, open-label, parallel-group, registry-linked, randomized controlled trial that studied the efficacy and safety of tenecteplase compared with alteplase for the treatment of patients with AIS. The study completed in April 2023.[24]

In total, 1,600 patients from Canada were included. They were randomized to receive either tenecteplase or alteplase, at a 1:1 ratio.

To be included, patients had to match the following criteria[24]:

- Be over 18 years old
- Have confirmed AIS and be eligible for IV thrombolysis within 4.5 hours of symptom onset

Patients with active or risk of haemorrhage were excluded.

**Further information/publications for AcT**

Clinicaltrials.gov (NCT03889249) – https://clinicaltrials.gov/study/NCT03889249

Publication (Menon et al. 2022[24]) – https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01054-6/fulltext

## EXTEND-IA TNK Part 1

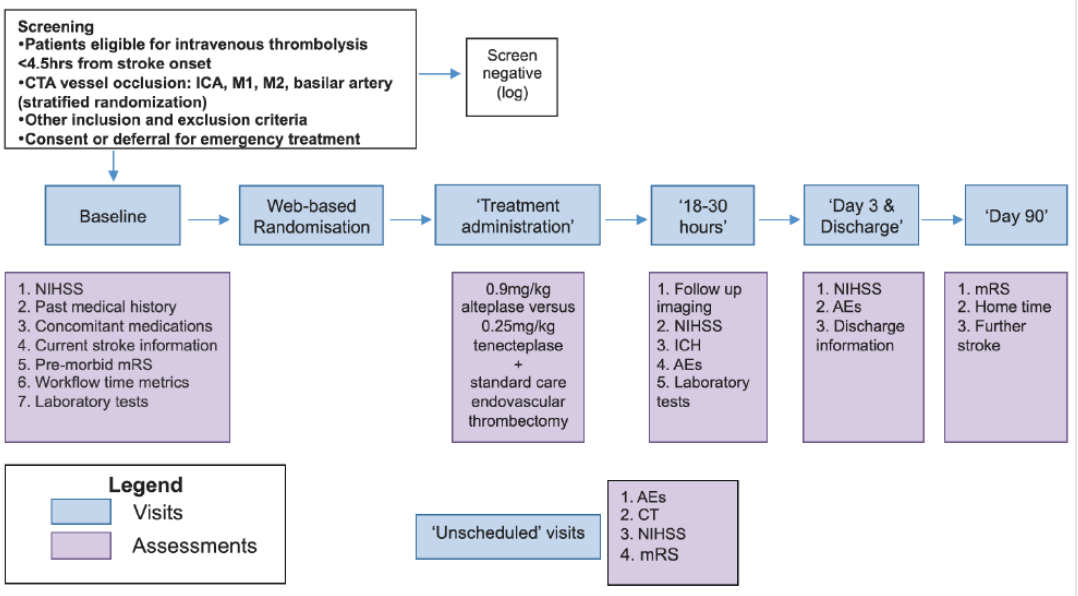
EXTEND-IA TNK Part 1 was a Phase II, prospective, multicentre, randomized, open-label, blinded-endpoint (PROBE) trial that studied the efficacy and safety of tenecteplase compared with alteplase before mechanical thrombectomy for the treatment of patients with AIS. It was completed in February 2018.[25]

In total, 204 patients from Australia and New Zealand were enrolled. They were randomized to receive either tenecteplase or alteplase, at a 1:1 ratio (i.e. equal numbers in each group). Figure 2 shows the design of the trial.

To be included, patients had to match the following criteria[25]:

- Be over 18 years of age
- Had confirmed AIS
- Were eligible for IV thrombolysis within 4.5 hours of symptom onset
- Were eligible for thrombectomy within 6 hours of symptom onset

**Figure 2: Study design of EXTEND-IA TNK Part 1**




**Key**: AEs, adverse events; CT, computed tomography; CTA, computed tomographic angiography; ICA, internal carotid artery; ICH, intracerebral haemorrhage; M1, first segment; M2, second segment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
**Notes**: Unscheduled visits were possible. These assessed AEs, CT, NIHSS and mRS.
**Sources**: Campbell et al. 2018.[25, 26]

### Further information/publications for EXTEND-IA TNK Part 1

Clinicaltrials.gov (NCT02388061) – https://clinicaltrials.gov/study/NCT02388061

Publication (Campbell et al. 2018[25]) – https://www.nejm.org/doi/10.1056/NEJMoa1716405

## 3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

**AcT**

In the AcT clinical trial, as summarized in Question 3d, patients received tenecteplase or alteplase for thrombolysis following AIS. Patients were assessed for between 90 and 120 days after an AIS.

**Primary endpoint: modified Rankin Scale (mRS) score 0–1 at 90–120 days**

The primary endpoint of the trial was the number of patients that recorded an mRS score of 0–1 at 90–120 days.[24] The mRS is a 6-point scale measure of disability and dependence for patients after a stroke: 0, no neurological deficit; 1, no clinically significant disability; 2, slight disability (able to handle own affairs without assistance but unable to carry out all previous activities); 3, moderate disability requiring some help (e.g. with shopping, cleaning and finances, but able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death.[24]

In the group of patients treated with tenecteplase, 36.9% had an mRS score of 0–1. In the alteplase-treated group, 34.8% had an mRS score of 0–1, showing comparable efficacy between the two treatment groups.[24]

**Secondary endpoint: mRS score 0–2 at 90–120 days**

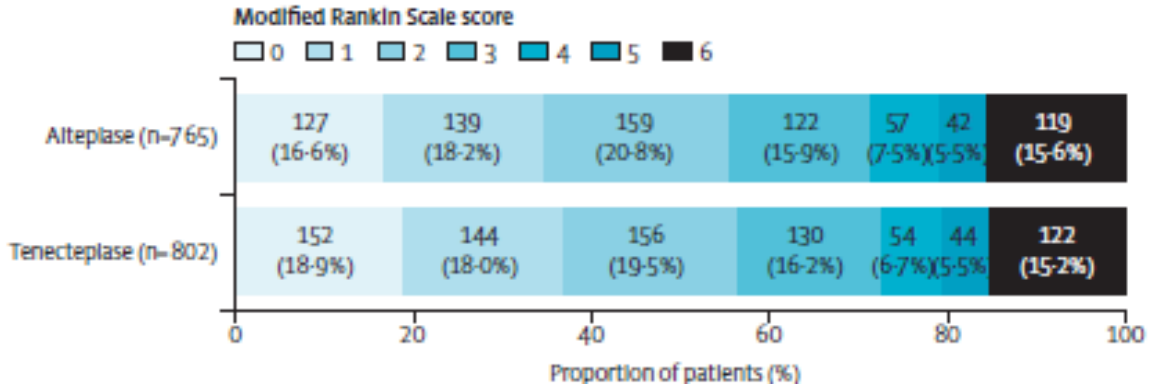
A secondary endpoint of the trial was the number of patients that recorded an mRS score of 0–2 at 90–120 days.[24]

In the group of patients treated with tenecteplase, 56.4% had an mRS score of 0–2. In the alteplase-treated group, 55.6% had an mRS score of 0–2, showing comparable efficacy between the two treatment groups.[24]

**Secondary endpoint: actual mRS score at 90–120 days**

Patients in both the tenecteplase and alteplase groups had median mRS scores of 2 (interquartile range [IQR]: 1–4) at 90–120 days, showing comparable function between the two groups (Figure 3).[24]

**Figure 3: Distribution of the mRS scores at 90–120 days, intention-to-treat population**




**Key:** mRS, modified Rankin Scale.
**Source:** Menon et al. 2022.[24]

**Secondary endpoint: return to baseline function**

Return to baseline function was measured in 1,454 of the 1,600 patients in the AcT trial.[24] Of the tenecteplase-treated patients, 29.6% showed a return to baseline function; this was comparable to the 27.9% of patients in the alteplase-treated group that recorded a return to baseline function.[24]

**Secondary endpoint: length of hospital stay**

Length of hospital stay was recorded in 1,481 of the 1,600 patients in the trial.[24] The median length of stay was 5 days (IQR: 2–11) in the patients treated with tenecteplase, and 5 days (IQR: 3–11) in the patients treated with alteplase, showing comparable lengths of stay for both treatment groups.[24]

**EXTEND-IA TNK Part 1**

As summarized in Question 3d, in this clinical trial, patients with AIS were treated with either tenecteplase or alteplase before mechanical thrombectomy. Patients were assessed up to 90 days after treatment.[25]

**Primary endpoint: reperfusion of greater than 50% at initial angiographic assessment**

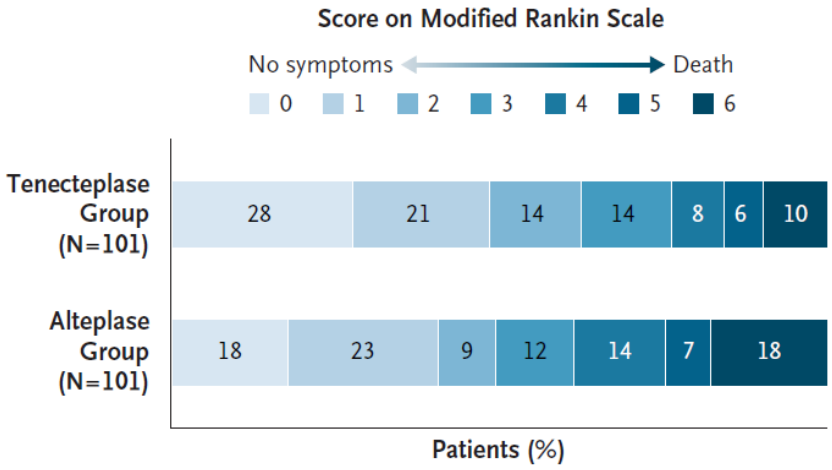
50% perfusion at initial angiographic assessment means a return of 50% or more of blood flow to the affected area of the brain confirmed using a CT or MRI scan.[25]

In patients treated with tenecteplase, 22% achieved greater than 50% reperfusion compared with 10% in the patients treated with alteplase. This was a significant improvement in the tenecteplase group relative to the alteplase group.[25]

**Secondary endpoint: median mRS score at 90 days**

Patients treated with tenecteplase had a median (average) score of 2 (IQR: 0–3), while those treated with alteplase had a median score of 3 (IQR: 1–5; Figure 4). This was a significant improvement in the tenecteplase group relative to the alteplase group.[25]

**Figure 4: Ordinal analysis of mRS score at 90 days in the intention-to-treat population of EXTEND-IA TNK Part 1**




**Key**: CSR, clinical study report; mRS, modified Rankin Scale.
**Source**: EXTEND-IA TNK Part 1 CSR[26]; Campbell et al. 2018.[25]

**Secondary endpoint: mRS score 0–2 at 90 days**

Any person with an mRS score of 0–2 or showing no change from baseline at Day 90 was recorded.[25] In the tenecteplase group, 64% of patients achieved an mRS score of 0–2 or no change from baseline function at 90 days, compared with 51%

in the alteplase group, showing comparable efficacy between the two treatment groups.[25]

**Secondary endpoint: mRS score 0–1 at 90 days**

Any person with an mRS score of 0–1 or showing no change from baseline at Day 90 was recorded.[25] In the tenecteplase-treated group, 51% of patients achieved an mRS score of 0–1 or no change from baseline function at 90 days compared with 43% in the alteplase-treated group, showing comparable efficacy between the two treatment groups.[25]

**Secondary endpoint: Early neurological improvement and NIHSS score at 24 hours and 72 hours**

The National Institutes of Health Stroke Scale (NIHSS score) is a measure of severity of stroke symptoms that scores between 0 and 42. It was used here to show early neurological improvement at 24 and 72 hours post-stroke.[25] A lower NIHSS score shows better function.

Compared with a baseline measurement, 71% of patients treated with tenecteplase showed an improvement in NIHSS score at 72 hours, and 68% of patients treated with alteplase showed an improvement in NIHSS score at 72 hours.[25]

Median NIHSS score at 24 hours was 3/42 (IQR: 1–12) among patients in the tenecteplase group and 6/42 (IQR: 2–14) among those in the alteplase group.[25] At 72 hours, the median NIHSS score was 2/42 (IQR: 0–10) among patients in the tenecteplase group and 3/42 (IQR: 1–13) among those in the alteplase group. These scores were comparable between the two treatment groups.[25]

## 3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life was recorded in the AcT trial. EQ-VAS and EQ-5D-5L domains (mobility, self-care, usual task, pain and anxiety) were measured after 90 days.[27] These are not specific measures for quality of life following a stroke, but they do capture many elements of activities of daily living. Overall, there were no differences observed between treatment groups for the EQ-VAS or EQ-5D-5L domains, demonstrating comparable effects on patient quality of life. Values are reported in Table 1, with more details in Document B, Section B.3.6.1.3.[27]

**Table 1: HRQL outcomes measured in the ITT population of the AcT trial**

| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of effect | Estimate (95% CI) |
|---|---|---|---|---|
| EQ-VAS at 90 days (n = 1,262), mean (SD) | 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) |

**Key**: CI, confidence interval; HRQL, health-related quality of life; ITT, intention-to-treat; SD, standard deviation; VAS, visual analogue scale.
**Notes**: * 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
Source: Menon et al, 2022[24]

## 3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

An adverse event is defined as any undesirable experience that occurs after a patient is given a treatment. For tenecteplase, the adverse events were generally manageable. The type and rate at which adverse events occurred for patients

receiving tenecteplase were similar to those for patients treated with alteplase. The reports of serious adverse events from both the AcT and EXTEND-IA TNK Part 1 trials are presented below.[24, 25]

**AcT trial**

The safety population of the AcT trial included 1,563 patients (800 treated with tenecteplase and 763 treated with alteplase).[24] There were no differences in safety outcomes between the two treatments. This includes no meaningful differences in the rate of 24-hour symptomatic intracerebral haemorrhage or mortality (90-day and overall) between the two treatment groups (symptomatic intracerebral haemorrhage is a brain bleed with increased risk after reperfusion therapy such as thrombolysis).[24] Further details on safety outcomes are presented in Document B, Section B.3.10.1.

**EXTEND-IA TNK Part 1**

Safety was analysed in all 202 patients that participated in the EXTEND-IA TNK Part 1 trial.[25] Safety was comparable between the tenecteplase- and alteplase-treated groups. In the tenecteplase group, 10 out of 101 patients died within 90 days; in the alteplase group, 18 out of 101 patients died. In both groups, the majority of deaths were due to progression of major stroke. Symptomatic intracerebral haemorrhage was recorded in one patient treated with tenecteplase and one patient treated with alteplase.[25]

## 3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Tenecteplase is a thrombolytic agent, meaning that it breaks down the blood clots that cause AIS. It is proposed that 25 mg vials of tenecteplase should be used for the treatment of adults with AIS within 4.5 hours from last known well and after exclusion of intracranial haemorrhage.

Tenecteplase provides a similar efficacy and safety profile to the current standard of care recommended by NICE for adults with AIS – alteplase – but is faster and easier to administer.

Clinical trials comparing tenecteplase and alteplase have shown the following:

- Tenecteplase and alteplase were comparable in terms of recovery of mRS score at 90 days – showing similar median mRS scores and proportion of patients with excellent functional recovery and functional independence[24, 25]
- The number of patients that recorded a return to baseline function at 90 days was comparable between tenecteplase- and alteplase-treated patients[24]
- Median length of hospital stay was comparable between tenecteplase- and alteplase-treated patients[24]
- Tenecteplase treatment increased the number of patients with reperfusion greater than 50% on initial angiographic assessment compared with alteplase[25]
- At both 24 and 72 hours after stroke, early neurological improvement measured by NIHSS score was comparable between tenecteplase- and alteplase-treated patients[25]
- There were no differences observed between the tenecteplase or alteplase treatment arms for the EQ-VAS or EQ-5D-5L domains used to measure the quality of life of patients after stroke[27]
- Safety outcomes were comparable between tenecteplase- and alteplase-treated patients, with no unexpected adverse events. There were no differences between tenecteplase and alteplase for symptomatic intracerebral haemorrhage, extracranial bleeding or mortality[24, 25]

Overall, the findings of AcT and EXTEND-IA TNK Part 1 show that tenecteplase and alteplase have equivalent health benefits.[24, 25] Combined with the quick and easy administration process, the comparable efficacy and safety outcomes make tenecteplase supplied as a 25 mg vial a valuable addition to the NICE-recommended clinical pathway for AIS.

## 3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Not applicable - no disadvantages are expected.

## 3j) Value and economic considerations

**Introduction for patients:**

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

**How the model reflects AIS**

The cost-comparison model captures the acute phase of symptom onset and treatment; this is defined as the first 72 hours after stroke onset. Tenecteplase and alteplase are administered during this time.

**Modelling how much a treatment extends life and improves quality of life**

The pivotal trials AcT and EXTEND-IA TNK Part 1 have demonstrated that tenecteplase has a similar efficacy and safety profile to alteplase. As such, the cost-comparison model assumes that the two treatments have identical outcomes in terms of survival, safety and patient quality of life.

**Modelling how the costs of treatment differ with the new treatment**

Tenecteplase has lower drug acquisition costs than alteplase.

**Uncertainty**

One potential area in which tenecteplase may offer benefits for patients versus alteplase is through its shorter administration time and, subsequently, the reduced need for healthcare resources such as specialist stroke nurses. Exploratory scenario analysis explored the potential impact of this on NHS resource use and showed that there may be additional cost-savings. Uncertainty in the inputs for demographic and safety data was also explored; tenecteplase was always cost-saving compared to alteplase.

**Results**

The results indicate that tenecteplase, which is assumed to be equally as effective as the current standard-of-care therapy, alteplase, offers a cost-saving option to the NHS due to lower treatment acquisition costs. Scenario analyses indicate further cost savings to the NHS if the shorter administration times lead to reduced NHS resource use.

## 3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Tenecteplase provides several benefits over alteplase for the treatment of people with AIS that have been recognised in recent clinical guidelines.[19, 20] This indication addresses the limitations of current off-label use.

Compared with alteplase, tenecteplase has a higher binding specificity to the fibrin found in blood clots, meaning that it forms stronger attachments to the net-like structure that forms the basis of blood clots.[21, 28, 29]

Tenecteplase takes approximately 10 seconds to administer, whereas alteplase takes approximately 1 hour. This means that patients are treated faster and patient monitoring is easier with tenecteplase.[21, 23]

### 3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

| |
|---|
| No equality issues are expected. |

## SECTION 4: Further information, glossary and references

### 4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

| |
|---|
| NHS stroke information \| https://www.nhs.uk/conditions/stroke/<br><br>Stroke Association \| https://www.stroke.org.uk/<br><br>NICE guidance for AIS \| https://www.nice.org.uk/guidance/ng128<br><br>**Further information/publications for AcT**<br><br>Clinicaltrials.gov (NCT03889249) \| https://clinicaltrials.gov/study/NCT03889249<br><br>Publication (Menon et al. 2022[24]) \| https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01054-6/fulltext |

**Further information/publications for EXTEND-IA TNK Part 1**

Clinicaltrials.gov (NCT02388061) | https://clinicaltrials.gov/study/NCT02388061

Publication (Campbell et al. 2018[25]) | https://www.nejm.org/doi/10.1056/NEJMoa1716405

Further information on NICE and the role of patients:

- Public Involvement at NICE
- NICE's guides and templates for patient involvement in HTAs
- EFPIA – Working together with patient groups (PDF)
- National Health Council Value Initiative

## 4b) Glossary of terms

- Adverse event (AE): any undesirable experience that occurs after a patient is given a treatment
- Acute ischaemic stroke (AIS): a stroke caused by blockage of the blood vessels supplying the brain, starving the brain of blood and oxygen and causing tissue damage
- Computed tomography (CT): A form of body scan that uses X-rays to take pictures of the inside of the body.
- Computed tomographic angiography (CTA): a CT scan combined with an injection of a special dye which allows pictures to be taken of blood vessels to analyse blood flow to organs and tissues
- EQ-5D-5L: a health-state questionnaire that assesses function across five areas: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Each area is given a 1–5 score, with 5 being extreme problems
- EQ-VAS: a health-state questionnaire that rates a patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The visual analogue scale can be used as a quantitative measure of health outcome that reflects the patient's own judgement
- Executive function: high-level cognitive skills used to control and coordinate other cognitive abilities
- Fibrin net: fibrin is the fibre-like protein that forms the basis of a blood clot; it forms a scaffold net base for a plug to stop further bleeding/blood flow

- Fibrin-specific plasminogen activator: a drug that specifically targets fibrin protein and activates the protein plasminogen to turn on the protein plasmin
- Initial angiographic assessment: the initial examination of a stroke patient for blood flow to the brain
- Internal carotid artery (ICA): artery that supplies blood to the brain, upper nose and eyes
- Intracerebral haemorrhage (ICH): a type of stroke where blood pools in the brain
- Large vessel occlusion (LVO): the obstruction of the large blood vessels supplying the brain
- M1/M2 segments: the segments of the middle cerebral artery, which branches from the ICA
- Magnetic resonance angiography (MRA): an MRI scan combined with an injection of a special dye which allows pictures to be taken of blood vessels to analyse blood flow to organs and tissues
- Magnetic resonance imaging (MRI): A form of body scan that uses radiowaves to take pictures of the inside of the body.
- Modified Rankin Scale (mRS): a 6-point disability scale assessment of patient function after a stroke
- National Institutes of Health Stroke Scale (NIHSS): a 42-point scale to assess the severity of a stroke by assessing patient neurological function after stroke across multiple areas of the body and activities
- Parenchymal haematoma: a brain bleed where blood pools in the parenchyma (functional tissue) of the brain
- Plasmin/plasminogen: plasmin is a protein that the body can switch on to break down the fibrin that makes up a blood clot when the blood clot is no longer needed. Plasminogen is the turned-off form of plasmin
- Thrombectomy (mechanical): surgical removal of a blood clot
- Thrombolysis: the breakdown of blood clots using medication
- Thrombolytic agent/drug: medication that breaks down blood clots

## 4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text: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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Single Technology Appraisal

# Tenecteplase for treating acute ischaemic stroke [ID6306]

# Clarification questions

**March 2024**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **Tenecteplase for treating acute ischaemic stroke [ID6306]. Clarification questions** | **1** | **No - Redacted** | **22/04/2024** |

## Section A: Clarification on effectiveness data

**A1. You mentioned at the decision problem call that you had access to preliminary effectiveness data from ATTEST-2. We have since spotted that results were presented at the World Stroke Conference 2023.* Could you provide the presentation from this conference and any other publications (posters, presentations etc.) that contain these results?**

ATTEST-2 (NCT02814409) is an ongoing Phase III, independent, investigator-initiated, prospective, multicentre, randomized, controlled trial to investigate the superiority of IV tenecteplase compared with alteplase for thrombolysis within 4.5 hours of the onset of acute ischaemic stroke (AIS) in adults.[1]

Preliminary results based on a database snapshot on 06 October 2023 were presented by Professor Keith Muir, the Principal Investigator of the ATTEST-2 trial, at the World Stroke Conference 2023[2], and at the UK Stroke Forum 2023.[3] ***Please note:*** this data has not yet been published.

Professor Muir has kindly allowed us to provide the below data from his presentation. However, please note the presentation was limited to preliminary results based on a database snapshot on 06 October 2023, which may be subject to minor changes following database lock and included limited data on secondary endpoints.

[redacted]

* https://www.medscape.com/viewarticle/997597?form=fpf and https://neuronewsinternational.com/tenecteplase-deemed-non-inferior-to-alteplase-in-suitable-ischaemic-stroke-patients/

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**A2. As noted in Table 7 of Document B Appendices, four RCTs comparing tenecteplase 0.25 mg/kg with alteplase 0.9 mg/kg in a relevant population were excluded from the systematic literature review (SLR):**

- **ATTEST (NCT01472926)**
- **TAAIS (ACTRN12608000466347)**
- **TASTE-A (NCT04071613)**
- **TRACE (NCT04676659)**

**Please confirm non-inferiority of tenecteplase 0.25 mg/kg with alteplase 0.9 mg/kg in these studies using the non-inferiority margins developed for AcT and EXTEND-IA TNK Part 1. This could be achieved through meta-analysis of the included studies or assessing each study separately.**

The four RCTs of interest are investigator-initiated studies; therefore the company does not have access to the trial data and cannot conduct additional analyses. Using results in the public domain are used, the company has assessed each of the four studies separately using the non-inferiority margins developed for the primary outcome in AcT. The primary outcome in AcT was the proportion of patients who had a score of 0 or 1 on the mRS at 90 days, up to 120 days after randomization.[4] Non-inferiority was met if the lower 95% confidence interval (CI) of the unadjusted difference in the proportion of patients who met the primary outcome between the tenecteplase and alteplase groups was more than -5%.

A summary of the available results for each of the four studies as compared to the primary outcome of AcT is presented in Table 4. The four additional studies did not present unadjusted difference data for mRS at 90 days. However, as the point-estimates all favour tenecteplase, non-inferiority can be assumed. Specifically, the observed proportion of patients who had a score of 0 or 1 on the mRS at 90 to 120 days after randomization was increased for the tenecteplase group in all four studies, with increases ranging from 1% to 32%.

**Table 4: Summary of outcomes - AcT**

| Trial | Study population | Intervention | Patients with mRS score 0-1 at 90-120 days post- stroke n/N (%) | Difference |
|---|---|---|---|---|
| AcT (NCT03889249)[4] | Adults with a diagnosis of ischaemic stroke causing disabling neurological deficit, presenting within 4.5 h of symptom onset, and eligible for thrombolysis per Canadian guidelines | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Tenecteplase: 296/802 (36.9%)<br>Alteplase: 266/765 (34.8%) | Unadjusted risk difference: 2.1% (95% CI: 2.6, 6.9) |
| ATTEST (NCT01472926)[5] | Adults with supratentorial ischaemic stroke eligible for intravenous thrombolysis within 4.5 h of onset | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Tenecteplase: 13/47 (28%)<br>Alteplase: 10/49 (20%) | Adjusted odds ratio: 1.8 (95% CI: 0.6, 5.5); p = 0.28 |
| TAAIS (ACTRN12608000466347)[6] | Adults less than 6 h after the onset of ischemic stroke | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Tenecteplase: 18/25 (72%)<br>Alteplase: 10/25 (40%) | Adjust p-value versus alteplase: p = 0.02 |
| TASTE-A (NCT04071613)[7] | Adults with ischaemic stroke in a mobile stroke unit who were eligible for thrombolytic treatment within 4.5 h of symptom onset | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Tenecteplase: 23/55 (42%)<br>Alteplase: 20/49 (41%) | Adjusted common odds ratio: 0.95 (95% CI: 0.38, 2.39), p = 0.92 |
| TRACE (NCT04676659)[8] | Adults with ischaemic stroke who were eligible for thrombolytic treatment within 3 h of symptom onset<br>NIHSS 4-25<br>Pre-stroke mRS 0f 0-2 | Tenecteplase 0.25 mg/kg (maximum 40 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Tenecteplase: 35/57 (64%)<br>Alteplase: 35/59 (59%) | Adjusted odds ratio versus alteplase: 1.20 (95% CI: 0.56 to 2.56) |
| **Key:** CI, confidence interval; mRS, modified Rankin Scale Score; NIHSS, National Institutes of Health Stroke Scale.<br>**Sources**: Bivard et al. 2022[7]; Huang et al. 2015[5]; Li et al. 2022[8]; Menon et al. 2022[4]; Parsons et al. 2012.[6] | | | | |

The company has also assessed each of the four studies separately using the non-inferiority margins developed for the primary outcome in EXTEND-IA TNK Part 1. The primary outcome EXTEND-IA TNK Part 1 was defined as the restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment.[9] Non-inferiority was established if the lower boundary of the two sided 95% CI of the unadjusted 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.

A summary of the available results for each of the four studies as compared to the primary outcome of EXTEND-IA TNK Part 1 is presented in Table 5. Two of the four studies present data for substantial reperfusion, but they do not present unadjusted difference data in the percentages of patients. In addition, there were differences in definitions of reperfusion, and for one study data were only available for a subgroup of the trial population (and so the comparison is not randomized). Collectively, this makes it difficult to draw conclusions. However, there is no evidence to suggest that tenecteplase non-inferiority cannot be assumed.

**Table 5: Summary of outcomes – EXTEND-IA TNK Part 1**

| Trial | Study population | Intervention | Substantial reperfusion at initial angiographic assessment | Difference |
|---|---|---|---|---|
| EXTEND-IA TNK PART 1 (NCT02388061)[9] | Adults with ischaemic stroke within 4.5 h after onset who had large vessel occlusion of the internal carotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Tenecteplase: 22/101 (22.0%)<br>Alteplase: 10/101 (10.0%) | Unadjusted difference in percentage points: 12 (95% CI: 2, 21); p = 0.002 |
| ATTEST (NCT01472926)[5] | Adults with supratentorial ischaemic stroke eligible for intravenous thrombolysis within 4.5 h of onset | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | No reperfusion data reported<br><br>Recanalisation at 24-48 hours (TIMI grade 2-3):<br>Tenecteplase: 21/32 (66%)<br>Alteplase: 26/35 (74%) | No reperfusion data reported<br><br>Recanalisation at 24-48 hours (TIMI grade 2-3):<br>Odds ratio (95% CI): 0.6 (0·2, 1·8), p=0.38 |
| TAAIS (ACTRN12608000466347)[6] | Adults less than 6 h after the onset of ischaemic stroke | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | Median percent reperfusion at 24 hours:<br><br>Tenecteplase: 100%<br>(range: 5.8, 100)<br>Alteplase: 61.4%<br>(range: -5.3, 100) | Adjusted p value vs alteplase: p < 0.001 |

| Trial | Study population | Intervention | Substantial reperfusion at initial angiographic assessment | Difference |
|---|---|---|---|---|
| TASTE-A (NCT04071613)[7] | Adults with ischaemic stroke in a mobile stroke unit who were eligible for thrombolytic treatment within 4.5 h of symptom onset | Tenecteplase 0.25 mg/kg (maximum 25 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | 50% reperfusion between ED CT perfusion and 24-hour perfusion imaging (MRI), data only available for a subgroup:<br><br>Tenecteplase: 33/35 (94%)<br>Alteplase: 34/35 (97%) | Adjusted effect size: 0.6 (95% CI: 0.048, 8.1); p = 0.72 |
| TRACE (NCT04676659)[8] | Adults with ischaemic stroke who were eligible for thrombolytic treatment within 3 h of symptom onset<br>NIHSS 4-25<br>Pre-stroke mRS 0f 0-2 | Tenecteplase 0.25 mg/kg (maximum 40 mg)<br>Alteplase 0.9 mg/kg (maximum 90 mg) | No reperfusion data reported | No reperfusion data reported |

**Key:** CT, computed tomography; CI, confidence interval, ED, emergency department; mRI, magnetic resonance imaging; mRS, modified Rankin Scale Score; NIHSS, National Institutes of Health Stroke Scale; TIMI, Thrombolysis in Myocardial Infarction.
**Sources**: Bivard et al. 2022[7]; Campbell et al. 2018[9]; Huang et al. 2015[5]; Li et al. 2022[8]; Parsons et al. 2012.[6]

**A3. The people recruited to the AcT trial were adults with a diagnosis of ischaemic stroke causing disabling neurological deficit. A disabling neurological deficit can be defined as a National Institute of Health Stroke Scale (NIHSS) score of 6 or more.**

a) **Was this the definition used for disabling neurological deficit when recruiting people to the AcT trial?**

b) **If this was the definition used for the AcT trial then we have not identified any data for people with a NIHSS score of 1 to 5. The clinical experts consulted by the EAG did note that these people may still be considered for treatment. Please could you offer clinical rationale for the generalisability of the results you have presented to these people.**

Patients were eligible for inclusion in the AcT trial if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit, presenting within 4.5 h of symptom onset, and eligible for thrombolysis with alteplase per the Canadian Stroke Best Practice Guidelines.[4,10,11]

The Canadian Stroke Best Practice Guidelines treatment inclusion criteria for AIS treatment with alteplase specifies diagnosis of ischaemic stroke causing *disabling* neurologic deficit in a patient who is 18 years of age or older; and time from last known well (onset of stroke symptoms) <4.5 hours before alteplase administration. These criteria are designed to guide clinical decision-making; however, the decision to use alteplase in these situations should be based on the clinical judgment of the treating physician.[1,3] For minor stroke, the Canadian guidelines suggest thrombolysis only in those with disabling deficits (i.e., significantly impacting functioning without qualification of specific deficits).[12]

A *post-hoc* exploratory analysis of the AcT trial evaluated the effectiveness and safety of tenecteplase compared with alteplase in the subgroup of patients, presenting with an NIHSS of 5 or less, eligible for standard-of-care thrombolysis based on the Canadian guidelines.[4] Of the 1,577 patients included in the intention-to-treat analysis of the AcT trial, 378 (24.0%) patients presented with an NIHSS of 0–5 with 194 (51.3%) patients receiving tenecteplase and 184 (48.7%) patients receiving alteplase. The baseline characteristics for patients with minor stroke

(NIHSS <6) in AcT are presented in Table 6. ***Please note:*** randomization in the AcT trial was not stratified by baseline NIHSS.

**Table 6: Baseline characteristics for patients with minor stroke (NIHSS <6) in AcT**

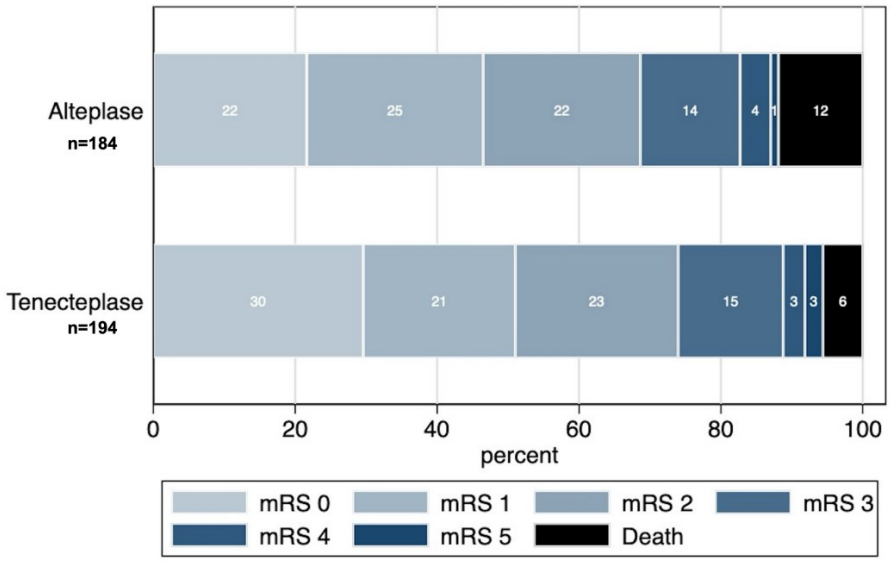
| Characteristic | Tenecteplase (n = 194) | Alteplase (n = 184) |
|---|---|---|
| Age, median (IQR), years | 72 (62–83) | 71 (59–81) |
| Female sex n (%) | 75 (38.7%) | 75 (40.8%) |
| Baseline NIHSS score, median (IQR) | 4 (3–5) | 4 (3–5) |
| Baseline ASPECTS score (n=143)*, median (IQR) | 9 (9–10) | 9 (9–10) |
| Occlusion site on baseline CT angiography (n=376)†, n (%) | | |
| Intracranial internal carotid artery | 3 (1.5%) | 0 (0%) |
| M1 segment MCA | 9 (4.7%) | 6 (3.3%) |
| M2 segment MCA | 42 (21.8%) | 17 (9.3%) |
| Other distal occlusions (MCA, ACA, PCA)‡ | 43 (22.3%) | 41 (22.4%) |
| Vertebrobasilar arterial system | 11 (5.7%) | 14 (7.6%) |
| Cervical internal carotid artery | 3 (1.5%) | 3 (1.6%) |
| No visible occlusions | 82 (42.5%) | 102 (55.7%) |
| Presence of large vessel occlusion on baseline CT angiography, n (%) | 13 (6.7%) | 6 (3.3%) |
| Type of enrolling centre, n (%) | | |
| Primary stroke centre | 14 (7.2%) | 8 (4.3%) |
| Comprehensive stroke centre | 180 (92.8%) | 176 (95.6%) |
| Workflow times, median (IQR), minutes | | |
| Stroke symptom onset to randomisation | 146 (100–212) | 149 (106–205) |
| Stroke symptom onset to start of thrombolysis | 150 (106–218) | 159 (111–214) |
| Baseline CT to arterial puncture (in patients undergoing EVT) | 78 (58–188) | 95 (51–216) |
| Arterial puncture to successful reperfusion (in patients undergoing EVT) | 33 (18–41) | 21 (13–25) |

**Key**: ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; CT, computed tomography; EVT, endovascular thrombectomy; IQR, interquartile range; M1, first segment; M2, second segment; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery.
**Notes**: Large vessel occlusion is defined as large vessel occlusion of the internal carotid artery, M1 segment MCA, or functional M1 segment MCA occlusion – i.e. all M2 segments MCA occluded on baseline CT angiography scan. If patients had more than one occlusion site, the most proximal occlusion is listed. *ASPECTS was available for patients who had ICA or MCA occlusion at baseline. †Two patients had baseline non-contrast CT but did not have a baseline CT angiography. ‡MCA (M3 and beyond), ACA (A2 and beyond) or PCA (P2 and beyond).
**Source**: Nair et al. 2024[4]

### *Efficacy outcomes*

The primary outcome (90–120-day mRS score of 0–1) occurred in 100 (51.8%) of 194 patients in the tenecteplase group and 86 (47.5%) of 184 patients in the alteplase group (adjusted risk ratio [RR] 1.14; 95%CI 0.92 to 1.40). The direction of the effect favoured tenecteplase across the full range of mRS scores. No heterogeneity of treatment effect on the primary outcome was observed across any of the clinically relevant subgroups (age, sex, ASPECTS score, occlusion site, large vessel occlusion, tandem occlusion).[4]

**Figure 2: Distribution of the modified Rankin scale scores at 90–120 days, intention-to-treat population**




**Notes:** 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.
**Source:** Nair et al. 2024.[4]

Secondary efficacy outcomes including mRS score of 0–2 at 90–120 days were achieved in 143 (74.1%) patients in the tenecteplase group and 126 (69.6%) patients in the alteplase group (adjusted RR 1.09; 95%CI 0.94 to 1.26), with a median (IQR) mRS of 1 (0–3) in tenecteplase versus 2 (1–3) in the alteplase group (adjusted RR 0.69; 95%CI 0.47 to 1.0). A summary of the efficacy endpoints for patients with minor stroke (NIHSS <6) from AcT are presented in Table 7.[4]

**Table 7: Summary of efficacy outcomes at 90–120 days for patients with minor stroke (NIHSS <6) from the AcT trial**

| Outcomes | Tenecteplase (n = 194) | Alteplase (n = 184) | Unadjusted risk ratio (95%CI) | Adjusted risk ratio (95%CI)* |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| mRS score 0–1 at 90–120 days, n (%) | 100 (51.8%) | 86 (47.5%) | 1.09 (0.88, 1.23) | 1.14 (0.92, 1.40) |
| **Secondary outcomes** | | | | |
| mRS score 0–2 at 90–120 days, n (%) | 143 (74.1%) | 126 (69.6%) | 1.06 (0.93, 1.20) | 1.09 (0.94, 1.26) |
| Actual mRS score at 90–120 days, median (IQR) | 1 (0–3) | 2 (1–3) | 0.74 (0.52, 1.07) | 0.69 (0.47, 1.00)† |
| Return to baseline function, n (%) | 80 (42.5%) | 61 (35.3%) | 1.20 (0.92, 1.56) | 1.20 (0.90, 1.59) |
| Length of hospital stay, median (IQR), days | 4 (2–8) | 4 (2–7) | −0.47 (−2.6 to 1.70) | 0.86 (0.79 to 0.93)‡ |

**Key**: CI, confidence interval; IQR, interquartile range; mRS, modified Rankin scale.

**Notes**: *Adjusted for age, sex, occlusion location as fixed-effects variables, and participating site as a random-effects variable. †Common OR is the OR for a unit increase in mRS score for tenecteplase versus alteplase. ‡Risk ratio using mixed-effects linear regression model adjusted for age, sex, occlusion location as fixed-effects variables and participating site as a random-effects variable.

**Source**: Nair et al. 2024[4]

### *Safety outcomes*

Symptomatic ICH occurred in five (2.6%) patients in the tenecteplase group and six (3.3%) patients in the alteplase group (adjusted RR 0.79; CI 0.24 to 2.54). There was a single patient with orolingual angioedema in each group and no patients with extracranial bleeding requiring blood transfusion. Fewer patients died within 90–120 days in the tenecteplase group compared with the alteplase group (11 (5.7%) and 20 (11.0%), respectively (adjusted HR 0.99; CI 0.96 to 1.02). The safety outcomes are shown in Table 8.[4]

**Table 8: Summary of safety outcomes for patients with minor stroke (NIHSS <6) in the AcT trial**

| Outcomes | Tenecteplase (n = 194) | Alteplase (n = 184) | Unadjusted risk ratio (95%CI) |
|---|---|---|---|
| Death within 90 days, n (%) | 11 (5.7%) | 20 (11.0%) | 0.99 (0.96, 1.02)* |
| Symptomatic intracerebral haemorrhage, n (%) | 5 (2.6%) | 6 (3.3%) | 0.79 (0.24, 2.54) |
| Extracranial bleeding requiring blood transfusions, n (%) | 0 (0%) | 0 (0%) | NA |
| Orolingual angioedema, n (%) | 1 (0.5%) | 1 (0.5%) | 0.94 (0.06, 15.05) |
| Other SAEs, n (%) | 17 (8.8%) | 17 (9.2%) | 0.94 (0.49, 1.80) |
| Imaging-identified intracranial haemorrhage, n (%) | 23 (11.9%) | 27 (14.7%) | 0.80 (0.48, 1.35) |
| Subarachnoid haemorrhage, n (%) | 5 (2.6%) | 4 (2.2%) | 1.18 (0.32, 4.34) |
| Subdural haemorrhage, n (%) | 0 (0%) | 1 (0.5%) | NA |
| Intraventricular haemorrhage, n (%) | 5 (2.6%) | 3 (1.6%) | 1.58 (0.38, 6.52) |
| HI1 (scattered small petechiae), n (%) | 1 (0.5%) | 5 (2.7%) | 0.18 (0.02, 1.59) |
| HI2 (confluent petechiae), n (%) | 12 (6.2%) | 13 (7.1%) | 0.86 (0.40 to 1.84) |
| PH1 (haematoma occupying < 30% of infarct with no substantive mass effect), n (%)† | 6 (3.1%) | 3 (1.6%) | 1.87 (0.47, 7.39) |
| PH2 (haematoma occupying ≥ 30% of infarct with obvious mass effect), n (%)‡ | 2 (1%) | 3 (1.6%) | 0.62 (0.10, 3.70) |

**Key**: CI, confidence interval; HI, haemorrhagic infarction; NA, not applicable; PH, parenchymal haematoma; SAE, serious adverse event.

**Notes**: Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification. *HR using Cox proportional hazard adjusted for age, sex and occlusion site. †Remote PH type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect. ‡Remote PH type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.

**Source**: Nair et al. 2024[4]

The results of this *post-hoc* analysis of patients with minor stroke (NIHSS <6) in the AcT trial are consistent with the overall results of the trial and demonstrated non-inferior efficacy and safety of tenecteplase compared to alteplase. [4]

**A4. The ATTEST trial safety outcomes, reported in Table 9 of Document B appendix, found a lower proportion of people in the tenecteplase arm sustained any intracerebral haemorrhage (ICH) compared with the alteplase arm (15% versus 27%). Within that, more people in the alteplase arm sustained a parenchymal haemorrhage, symptomatic ICH (ECASS II14 definition), and symptomatic ICH (SITS-MOST23 definition). Please provide a clinical rationale for these differences.**

The company was not involved in the ATTEST trial. It was an investigator-initiated open-label, single-centre phase 2 study at the Institute of Neurological Sciences, Glasgow, Scotland (n=102). The trial was intended to inform the design of a larger definitive study (ATTEST-2) by yielding information about potential recruitment rates, incidence of relevant imaging abnormalities, and distribution of outcome events.[5] It is not appropriate to draw conclusions from numerical differences between the arms, and providing a clinical rationale for differences in ICH rate is of limited value. However, there are two factors that could, theoretically, be relevant.

Firstly, a higher proportion of patients with prognostically important comorbidities, such as hypertension (43% in the tenecteplase group compared to 57% in the alteplase group) may account for differences in the numbers of patients who sustained any ICH.

Secondly, the pharmacological properties of the drugs may contribute to differences in ICH rates. Due to its greater fibrin specificity, tenecteplase may cause less systemic plasminogen activation than alteplase, potentially reducing the risk of ICH. The company has not investigated this in clinical trials; however, the investigators leading the ATTEST trial conducted a sub-study to compare the effects of tenecteplase and alteplase on coagulation and the fibrinolytic system and to explore potential associations between hypofibrinogenaemia and ICH.[13]

Of 104 participants in the ATTEST trial, 30 participated in the sub-study (alteplase n=14, tenecteplase n=16). Tenecteplase was associated with less disruption to the coagulation and fibrinolytic systems compared with alteplase, which was consistent with the trend toward reduced incidence of ICH observed in the ATTEST trial. Markers of clot lysis efficacy (D-dimer, fibrin degradation products and prothrombin fragments F1+2) were the same for both drugs. Six patients had ICH post-thrombolysis (four with alteplase and two with tenecteplase). None were considered symptomatic using either the ECASS II or SITS-MOST definition and binary logistic regression found no association between ICH and the change of fibrinogen, probably because of the small sample size].[13]

**A5. The serious adverse events (SAE) outcomes from days 7 to 90 in the ATTEST trial, reported in Table 10 of the Document B appendix, demonstrate different safety profiles between alteplase and tenecteplase. Please can you comment on or provide a clinical rationale for these differences.**

- **18 (35%) of participants in the tenecteplase arm sustained at least one SAEs compared with 7 (14%) in the alteplase arm**
- **4 (8%) of participants in the tenecteplase arm had a new ischaemic stroke compared with 2 (4%) in the alteplase arm**
- **There were also higher proportions in the tenecteplase arm who had a range of other SAEs, such as planned medical procedures, gastrointestinal bleeding, other extracranial bleeding, pneumonia, hypotension, VTE, atrial fibrillation, abdominal pain, constipation, diarrhoea, chest pain, and renal impairment.**

The company was not involved in the ATTEST trial. It was an investigator-initiated was an open-label, single-centre phase 2 study at the Institute of Neurological Sciences, Glasgow, Scotland (n=104). The trial was intended to inform the design of a larger definitive study (ATTEST-2) by yielding information about potential recruitment rates, incidence of relevant imaging abnormalities, and distribution of outcome events.[5] It is not appropriate to draw conclusions from numerical differences between the arms, and providing a clinical rationale for differences is of limited value.

Given the short half-life of both thrombolytic agents (22 minutes for tenecteplase and 3.5 minutes for alteplase[14]), SAEs that occur beyond 24 hours may be unrelated to the study drug. Up to day 7, SAEs considered probably or definitely related to drug treatment were reported in three (6%) patients given tenecteplase and five (10%), patients given alteplase.[5]

Factors that could affect the number of SAEs reported during the trial include:

- The open-label nature of the trial may have contributed to observer bias; increased vigilance may have contributed to increased reporting of adverse events.

- Older age at baseline (mean age 71 years), and a higher proportion of patients with prognostically important comorbidities such as previous stroke or transient ischaemic attack (26% in the tenecteplase group compared to 22% in the alteplase group) and atrial fibrillation (40% in the tenecteplase group and 31% in the alteplase group) may account for differences in the number of patients who had a new ischaemic stroke between days 7-90 of follow-up.

## Section B: Clarification on cost-effectiveness data

**B1. Please provide full details of exactly where the weight data was taken from in the two references used (SSNAP and HSE). Please point to the page numbers in the references supplied.**

The mean weight of patients used in the model is calculated by combining information from SSNAP and HSE.[15,16] In the references supplied, the mean weights for males and females used in the model are taken from the HSE 2021 survey. The mean weight for males was 85.1 kg (Table 7, cell AC28) and 71.8 kg for females (Table 7, cell AC72). These values were multiplied by the weighted mix of males and females. For the SSNAP data, these came from the January-March 2023 data, with values of 53.6% for males (F. Casemix, cell E32) and 46.4% for females (F. Casemix, cell E30). These data were incorrectly classified as April 2022-March 2023 data in the submission (the URL is correct). The weighted average of these values resulted in mean weight used in the model calculations of 78.92 kg. The most recently available SSNAP data are for October-December 2023, with values of

53.0% for males (F. Casemix, cell E32) and 47.0% for females (F. Casemix, cell E30). Using this most recent data in the model results in a mean weight of 78.84 kg and cost-savings of £[redacted](original cost savings £[redacted], difference less than £1).

**B2. Please provide the mean patient weight and standard deviation for the AcT and EXTEND-IA TNK trials.**

In the AcT trial the mean (standard deviation) weight was [redacted] kg ([redacted]) in the tenecteplase group and [redacted] kg ([redacted]) in the alteplase group. Data on mean weight are not available for EXTEND-IA TNK.

Both AcT and EXTEND-IA TNK are investigator-initiated studies; therefore the company does not have access to the trial data outside of what has been presented.

**B3. When will the 25mg vial of tenecteplase become available?**

Marketing authorisation is still pending, with a best-case authorisation date of [redacted]. Anticipated UK launch remains [redacted].

## Section C: Textual clarification and additional points

**C1. It appears that you have omitted "alteplase" as a search term in ClinicalTrials.gov (table 4 in Doc B appendices). Could you confirm that no important studies were missed due to this omission, or is this a transcription error?**

ClinicalTrials.Gov uses MeSH headings or Medical Language System terms which automatically picks up variations and synonyms of the heading.

Please see below for results for a search undertaken on 12.4.24 in ClinicalTrials.gov which shows that the MeSH heading for "tissue plasminogen activator" is picking up all trials which include alteplase:

| Intervention field | Results |
|---|---|
| Alteplase | 390 |

| | |
|---|---|
| Tissue Plasminogen Activator | 465 |
| Tissue Plasminogen Activator OR alteplase | 465 |

**C2. Line #15 in the Cochrane library search strategy (table 3 in Doc B appendices) is as follows: Shea, #5-`#14. Could you confirm that the line should read {OR #5-#14} and that the current line is a transcription error?**

Yes, that is correct. This is a transcription error, and the unformatted strategy indicates that this was run as {or #5-#14} and has now been amended in the search strategy tables.

**C3. It is stated that "Bibliography checks of recent relevant SLR publications published between 2020 and 2023 (identified by database searches) were reviewed to identify potentially relevant primary studies". However, a search for SLRs was not performed, except in the Cochrane library. Can you confirm that bibliography checks of only Cochrane SLRs was performed, or did you include checks of SRs that were retrieved by the RCT filters?**

Bibliography checks were conducted on any recent and relevant SLRs that may have been picked up through any of the electronic database searches.

**C4. The "records identified from" numbers in the clinical PRISMA diagram (Figure 1 in Doc B appendices) do not align with the search strategy numbers (Tables 1-5). Similarly, the numbers in the economics PRISMA (Figure 6) do not align with the search strategy numbers (Tables 19-21). Numbers of studies provided in the text are often also inconsistent with the PRISMA diagrams. Can you explain why this is, and which are the current numbers?**

For the clinical SLR, the search strategies included a transcription error. The search strategy tables have been updated within Doc B Appendices and the numbers now match the PRISMA figure.

For the economic SLR, the search strategies included a transcription error. The search strategy tables have been updated within Doc B Appendices and the numbers now match the PRISMA figure.

Number of studies in the text have also now been updated to reflect the numbers reflected in the PRSIMA tables, for both clinical and economic sections. Inconsistencies were due to transcription errors.

## References


1. Clinicaltrials.gov. Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST2). 2016. (Updated: 29 March 2018) Available at: https://clinicaltrials.gov/study/NCT02814409. Accessed: 12 April 2024.

2. Muir K, et al. Tenecteplase versus Alteplase for Acute Stroke within 4.5h of onset: the second Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2). Oral Presentation. 15th World Stroke Congress, 10-12 October 2023, Toronto, Canada. Presented at:

3. Muir K, et al. Tenecteplase versus Alteplase for Acute Stroke within 4.5h of onset: the second Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2). Oral Presentation. UK Stroke Forum, 4-6 December 2023, Birmingham, United Kingdom. Presented at:

4. Menon BK, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet 2022;400(10347);161-169.

5. Huang X, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol 2015;14(4):368-376.

6. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. NEJM. 2012; 366(12):1099-107.

7. Bivard A, Zhao H, Churilov L, et al. Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. Lancet Neurol. 2022; 21(6):520-.

8. 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 and Vascular Neurology. 2022; 7(1):47-53.

9. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med. 2018; 378(17):1573-82.

10. Sajobi T, et al. AcT Trial: Protocol for a Pragmatic Registry-Linked Randomized Clinical Trial. Stroke Vasc Intervent Neurol 2022;2;e000447.

11. Boulanger J, et al. Canadian stroke best practice recommendations for acute stroke management: prehospital, emergency department, and acute inpatient stroke care, 6th edition, update 2018. Int J Stroke 2018;13:949–984.

12. Nair R, et al. Intravenous tenecteplase compared with alteplase for minor ischaemic stroke: a secondary analysis of the AcT randomised clinical trial. Stroke Vasc Neurol 2024; 0. doi:10.1136/svn-2023-002828.

13. Huang X, et al. Coagulation and Fibrinolytic Activity of Tenecteplase and Alteplase in Acute Ischemic Stroke. Stroke 2015;46(12):3543-6.

14. Miller SE, Warach SJ. Evolving thrombolytics: from alteplase to tenecteplase. Neurotherapeutics 2023; 20(3):664-678.

15. Sentinel Stroke National Audit Programme. SSNAP Annual Portfolio April 2022-March 2023 Admission and Discharges. 2023. Available at: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx. Accessed: 1 March 2024.

16. NHS England. Health Survey for England. 2021. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021. Accessed: November 2023.

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal: cost-comparison

# Tenecteplase for thrombolytic treatment of acute ischaemic stroke [ID6306]

## Document B

## Appendices

**March 2024**



# Contents





# List of Abbreviations

| | |
|---|---|
| AIS | Acute ischaemic stroke |
| CDSR | Cochrane Database of Systematic Reviews |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| EVT | Endovascular thrombectomy |
| HCRU | Healthcare resource use |
| HRQL | Health-related quality of life |
| ITT | Intention to treat |
| IVT | Intravenous thrombolysis |
| LOS | Length of stay |
| LVO | Large vessel occlusion |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| mRS | Modified Rankin Scale |
| NICE | National Institute for Health and Care Excellence |
| NIHSS | National Institute of Health Stroke Score |
| NIS | Nationwide Inpatient Sample |
| OPTIMISE | Optimizing Patient Treatment in Major Ischemic Stroke With EVT |
| PICOS | Population, intervention, comparators, outcome, study design |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RCT | Randomized controlled trial |
| RoB | Risk of bias |
| SLR | Systematic literature review |
| SmPC | Summary of product characteristics |
| SoC | Standard of care |



# Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

## *C.1. SmPC*

A copy of the draft SmPC document for Metalyse 25 mg is provided below:

[redacted]

## *C.2. UK public assessment report*

The UK public assessment report is not yet available. Marketing authorisation is still pending, with a best-case authorisation date of [redacted]

# Appendix D: Identification, selection and synthesis of clinical evidence

## *D.1. Identification and selection of relevant studies*

A global systematic literature review (SLR) was conducted to identify the current available evidence on the clinical efficacy and safety of tenecteplase and alteplase administered to patients with acute ischaemic stroke (AIS) within the first 4.5 hours of symptom onset.

### D.1.1 Search strategy

Searches were conducted on 11 September 2023 (timeframe covered database inception to 8 September 2023) in Ovid MEDLINE®, Ovid Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Clinicaltrials.gov and International Clinical Trials Registry Platform (ICTRP).

The search terms used for each database are presented in Table 1, Table 2, Table 3, Table 4 and Table 5.

**Table 1: Ovid MEDLINE ALL: 1946 to July 19 2023. Searched: 20 July 2023**

| # | Search terms | |
|---|---|---|
| Disease terms | | |
| 1 | ischemic stroke/ | 10,097 |
| 2 | (isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion or AIS or LVO).ti,ab,kf. /freq=3 | 36,609 |
| 3 | ((isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion) adj4 (time sensitive or time constrain$ or time window or symptom onset or symptom on-set or time$1 to treatment or acute)).ti,ab,kf. | 26,915 |
| 4 | or/1-3 | 50,616 |
| Interventions | | |
| 5 | Tissue Plasminogen Activator/ | 20,568 |
| 6 | (alteplase or actilyse or activacin or activase or g-11021 or g11021 or g-11035 or g11035 or g-11044 or g11044 or gmk-527 or gmk527 or ly-210825 or ly218025 or lysatec rt pa or mmr-701 or mmr701 or td-2061 or td2061 or ((tissue or t) adj2 (plasminogen activator$ or activator d 44)) or tisokinase or 105857-23-6).ti,ab,kf,rn. | 23,367 |
| 7 | Tenecteplase/ | 529 |
| 8 | (5hrombectomy or metalyse or r-tpr-012 or rg-3625 or rg3625 or tenecterel or tnk-tpa or tnkase or 191588-94-0).ti,ab,kf,rn. | 884 |
| 9 | Thrombectomy/ | 10,575 |
| 10 | ((mechanical adj (5hrombectom$ or thrombolysis)) or 5hrombectomy$).ti,ab,kf. | 17,269 |
| 11 | Fibrinolysis/ | 21,794 |
| 12 | (fibrinolys?s or fibrin clot lysis or fibrin$ degradation or fibrin splitting).ti,ab,kf. | 24,102 |
| 13 | Thrombolytic Therapy/ | 26,481 |
| 14 | ((fibrinolytic or thrombolytic or thromboly?s) adj (treatment$ or therap$)).ti,ab,kf. | 38,343 |
| 15 | or/5-14 | 116,792 |
| Trials | | |
| 16 | (randomized controlled trial or controlled clinical trial).pt. | 690,018 |
| 17 | (randomized or placebo or randomly).ab. | 1,081,637 |
| 18 | clinical trials as topic.sh. | 201,225 |
| 19 | trial.ti. | 292,288 |
| 20 | or/16-19 | 1,546,343 |
| 21 | exp animals/ not humans.sh. | 5,153,293 |
| 22 | 20 not 21 | 1,423,520 |
| 23 | 4 and 15 and 22 | 2,387 |
| Excluded studies | | |



| | | |
|---|---|---|
| 24 | (letter or comment or editorial).pt. | 2,187,259 |
| 25 | (Hemorrhagic Stroke/ or Ischemic Attack, Transient/) not ischemic stroke/ | 21,775 |
| 26 | 23 not (24 or 25) | 2,314 |
| RCT filter from: Cochrane Handbook [1] | | |

**Table 2: Ovid Embase: 1974 to July 19 2023. Searched: 20 July 2023**

| # | Search terms | |
|---|---|---|
| Disease terms | | |
| 1 | acute ischemic stroke/ | 9,319 |
| 2 | *ischemic stroke/ | 7,659 |
| 3 | (isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion or AIS or LVO).ti,ab,kw. /freq=3 | 56,617 |
| 4 | ((isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion) adj4 (time sensitive or time constrain$ or time window or symptom onset or symptom on-set or time$1 to treatment or acute)).ti,ab,kw. | 46,267 |
| 5 | or/1-4 | 82,030 |
| Interventions | | |
| 6 | Alteplase/ | 23,309 |
| 7 | (alteplase or actilyse or activacin or activase or g-11021 or g11021 or g-11035 or g11035 or g-11044 or g11044 or gmk-527 or gmk527 or ly-210825 or ly218025 or lysatec rt pa or mmr-701 or mmr701 or td-2061 or td2061 or ((tissue or t) adj2 (plasminogen activator$ or activator d 44)) or tisokinase or 105857-23-6).ti,ab,kw,rn. | 44,135 |
| 8 | Tenecteplase/ | 3,340 |
| 9 | (tenecteplase or metalyse or r-tpr-012 or rg-3625 or rg3625 or tenecterel or tnk-tpa or tnkase or 191588-94-0).ti,ab,kw,rn. | 3,453 |
| 10 | mechanical thrombectomy/ or thrombectomy/ | 29,966 |
| 11 | ((mechanical adj (embolectom$ or thrombolysis)) or thrombectom$).ti,ab,kw. | 29,117 |
| 12 | fibrinolysis/ | 37,194 |
| 13 | (fibrinolys?s or fibrin clot lysis or fibrin$ degradation or fibrin splitting).ti,ab,kw. | 30,694 |
| 14 | fibrinolytic therapy/ | 27,867 |
| 15 | ((fibrinolytic or thrombolytic or thromboly?s) adj (treatment$ or therap$)).ti,ab,kw. | 54,246 |
| 16 | or/6-15 | 168,641 |
| Trials | | |



| | | |
|---|---|---|
| 17 | Randomized controlled trial/ or Controlled clinical trial/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ | 1,932,476 |
| 18 | (random$ or placebo or (open adj label) or parallel group$1 or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or (crossover or cross over) or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or (assigned or allocated) or (controlled adj7 (study or design or trial)) or (volunteer or volunteers)).ti,ab. | 2,902,023 |
| 19 | (compare or compared or comparison or trial).ti. | 989,011 |
| 20 | ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. | 2,773,393 |
| 21 | or/17-20 | 6,316,622 |
| 22 | (random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) | 9,594 |
| 23 | Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) | 360,295 |
| 24 | (((case adj control$) and random$) not randomi?ed controlled).ti,ab. | 21,530 |
| 25 | (Systematic review not (trial or study)).ti. | 258,944 |
| 26 | (nonrandom$ not random$).ti,ab. | 18,933 |
| 27 | Random field$.ti,ab. | 2,959 |
| 28 | (random cluster adj3 sampl$).ti,ab. | 1,578 |
| 29 | (review.ab. and review.pt.) not trial.ti. | 1,128,667 |
| 30 | we searched.ab. and (review.ti. or review.pt.) | 49,232 |
| 31 | update review.ab. | 136 |
| 32 | (databases adj4 searched).ab. | 62,280 |
| 33 | (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ | 1,219,722 |
| 34 | Animal experiment/ not (human experiment/ or human/) | 2,561,951 |
| 35 | or/22-34 | 4,337,577 |
| 36 | 21 not 35 | 5,573,353 |
| 37 | 5 and 16 and 36 | 7,413 |
| 38 | (editorial or letter or comment or note).pt. | 3,023,660 |
| 39 | preprint.db. | 85,076 |
| 40 | or/38-39 | 3,108,736 |
| Excluded studies | | |
| 41 | (brain hemorrhage/ or transient ischemic attack/) not (acute ischemic stroke/ or ischemic stroke/) | 165,175 |
| 42 | (conference abstract or conference paper).pt. | 5,644,700 |
| 43 | or/40-42 | 8,869,412 |
| 44 | 37 not 43 | 3,011 |



| | | |
|---|---|---|
| 45 | limit 42 to yr="2020 -Current" | 1,042,810 |
| 46 | 37 and 45 | 958 |
| 47 | 44 or 46 | 3,969 |
| RCT filter from: Cochrane Handbook [1] | | |

**Table 3: The Cochrane Library: CDSR up to Issue 7, July 2023, CENTRAL up to Issue 7, July 2023. Searched: 25 July 2023**

| # | Search terms | |
|---|---|---|
| Disease terms | | |
| #1 | MeSH descriptor: [Ischemic Stroke] this term only | 902 |
| #2 | ((ischemic-stroke* or ischaemic-stroke* or cryptogenic-embolism-stroke* or cryptogenic-stroke* or thrombotic-stroke* or embolic-stroke or large-vessel-occlusion) near/6 (time-sensitive or time-constrain* or time-window or symptom-onset or symptom-on-set or time* next to-treatment or acute)):ti,ab,kw | 6,643 |
| #3 | (time-sensitive or time-constrain* or time-window or symptom-onset or symptom-on-set or time* next to-treatment or acute):ti,ab,kw | 171,792 |
| #4 | (#1 and #3) or #2 | 6,732 |
| Interventions | | |
| #5 | MeSH descriptor: [Tissue Plasminogen Activator] this term only | 2,121 |
| #6 | (alteplase or actilyse or activacin or activase or g-11021 or g11021 or g-11035 or g11035 or g-11044 or g11044 or gmk-527 or gmk527 or ly-210825 or ly218025 or lysatec-rt-pa or mmr-701 or mmr701 or td-2061 or td2061 or ((tissue or t) near/2 (plasminogen-activator* or activator-d-44)) or tisokinase):ti,ab,kw | 4,577 |
| #7 | MeSH descriptor: [Tenecteplase] this term only | 198 |
| #8 | (tenecteplase or metalyse or r-tpr-012 or rg-3625 or rg3625 or tenecterel or tnk-tpa or tnkase):ti,ab,kw | 510 |
| #9 | MeSH descriptor: [Thrombectomy] this term only | 624 |
| #10 | ((mechanical next (embolectom* or thrombolysis)) or thrombectom*):ti,ab,kw | 2,215 |
| #11 | MeSH descriptor: [Fibrinolysis] this term only | 1,179 |
| #12 | (fibrinolyses or fibrinolysis or fibrin-clot-lysis or fibrin* next degradation or fibrin-splitting):ti,ab,kw | 3,538 |
| #13 | MeSH descriptor: [Thrombolytic Therapy] this term only | 2,229 |
| #14 | ((fibrinolytic or thrombolytic or thrombolyes or thrombolyis) next (treatment* or therap*)):ti,ab,kw | 5,846 |
| #15 | Shea, #5-`#14 | 12,716 |
| #16 | #4 and #15 | 2,486 |
| Excluded studies | | |
| #17 | MeSH descriptor: [Hemorrhagic Stroke] explode all trees | 39 |



| | | |
|---|---|---|
| #18 | MeSH descriptor: [Ischemic Attack, Transient] explode all trees | 40 |
| #19 | MeSH descriptor: [Ischemic Stroke] explode all trees | 976 |
| #20 | (#17 or #18) not #19 | 971 |
| #21 | #16 not #20 with Cochrane Library, in Trials | 942 |
| #22 | (trialsearch or clinicaltrials.gov):so | 2,465 |
| Trials | | |
| #23 | #21 not #22 | 2,014 |
| Reviews | | |
| #24 | #16 not #20 with Cochrane Library, in Cochrane Reviews | 11 |

**Table 4: ClinicalTrials.gov (www.clinicaltrials.gov). Searched: 20 July 2023**

| **Condition or disease** | |
|---|---|
| Ischemic Stroke, Acute | |
| **Intervention/Treatment** | |
| Tissue plasminogen activator OR tenecteplase OR Thrombectomy OR fibrinolysis OR Thrombolytic Therapy | |
| **Results** | **434** |

**Table 5: International Clinical Trials Registry Platform (ICTRP) (https://apps.who.int/trialsearch/). Searched: 25 July 2023**

| **Title** | |
|---|---|
| acute ischaemic stroke OR acute ischemic stroke | |
| **Intervention/Treatment** | |
| Tissue plasminogen activator OR acteplase OR tenecteplase OR Thrombectomy OR fibrinolysis OR Thrombolytic Therapy | |
| **Results** | **42** |

Electronic database searches were supplemented by conducting grey literature searches of the following conference proceedings from the past two years (2021–2023):

- World Stroke Congress
  - 14th World Stroke Congress 2022
  - 13th World Stroke Congress 2021
- International Stroke Conference

  - 20th American Stroke Association International Stroke Conference 2021
  - 21st American Stroke Association International Stroke Conference 2022
  - 22nd American Stroke Association International Stroke Conference 2023
- European Stroke Organisation Conference
  - 9th Annual European Stroke Organisation Conference 2023
  - 8th Annual European Stroke Organisation Conference 2022
  - 7th Annual European Stroke Organisation Conference 2021
- Annual Meeting of the American Association of Neurological Surgeons
  - 73rd Annual American Academy of Neurology 2021
  - 74th Annual American Academy of Neurology 2022
  - 75th Annual American Academy of Neurology 2023

Bibliography checks of recent relevant SLR publications published between 2020 and 2023 (identified by database searches) were reviewed to identify potentially relevant primary studies that may not have been captured by the database searches.

A hand-search of https://www.medrxiv.org/ (incorporating keywords such as ‘tenecteplase’, ‘alteplase’ and ‘AIS and thrombolysis’) was conducted to identify non-peer-reviewed manuscripts. The server was searched on the 11 October 2023 with no timeframe cut-off.

### D.1.2 Study selection

Bibliographic details and abstracts of all citations retrieved by the electronic database searches were downloaded into EndNote® and duplicate references were removed.

Before records were transferred from EndNote to Covidence, EndNote filters were applied as a pre-screen to identify and exclude noticeably irrelevant records. Pre-screen exclusion criteria included animal studies (e.g. terms 'mice' or 'murine'), paediatric populations (e.g. terms 'child,' 'children,' or 'adolescent'), and certain study

types (e.g. cohort, case reports, case series, narrative reviews, pharmacokinetic studies). Excluded records were retained in the EndNote library and documented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. A second reviewer verified the irrelevance of record titles.

Title and abstracts were independently assessed by two reviewers in line with the population, intervention, comparators, outcome and study design (PICOS) criteria (presented in Table 6). Studies that did not meet eligibility criteria were excluded. Full text articles of potentially relevant records were retrieved and PICOS eligibility criteria was reapplied by two independent reviewers. Any discrepancies between the two reviewers were resolved by consensus or involvement of a third reviewer. Reasons for exclusion were documented by reviewers and were compiled in a PRISMA flow diagram, allowing full traceability of included and excluded studies.[2] The studies that met inclusion criteria underwent data extraction.

All data were extracted using a piloted data extraction grid in Microsoft Excel® that had been agreed upon and signed off by BI. Publications reporting data from the same trial were grouped. A publication which provided duplicated trial data would not be extracted, but still met inclusion criteria for the review. Data extraction was completed by a single reviewer and independently checked by a second reviewer for accuracy. Any discrepancies were resolved by consensus or involvement of a third reviewer.

**Table 6: PICOS eligibility criteria for the identification of eligible studies**

| PICOS elements | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | Adult patients (≥ 18 years old) presenting with AIS symptoms | • Patients with haemorrhagic stroke, brain stem stroke, TIA, or stroke of unknown causes<br>• Paediatric population (< 18 years old) |
| Intervention | Thrombolysis treatments for the initial management of ischaemic stroke (defined as administered within 4.5 hours of symptom onset) e.g. pharmaco-induced thrombolysis, with or without concurrent mechanical removal. | Treatments for the management of ischaemic stroke outside the acute setting i.e. secondary prevention strategies/therapies.<br>• TNK or ALT in combination with pharmacotherapy (e.g. aspirin, |

| | | |
|---|---|---|
| | • TNK with or without thrombectomy<br>• ALT with or without thrombectomy | antiplatelet, neuroprotectant, antithrombotic)<br>• Other thrombolytic therapies (e.g. urokinase, staphylokinase) |
| Comparator | • ALT with or without thrombectomy[†]<br>• Placebo or SoC<br>• Thrombectomy alone | • Any comparator in combination with pharmacotherapy (e.g. aspirin, antiplatelet, neuroprotectant, antithrombotic) |
| Outcomes | Short- and long-term outcomes relating to initial AIS management (included but not limited to):<br>• Disability (modified Rankin Scale)<br>• Proportion of patients with angiographic reperfusion<br>• Intracranial haemorrhage<br>• Functional recovery<br>• Neurological deficit<br>• Mortality<br>• Survival rate<br>• Length of hospital stay<br>• Adverse effects of treatment | Outcomes not listed |
| Study design | • RCTs<br>• Controlled trials (non-RCTs)<br>• Non-comparative (single-arm) trials | • Pharmacokinetics studies<br>• Pilot studies<br>• Observational studies and RWE (e.g. case-control, cohort, case series)<br>• Animal or in vitro studies |
| Publication Type | • Peer-reviewed publications<br>• Non-peer-reviewed manuscripts<br>• Conference abstracts<br>• Clinical trial registries including ongoing trials | • SLR[‡] and narrative reviews<br>• HTA reports/submissions<br>• Editorials, comments, notes<br>• Clinical trial protocols |
| Geography | No restrictions | None |
| Language | English language at full text | Non-English language |
| Timeframe | No restrictions | None |

**Key:** AIS, acute ischaemic stroke; ALT, alteplase; HTA, health technology assessment; PICOS, population, intervention, comparator, outcome, study type; RCT, randomized controlled trial; RWE, real-world evidence; SLR, systematic literature review; SoC, standard of care; TIA, transient ischaemic attack; TNK, tenecteplase.
**Notes:** [†] Studies assessing ALT vs ALT (with/without thrombectomy) will not be considered eligible for inclusion in the clinical SLR. [‡] Systematic reviews and meta-analyses will be used only to identify potentially relevant primary studies that have not been found through database searches.



An overview of the number of records included at each stage of the review during the study selection process is presented in Figure 1.

The literature search for the review period of database inception to 8 September 2023 identified a total of 8,992 records from electronic database searches. After the removal of duplicates (n = 2,306), and removal of irrelevant records at pre-screen (n = 121), 6,565 titles and abstracts were assessed using PICOS criteria, of which 6,143 were excluded. Several articles did not progress through full text screening due to inability to retrieve the full text (n = 9). Full texts of the remaining 413 publications were retrieved and 333 were excluded when eligibility criteria were reapplied.

In addition, 181 records were identified through supplementary search sources. Of those, 150 records were identified as duplicates or had already been identified from the electronic database search. The remaining 31 records were assessed for eligibility and 29 records were excluded. In total, 82 publications met the eligibility criteria and were included in the review, reporting 32 unique trials and eight pooled analyses.

The SLR prioritized 45 records for data synthesis. Eligible records were grouped by trial and prioritization was based on primary publication of the trial. Any linked publications with new data, or subgroups of interest related to vessel occlusion, were also included. Therefore, 27 unique trials reported by 39 publications were included in the full data synthesis, and six trial registry records reporting six ongoing trials were included in a summary data synthesis (as results of these trials were not yet published at time of review).

Of these studies, only two (AcT and EXTEND-IA TNK Part 1) were considered relevant to the decision problem specified in the final scope (Table 1, Document B). These two studies have been used to support the application for marketing authorization and are the largest, most robust, Phase II and III randomised, controlled, non-inferiority trials directly comparing the relevant dose of tenecteplase to the comparator of interest in this submission, alteplase.

Table 7 presents the RCTs and other studies highlighted by the SLR search that were excluded; reasons for exclusion are listed for all excluded studies.

**Figure 1: PRISMA flow diagram illustrating the study selection process**

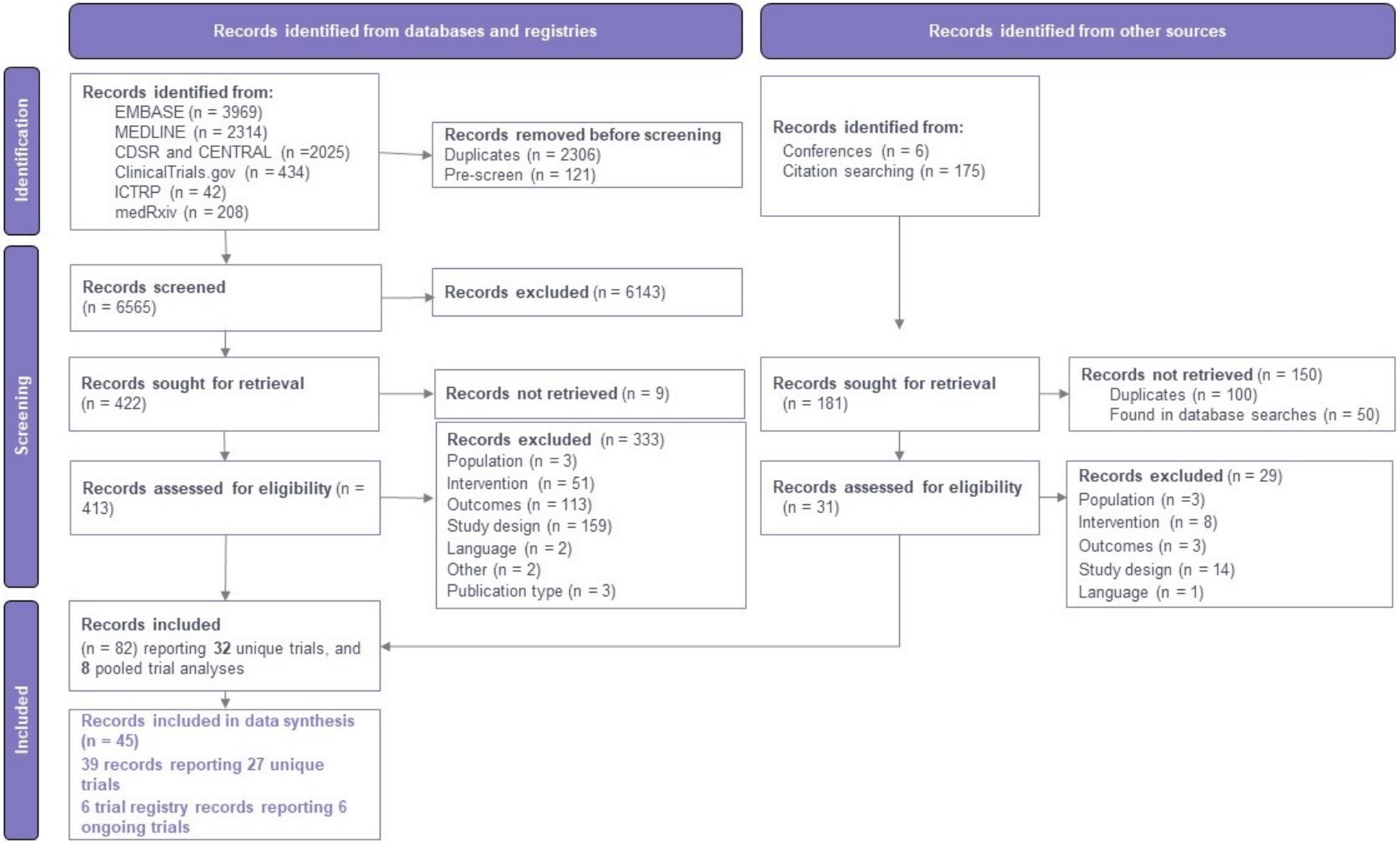




**Table 7: Summary of included and excluded studies**

| Type of study | Name of study | Reference | Reason for exclusion from submission |
|---|---|---|---|
| RCT | AcT (NCT03889249) | Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet. 2022; 400(10347):161-9. | Not applicable |
| | EXTEND-IA TNK Part 1 (NCT02388061) | Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. N Engl J Med. 2018; 378(17):1573-82. | Not applicable |
| | EXTEND-IA TNK Part 2 (NCT03340493) | Alemseged F, Ng FC, Williams C, et al. Tenecteplase vs Alteplase Before Endovascular Therapy in Basilar Artery Occlusion. Neurology. 2021; 96(9):e1272-e7. | No head-to-head comparison of tenecteplase to alteplase, tenecteplase 0.25mg/kg versus tenecteplase 0.40 mg/kg, which is not the relevant dose that will be used in clinical practice. |
| | ECASS II | Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 352 1245-51 (1998). Available at: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00273740/full. | Alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| | ECASS III (NCT00153036) | Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. New England Journal of Medicine. 2008; 359(13):1317-29. | Alteplase versus placebo, no head-to-head comparison of teneteplase to alteplase |
| | MR CLEAN–NO IV (ISRCTN80619088) | LeCouffe N, Kappelhof M, Treurniet KM, et al. A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke. NEJM. 2021; 385(20):1833-44. | Alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| | NOR-TEST (NCT01949948) | Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR- | Dose of tenecteplase was 0.40 mg/kg, which is not the relevant |



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| | | TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017; 16(10):781-8. | dose that will be used in clinical practice. |
| | NOR-TEST 2A (NCT03854500) | Kvistad CE, Naess H, Helleberg BH, et al. 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. Lancet Neurol. 2022; 21(6):511-9. | Dose of tenecteplase was 0.40 mg/kg, which is not the relevant dose that will be used in clinical practice. |
| | TRACE-2 (NCT04797013) | Wang Y, Li S, Pan Y, et al. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial. Lancet. 2023; 401(10377):645-54. | Chinese population only |
| | ATTEST (NCT01472926) | Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol. 2015; 14(4):368-76. | Small, single-centre study |
| | TNK-S2B (NCT00252239) | Haley EC, Jr., Thompson JLP, Grotta JC, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. Stroke. 2010; 41(4):707-11. | Small study which was prematurely terminated for slow enrolment, only included 31 patients treated with tenecteplase 0.25mg/kg and included 0.1 mg/kg tenecteplase and 0.40 mg/kg of tenecteplase, which are not relevant doses that will be used in clinical practice. |
| | TAAIS (ACTRN12608000466347) | Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. NEJM. 2012; 366(12):1099-107. | Small study, only 25 patients treated with 0.25 mg/kg tenecteplase, other doses not relevant to clinical practice |
| | TASTE-A (NCT04071613) | Bivard A, Zhao H, Churilov L, et al. Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the | Small study, only 49 patients treated with 0.25mg/kg tenecteplase, in a mobile |


 

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| | | Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. Lancet Neurol. 2022; 21(6):520-7. | stroke unit which is not relevant to UK clinical practice. |
| | TRACE (NCT04676659) | 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 and Vascular Neurology. 2022; 7(1):47-53. | Chinese population only, only 57 patients treated with 0.25 mg/kg tenecteplase, other doses not relevant to clinical practice |
| | DEVT (ChiCTR-IOR-17013568) | Zi W, Qiu Z, Li F, et al. Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke: The DEVT Randomized Clinical Trial. JAMA. 2021; 325(3):234-43. | Chinese population only, alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| | DIRECT-MT (NCT03469206) | Yang P, Zhang Y, Zhang L, et al. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. NEJM. 2020; 382(21):1981-93. | Alteplase vs placebo, no head-to-head comparison of tenecteplase to alteplase |
| | ECASS | Steiner T, Bluhmki E, Kaste M, et al. The ECASS 3-hour cohort. Secondary analysis of ECASS data by time stratification. ECASS Study Group. European Cooperative Acute Stroke Study. Cerebrovascular Diseases. 1998; 8(4):198-203. | Alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| | NINDS | The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke. 1997; 28(11):2109-18. | Alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| | Rajappa et al. 2018 | Rajappa S and Siivakumar S. Safety and efficacy of tenecteplase compared to alteplase in acute ischaemic stroke. IJS. 2018; 13(2):9-10. | Indian population only, dose of tenecteplase was 0.20 mg/kg, which is not the relevant dose that will be used in clinical practice. |
| | SKIP (UMIN000021488) | Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke: The SKIP Randomized Clinical Trial. JAMA. 2021; 325(3):244-53. | Japanese population only, alteplase versus placebo,no head-to-head comparison of tenecteplase to alteplase |



 

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|---|---|---|---|
| | SWIFT DIRECT (NCT03192332) | Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet. 2022; 400(10346):104-15. | Alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| | TESPI | Lorenzano S, Vestri A and Toni D. TESPI(thrombolysis in elderly stroke patients in Italy): randomized controlled trial of alteplase versus standard treatment in patients aged >80 years within 3hrs after stroke onset. European Stroke Journal. 2017; 2(1):7. | Alteplase versus placebo, no head-to-head comparison of tenecteplase to alteplase |
| Non-RCT | Huu An et al. 2022 | Huu An N, Dang Luu V, Duy Ton M, et al. Thrombectomy Alone versus Bridging Therapy in Acute Ischemic Stroke: Preliminary Results of an Experimental Trial. Clin Ter. 2022; 173(2):107-14. | Alteplase versus placebo, no head-to-head RCT comparison of tenecteplase to alteplase |
| Single-arm | J-ACT | Yamaguchi T, Mori E, Minematsu K, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke. 2006; 37(7):1810-5. | Single-arm, no head-to-head comparison of tenecteplase to alteplase |
| | NCT02930837 | Zheng H, Yang Y, Chen H, et al. Thrombolysis with alteplase 3-4.5 hours after acute ischaemic stroke: the first multicentre, phase III trial in China. Stroke and Vascular Neurology. 2020; 5(3):285-90. | Single-arm, no head-to-head comparison of tenecteplase to alteplase |
| | CTRI/2015/02/005556[3] | Ramakrishnan T, Kumaravelu S, Narayan S, et al. Efficacy and Safety of Intravenous Tenecteplase Bolus in Acute Ischemic Stroke: results of Two Open-Label, Multicenter Trials. American Journal of Cardiovascular Drugs. 2018; 18(5):387-95 | Single-arm, no head-to-head comparison of tenecteplase to alteplase, doses of tenecteplase were 0.10mg/kg and 0.20 mg/kg, which are not the relevant doses that will be used in clinical practice |
| | J-ACT II (NCT00412867) | ClinicalTrials.gov. Post-marketing Clinical Study of Alteplase for Acute Ischemic Stroke Japan Alteplase Clinical Trial II: J-ACT II. https://classic.clinicaltrials.gov/ct2/show/NCT00412867 | Single-arm, no head-to-head comparison of tenecteplase to alteplase |
| **Key:** RCT, randomized controlled trial. | | | |

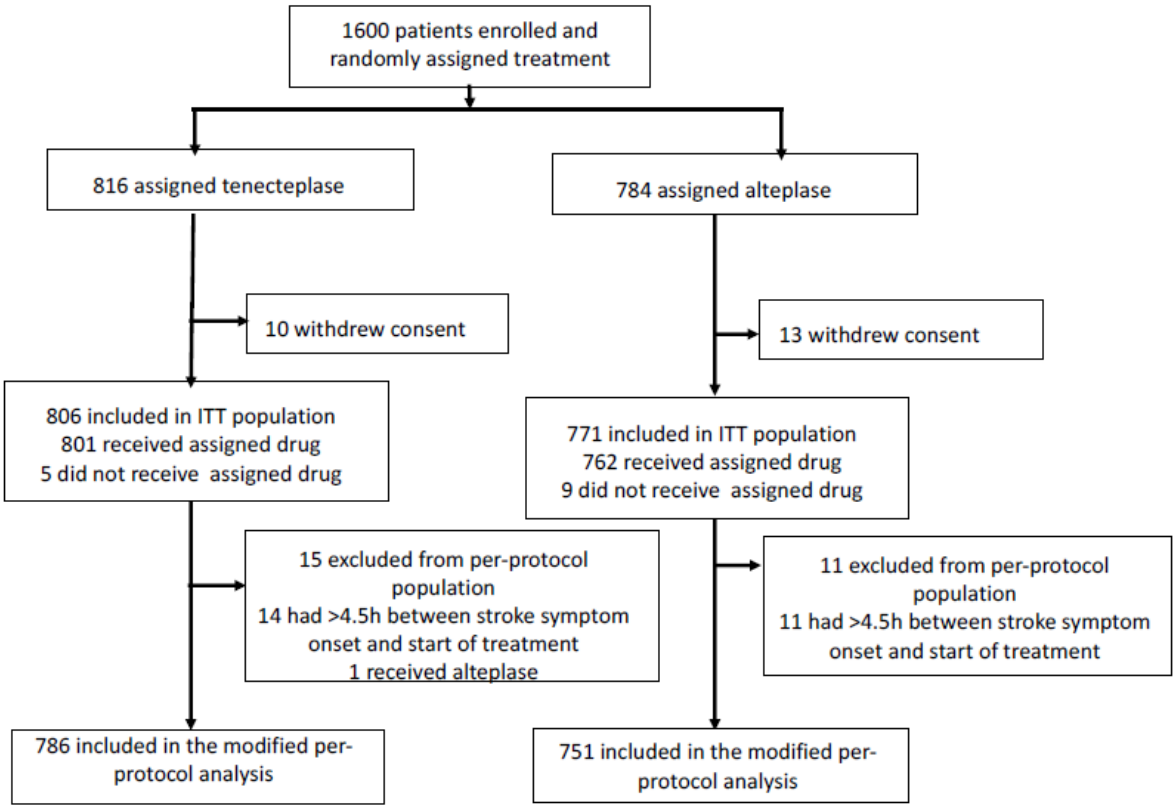

 

## *D.2. Participant flow in the relevant randomised control trials*

### D.2.1 AcT

From 10 December, 2019 to 25 January, 2022, 1,600 patients were enrolled across Canada.[4] A total of 816 patients were assigned to receive tenecteplase and 784 were assigned to receive alteplase. Of these, 23 (1.4%) withdrew consent from the study, leaving 1,577 patients comprising the intention to treat (ITT) population, with 806 assigned to receive tenecteplase, and 771 to receive alteplase.

**Figure 2: CONSORT diagram for AcT trial**




**Key:** ITT, intention to treat
**Source:** Menon et al. 2022.[4]

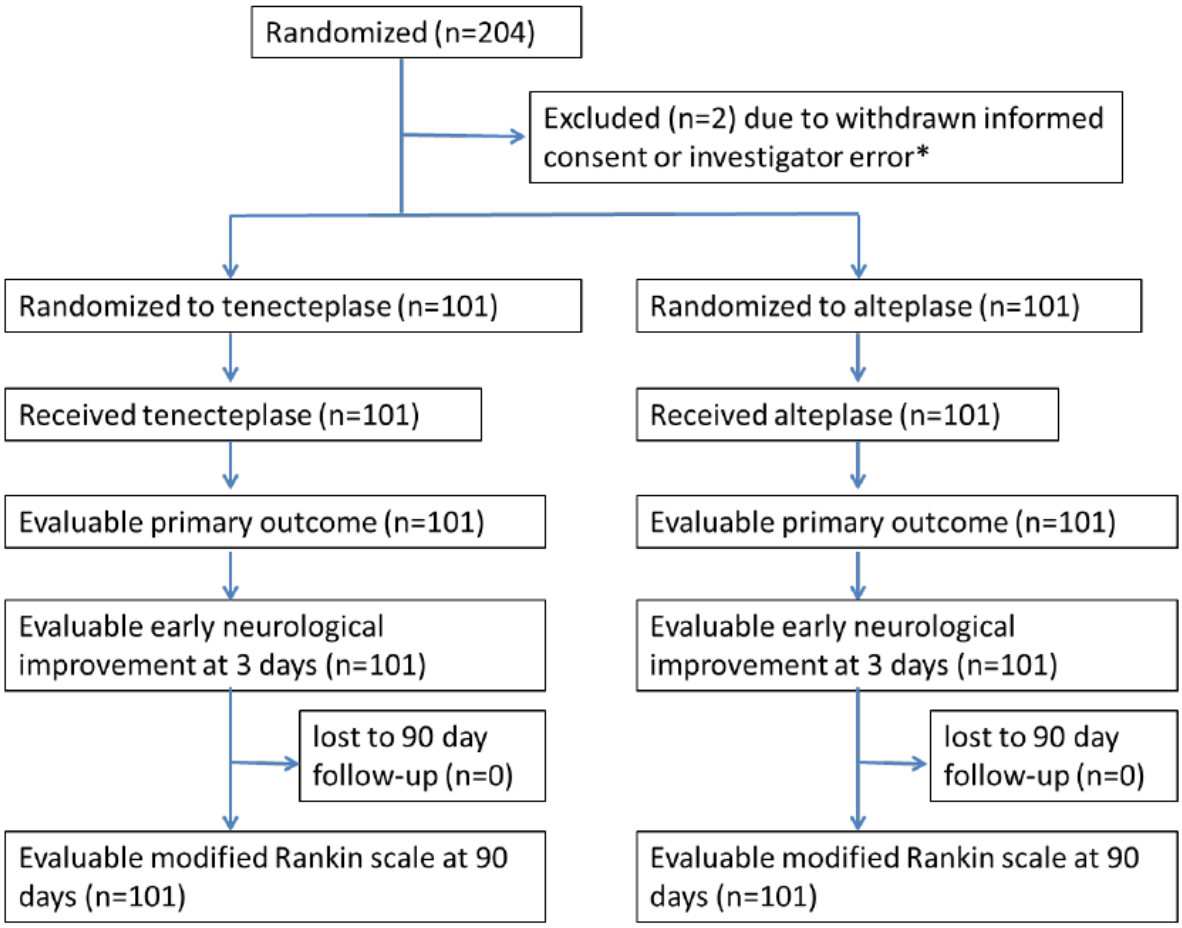
### D.2.2 EXTEND-IA TNK Part 1

From March 2015 to October 2017, 204 patients were enrolled at 12 centres in Australia and at one centre in New Zealand.[5] A total of 101 patients were assigned to receive tenecteplase and 101 were assigned to receive alteplase. Two were excluded; one owing to withdrawal of consent and one owing to withdrawal by the

enrolling physician before treatment was commenced, due to an error in assessing patient eligibility. There were two patients in Part 1 who received the cardiac dose of 0.5 mg/kg due to nursing error, but this did not cause adverse consequences. No patients were lost to follow up.

**Figure 3: CONSORT diagram for EXTEND-IA TNK Trial**




**Source:** Campbell et al. 2018.[5]

## *D.3. Quality assessment for each study*

AcT and EXTEND-IA TNK Part 1 were conducted in accordance with the ethical principles of Good Clinical Practice and were both considered to be good-quality studies. A complete quality assessment in accordance with the Cochrane risk-of-bias tool is presented in Table 8. The overall risk of bias for both studies is considered to be low.

**Table 8: Summary of risk of bias assessments**

| Study | Domain 1<br>Was the method used to generate random allocation adequate? | Domain 2<br>Was the allocation adequately concealed? | Domain 3<br>Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease? | Domain 4<br>Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? | Domain 5<br>Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | Domain 6<br>Is there any evidence to suggest that the authors measured more outcomes than they reported? | Domain 7<br>Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? |
|---|---|---|---|---|---|---|---|
| Menon, AcT[4] (NCT03889249) [6] | Yes | Yes | Yes | No | No | Yes | Yes |
| Campbell, EXTEND-IA TNK[5] (NCT02388061) [7] | Yes | Yes | Yes | No | No | No | Yes |

# Appendix E: Subgroup analysis

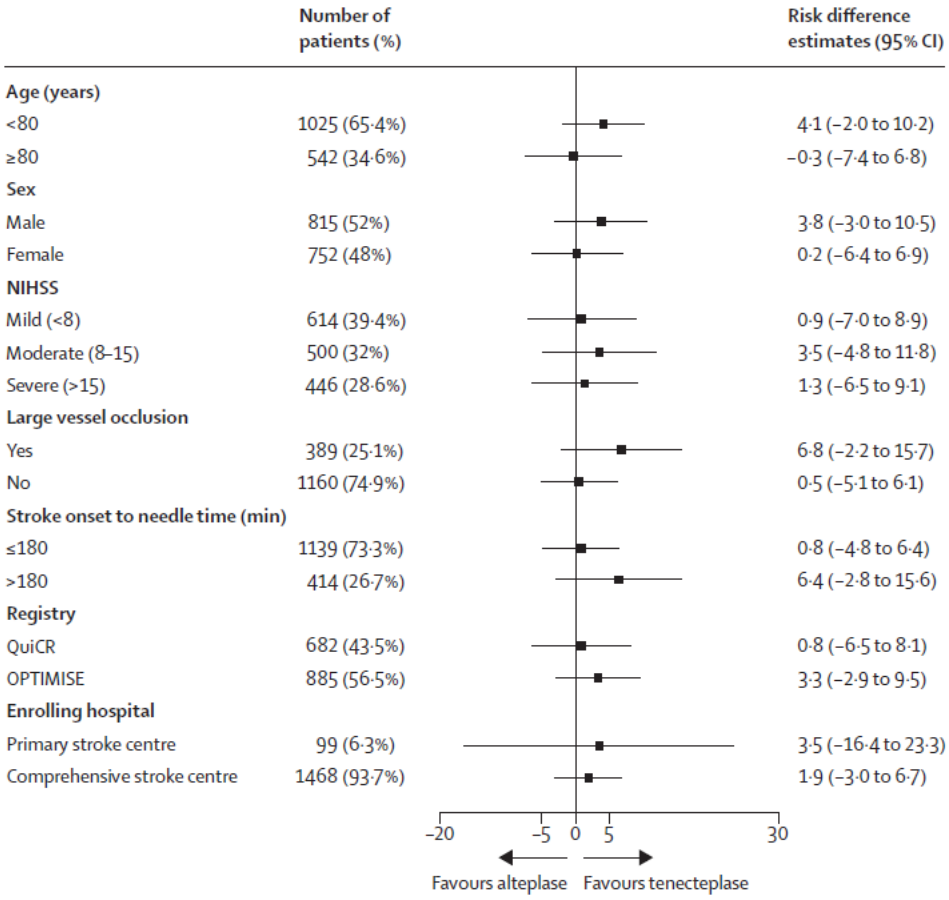
## *E.1. AcT trial clinical efficacy outcomes*

In the AcT trial, prespecified subgroup analysis was conducted for the primary outcome of the trial, modified Rankin Scale (mRS) score 0–1 at 90–120 days.[8] This analysis was exploratory. A forest plot presenting the unadjusted risk difference estimates in the ITT population of the AcT trial is presented in Figure 4, with positive scores favouring tenecteplase. No heterogeneity of treatment effect was observed across any prespecified subgroups.[8]



**Figure 4: Forest plot of unadjusted risk difference estimates for the primary outcome (modified Rankin Scale score of 0–1) stratified by prespecified subgroups, ITT population**




**Key:** CI, confidence interval; NIHSS, National Institute of Health Stroke Score; OPTMISE, Optimizing Patient Treatment in Major Ischemic Stroke With EVT; QuiCR, Quality Improvement and Clinical Research.
**Source**: Menon et al. 2022.[4]

## *E.2. AcT trial safety outcomes*

In the AcT trial, prespecified subgroup analysis was conducted for the safety outcome of the trial, death up to Day 90. Results are presented in Figure 5.[8] The subgroups for which the point estimates were not in favour of tenecteplase were: female, age ≤ 80 years, National Institute of Health Stroke Score (NIHSS) 8–15, Optimizing Patient Treatment in Major Ischemic Stroke With EVT (endovascular thrombectomy) (OPTIMISE) registry, comprehensive stroke centres and patients without large vessel

occlusion (LVO). For NIHSS 8–15, the result was statistically significant in favour of alteplase and for NIHSS < 8 it was statistically significant in favour of tenecteplase.[8]

**Figure 5: Forest plot of death within 90 days (AcT) Risk difference by subgroups – SAF population ([redacted])**

**Source**: AcT CSR Revision 1.[8]



# Appendix F: Adverse reactions

ATTEST is a single-centre, phase 2, prospective, randomised, open-label, blinded end-point evaluation study, adults with supratentorial ischaemic stroke eligible for intravenous thrombolysis (IVT) within 4.5 hours of onset were recruited from The Institute of Neurological Sciences, Glasgow, Scotland.[9] Patients were randomly assigned (1:1) to receive tenecteplase 0.25 mg/kg (maximum 25 mg) or alteplase 0.9 mg/kg (maximum 90 mg). Between 1 January 2012, and 7 September 2013, 355 patients were screened, of whom 157 were eligible for IVT, and 104 patients were enrolled. Of these, 52 were assigned to the alteplase group and 52 to tenecteplase.

The safety population included 52 patients given tenecteplase and 51 given alteplase.[9] A summary of the key safety outcomes reported in the ATTEST trial is provided in Table 9. Intracerebral haemorrhage of any kind was seen in eight patients (15%) in the tenecteplase group and 14 (27%) in the alteplase group (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 symptomatic intracerebral haemorrhage, with either SITS-MOST definition or ECASS II definition, did not differ between treatment groups.[9]

**Table 9: Safety outcomes in the per-protocol analysis in ATTEST**

| | **Tenecteplase (n = 52)** | **Alteplase (n = 51)** | **p value*** | **Odds ratio (95% CI)** |
|---|---|---|---|---|
| Any ICH | 8/52 (15%) | 14/51 (27%) | 0.09 | 0.4 (0.2, 1.2) |
| Any parenchymal haemorrhage | 1/52 (2%) | 5/51 (10%) | 0.12 | - |
| Parenchymal haemorrhage type 2 | 0/52 (0%) | 3/51 (6%) | 0.94 | |
| Symptomatic ICH (ECASS II14 definition) | 3/52 (6%) | 4/51 (8%) | 0.59 | 0.6 (0.1, 3.2) |

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|---|---|---|---|---|
| Symptomatic ICH (SITS-MOST23 definition) | 1/52 (2%) | 2/51 (4%) | 0.50 | 0.4 (0.04, 5.1) |

**Key:** ICH, intracerebral haemorrhage; IQR, interquartile range; SD, standard deviation.
**Notes:** Data are mean (SD), n (%), n/N (%), or median (IQR), unless otherwise shown. *Calculated from linear or logistic regression models that adjust for stratification variables and are a test for difference between groups.
**Source:** Huang et al. 2015.[9]

A summary of the serious adverse events reported in the ATTEST trial is provided in Table 10. Up to day 90, 32 serious adverse events (62%) were noted in 22 (42%) patients given tenecteplase and 16 (31%) patients given alteplase, including intracerebral haemorrhage events fulfilling criteria for seriousness.[9]

**Table 10: Serious adverse events in ATTEST**

| SAEs, n (%) | Tenecteplase (n =2) | Alteplase (n = 51) |
|---|---|---|
| **All SAEs to day 90** | 32 (62) | 16 (31) |
| **Up to day 7** | | |
| Number of participants with one or more SAE | 8 (15) | 9 (18) |
| Probably or definitely related to study drug | 3 (6) | 5 (10) |
| All SAEs within 7 days | 8 (15) | 9 (18) |
| Probably or definitely related to study drug | 3 (6) | 5 (10) |
| Angio-oedema | 1 (2) | 0 |
| New ischaemic stroke | 2 (4) | 0 |
| Epistaxis | 1 (2) | 0 |
| Pneumonia | 2 (4) | 2 (4) |
| Intracerebral haemorrhage | 1 (2) | 5 (10) |
| Other | | |
| Chest pain | 1 (2) | 0 |
| Malignant glioma | 0 | 1 (2) |
| General deterioration | 0 | 1 (2) |
| **Days 7–90** | | |
| Number of participants with one or more SAE | 18 (35) | 7 (14) |
| All SAEs days 7–90 | 24 (46) | 7 (14) |
| Gastrointestinal bleeding | 2 (4) | 0 |

| | | |
|---|---|---|
| New ischaemic stroke | 4 (8) | 2 (4) |
| Other extracranial bleeding | 2 (4) | 0 |
| Pneumonia | 2 (4) | 0 |
| Venous thromboembolism | 1 (2) | 0 |
| Other | | |
| Atrial fibrillation | 3 (6) | 1 (2) |
| Abdominal pain, constipation, diarrhoea | 3 (6) | 0 |
| Chest pain | 3 (6) | 0 |
| Gastroenteritis | 0 | 1 (2) |
| Fall | 1 (2) | 1 (2) |
| Planned medical procedures | 5 (10) | 1 (2) |
| Dehydration | 1 (2) | 0 |
| Depression | 0 | 1 (2) |
| Renal impairment | 3 (6) | 0 |
| Hypotension | 2 (4) | 0 |

**Key:** SAEs, serious adverse events.
**Notes:** Data are number of events (%), more than one event can occur in any participant.
**Source:** Huang et al. 2015.[9]



# Appendix G: Cost and healthcare resource identification, measurement and valuation

## *G.1. Objective*

An economic SLR was conducted to identify published evidence to support the development of the cost-comparison model for tenecteplase.

The review aimed to assess:

- 1) The costs and healthcare resource use (HCRU) associated with AIS management
- 2) The evidence on current health economic models for AIS

This National Institute for Health and Care Excellence (NICE) cost comparison submission of tenecteplase uses a cost comparison model, which is of a more narrow scope than the economic SLR. Because of this, model specifications and results from cost-utility analyses were not of interest. This SLR focuses on the costs and resource uses that are necessary to inform the cost comparison analysis only. Alteplase is the only relevant comparator for tenecteplase, given that it is currently the only licenced treatment for AIS in the UK.

## *G.2. Methods*

### G.2.1 Identification and selection of relevant studies

#### *G.2.1.1 Search Strategy*

An SLR protocol was designed a priori following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols checklist.[10] The systematic review has been reported according to PRISMA standards[2] and adheres to NICE requirements. This protocol is registered with PROSPERO (Registration number: CRD42023434098).

Search strategies are presented in Section G.6. Searches were conducted in the following databases:

- Ovid MEDLINE and Embase (24 May 2023)
- Ovid EconLit (1 June 2023)
- International Network of Agencies for Health Technology Assessment (INAHTA) (7 June 2023)

A pre-agreed selection of conferences (2020–2023), bibliographies of relevant SLRs and relevant health technology assessment agencies were also searched for published data. No language restrictions were applied and only studies published in the last 10 years (2013–2023) were eligible for inclusion.

#### *G.2.1.2 Study selection*

Records were assessed against the pre-defined PICOS eligibility criteria presented in Table 11. Titles and abstracts were independently assessed by two reviewers, with disagreements adjudicated by a third independent reviewer. Full texts were assessed in the same manner.

Studies were eligible for inclusion if they were conducted in the following regions: Australia, Brazil, China, Europe (France, Italy, Germany, Spain, and the UK), Japan, Kingdom of Saudi Arabia, and the US.

#### G.2.1.3 Inclusion/Exclusion Criteria

**Table 11: SLR | PICOS relevant for the NICE cost comparison submission (UK cost and resource use outcomes)**

| PICOS elements | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | • The population will be kept broad to include adult patients (18+) with ischaemic stroke<br>• Subpopulation of interest: patients presenting with AIS symptoms | • Patients with haemorrhagic stroke, brain stem stroke, TIA, or stroke of unknown causes<br>• Paediatric population (< 18 years old) |
| **Intervention/ Comparators** | Pharmaco-induced thrombolysis for the initial management of ischaemic | • Studies focusing on mechanical thrombectomy |

| | | |
|---|---|---|
| | stroke, with or without mechanical thrombectomy or secondary prevention therapies[†] | without a thrombolysis comparison arm<br>• Secondary prevention therapies or long-term treatment with no reference to any treatment used for the initial management of ischaemic stroke |
| **Outcomes** | Short and long-term effects of treatment for both patients and caregivers reported as:<br>• HRQL data using validated instruments<br>• Symptoms (patient-reported or through physician)<br>• Utility and disutility data for relevant health states<br>• Functional impairment and activity limitations | Outcomes not listed |
| **Study design** | • Prospective and retrospective observational studies (cohort, case-control, cross-sectional)<br>• RWE<br>• Direct elicitation studies<br>• Clinical trial studies reporting HRQL data | • Case series and case reports<br>• BIMs<br>• Animal or in vitro studies |
| **Publication Type** | • Peer-reviewed publications<br>• Conference abstracts (published in the last 2 years)<br>• Completed HTAs | • SLRs[‡] and narrative reviews<br>• Editorials, letters or comments, notes<br>• Suspended or ongoing/ incomplete HTAs |
| **Geography** | Australia, Brazil, China, Europe (France, Italy, Germany, Spain and the UK), Japan, Kingdom of Saudi Arabia, US | Regions/countries not listed |
| **Language** | English language at full-text | Non-English language[§] |
| **Timeframe** | 2013 to present (the last ten years) | Prior to 2013 |

**Key:** AIS, acute ischaemic stroke; BIM, budget impact model; HRQL, health-related quality of life; HTA, health technology assessment; PICOS, population, intervention, comparator, outcome, study type; RWE, real-world evidence; SLR, systematic literature review; TIA, transient ischaemic attack
**Notes:** [†] Studies will only be eligible for inclusion if 100% of patients in a treatment arm received thrombolytic therapy. Patient populations receiving a variety of treatments based on specific treatment criteria will be excluded. [‡] Systematic reviews and meta-analyses will be used only to identify potentially relevant primary studies that have not been found through database searches. [§] HEOR will provide a list of potentially relevant non-English language publications.



#### *G.2.1.4* Screening

#### *G.2.1.5* Data Extraction

All data were extracted by a single reviewer and independently checked by a second reviewer for accuracy. Discrepancies were resolved by consensus.

#### *G.2.1.6* *Quality Assessment*

Risk of bias (RoB) assessment was conducted for economic evaluations using the Drummond 36-item checklist.[11] The Centre for Review and Dissemination tool was used for randomized controlled trials (RCTs)[12], and the Joanna Briggs Institute tools were applied to all other study designs (including cross-sectional, cohort, case control, and other comparative studies).[13]

All RoB assessments were performed by a single reviewer and validated by a second reviewer. For studies with multiple associated publications, RoB assessment was only conducted on the primary publication.

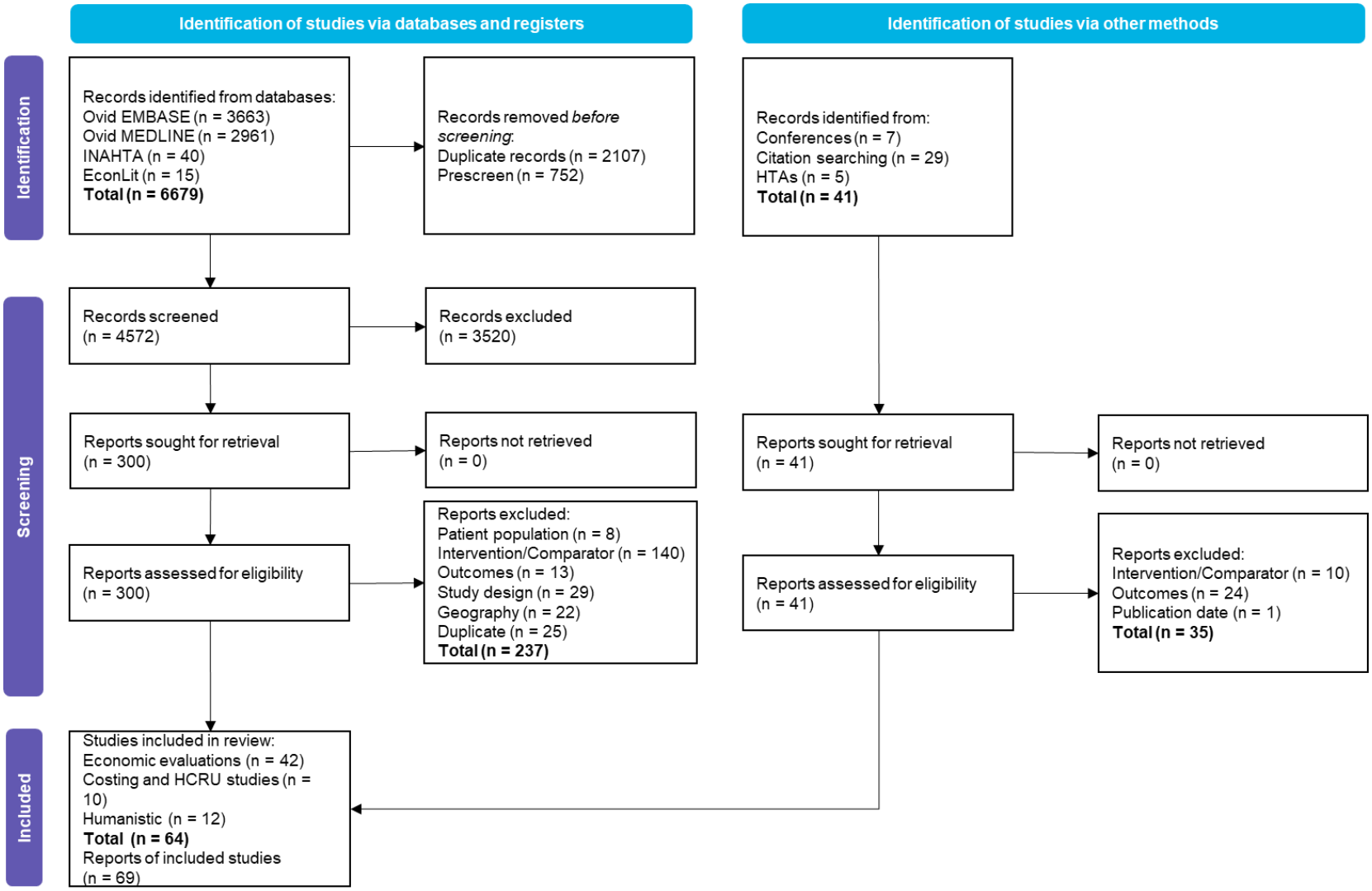
## *G.3. Results*

### G.3.1 Economic studies relevant for NICE cost comparison submission (reporting cost and resource use outcomes in UK)

In total, 6,679 records were identified from database and registry searches (Figure 6). After deduplication and pre-screening, 4,572 records were screened at title and abstract level. At full-text level, 300 records were screened and 237 were excluded. Handsearching identified 41 records, of which six were included. Overall, 69 records were included in the final review, of which 64 were unique studies. Economic evaluations were reported in 42 studies; primary costing or HCRU outcomes were reported in 10 studies; and HRQL outcomes only were reported in 12 studies (these are not relevant to the cost-comparison submission but included here for completeness).

## Figure 6: PRISMA flowchart




**Key:** HCRU, healthcare resource use; HTA, health technology assessment.

### G.3.2 Description of identified studies

#### *G.3.2.1 Primary costing studies (not including cost-effectiveness studies)*

In total, the review identified nine publications reporting eight unique primary costing studies. Table 12 provides a summary covering study design, geography and treatment comparisons of the unique primary costing studies included in the review.

Most included studies were retrospective observational studies, seven of which were analyses of AIS patient databases and one of which used a case-control control design. All but one of the studies were conducted in the US; the remaining study was conducted in Brazil. The most common comparison of treatments was IVT alone vs EVT alone, which was assessed in five studies. Comparisons of tenecteplase vs alteplase, IVT alone vs standard of care (SoC), and IVT prior to EVT vs EVT alone were assessed in one study each.

**Table 12: Primary costing studies characteristics**

| **Study Design** | | |
|---|---|---|
| Prospective cohort | 2 (25) | Etges 2022;[14] Warach 2022[15] |
| Retrospective case-control | 1 (13) | Kwok 2023[16] |
| Retrospective database study | 5 (63) | Hailat 2021;[17] Joo 2016;[18] Rai 2015;[19] Rai 2016;[20] Sonig 2016[21] |
| Geography | | |
| Australia | 0 (0) | NA |
| Brazil | 1 (12) | Etges 2022;[14] |
| Canada | 0 (0) | NA |
| China | 0 (0) | NA |
| Europe | 0 (0) | NA |
| France | 0 (0) | NA |
| Germany | 0 (0) | NA |
| Italy | 0 (0) | NA |
| Kingdom of Saudi Arabia | 0 (0) | NA |

| | | |
|---|---|---|
| Spain | 0 (0) | NA |
| UK | 0 (0) | NA |
| US | 7 (88) | Hailat 2021;[17] Joo 2016;[18] Kwok 2023;[16] Rai 2015;[19] Rai 2016;[20] Sonig 2016;[21] Warach 2022[15] |
| Treatment comparisons | | |
| Tenecteplase vs alteplase | 1 (13) | Warach 2022[15] |
| IVT vs EVT | 4 (50) | Etges 2022;[14]; Hailat 2021;[17] Rai 2015;[19] Sonig 2016[21] |
| IVT vs SoC | 1 (13) | Joo 2016[18] |
| IVT + EVT vs EVT | 1 (13) | Kwok 2023[16] |
| IVT | 1 (13) | Rai 2016[20] |
| **Key:** EVT, endovascular treatment; IVT, intravenous thrombolysis; NA, not applicable; SoC, standard of care. | | |

Identified cost studies can be grouped into two categories: costs based on treatments received for AIS and costs based on other comparisons. An overview of the costs reported in these studies is presented in Table 13.

#### *G.3.2.1.1. Treatment comparison costs*

One prospective cohort study reported a comparison of the median cost per hospital admission for patients treated with tenecteplase vs alteplase. Hospital encounters were found to cost less for patients treated with tenecteplase compared with alteplase, largely due to the lower pharmacy costs attributed to tenecteplase treatment.[15]

Two retrospective database studies reported a comparison of IVT alone vs EVT alone, one using the Michigan Value Collaborative registry and the other using a database of AIS patients treated at a medical centre in Virginia (Hailat et al.).[17] The latter study found that mean 90-day hospital episode costs were significantly higher when patients were treated with EVT alone than when patients were treated with IVT alone, primarily due to higher costs related to readmissions and the post-acute phase. Rai and Evans[19] reported that EVT alone was associated with significantly higher mean hospital charges, total costs, direct costs, and payments than IVT alone.

Another retrospective database study compared the cost of patients treated with IVT alone compared with patients not treated with IVT, using the MarketScan Commercial Claims and Encounters Inpatient Database. Inpatient costs per hospitalization were significantly higher in the IVT group than the non-IVT group.[18]

A retrospective case-control study reported a comparison of IVT prior to EVT vs EVT alone, using the Nationwide Inpatient Sample (NIS). There was no significant increase in the median cost of hospitalization when IVT was used as an adjunct to EVT in patients with AIS.[16]

Lastly, a Brazilian prospective cohort study reported the cost of treating patients with AIS with IVT, EVT, or IVT prior to EVT. Mean costs were found to be highest after EVT treatment, followed by IVT prior to EVT treatment, and then IVT alone.[14]

*G.3.2.1.2. Other comparison costs*

One retrospective database study reported a comparison of the costs of IVT in patients who experienced AIS with LVO compared with no LVO. The study used a database of patients with AIS who were treated at a medical centre in Virginia. Mean hospital costs were significantly higher in patients with LVO, likely because LVO strokes incur higher morbidity and mortality than non-LVO strokes.[20]

Another retrospective database study aimed to evaluate the impact of transferring patients with stroke from one facility to a centre where they received some form of active stroke treatment, using the NIS. Mean hospitalization costs were significantly higher for a transferred patient compared with a direct admission.[21]

**Table 13: Overview of primary costing studies**

| Author, year, country | Title | Study aim | Group comparison (n) | Cost description | Currency (year) | Value | Between group comparison | Source | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment comparison costs** | | | | | | | | | |
| Hailat, 2021[17]<br><br>US | The Effect of Endovascular Procedure and Tissue Plasminogen Activator Treatments on 90 Days Episode Payments Among Ischaemic Stroke Patients | To compare 90-day episode payments for EVT and tPA treatments for patients with AIS | EVT (with and without tPA) (1,775) | Mean (SD) costs for total episode | USD (NR) | 37,923 (25,481) | p < 0.01 | Michigan Value Collaborative registry, January 2014–June 2019 | EVT and tPA treatments significantly affect 90-day episode payments - primarily due to higher readmission and post-acute phase payments |
| | | | IV or IA tPA only (4,889) | | USD (NR) | 32,764 (21,160) | | | |
| | | | non-EVT or tPA (40,571) | | USD (NR) | 28,726 (23,796) | | | |
| Joo, 2016[18]<br>US | Use of intravenous tissue plasminogen activator and hospital costs for patients with AIS aged 18–64 years in the USA | To examine IV tPA use among patients aged 18–64 years with a primary diagnosis of AIS in the USA | Primary diagnosis of AIS (39,149) | Mean (SD) inpatient cost per hospitalization | USD (2013) | 20,331 (NR) | NA | MarketScan Commercial Claims and Encounters Inpatient Database, 2010–2013 | Inpatient cost per AIS hospitalization is substantial, especially for those who received IV tPA |
| | | | Received IV tPA (2,546) | | USD (2013) | 31,369 (NR) | p < 0.01 | | |
| | | | Non-tPA group (36, 603) | | USD (2013) | 19,563 (NR) | | | |

| Author, year, country | Title | Study aim | Group comparison (n) | Cost description | Currency (year) | Value | Between group comparison | Source | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| | | and inpatient costs per hospitalization by IV tPA use status among these patients | | | | | | | |
| Kwok, 2023[16] US | Intra-arterial thrombolysis as adjunct to mechanical thrombectomy in AIS patients in the United States: A case control analysis | To evaluate the cost and length of hospitalization associated with intra-arterial thrombolysis as adjunct to mechanical thrombectomy | Intra-arterial thrombolysis (1,990) | Median (IQR) hospital cost | USD (NR) | 36,992 (28,361–4,336) | p = 0.37 | NIS, 2017–2019 | There was no increase in the cost of hospitalization associated with the use of IA thrombolysis as adjunct to mechanical thrombectomy in patients with AIS |
| | | | Not receiving intra-arterial thrombolysis (1,990) | | USD (NR) | 35,440 (24,383–50,438) | | | |
| Rai, 2015[19] | Hospital-based | To compare a | Endovascular therapy (141) | | USD (NR) | 69,590 | p < 0.01 | Patients treated | Endovascular therapy was |

| Author, year, country | Title | Study aim | Group comparison (n) | Cost description | Currency (year) | Value | Between group comparison | Source | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| US | financial analysis of endovascular therapy and intravenous thrombolysis for large vessel AIS: the 'bottom line' | hospital's costs and reimbursements for IV thrombolysis and endovascular therapy for AIS | Intra-arterial thrombolysis (124) | Mean hospital charges | USD (NR) | 44,303 | | with IVT and EVT for AIS at an academic medical centre in Virginia | associated with higher cost–recovery than IV thrombolysis in patients with large vessel strokes |
| | | | Endovascular therapy (141) | Mean total cost | USD (NR) | 28,009 | p < 0.01 | | |
| | | | IA thrombolysis (124) | | USD (NR) | 18,479 | | | |
| | | | Endovascular therapy (141) | Mean direct cost | USD (NR) | 19,546 | p < 0.01 | | |
| | | | IA thrombolysis (124) | | USD (NR) | 13,120 | | | |
| | | | Endovascular therapy (141) | Mean payments | USD (NR) | 28,485 | p < 0.01 | | |
| | | | Intra-arterial thrombolysis (124) | | USD (NR) | 16,727 | | | |
| Warach, 2022[15] US | Prospective Observational Cohort Study of Tenecteplase Versus Alteplase in Routine Clinical Practice | To evaluate whether tenecteplase use in routine clinical practice reduced thrombolytic workflow | Tenecteplase-treated (234) | Median cost per hospital encounter | USD | 13,382 | p < 0.01 | Patients treated with an IV thrombolytic for AIS at the 10 Ascension Seton Hospitals in Texas, | Median cost per hospital encounter was less for tenecteplase cases than for alteplase |
| | | | Alteplase-treated (354) | | USD | 15,841 | | | |

| Author, year, country | Title | Study aim | Group comparison (n) | Cost description | Currency (year) | Value | Between group comparison | Source | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| | | times with noninferior clinical outcomes | | | | | | September 2017–December 2020 | |
| Etges, 2022[14] Brazil | Moving the Brazilian ischaemic stroke pathway to a value-based care: introduction of a risk-adjusted cost estimate model for stroke treatment | To introduce a clinical risk- and outcome-adjusted cost estimate model sustained on time-driven activity-based costing to estimate the individual cost of AIS treatment | Consecutive patients with diagnosis of ischaemic stroke (822) | Mean (SD) cost | International dollars (2019) | 4,499 (7,970) | NR | AIS patients in three Brazilian stroke centres | Patients treated with EVT, or IVT prior to EVT consumed more resources than patients treated with IVT alone and consequently registered higher costs |
| | | | IVT (176) | | International dollars (2019) | 6,205 (NR) | | | |
| | | | EVT (73) | | International dollars (2019) | 16,311 (NR) | | | |
| | | | IVT + EVT (155) | | International dollars (2019) | 13,351 (NR) | | | |
| **Costs based on other comparisons** | | | | | | | | | |
| Rai, 2016[20] US | Intravenous thrombolysis of LVOs is associated | To determine whether intravenous | LVO (119) | Total mean (SD) cost per patient | USD (NR) | 18,815 (14,262) | p = 0.04 | Patients treated with IVT for AIS at an | The presence of LVO is associated with significantly |
| | | | No LVO (104) | | USD (NR) | 15,174 (11,769) | | | |

| Author, year, country | Title | Study aim | Group comparison (n) | Cost description | Currency (year) | Value | Between group comparison | Source | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| | with higher hospital costs than small vessel strokes: a rationale for developing stroke severity-based financial models | thrombolysis costs are related to the presence or absence of LVO | | | | | | academic medical centre in Virginia | higher hospital costs vs patients without LVO |
| Sonig, 2016[21] US | Impact of transfer status on hospitalization cost and discharge disposition for AIS across the US | To evaluate the impact of transferring patients with stroke from one facility to a centre where they received some form of active stroke intervention | Direct admissions<br>Transferred patients | Mean hospitalization cost | USD (NR)<br>USD (NR) | USD 70,325<br>USD 97,547 | p < 0.01; OR 1.70, 95% CI 1.5–1.8 | NIS, 2008–2010 | Hospital cost for AIS intervention is significantly higher for a transferred patient than for a direct admission |

| Author, year, country | Title | Study aim | Group comparison (n) | Cost description | Currency (year) | Value | Between group comparison | Source | Conclusion |
|---|---|---|---|---|---|---|---|---|---|
| **Key:** AIS, acute ischaemic stroke; EVT, endovascular treatment; IA, intra-arterial; IQR, interquartile range; IV, intravenous; IVT, intravenous thrombolysis; LVO, large vessel occlusion; NIS, Nationwide Inpatient Sample; NR, not reported; SD, standard deviation; tPA, tissue plasminogen activator. | | | | | | | | | |

### *G.3.2.2 HCRU studies*

In total, the review identified 18 publications reporting 19 unique studies that covered discharge destination, hospitalization, length of stay (LOS), outpatient/caregiver HCRU. Table 14 provides a summary covering the study design, geography, and treatment comparisons of the unique studies that reported HCRU.

Studies were heterogeneous in design and were either within-trial analyses (n = 7), retrospective database studies (n = 4), cost-effectiveness models (n = 4), prospective cohort studies (n = 2), RCTs (n = 1), or retrospective cross-sectional studies (n = 1).

Most studies were conducted in the US (n = 8). Other geographical locations included Australia (n = 3), Brazil (n = 2), China (n = 2), Canada (n = 1), France (n = 1), international (n = 1), and the UK (n = 1).

There were differences in the treatments assessed within the studies. IVT prior to EVT compared with IVT alone (n = 5) and IVT alone compared with SoC (n = 5) were the most frequent treatment comparisons, followed by IVT alone compared with EVT alone (n = 2), tenecteplase compared with alteplase (n = 2), IVT alone compared with EVT alone and IVT prior to EVT (n = 2), and IVT prior to EVT compared with EVT alone (n = 1). Additionally, two studies compared patients receiving IVT: an RCT that evaluated very early mobilization after IVT treatment for AIS compared with standard treatment[22], and one that evaluated outcomes in LVO and patients with non-LVO AIS after IVT treatment.[20]

**Table 14: Characteristics of included HCRU studies**

| Category | Studies, n (%) | References |
|---|---|---|
| **Study Design** | | |
| Cost-effectiveness model | 4 (21) | Joo 2016[18]; Kazley 2013;[23] NICE 2012;[24] Tan Tanny 2013[25] |
| Prospective cohort | 2 (11) | Etges 2022;[14]; Warach 2022[15] |
| RCT | 1 (5) | Anjos 2023[22] |
| Retrospective database study | 4 (21) | Joo 2016;[18] Rai 2015;[19] Rai 2016;[20] Sonig 2016[21] |
| Retrospective cross-sectional | 1 (5) | Nagaraja 2021[26] |
| Within-trial analyses | 7 (37) | Campbell 2017;[27] Gao 2020;[28] Ma 2023;[29] Sevick 2021;[30] Shireman 2017;[31] Simpson 2017;[32] Yan 2015[33] |
| **Geography** | | |
| Australia | 3 (16) | Campbell 2017;[27] Gao 2020;[28] Tan Tanny 2013[25] |
| Brazil | 2 (11) | Anjos 2023;[22] Etges 2022;[14] |
| Canada | 1 (5) | Sevick 2021[30] |
| China | 2 (11) | Ma 2023;[29] Yan 2015[33] |
| Europe | 0 (0) | NA |
| France | 1 (5) | Kabore 2019[34] |
| Germany | 0 (0) | NA |
| International | 1 (5) | Simpson 2017[32] |
| Italy | 0 (0) | NA |
| Kingdom of Saudi Arabia | 0 (0) | NA |
| Spain | 0 (0) | NA |
| UK | 1 (5) | NICE 2012[24] |
| US | 8 (42) | Joo 2016; Kazley 2013;[23] Nagaraja 2017; Rai 2015; Rai 2016; Shireman 2017;[31] Sonig 2016; Warach 2022[15] |
| **Treatment comparisons** | | |
| Tenecteplase vs alteplase | 2 (11) | Gao 2020;[28] Warach 2022[15] |
| IVT vs EVT | 2 (11) | Etges 2022 ;[14] ; Rai 2015[19] |
| IVT vs SoC | 5 (26) | Joo 2016; Kazley 2013;[23] Tan Tanny, 2013;[25] Yan 2015[33] |
| IVT vs IVT + EVT | 5 (26) | Campbell 2017;[27] Kabore 2021;[34] NICE 2012;[24] Sevick 2021;[30] Shireman 2017;[31] Simpson 2017[32] |



| | | |
|---|---|---|
| IVT + EVT vs EVT | 1 (5) | Ma 2023[29] |
| IVT | 2 (11) | Anjos 2023;[22] Rai 2016[20] |
| IVT vs EVT vs IVT + EVT | 2 (11) | Nagaraja 2021;[26] Sonig 2016[21] |
| **Key:** EVT, endovascular treatment; IVT, intravenous thrombolysis; NA, not applicable; RCT, randomized controlled trial; SoC, standard of care. | | |

#### *G.3.2.2.1. Hospitalization*

Hospitalization data was reported in three studies (Table 15). No significant difference was reported in rehospitalization days or readmissions between patients treated with IVT alone and patients treated with IVT prior to EVT.[30, 31] Similarly, no significant difference in the number of rehospitalization days was reported in patients treated with IVT prior to EVT or EVT alone.[29]

#### *G.3.2.2.2. LOS*

LOS data was reported in 14 studies (Table 16). Two studies reported that patients treated with IVT alone stayed in hospital for fewer days compared with patients treated with SoC.[18, 33] Another study reported that patients with AIS with LVO spent longer in hospital than patients with non-LVO AIS.[20] No other studies reported significant differences in LOS between treatment arms; populations and study designs were too heterogenous to assess trends in LOS between treatments.

#### *G.3.2.2.3. Discharge destination*

Discharge destination was reported in seven studies (Table 17). One study found that patients treated with IVT alone compared with SoC were more likely to be discharged home than to a rehabilitation facility.[18] Another study found that patients who were directly admitted were significantly more likely to be discharged home than patients who were transferred in from another facility, regardless of treatment received.[21] No other studies reported significant differences in discharge destination after treatment for AIS.

#### *G.3.2.2.4. Outpatient*

Outpatient HCRU data was reported in two studies, both of which compared IVT alone with IVT prior to EVT (Table 18). Neither study reported a significant difference in emergency room visits, physician visits, outpatient rehabilitation, or ambulatory care visits between the two groups.[30, 31]

**Table 15: Hospitalization data reported in included HCRU studies**

| Author, year, country | Study arm | Subgroup | Description | Unit of HCRU | Time point | HCRU measure, mean (SD) | p-value |
|---|---|---|---|---|---|---|---|
| **IVT vs IVT + EVT** | | | | | | | |
| Shireman, 2017[31]<br><br>US | tPA + SST (98) | NA | Rehospitalization | Days | ≤ 90 days post-stroke | 0.2 (0.5) | 0.92 |
| | tPA (92) | | Rehospitalization | Days | ≤ 90 days post-stroke | 0.2 (0.5) | |
| Sevick, 2021[30]<br><br>US | Alteplase + EVT (52) | mRS 0–2 | Readmissions | Per patient | ≤ 90 days post-stroke | 0.2 (0.4) | NR |
| | | mRS 3–5 | Readmissions | Per patient | ≤ 90 days post-stroke | 0.4 (0.7) | NR |
| | | mRS 6 | Readmissions | Per patient | ≤ 90 days post-stroke | 1.0 (1.4) | NR |
| | Alteplase (47) | mRS 0–2 | Readmissions | Per patient | ≤ 90 days post-stroke | 0.3 (0.5) | NR |
| | | mRS 3–5 | Readmissions | Per patient | ≤ 90 days post-stroke | 0.2 (0.5) | NR |
| | | mRS 6 | Readmissions | Per patient | ≤ 90 days post-stroke | 0.5 (0.6) | NR |
| **IVT + EVT vs EVT** | | | | | | | |
| Ma, 2023[29]<br>China | Alteplase + MT (328) | NA | Rehospitalization | Days | ≤ 90 days post-stroke | 0.8 (0.4) | 0.47 |
| | MT (326) | | Rehospitalization | Days | ≤ 90 days post-stroke | 1.1 (0.4) | |

**Key:** EVT, endovascular treatment; HCRU, healthcare resource use; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NA, not applicable; SD, standard deviation; SST, stent-retriever thrombectomy.; tPA, tissue plasminogen activator

**Table 16: LOS data reported in included HCRU studies**

| Author, year, country | Study arm (n) | Subgroup | Description | Unit of HCRU | Time point | Patients with HCRU measure, n (%) | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Tenecteplase vs alteplase** | | | | | | | | |
| Gao, 2020[28] Australia | Tenecteplase (101) | NA | Duration of acute hospitalization | Days | NA | NR | Median (IQR): 6.0 (3.0–11.0) | 0.79 |
| | Alteplase (101) | | Duration of acute hospitalization | Days | NA | NR | Median (IQR): 6.0 (3.0–10.1) | |
| Warach, 2022[15] US | Alteplase (354) | NA | LOS | Days | Index hospitalization | NA | Median (IQR): 4.0 (2.6–7.1) | 0.38 |
| | Tenecteplase (234) | | LOS | Days | Index hospitalization | NA | Median (IQR): 4.4 (2.9–6.9) | |
| **IVT vs SoC** | | | | | | | | |
| Yan, 2015[33] China | SoC (73) | NA | LOS | Days | Index hospitalization | NR | 18.4 (8.4) | 0.04 |
| | Alteplase (69) | | LOS | Days | Index hospitalization | NR | 14.5 (8.0) | |
| Kazley, 2013[23] US | tPA (NA) | NA | Hospital days | Days | 6 years post-stroke | NA | 10.9 (NR) | NR |
| | Placebo (NA) | | Hospital days | Days | 6 years post-stroke | NA | 12.4 (NR) | NR |
| Joo, 2016[18] US | No tPA (36,603) | NA | LOS, < 2 days | NA | Index hospitalization | 6,296 (17) | NA | < 0.01 |
| | tPA (2,546) | | LOS, < 2 days | NA | Index hospitalization | 191 (8) | NA | |
| | No tPA (36,603) | | LOS, 2–4 days | NA | Index hospitalization | 20,278 (55) | NA | 0.44 |

| Author, year, country | Study arm (n) | Subgroup | Description | Unit of HCRU | Time point | Patients with HCRU measure, n (%) | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| | tPA (2,546) | | LOS, 2–4 days | NA | Index hospitalization | 1,433 (56) | NA | |
| | No tPA (36,603) | | LOS, ≥ 5 days | NA | Index hospitalization | 10,029 (27) | NA | < 0.01 |
| | tPA (2,546) | | LOS, ≥ 5 days | NA | Index hospitalization | 922 (36) | NA | |
| | No tPA (36,603) | | LOS | Days | Index hospitalization | NA | 4.1 (NR) | < 0.01 |
| | tPA (2,546) | | LOS | Days | Index hospitalization | NA | 4.6 (NR) | |
| **IVT vs EVT** | | | | | | | | |
| Etges, 2022[14] Brazil | tPA (176) | NA | ER LOS | Days | Index hospitalization | NA | 1.3 (NR) | NR |
| | | | Hemodynamic LOS | Days | Index hospitalization | NA | 0.1 (NR) | NR |
| | | | ICU LOS | Days | Index hospitalization | NA | 3.8 (NR) | NR |
| | | | Stroke unit LOS | Days | Index hospitalization | NA | 7.2 (NR) | NR |
| | | | Ward LOS | Days | Index hospitalization | NA | 4.4 (NR) | NR |
| | | | Total LOS | Days | Index hospitalization | NA | 16.8 (NR) | NR |
| | EVT (73) | | ER LOS | Days | Index hospitalization | NA | 1.0 (NR) | NR |
| | | | Hemodynamic LOS | Days | Index hospitalization | NA | 0.09 (NR) | NR |
| | | | ICU LOS | Days | Index hospitalization | NA | 15.6 (NR) | NR |
| | | | Stroke unit LOS | Days | Index hospitalization | NA | 8.0 (NR) | NR |
| | | | Ward LOS | Days | Index hospitalization | NA | 7.0 (NR) | NR |
| | | | Total LOS | Days | Index hospitalization | NA | 31.7 (NR) | NR |
| Rai, 2015[19] | EVT (141) | | LOS | Days | Index hospitalization | NA | 7.4 (8.0) | NR |

| Author, year, country | Study arm (n) | Subgroup | Description | Unit of HCRU | Time point | Patients with HCRU measure, n (%) | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| US | Alteplase (124) | Died in hospital | LOS | Days | Index hospitalization | NA | 5.3 (5.0) | NR |
| | EVT (141) | Survived in hospital | LOS | Days | Index hospitalization | NA | 8.9 (6.8) | NR |
| | Alteplase (124) | | LOS | Days | Index hospitalization | NA | 8.0 (7.0) | NR |
| | EVT (141) | mRS 0–2 | LOS | Days | Index hospitalization | NA | 6.9 (6.0) | NR |
| | Alteplase (124) | | LOS | Days | Index hospitalization | NA | 5.0 (2.6) | NR |
| | EVT (141) | mRS > 2 | LOS | Days | Index hospitalization | NA | 9.6 (8.0) | NR |
| | Alteplase (124) | | LOS | Days | Index hospitalization | NA | 8.6 (8.0) | NR |
| | EVT (141) | NA | LOS | Days | Index hospitalization | NA | 8.5 (7.2) | NR |
| | Alteplase (124) | | LOS | Days | Index hospitalization | NA | 7.4 (6.8) | NR |
| **IVT vs IVT + EVT** | | | | | | | | |
| Campbell, 2017[27] Australia | Alteplase + EVT (35) | NA | Acute stroke unit LOS | Days | ≤ 90 days post-stroke | NR | 8.0 (NR) | NR |
| | Alteplase only (35) | | Acute stroke unit LOS | Days | ≤ 90 days post-stroke | NR | 12.0 (NR) | NR |
| | Alteplase + EVT (35) | | Intensive care utilization | Hours | ≤ 90 days post-stroke | NR | 9.0 (NR) | NR |
| | Alteplase only (35) | | Intensive care utilization | Hours | ≤ 90 days post-stroke | NR | 11.0 (NR) | NR |
| | Alteplase + EVT (35) | | Rehabilitation LOS | Days | ≤ 90 days post-stroke | NR | 14.0 (NR) | NR |

| Author, year, country | Study arm (n) | Subgroup | Description | Unit of HCRU | Time point | Patients with HCRU measure, n (%) | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| | Alteplase only (35) | | Rehabilitation LOS | Days | ≤ 90 days post-stroke | NR | 33.0 (NR) | NR |
| Sevick, 2021[30] US | Alteplase + EVT (52) | mRS 0–2 | Readmission LOS | Days | ≤ 90 days post-stroke | NR | 14.3 (13.9) | NR |
| | | mRS 3–5 | Readmission LOS | Days | ≤ 90 days post-stroke | NR | 39.0 (25.7) | NR |
| | | mRS 6 | Readmission LOS | Days | ≤ 90 days post-stroke | NR | 6.0 (2.8) | NR |
| | Alteplase (47) | mRS 0–2 | Readmission LOS | Days | ≤ 90 days post-stroke | NR | 40.3 (46.1) | NR |
| | | mRS 3–5 | Readmission LOS | Days | ≤ 90 days post-stroke | NR | 46.5 (56.1) | NR |
| | | mRS 6 | Readmission LOS | Days | ≤ 90 days post-stroke | NR | 3.0 (1.41) | NR |
| Shireman, 2017[31] US | tPA + SST (98) | NA | LOS | Days | Index hospitalization | 9 (NR) | 6.3 (NR) | 0.88 |
| | tPA (92) | | LOS | Days | Index hospitalization | 9 (NR) | 6.0 (NR) | |
| | tPA + SST (98) | | ICU LOS | Days | Index hospitalization | 4 (NR) | 3.9 (NR) | 0.94 |
| | tPA (92) | | ICU LOS | Days | Index hospitalization | 4.0 (NR) | 4.5 (NR) | |
| **Other** | | | | | | | | |
| Anjos, 2023[22] Brazil | Very early mobilization (51) | NA | LOS | Days | Index hospitalization | NA | Median (IQR): 6.0 (4.0–7.0) | 0.69 |

| Author, year, country | Study arm (n) | Subgroup | Description | Unit of HCRU | Time point | Patients with HCRU measure, n (%) | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| | Usual care after alteplase (53) | | LOS | Days | Index hospitalization | NA | Median (IQR): 5.0 (4.0–8.0) | |
| Nagaraja, 2021[26] US | tPA (2,275) | NA | Prolonged LOS | Days | Index hospitalization | 134 (6) | Median (IQR): 2.0 (1.0–4.0) | < 0.01 |
| | | | Prolonged LOS | Days | Index hospitalization | 180 (8) | Median (IQR): 3.0 (2.0–5.0) | < 0.01 |
| | | | Prolonged LOS | Days | Index hospitalization | 239 (11) | Median (IQR): 4.0 (2.0–6.0) | < 0.01 |
| | MT (590) | | Prolonged LOS | Days | Index hospitalization | 150 (25) | Median (IQR): 6.0 (3.0–9.0) | < 0.01 |
| | | | Prolonged LOS | Days | Index hospitalization | 175 (30) | Median (IQR): 6.0 (3.0–10.0) | < 0.01 |
| | | | Prolonged LOS | Days | Index hospitalization | 150 (26) | Median (IQR): 6.0 (3.0–9.0) | < 0.01 |
| | tPA + MT (165) | | Prolonged LOS | Days | Index hospitalization | 65 (39) | Median (IQR): 6.0 (3.0–11.0) | < 0.01 |
| | | | Prolonged LOS | Days | Index hospitalization | 39 (24) | Median (IQR): 5.0 (3.0–9.0) | < 0.01 |

| Author, year, country | Study arm (n) | Subgroup | Description | Unit of HCRU | Time point | Patients with HCRU measure, n (%) | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| | | | Prolonged LOS | Days | Index hospitalization | 40 (24) | Median (IQR): 5.0 (3.0–9.0) | < 0.01 |
| Rai, 2016[20]<br><br>US | Alteplase (223) | AIS with LVO | Admission duration | Days | Index hospitalization | NA | 7.5 (6.9) | < 0.01 |
| | | AIS without LVO | Admission duration | Days | Index hospitalization | NA | 4.9 (4.2) | |
| | | AIS with LVO | LOS for patients who survived the admission | Days | Index hospitalization | NA | 8.3 (7.0) | < 0.01 |
| | | AIS without LVO | LOS for patients who survived the admission | Days | Index hospitalization | NA | 4.5 (3.7) | |
| Sonig, 2016[21]<br>US | tPA, EVT, and tPA + EVT | NA | Patients in the direct admission cohort | Days | Index hospitalization | 6 (NR) | 5.9 (NR) | NR |
| | | | Patient in the transfer cohort | Days | Index hospitalization | 7 (NR) | 6.0 (NR) | NR |

**Key:** ER, emergency room; EVT, endovascular treatment; HCRU, healthcare resource use; ICU, intensive care unit; IQR, interquartile range; IVT, intravenous thrombolysis; LOS, length of stay; LVO, large vessel occlusion; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NA, not applicable; SD, standard deviation; SST, stent-retriever thrombectomy; tPA, tissue plasminogen activator.

**Table 17: Discharge destination data reported in included HCRU studies**

| Author, year, country | Study arm (n) | Subgroup | Description | Patients with HCRU measure, n (%) | p-value |
|---|---|---|---|---|---|
| **Tenecteplase vs alteplase** | | | | | |
| Gao, 2020[28] Australia | Tenecteplase (101) | NA | Discharged from hospital to home | 38 (38) | 0.57 |
| | Alteplase (101) | | Discharged from hospital to home | 32 (32) | |
| | Tenecteplase (101) | | Discharged via fast-stream inpatient rehabilitation | 9 (9) | 0.57 |
| | Alteplase (101) | | Discharged via fast-stream inpatient rehabilitation | 8 (8) | |
| | Tenecteplase (101) | | Discharged via slow-stream inpatient rehabilitation | 37 (37) | 0.57 |
| | Alteplase (101) | | Discharged via slow-stream inpatient rehabilitation | 32 (32) | |
| | Tenecteplase (101) | | Discharged to low-level care (hostel) | 6 (6) | 0.57 |
| | Alteplase (101) | | Discharged to low-level care (hostel) | 10 (10) | |
| | Tenecteplase (101) | | Discharged to nursing home/transitional care | 2 (2) | 0.57 |
| | Alteplase (101) | | Discharged to nursing home/transitional care | 2 (2) | |
| | Tenecteplase (101) | | Discharged to palliative care | 2 (2) | 0.57 |
| | Alteplase (101) | | Discharged to palliative care | 6 (6) | |
| | Tenecteplase (101) | | Discharged to other location | 7 (7) | 0.57 |
| | Alteplase (101) | | Discharged to other location | 11 (11) | |

| Author, year, country | Study arm (n) | Subgroup | Description | Patients with HCRU measure, n (%) | p-value |
|---|---|---|---|---|---|
| **IVT vs SoC** | | | | | |
| Joo, 2016[18] US | No tPA (36,603) | NA | Discharged home | NR (76) | < 0.01 |
| | tPA (2,546) | | Discharged home | NR (67) | |
| | No tPA (36,603) | | Discharged to rehabilitation facility | NR (14) | < 0.01 |
| | tPA (2,546) | | Discharged to rehabilitation facility | NR (21) | |
| | No tPA (36,603) | | Discharged to short-term hospital/skilled nursing facility/other† | NR (9) | 0.29 |
| | tPA (2,546) | | Discharged to short-term hospital/skilled-nursing facility/other† | NR (9) | |
| | No tPA (36,603) | | Died | NR (2) | < 0.01 |
| | tPA (2,546) | | Died | NR (3) | |
| Kazley, 2013[23] US | tPA (NA) | NA | Discharged home | NR (46) | NR |
| | Placebo (NA) | | Discharged home | NR (36) | NR |
| | tPA (NA) | | Rehabilitation to nursing home | NR (18) | NR |
| | Placebo (NA) | | Rehabilitation to nursing home | NR (18) | NR |
| NICE, 2012[24] UK | Alteplase, SoC (NA) | Mild stroke | Proportion discharged home | NR (100) | NR |
| | | Moderate stroke | Proportion discharged home | NR (96) | NR |
| | | | Proportion discharged to an institution | NR (1) | NR |
| | | Severe stroke | Proportion discharged home | NR (73) | NR |
| | | | Proportion discharged to an institution | NR (17) | NR |
| **IVT vs IVT + EVT** | | | | | |
| Simpson, 2017[32] US | tPA + EVT (NR) | NA | Rehabilitation hospital | NR (43) | NR |
| | | | Home | NR (30) | NR |
| | | | Nursing home | NR (6) | NR |

| Author, year, country | Study arm (n) | Subgroup | Description | Patients with HCRU measure, n (%) | p-value |
|---|---|---|---|---|---|
| | tPA (NR) | | Rehabilitation hospital | NR (45) | NR |
| | | | Home | NR (27) | NR |
| | | | Nursing home | NR (9) | NR |
| **Other** | | | | | |
| Tan Tanny, 2013[25] Australia | tPA (378) | NA | Independent at home | 16 (4) | NR |
| | | | Home with relatives | 60 (16) | NR |
| | | | Home with community support | 44 (12) | NR |
| | | | Inpatient rehabilitation | 119 (32) | NR |
| | | | Geriatric evaluation and management unit | 69 (18) | NR |
| | | | Palliative | 9 (2) | NR |
| | | | Death | 51 (13) | NR |
| | | | Other | 8 (2) | NR |
| | | | Unknown | 2 (1) | NR |
| Nagaraja, 2021[26] US | tPA (2,275) | 18–45 years | Discharge to home | 1,561 (69) | NR |
| | | 46–80 years | Discharge to home | 1,108 (49) | NR |
| | | > 80 years | Discharge to home | 382 (17) | NR |
| | MT (590) | 18–45 years | Discharge to home | 250 (42) | NR |
| | | 46–80 years | Discharge to home | 129 (22) | NR |
| | | > 80 years | Discharge to home | 35 (6) | NR |
| | tPA + MT (165) | 18–45 years | Discharge to home | 100 (61) | NR |
| | | 46–80 years | Discharge to home | 56 (34) | NR |
| | | > 80 years | Discharge to home | 16 (10) | NR |
| Sonig, 2016[21] US | tPA (48,362) | Direct admissions | OTR discharge disposition‡ | 32,115 (NR) | < 0.01 |
| | | | Discharged home | 14,070 (30) | |

| Author, year, country | Study arm (n) | Subgroup | Description | Patients with HCRU measure, n (%) | p-value |
|---|---|---|---|---|---|
| | | Transferred in from another facility | OTR discharge disposition‡ | 1,754 (NR) | < 0.01 |
| | | | Discharged home | 423 (19) | |
| | tPA + EVT (4,342) | Direct admissions | OTR discharge disposition‡ | 2,895 (NR) | < 0.01 |
| | | | Discharged home | 533 (16) | |
| | | Transferred in from another facility | OTR discharge disposition‡ | 844 (NR) | < 0.01 |
| | | | Discharged home | 70 (8) | |
| | EVT (3,209) | Direct admissions | OTR discharge disposition‡ | 1,657 (NR) | < 0.01 |
| | | | Discharged home | 298 (15) | |
| | | Transferred in from another facility | OTR discharge disposition‡ | 1,126 (NR) | < 0.01 |
| | | | Discharged home | 128 (10) | |
| | tPA, EVT, and tPA + EVT (55,913) | White | OTR discharge disposition‡ | 25,994 (NA) | < 0.01 |
| | | Black | OTR discharge disposition‡ | 11,402 (NA) | < 0.01 |
| | | Hispanic | OTR discharge disposition‡ | 2,001 (NA) | < 0.01 |
| | | Asian or Pacific Islander | OTR discharge disposition‡ | 895 (NA) | < 0.01 |
| | | Native American | OTR discharge disposition‡ | 120 (NA) | < 0.01 |
| | | White | Discharged home | 9,889 (NA) | < 0.01 |
| | | Black | Discharged home | 4,232 (NA) | < 0.01 |
| | | Hispanic | Discharged home | 932 (NA) | < 0.01 |
| | | Asian or Pacific Islander | Discharged home | 353 (NA) | < 0.01 |
| | | Native American | Discharged home | 95 (NA) | < 0.01 |

| Author, year, country | Study arm (n) | Subgroup | Description | Patients with HCRU measure, n (%) | p-value |
|---|---|---|---|---|---|
| **Key:** EVT, endovascular treatment; HCRU, healthcare resource use; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; NA, not applicable; NR, not reported; OTR, other than routine; SoC, standard of care; tPA, tissue plasminogen activator.<br>**Notes**: † Other discharge status included transferring to a federal hospital, critical access hospital, hospice, long-term care facility, and all other discharge status; ‡ OTR discharge dispositions included final outcomes like transfer to a short-term hospital facility, skilled nursing facility, intermediate care, or home health care, transfer against medical advice, and death. | | | | | |

## Table 18: Outpatient data reported in included HCRU studies

| Study identifier | Study arm (n) | Subgroup | Description | Unit of HCRU | Timepoint | Patients with HCRU measure, % | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| **IVT vs IVT + EVT** | | | | | | | | |
| Shireman, 2017[31] US | tPA + SST (98) | NA | ER visit | Visits | ≤ 90 days post-stroke | 9 (9) | 0.1 (0.4) | 0.11 |
| | tPA (92) | | ER visit | Visits | ≤ 90 days post-stroke | 2 (2) | 0.0 (0.2) | |
| | tPA + SST (98) | | Physician visits | Visits | ≤ 90 days post-stroke | 52 (53) | 1.7 (3.9) | 0.56 |
| | tPA (92) | | Physician visits | Visits | ≤ 90 days post-stroke | 40 (44) | 2.0 (5.1) | |
| | tPA + SST (98) | | Outpatient rehabilitation | Visits | ≤ 90 days post-stroke | 18 (18) | 3.5 (10.3) | 0.23 |
| | tPA (92) | | Outpatient rehabilitation | Visits | ≤ 90 days post-stroke | 21 (23) | 6.8 (25.0) | |
| Sevick, 2021[30] | Alteplase + EVT (52) | mRS 0–2 | Ambulatory care visits | Mean | ≤ 90 days post-stroke | NA | 1.0 (1.5) | NR |

| Study identifier | Study arm (n) | Subgroup | Description | Unit of HCRU | Timepoint | Patients with HCRU measure, % | HCRU measure mean (SD) | p-value |
|---|---|---|---|---|---|---|---|---|
| US | | mRS 3–5 | Ambulatory care visits | Mean | ≤ 90 days post-stroke | NA | 1.7 (2.3) | NR |
| | | mRS 6 | Ambulatory care visits | Mean | ≤ 90 days post-stroke | NA | 0.0 (NR) | NR |
| | Alteplase (47) | mRS 0–2 | Ambulatory care visits | Mean | ≤ 90 days post-stroke | NA | 0.7 (1.2) | NR |
| | | mRS 3–5 | Ambulatory care visits | Mean | ≤ 90 days post-stroke | NA | 2.7 (2.5) | NR |
| | | mRS 6 | Ambulatory care visits | Mean | ≤ 90 days post-stroke | NA | 0.0 (0.0) | NR |
| | Alteplase + EVT (52) | NA | Physiatrist consult | Number | ≤ 90 days post-stroke | NA | 49.0 (NR) | NA |
| | Alteplase (47) | | Physiatrist consult | Number | ≤ 90 days post-stroke | NA | 49.0 (NR) | NA |

**Key:** EVT, endovascular treatment; HCRU, healthcare resource use; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NA, not applicable; NR, not reported; SD, standard deviation; SST, stent-retriever thrombectomy.

## *G.4. Discussion*

### G.4.1 Costs and HCRU

The most frequently reported model input costs were the direct healthcare costs of managing AIS in both the acute post-treatment phase and in the long-term. Where these total costs were described in terms of their component resource costs, the costs of each individual resource were not frequently reported. Individual resource costs that were reported included drugs, procedures, consumables, inpatient and outpatient services, adverse event management, and professional costs. Cost data were identified across multiple geographies, and there was a trend that treatment regimens which included EVT were associated with higher costs.

Relatively few non-economic evaluation costing studies were identified by the review. These studies were predominantly conducted in the US and were retrospective analyses of databases of patients with AIS. The most frequently reported comparison was between the cost of IVT and EVT, and there was a general trend that EVT had higher healthcare costs. The evidence of the indirect costs or costs to caregivers of AIS was sparse.

A comparison of the cost of tenecteplase with alteplase was reported in two studies: the previously described economic evaluation published by Gao et al.[28], and a prospective cohort study comparing treatment workflow times in clinical practice.[15] Gao et al. found that costs at 3 months were lower with tenecteplase than with alteplase, although this difference was not deemed to be significant ($p = 0.13$). In Warach et al.[15], tenecteplase was associated with a significantly lower hospital admission cost than alteplase. Cost savings were primarily attributed to differences in pharmacy costs.

HCRU was mainly reported in cost-effectiveness models and within-trial economic analyses and was most often described in terms of hospitalization, LOS and discharge destination. Limited caregiver HCRU data were identified; evidence related to the use of tenecteplase was not frequently reported. Door-to-needle and door-in-door-out times were found to be significantly lower for tenecteplase compared with alteplase. However, this evidence was generated from a stroke

service in a single region where ground transportation was not initiated until alteplase infusion was complete. Similar results associated with tenecteplase may not generalize to regions where the emergency medical system accepts patients with alteplase running.[15]

## *G.5. Conclusion*

This review provides an overview of the economic and humanistic burden of AIS, providing evidence on published costs and HCRU after treatment for AIS. The evidence found in this review will assist in the development of cost-effectiveness models to assess the cost-effectiveness of tenecteplase treatment for AIS across a variety of settings.

## *G.6. Search strategies*

**Table 19: SLR | Economic Outcomes – Ovid MEDLINE (Search date: 25 May 2023)**

| # | Search terms | Number of records |
|---|---|---|
| **Disease terms** | | |
| 1 | ischemic stroke/ | 9427 |
| 2 | (isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion or AIS or LVO).ti,ab,kf. /freq=3 | 35770 |
| 3 | ((isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion) adj4 (time sensitive or time constrain$ or time window or symptom onset or symptom on-set or time$1 to treatment or acute)).ti,ab,kf. | 26335 |
| 4 | or/1-3 | 49465 |
| **Economic terms** | | |
| 5 | Absenteeism/ or Efficiency/ or Caregiver Burden/ or Caregivers/ | 74487 |
| 6 | ((human$ or social$ or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$ or care-giver or psychologic$ or emotional or psychosocial or social) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$ or cost$)).ti,ab,kf. | 235741 |
| 7 | ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab,kf. | 13270 |

| | | |
|---|---|---|
| 8 | ((emergenc$ or domestic$ or famil$ or carer$ or caregiver$ or care-giver$) adj3 leave$).ti,ab,kf. | 1152 |
| 9 | (cost adj2 (illness$ or disease$ or sickness$)).ti,ab,kf. | 4339 |
| 10 | ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,kf. | 2217 |
| 11 | ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention$ or trip or trips or visit$ or stay$ or admission$ or admitted)).ti,ab,kf. | 211821 |
| 12 | ((GP or general practitioner$ or doctor$ or clinician$ or specialist$ or physician$) adj2 (appointment$ or attention$ or trip or trips or visit$)).ti,ab,kf. | 15773 |
| 13 | Cost-Benefit Analysis/ or Health Care Costs/ or Economics, Pharmaceutical/ | 128651 |
| 14 | ((econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$) not (energy or oxygen or metabolic)).ti,ab,kf. /freq=3 | 197972 |
| 15 | or/5-14 | 758919 |
| 16 | 4 and 15 | 2460 |
| **Humanistic terms** | | |
| 17 | Quality-Adjusted Life Years/ or Health Status/ | 104702 |
| 18 | (quality adjusted or adjusted life year$).ti,ab,kf. | 23326 |
| 19 | (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. | 14541 |
| 20 | (illness state$1 or health state$1).ti,ab,kf. | 8347 |
| 21 | (hui or hui1 or hui2 or hui3).ti,ab,kf. | 1966 |
| 22 | (multiattribute$ or multi attribute$).ti,ab,kf. | 1311 |
| 23 | ((utility or disutility) adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. | 20156 |
| 24 | (utilities or disutilities).ti,ab,kf. | 9429 |
| 25 | (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. | 17215 |
| 26 | (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. | 5962 |
| 27 | (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. | 26514 |
| 28 | (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. | 2368 |
| 29 | "quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. | 15541 |
| 30 | "quality of life"/ and ec.fs. | 10875 |
| 31 | "quality of life"/ and (health adj3 status).ti,ab,kf. | 11715 |
| 32 | (qol or hrqol or quality of life).ti,kf. | 116898 |
| 33 | ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. | 132837 |



| | | |
|---|---|---|
| 34 | or/17-33 | 351976 |
| 35 | 4 and 34 | 830 |
| 36 | Patient Reported Outcome Measures/ | 13519 |
| 37 | ((patient$ or self) adj2 (report$ or apprais$) adj2 (rate$ or rating$ or response$ or evaluat$ or outcome$ or assess$ or measure$)).ti,ab,kf. | 85095 |
| 38 | ((function$ or health) adj2 status adj2 report$).ti,ab,kf. | 3306 |
| 39 | (PROM$1 or PRO$1).ti,ab,kf. | 306560 |
| 40 | or/36-39 | 385494 |
| 41 | 4 and 40 | 883 |
| 42 | exp Models, Economic/ | 16219 |
| 43 | Models, Theoretical/ | 162203 |
| 44 | Markov Chains/ | 15982 |
| 45 | Monte Carlo Method/ | 32237 |
| 46 | exp decision theory/ | 13288 |
| 47 | Decision Trees/ | 12099 |
| 48 | ((monte carlo adj2 (simulation$ or method$ or model$ or technique$)) or markov).ti,ab. | 65482 |
| 49 | (econom$ model$ or econom$ evaluat$).ti,ab,kf. | 21613 |
| 50 | (cost effective$ or cost utilit$ or cost minimi$ or cost compar$).ti. | 37239 |
| 51 | (decision$ adj2 (tree$ or analy$ or model$ or theor$ or threshold$)).ti,ab. | 39457 |
| 52 | or/42-51 | 334198 |
| 53 | 4 and 52 | 539 |
| 54 | 16 or 35 or 41 or 53 | 4107 |
| 55 | exp animals/ not exp humans/ | 5134710 |
| 56 | (editorial or letter or comment).pt. | 2170443 |
| 57 | (Hemorrhagic Stroke/ or Ischemic Attack, Transient/) not ischemic stroke/ | 21719 |
| 58 | 54 not (55 or 56 or 57) | 3741 |
| 59 | limit 58 to yr="2013 -Current" | 2961 |
| **Notes:** Humanistic burden filter adapted with additional cost terms from: Clayton S, et al.[35] HRQL filter adapted from: Sutherland CS, et al.[36] Economic models filter adapted from: Vale L, et al.[37] | | |

## Table 20: SLR | Economic Outcomes – Ovid Embase search (Search date: 25 May 2023)

| # | Search terms | Number of records |
|---|---|---|
| Disease terms | | |
| 1 | acute ischemic stroke/ | 8742 |
| 2 | *ischemic stroke/ | 7347 |



| | | |
|---|---|---|
| 3 | (isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion or AIS or LVO).ti,ab,kw. /freq=3 | 57064 |
| 4 | ((isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion) adj4 (time sensitive or time constrain$ or time window or symptom onset or symptom on-set or time$1 to treatment or acute)).ti,ab,kw. | 46641 |
| 5 | or/1-4 | 82498 |
| Economic terms | | |
| 6 | Productivity/ or Absenteeism/ or Caregiver Burden/ or Caregiver/ or Work Disability/ | 191167 |
| 7 | ((human$ or social$ or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$ or care-giver or psychologic$ or emotional or psychosocial or social) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$ or cost$)).ti,ab,kw. | 313106 |
| 8 | ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab,kw. | 18741 |
| 9 | ((emergenc$ or domestic$ or famil$ or carer$ or caregiver$ or care-giver$) adj3 leave$).ti,ab,kw. | 1427 |
| 10 | (cost adj2 (illness$ or disease$ or sickness$)).ti,ab,kw. | 5873 |
| 11 | ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,kw. | 3283 |
| 12 | ((ambulatory or ambulance or hospital or A&E or emergency) adj2 (attention$ or trip or trips or visit$ or stay$ or admission$ or admitted)).ti,ab,kw. | 353876 |
| 13 | ((GP or general practitioner$ or doctor$ or clinician$ or specialist$ or physician$) adj2 (appointment$ or attention$ or trip or trips or visit$)).ti,ab,kw. | 25065 |
| 14 | Health Economics/ or Economic Evaluation/ or Health Care Cost/ or pharmacoeconomics/ | 274530 |
| 15 | ((econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$) not (energy or oxygen or metabolic)).ti,ab,kw. /freq=3 | 278707 |
| 16 | or/6-15 | 1255510 |
| 17 | 5 and 16 | 4755 |
| Humanistic terms | | |
| 18 | Quality-Adjusted Life Year/ or Short Form 36/ or Health Status/ | 219119 |
| 19 | (quality adjusted or adjusted life year$).ti,ab,kw. | 34420 |
| 20 | (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. | 27506 |
| 21 | (illness state$1 or health state$1).ti,ab,kw. | 14733 |
| 22 | (hui or hui1 or hui2 or hui3).ti,ab,kw. | 3108 |
| 23 | (multiattribute$ or multi attribute$).ti,ab,kw. | 1570 |
| 24 | ((utility or disutility) adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. | 31878 |



| | | |
|---|---|---|
| 25 | (utilities or disutilities).ti,ab,kw. | 15407 |
| 26 | (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. | 31407 |
| 27 | (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. | 9088 |
| 28 | (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. | 46042 |
| 29 | (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. | 3553 |
| 30 | "quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw. | 33403 |
| 31 | "quality of life"/ and ec.fs. | 59537 |
| 32 | "quality of life"/ and (health adj3 status).ti,ab,kw. | 20215 |
| 33 | (qol or hrqol or quality of life).ti,kw. | 178415 |
| 34 | ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. | 224240 |
| 35 | or/18-34 | 611583 |
| 36 | 5 and 35 | 1559 |
| 37 | patient-reported outcome/ | 54203 |
| 38 | ((patient$ or self) adj2 (report$ or apprais$) adj2 (rate$ or rating$ or response$ or evaluat$ or outcome$ or assess$ or measure$)).ti,ab,kw. | 120958 |
| 39 | ((function$ or health) adj2 status adj2 report$).ti,ab,kw. | 4446 |
| 40 | (PROM$1 or PRO$1).ti,ab,kw. | 457323 |
| 41 | or/37-40 | 573808 |
| 42 | 5 and 41 | 1425 |
| 43 | exp economic model/ | 3773 |
| 44 | theoretical model/ | 89969 |
| 45 | nonbiological model/ | 48463 |
| 46 | markov chain/ | 10352 |
| 47 | monte carlo method/ | 51068 |
| 48 | exp decision theory/ | 1849 |
| 49 | decision tree/ | 21800 |
| 50 | ((monte carlo adj2 (simulation$ or method$ or model$ or technique$)) or markov).ti,ab. | 75178 |
| 51 | (econom$ model$ or econom$ evaluat$).ti,ab. | 28812 |
| 52 | (cost effective$ or cost utilit$ or cost minimi$ or cost compar$).ti. | 56292 |
| 53 | (decision$ adj2 (tree$ or analy$ or model$ or theor$ or threshold$)).ti,ab. | 53944 |
| 54 | or/43-53 | 346340 |
| 55 | 5 and 54 | 805 |
| 56 | 17 or 36 or 42 or 55 | 7403 |



| | | |
|---|---|---|
| 57 | exp animal/ or exp animal experiment/ or nonhuman/ | 32941068 |
| 58 | (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or animal or pig or pigs or porcine or rabbit or rabbits or animal or animals or dog or dogs or cat or cats or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. | 6947973 |
| 59 | or/57-58 | 33151141 |
| 60 | exp human/ or exp human experiment/ | 25654381 |
| 61 | 59 not (59 and 60) | 7497955 |
| 62 | (editorial or letter or comment or note).pt. | 3038982 |
| 63 | preprint.db. | 75220 |
| 64 | or/62-63 | 3114202 |
| 65 | (brain hemorrhage/ or transient ischemic attack/) not (acute ischemic stroke/ or ischemic stroke/) | 165416 |
| 66 | (conference abstract or conference paper).pt. | 5569471 |
| 67 | 56 not (61 or 64 or 65 or 66) | 3660 |
| 68 | limit 66 to yr="2020 -Current" | 976658 |
| 69 | 56 and 68 | 735 |
| 70 | 67 or 69 | 4395 |
| 71 | limit 70 to yr="2013 -Current" | 3663 |
| **Notes:** Humanistic burden filter adapted with additional cost terms from: Clayton S, et al.[35]; HRQoL filter adapted from: Sutherland CS, et al.[36] Economic models filter adapted from: Vale L, et al.[37] | | |

**Table 21: SLR | Economic Outcomes – Ovid EconLit (Search date: 7 June 2023)**

| # | Search terms | Number of records |
|---|---|---|
| 1 | (isch?emic stroke$ or cryptogenic embolism stroke$ or cryptogenic stroke$ or thrombotic stroke$ or embolic stroke or large vessel occlusion).ti,ab. | 23 |
| 2 | limit 1 to yr="2013 -Current" | 15 |

**Table 22: SLR | Economic Outcomes – INAHTA search (Search date: 7 June 2023)**

| # | Search terms | Number of records |
|---|---|---|
| 1 | (ischemic stroke*" or "ischaemic stroke*" or "cryptogenic embolism stroke*" or "cryptogenic stroke*" or "thrombotic stroke*" or "embolic stroke*" or "large vessel occlusion") OR ("Ischemic Stroke"[mh]) | 82 |
| 2 | 2013-2023 | 40 |



# Appendix H: Price details of treatments included in the submission

## *H.1. Price of intervention and comparator*

Table 23 and Table 24 outline the total acquisition costs for tenecteplase and alteplase, respectively. Acquisition costs apply when treatment is administered, and in line with clinical practice and the previous NICE TA264[24], no vial sharing was assumed in the model base case. Therefore, the cost calculation used in the model calculated the number of vials used per administration multiplied by the acquisition costs. The average patient weight used to inform dosing calculations was obtained from Health Survey England 2021 and Sentinel Stroke National Audit Programme 2023 and reflected the average weight of patients with stroke in the UK, consistent with findings from the Act trial. For tenecteplase, the mean required dose per patients is 19.7 mg, requiring one vial of tenecteplase at a cost of [redacted] Further details on treatment with alteplase, is provided in Appendix H.2.

**Table 23: Tenecteplase acquisition costs**

| Name | Form | Vial size (mg) | Acquisition price | Dose (mg/kg) | Mean dose (mg) | Num. of vials | Cost | Source |
|---|---|---|---|---|---|---|---|---|
| Tenecteplase | Injection | 25 | [redacted] | 0.25 | 19.73 | 1 | [redacted] | List price |

**Table 24: Alteplase acquisition costs**

| Name | Form | Vial size (mg) | Acquisition price | Dose (mg/kg) | Mean dose (mg) | Cost | Source |
|---|---|---|---|---|---|---|---|
| Alteplase (used in initial injection) | Injection | 10 | £172.80 | 0.9 | 7.10 | £172.80 | BNF[38] |
| Alteplase (remainder of dosage over 1 hour) | Injection | 10 | £172.80 | 0.81 | 63.93 | £694.92 | BNF[38] |
| | Injection | 20 | £259.20 | | | | BNF[38] |
| | Infusion | 50 | £432.00 | | | | BNF[38] |
| | | | | | **Total cost** | £867.72 | |

## *H.2. Alteplase subsequent cost calculation*

For alteplase, calculations consider patient distributions across dosing options and treatment regimens when multiple options are available. The method used in the model calculated the number of vials used per administration based on each dose band, with weight assumed to be normally distributed. Alteplase requires an initial administration of 0.09 mg/kg and a subsequent administration of 0.81 mg/kg. For initial injection, a 10 mg dose option was assumed to always be used. Therefore, for the remaining injection, the maximum dose was 80 mg. Calculated weight distributions and associated pack needs for alteplase are presented in Table 25. This gives a combined total cost of £867.72 for alteplase.

**Table 25: Alteplase subsequent administration pack needs**

| Weight (kg, up to) | Dose | Vial costs | | | Weight dist. | Cost |
|---|---|---|---|---|---|---|
| | | *£172.80* | *£259.20* | *£432.00* | | |
| | | Vial size | | | | |

| | | 10 | 20 | 50 | | |
|---|---|---|---|---|---|---|
| 12.3 | 10 | 1 | 0 | 0 | 0.00% | £0.00 |
| 24.7 | 20 | 0 | 1 | 0 | 0.00% | £0.00 |
| 37.0 | 30 | 0 | 0 | 1 | 0.00% | £0.00 |
| 49.4 | 40 | 0 | 0 | 1 | 0.01% | £0.04 |
| 61.7 | 50 | 0 | 0 | 1 | 1.46% | £6.30 |
| 74.1 | 60 | 1 | 0 | 1 | 25.49% | £154.15 |
| 86.4 | 70 | 0 | 1 | 1 | 55.94% | £386.68 |
| 98.8 | 80 | 0 | 0 | 2 | 17.10% | £147.76 |
| Total | | | | | | £694.92 |
| Note: Dose given at (mg/kg): 0.81. Max dose (mg): 80. | | | | | | |

# Appendix I: Checklist of confidential information

This is submitted as a separate document.



# Appendix J: Further information on clinical guidelines

The following information expands on the guidelines outlined in Table 3 of Document B.

## *J.1. 2019 NICE Guideline on the treatment of stroke and transient ischaemic attack (NG5128)*

Take into account the person's overall clinical status and the extent of established infarction on initial brain imaging to inform decisions about thrombectomy. Select people who have:

- A pre-stroke functional status of less than 3 on the modified Rankin scale, and
- A score of more than 5 on the NIHSS

In May 2019, not all devices with a CE mark for thrombectomy were intended by the manufacturer for use as recommended here. The healthcare professional should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. Medicines and Healthcare products Regulatory Agency (MHRA) advice remains to use CE-marked devices for their intended purpose where possible. See MHRA's guidance on off-label use of a medical device for further information.

## *J.2. 2023 National Clinical Guideline for Stroke for the UK and Ireland*

Table 26 explains the eligibility criteria for extending the period of thrombolysis with alteplase from stroke onset or wake-up stroke.

**Table 26: 2023 National Clinical Guideline for Stroke for the UK and Ireland Eligibility criteria for extending thrombolysis with alteplase to 4.5–9 hours and wake-up stroke**

| | Time window | Imaging | Imaging criteria |
|---|---|---|---|
| Wake-up stroke | >4.5 hours from last seen well, no upper limit | MRI DWI-FLAIR mismatch | DWI lesion and no FLAIR lesion |
| Wake-up stroke or unknown onset time | >4.5 hours from last seen well, and within 9 hours of the midpoint of sleep. The midpoint of sleep is the time halfway between going to bed and waking up | CT or MRI core-perfusion mismatch | Suggested: mismatch ratio greater than 1.2, a mismatch volume greater than 10 mL, and an ischaemic core volume <70 mL |
| Known onset time | 4.5-9 hours | CT or MRI core-perfusion mismatch | Suggested: mismatch ratio greater than 1.2, a mismatch volume greater than 10 mL, and an ischaemic core volume <70 mL |

**Key:** CT, computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.
**Source:** 2023 National Clinical Guideline for Stroke for the UK and Ireland.[39]

# Appendix K: Further presentation of information from AcT and EXTEND-IA TNK Part 1

## *K.1. Summary of AcT and EXTEND-IA TNK Part 1*

Table 27 presents a summary of the trial methodology of AcT and EXTEND-IA TNK Part 1.

**Table 27: Summary of AcT and EXTEND-IA TNK Part 1 methodology**

| Trial Name | AcT (NCT03889249) | EXTEND-IA TNK Part 1 (NCT02388061) |
|---|---|---|
| Trial design | Phase III, multicentre, open-label, parallel-group, registry-linked, RCT | Phase II, prospective, multicentre, randomized open-label, blinded endpoint (PROBE) design trial |
| Location | 22 primary and CSCs in Canada | 12 sites across Australia and one site in New Zealand |
| Key eligibility criteria for patients | **Inclusion Criteria:**<br>Inclusion criteria was pragmatic and informed by Canadian Best Practices<br>• All patients with AIS eligible to receive intravenous alteplase as per standard care will be eligible for enrolment in the proposed trial<br>• Patients eligible for endovascular thrombectomy in addition to intravenous thrombolysis are eligible for enrolment<br>**Exclusion Criteria:**<br>• Contraindications to intravenous thrombolysis as used by treating physicians as current standard of care apply<br>• The benefits of thrombolysis with intravenous alteplase in the paediatric population is unknown. Therefore, any patient < 18 years of age may not be enrolled<br>• Women with pregnancy known to the investigator by history or examination, without requiring pregnancy testing, may only be | **Inclusion criteria:**<br>• Patients ≥18 years, presenting with acute ischaemic stroke eligible using standard criteria to receive IV thrombolysis within 4.5 hours of stroke onset<br>• Patient, family member or legally responsible person depending on local ethics requirements has given informed consent<br>• Endovascular thrombectomy can commence (groin puncture) within 6 hours of stroke onset<br>**Imaging inclusion criteria:**<br>• Arterial occlusion on CTA or MRA of the ICA, basilar, M1 or M2<br>• Mismatch **criterion removed in protocol v3 12-10-16 after approximately 80 patients enrolled**- Using CT perfusion imaging or MR perfusion imaging or DWI with a $T_{max}$ > 6 second delay perfusion volume and either CTrCBF or DWI ischaemic core volume (not applicable to patients with basilar artery occlusion) |



| | | |
|---|---|---|
| | enrolled in consultation with an expert stroke physician (either in person or through telestroke) | – Mismatch ratio > 1.2<br>– Absolute mismatch volume > 10 ml<br>– Ischaemic core lesion volume < 70 ml<br>**Exclusion criteria:**<br>• ICH identified by CT or MRI<br>• Rapidly improving symptoms at the discretion of the investigator<br>• Pre-stroke mRS score of ≥ 4 (indicating major previous disability)<br>• Hypodensity in > 1/3 MCA territory or equivalent proportion of basilar artery territory on non-contrast CT<br>• Contraindication to imaging with contrast agents<br>• Any terminal illness such that the patient would not be expected to survive more than 1 year<br>• Any condition that, in the judgment of the investigator, could impose hazards to the patient if study therapy is initiated, or affect the participation of the patient in the study<br>• Pregnant women |
| Settings and locations where the data were collected | A total of 1,600 patients were enrolled and treated at 22 stroke centres across Canada | A total of 202 patients were enrolled and treated at one of the 13 trial sites in Australia and New Zealand |
| Trial drugs | **Investigational arm: Tenecteplase**<br>Patients received a single bolus injection of tenecteplase at 0.25 mg/kg of body weight (maximum 25 mg)<br>**Standard of care arm: Alteplase**<br>Patients received a 0.09 mg/kg bolus injection of alteplase followed by a 60 minute infusion of the remaining 0.81 mg/kg of alteplase (maximum 90 mg) | **Investigational arm: Tenecteplase**<br>Patients received a single 10 second bolus injection of tenecteplase at 0.25 mg/kg of body weight (maximum 25 mg)<br>**Standard of care arm: Alteplase**<br>Patients received alteplase at 0.9 mg/kg of body weight (maximum 90 mg) |
| Permitted and disallowed | Standards of care per CSBPR applicable to any patient receiving | No anticoagulants or antiplatelet agents were to be given within 24 |



| | | |
|---|---|---|
| concomitant medication | intravenous alteplase apply to patients in both arms of the trial. No medications were prohibited except those considered as such based on best practices. There were no additional trial-specific management recommendations | hours of administration of the investigational product |
| Primary endpoints | Proportion of patients with a 90–120 day mRS score of 0–1 | Angiographic reperfusion (mTICI) at baseline angiogram |
| Other outcomes used in the economic model/specified in the scope | • Actual 90–120 day mRS score<br>• 90–120 day mRS score of 0–2<br>• Return to baseline level of functioning at 90–120 days<br>• EQ-5D-5L at 90–120 days<br>• EQ-VAS at 90–120 days<br>• Discharge destination (home, early supported discharge, rehabilitation facility, long-term care, death)<br>• Door-to-needle time<br>• DIDO times at PSCs<br>• Proportion of patients administered EVT<br>• Home time (defined as number of days subject spends at home after index stroke event)<br>• Cognition assessed via a brief, online cognitive assessment tool (feasibility sub-study only)<br>• All-cause mortality (death) at 90 days (and overall)<br>• Symptomatic ICH post-acute stroke treatment by CT/MRI (Time Frame: 24 hours days from Baseline-[Randomization]); AcT defines symptomatic ICH as intracerebral haemorrhage that, in the opinion of the investigator, is temporally related to and directly responsible for worsening of the neurological condition | • NIHSS at 24 hours and 3 days<br>• mRS at 3 months<br>• mRS 0–1 or no change from baseline at 3 months<br>• mRS 0–2 or no change from baseline at 3 months<br>• Symptomatic intracranial haemorrhage<br>• Mortality within 90 days |
| Other outcomes of interest | • Recanalization status (mTICI score) at first angiographic acquisition in patients taken to the angio suite for the purpose of administering EVT | • MR Perfusion (or CT Perfusion) - Reperfusion at 24hrs<br>• MRA (or CTA) - Recanalization at 24hrs DWI |



| | | |
|---|---|---|
| | • Door-to-groin puncture time in patients undergoing EVT<br>• CT-to-puncture time in patients undergoing EVT | • Ischaemic core volume at 24hrs |
| Pre-planned subgroups | • Age (< 80 vs 80+ years)<br>• Sex (male vs female)<br>• Baseline stroke severity (NIHSS score of < 8 vs 8–15 vs > 15)<br>• Symptom onset-to-needle time (≤ 180 vs > 180 min)<br>• Large vessel occlusion (no vs yes) defined as ICA, M1 segment MCA occlusion, or functional M1 MCA occlusion (i.e. all ipsilateral M2-MCA segments) on baseline CT angiography scan<br>• Type of enrolling centre (CSC vs PSC),Source registry (OPTIMISE vs QuiCR) | Not applicable |

**Key**: AIS, acute ischaemic stroke; CSBPR, Canadian Stroke Best Practices; CSC, comprehensive stroke centre; CT, computed tomography; CTA, computed tomography angiography; DIDO, door-in-door-out; DWI, diffusion-weighted imaging; EVT, endovascular thrombectomy; ICA, internal carotid artery; ICH, intracranial haemorrhage; IV, intravenous; MCA, middle cerebral artery; MR, magnetic resonance; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale score; mTICI, modified treatment in cerebral ischaemia; NIHSS, National Institutes of Health Stroke Scale; OPTIMISE, Optimizing Patient Treatment in Major Ischemic Stroke with EVT; PSC, primary stroke centre; QuiCR, Quality Improvement and Clinical Research; RCT, randomized controlled trial.
**Source**: Clinicaltrials.gov (NCT02388061)[7]; EXTEND-IA TNK Part 1 CSR[40]; Campbell et al. 2018[5]; Menon et al. 2022[4]; AcT CSR Revision 1[8]; Clinicaltrials.gov (NCT03889249).[6]

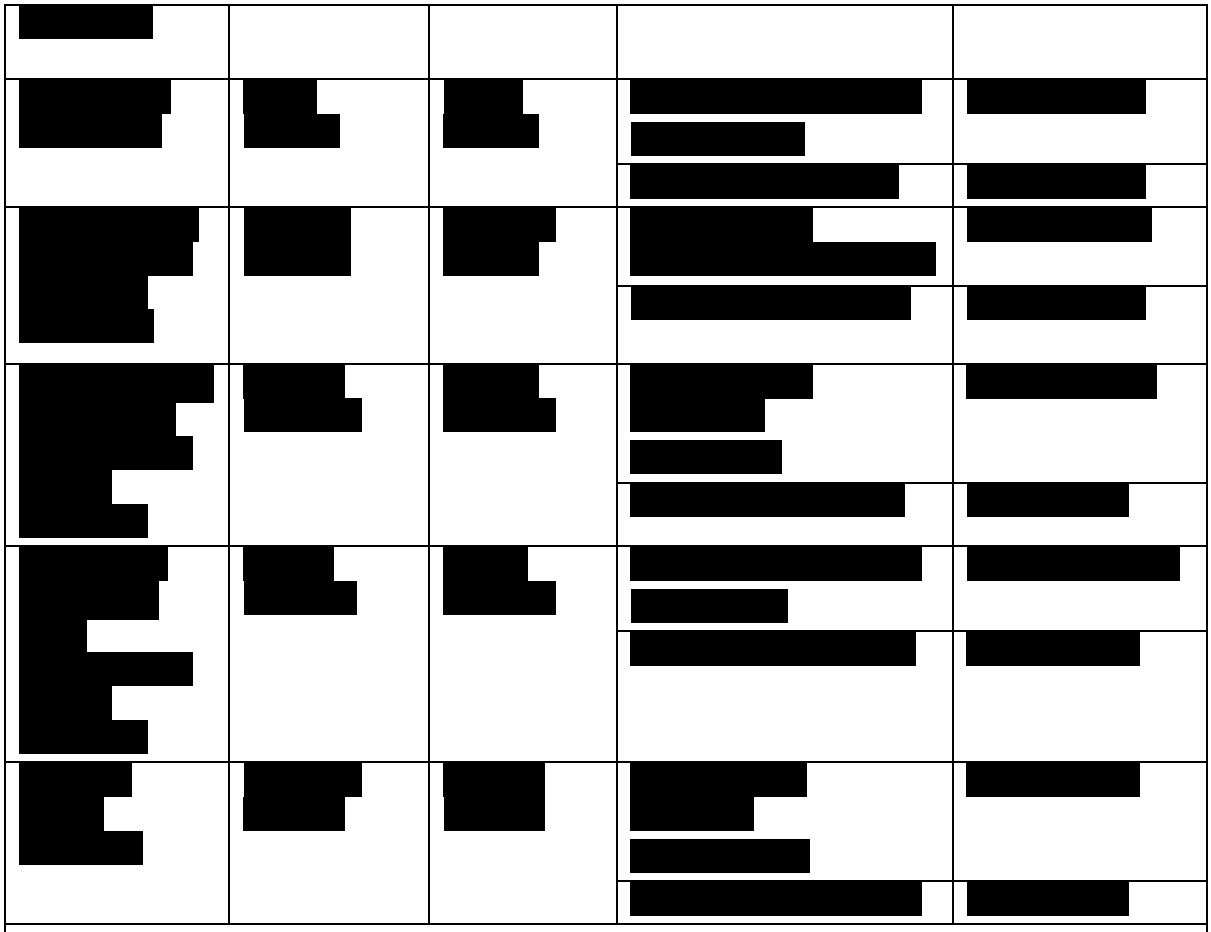
## *K.2. AcT trial: Presentation of further secondary endpoints*

### Table 28: Further secondary endpoints in the AcT trial

| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of Effect | Estimate (95% CI) |
|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |





**Key**: CI, confidence interval; eTICI, expanded treatment in cerebral ischaemia; EVT, endovascular thrombectomy; OPTIMISE, Optimizing Patient Treatment in Major Ischemic Stroke with EVT; QuiCR, Quality Improvement and Clinical Research; rAOL, revised arterial occlusion scale.
**Notes**: * Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time and source registry (QuiCR vs OPTIMISE) as fixed effects variables, and "site" as a random effects variable.
**Source**: Menon et al. 2022[4]; AcT CSR Revision 1.[8]

## *K.3. EXTEND-IA TNK Part 1: Procedural characteristics and the incidence of reperfusion according to the site of vessel occlusion*

**Table 29: Additional procedural characteristics**

| Thrombectomy procedural characteristics | Tenecteplase (n = 101) | Alteplase (n = 101) | p-value |
|---|---|---|---|
| Time (min) from arterial puncture to mTICI 2b/3 or completion, median (IQR) | 28 (15–53) | 35 (20–53) | 0.09 |

| | | | |
|---|---|---|---|
| Time (min) from stroke onset to mTICI 2b/3 or completion, median (IQR) | 203 (175–255) | 232 (185–268) | 0.07 |
| **Patients with substantial reperfusion at initial angiogram** | 22/101 (22%) | 10/101 (10%) | 0.02 |
| Intracranial ICA | 1/24 (4.2%) | 3/24 (12.5%) | |
| Basilar artery | 1/3 (33%) | 1/3 (33%) | |
| M1 MCA | 14/59 (24%) | 4/60 (6.7%) | |
| M2 MCA | 6/15 (40%) | 2/14 (14%) | |
| General anaesthesia | 28/98 (29%) | 40/99 (40%) | 0.08 |
| Number of device passes (median, IQR) | 1 (1–1) | 1 (1–2) | 0.14 |
| Carotid stent required | 10/97 (10%) | 12/99 (12%) | 0.14 |
| **Final mTICI 2b/3** | 83/97 (86%) | 80/99 (81%) | 0.45 |
| 3 | 16/97 (16%) | 10/99 (10%) | |
| 2c | 17/97 (18%) | 13/99 (13%) | |
| 2b | 50/97 (52%) | 57/99 (57%) | |
| 2a | 10/97 (10%) | 9/99 (9%) | |
| 1 | 1/97 (1%) | 2/99 (2%) | |
| 0 | 3/97 (3%) | 8/99 (8%) | |

**Key**: ICA; internal carotid artery, IQR, interquartile range; MCA, middle cerebral artery; mTICI, modified treatment in cerebral ischaemia.
**Source**: Campbell et al. 2018.[5]

## *K.4. EXTEND-IA TNK Part 1 – Further information on Adverse Events*

In the tenecteplase group, one patient had a symptomatic intracerebral haemorrhage which required an external ventricular drain.[5] They survived and are living at home with an mRS of 2 at 3 months. One patient in the alteplase had a symptomatic intracerebral haemorrhage which led to development of parenchymal haematoma and death. These were not significantly different (risk ratio of 1.0 [95% CI: 0.1, 15.9], p = 0.99; odds ratio of 1.0 [95% CI: 1.0, 16.2], p = 0.99).

Parenchymal haematoma was observed in six patients in the tenecteplase group and five patients in the alteplase group.[5] These were not significantly different (risk ratio of 1.2 [95% CI: 0.4, 3.8], p = 0.76; and an odds ratio of 1.2 [95% CI: 0.4, 4.1], p = 0.76).

Further information on the safety evaluation for EXTEND-IA TNK Part 1 is presented in Table 30.

**Table 30: Safety evaluation**

| | |
|---|---|
| Deaths | **IV alteplase group (n = 18)**<br>• Fourteen deaths related to progression of major stroke (including one who had no attempt at thrombectomy and one who had failed vascular access)<br>• Three deaths related to cardiac events (one myocardial infarction, one cardiac failure, one cardiac tamponade)<br>• One death related to symptomatic haemorrhage<br>**IV tenecteplase group (n = 10)**<br>• Nine deaths related to progression of major stroke (including two who had no attempt at thrombectomy and one who had failed vascular access)<br>• One death related to metastatic cancer diagnosed after presentation |
| Symptomatic intracerebral haemorrhage | **IV alteplase group (n = 1)**<br>• Parenchymal hematoma contralateral to the infarct in a patient who did not require thrombectomy due to substantial reperfusion at initial angiogram – fatal<br>**IV tenecteplase group (n = 1)**<br>• Intraventricular haemorrhage requiring external ventricular drain in a patient who proceeded directly from thrombectomy to carotid endarterectomy and was fully heparinized during the surgery. The patient survived and was living at home with an mRS of 2 at 3 months |
| Groin haematoma and arterial access complications | • Three patients receiving alteplase and one patient receiving tenecteplase developed groin hematoma<br>• None required transfusion<br>• One patient receiving alteplase developed a femoral artery pseudoaneurysm and one patient receiving tenecteplase developed post-procedure leg ischaemia distal to the puncture site. Both recovered without further complication |
| **Key**: IV, intravenous; mRS, modified Rankin scale score.<br>**Source**: Campbell et al. 2018[5]; EXTEND-IA TNK Part 1 CSR.[40] | |



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NICE National Institute for Health and Care Excellence

# Cost Comparison Appraisal

# Tenecteplase for treating acute ischaemic stroke [ID6306]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

NICE National Institute for Health and Care Excellence

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | Association of British Neurologists |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No<br>A specialist in the treatment of people with this condition? Yes or No<br>A specialist in the clinical evidence base for this condition or technology? Yes or No<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | Please enter the standard description of the ABN. |
| **5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | Does the ABN receive funding from the manufacturer of Tenectaplase? |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | I assume no links with tobacco industry. |

## The aim of treatment for this condition

| | |
|---|---|
| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | The main aim of the treatment is to reduce the disability associated with acute ischaemia of the brain by using a drug which promotes the breaking up of one or more clots which are blocking one or more arteries supplying blood to the brain. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | A clinically significant treatment response is best assessed as a reduction in the numbers of patients with associated disability, and dependency, as a result of receiving the treatment. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | Although the current approved treatment (tissue plasminogen activating factor) is estimated to reduce dependency, on average, in one patient for every ten patients treated (with marked differences in those treated earlier in the 4.5-hour window compared to those treated towards the end) it is given as a single injection and then an infusion over one hour. If a treatment was available with an equivalent beneficial effect was available, that could be given as a single injection, it would be a useful development in treatment options. |

## What is the expected place of the technology in current practice?

| | |
|---|---|
| **9. How is the condition currently treated in the NHS?** | As above |

| | |
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| **9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?** | NICE guidelines on thrombolysis in acute stroke and National Clinical Guideline for Stroke for the UK and Ireland. |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | The pathway of care is well defined and there are not major differences of opinion between professionals across the NHS about the importance of thrombolysis in acute stroke. |
| **9c. What impact would the technology have on the current pathway of care?** | Tenecteplase would make it easier for thrombolysis to be administered and accelerate the movement of patients along the stroke pathway. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | Tenecteplase would be used in a very similar way to the current treatment (tPA). |
| **10a. How does healthcare resource use differ between the technology and current care?** | Tenecteplase would be used in the same way as the current treatment. As it takes less time to administer it will potentially free up nursing and equipment resources. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Acute ischaemic stroke, in emergency units and acute medical units. |
| **10c. What investment is needed to introduce the technology? (For example,** | No new facilities would be required to introduce the technology. |

| | |
|---|---|
| **for facilities, equipment, or training.)** | |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | The main benefit would be in a reduction in the time taken to administer thrombolysis. |
| **11a. Do you expect the technology to increase length of life more than current care?** | The treatment effect would be roughly equivalent. |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | The effect on quality of life is likely to be equivalent to current treatment. |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | For patients who are restless or combative or who may be reluctant or unable to tolerate an IV infusion for an hour this treatment would be very useful. |

## The use of the technology

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|---|---|
| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant** | The treatment will be easier to give, quicker, and will not require a syringe driver to be set up. |

| | |
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| **treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | The treatment is given over a short time (10 seconds) so it is unlikely that rules will be required about stopping the treatment. The conditions and rules for giving the treatment will be the same as those for the current treatment. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | No |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Current need will be met but very much more quickly. |
| **16a. Is the technology a 'step-change' in the** | The new treatment is a step in the right direction more than a step change. |

| | |
|---|---|
| **management of the condition?** | |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | No |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Tenectaplase has a similar profile of side effects and benefits as the current treatment, with No significant increase in ICH (or mortality) in any RCT, although slightly higher numerically in ATTEST-2 and AcT. Reduced ICH incidence in observational studies. |

## Sources of evidence

| | |
|---|---|
| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Yes |
| **18a. If not, how could the results be extrapolated to the UK setting?** | |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | Reduction in dependency in those treated, and this was measured in the trials. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | |

| | |
|---|---|
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | No |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA264?** | No |
| **21. How do data on real-world experience compare with the trial data?** | Data from New Zealand, France, USA indicate reduced ICH, higher mRS 0-2, reduced workflow times in real world scenarios. |

**Topic-specific questions**

How clinically similar are tenecteplase and its comparators (alteplase)?

Are there likely to be any differences between the populations who would receive tenecteplase compared to those who would receive alteplase?

## Equality

| | |
|---|---|
| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | No |
| **22b. Consider whether these issues are different from issues with current care and why.** | |

## Key messages

| | |
|---|---|
| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | Tenecteplase is a useful addition to the treatments we can use in acute ischaemic stroke<br><br>The period of administration (10 second injection) is usefully quicker than the hour required to give the treatment most commonly used now (tPA).<br><br>No major changes will be required in facilities or care pathways to use Tenecteplase, and no new or unfamiliar equipment will be needed. In fact, nursing time and equipment will be spared.<br><br>The shorter administration time may result in patients being moved more quickly to acute stroke wards.<br><br>The same vigilance about the diagnosis of the location and nature of the pathology in patients presenting with neurological deficits will be required to ensure that the treatment is used - or not used - appropriately. |

Thank you for your time.

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NICE National Institute for Health and Care Excellence

# Cost Comparison Appraisal

# Tenecteplase for treating acute ischaemic stroke [ID6306]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | British and Irish Association of Stroke Physicians |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes |
| **5a. Brief description of the organisation (including who funds it).** | Professional body representing stroke physicians aiming to promote excellent stroke care. Funded by member subscriptions. |
| **5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | No |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No |

## The aim of treatment for this condition

| | |
|---|---|
| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | To improve clinical outcomes following ischaemic stroke through reducing disability or reducing death. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | Reduction in functional deficit as measured on any scale. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | Yes |

## What is the expected place of the technology in current practice?

| | |
|---|---|
| **9. How is the condition currently treated in the NHS?** | Using an alternative thrombolytic - alteplase |
| **9a. Are any clinical guidelines used in the** | Yes – multiple, from the UK National Stroke Guidelines to those produced by the European Stroke Organisation or the American Heart Association (this is not an exhaustive list) |

| | |
|---|---|
| **treatment of the condition, and if so, which?** | |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | Yes- pathway well described, there will be some local variation in pathways but this is minimal. |
| **9c. What impact would the technology have on the current pathway of care?** | Improve - There is clear evidence that the faster reperfusion therapy (encompassing intravenous (IV) thrombolysis and mechanical thrombectomy) is given, the more brain tissue is preserved and the better the outcome; reducing disability and death. The optimal management for ischaemic stroke patients is IV thrombolysis followed by thrombectomy as quickly as possible. In the UK we currently have a 'drip and ship' model where patients receive IV thrombolysis at their local hospital and are then transferred urgently to the closest neuroscience centre for thrombectomy. Alteplase (current pathway) is given via a single bolus and then an hour long infusion. Tenecteplase has similar clinical benefits to alteplase and can be given in a single bolus only (rather than an hour infusion). This will significantly speed up transfer to neuroscience centres, improving outcome. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | Yes. |
| **10a. How does healthcare resource use differ between the technology and current care?** | Less resource needed for the technology as less nursing time needed to monitor single bolus rather than hour long infusion. Less nursing resource needed to facilitate ambulance transfers. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Secondary care and tertiary care in acute stroke centres mainly. |

| | |
|---|---|
| **10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)** | Minimal. |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | Yes – see above answer 9c with regards to easier transfer for patients for mechanical thrombectomy. |
| **11a. Do you expect the technology to increase length of life more than current care?** | Yes |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | Yes |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | Probably not – there is some debate about using Tenecteplase in patients who present later post ischaemic stroke. |

## The use of the technology

| | |
|---|---|
| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are** | Easier – see 9c<br><br>No need for 1 hour intensive nursing input and use of infusion pumps. |

| | |
|---|---|
| **there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | No. No. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | Yes. Easier transfers, this will release nurses to look after other patients. Use of multiple ambulance transfers (ie into hospital and then later to the neuroscience centre) is likely to be more streamlined in such cases in addition. |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Yes. |

| | |
|---|---|
| **16a. Is the technology a 'step-change' in the management of the condition?** | No |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | There are a limited number of interventional neuroradiologists to perform mechanical thrombectomy. These operators must be concentrated in a small number of specialist centres. Anything which speeds up this necessary 'drip and ship' model would be of great benefit. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | Nil significantly over current standard. Non inferior to alteplase. |

## Sources of evidence

| | |
|---|---|
| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Yes |
| **18a. If not, how could the results be extrapolated to the UK setting?** | |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | Function post stroke – yes. |
| **18c. If surrogate outcome measures were used, do they adequately predict** | NA |

| | |
|---|---|
| **long-term clinical outcomes?** | |
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | No |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No |
| **20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA264?** | No |
| **21. How do data on real-world experience compare with the trial data?** | Corroborate as far as I know. |

**Topic-specific questions**

How clinically similar are tenecteplase and its comparators (alteplase)?

Very – proven to be non inferior, only main difference is mode of action.

Are there likely to be any differences between the populations who would receive tenecteplase compared to those who would receive alteplase?

Probably not – evidence is awaited but there may be some patients (a small number) who present late after stroke in whom Tenecteplase not proven to be non inferior therefore alteplase may be preferred but I think that this is likely to be a very small number of patients.

**Equality**

| | |
|---|---|
| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | No |
| **22b. Consider whether these issues are different from issues with current care and why.** | No |

## Key messages

| | |
|---|---|
| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • Tenecteplase is non inferior to alteplase<br>• Tenecteplase is significantly easier to administer requiring less resource<br>• This ease of administration will facilitate transfers between hospitals for mechanical thrombectomy therefore reducing inequality<br>• BIASP recommends switching to tenecteplase |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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# Cost Comparison Appraisal

# Tenecteplase for treating acute ischaemic stroke [ID6306]

# Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

## About you

| | |
|---|---|
| **1. Your name** | [redacted] |
| **2. Name of organisation** | St Georges University Hospital |
| **3. Job title or position** | [redacted] |
| **4. Are you (please select Yes or No):** | An employee or representative of a healthcare professional organisation that represents clinicians? Yes<br>A specialist in the treatment of people with this condition? Yes<br>A specialist in the clinical evidence base for this condition or technology? Yes or No<br>Other (please specify): |
| **5a. Brief description of the organisation (including who funds it).** | Large Teaching Hospital.<br>Tertiary Centre for Stroke. |
| **5b. Has the organisation received any funding from the manufacturers of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.]**<br>**If so, please state the name of manufacturer, amount, and purpose of funding.** | No. |
| **5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?** | No. |

## The aim of treatment for this condition

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| **6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)** | To stop progression and improve outcomes. |
| **7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)** | Reduction in NIHSS 24 hours post thrombolysis. |
| **8. In your view, is there an unmet need for patients and healthcare professionals in this condition?** | This treatment speeds up the pathway. Patients will complete treatment faster and this is important for those who later undergo thrombectomy. |

## What is the expected place of the technology in current practice?

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| **9. How is the condition currently treated in the NHS?** | Alteplase. |
| **9a. Are any clinical guidelines used in the** | Yes – NICE guidelines. |

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| **treatment of the condition, and if so, which?** | |
| **9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)** | Yes – same treatment across all trusts in SWL. |
| **9c. What impact would the technology have on the current pathway of care?** | An additional treatment option in thrombolysis for acute ischaemic stroke. |
| **10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?** | Yes. |
| **10a. How does healthcare resource use differ between the technology and current care?** | Nil additional resources required. |
| **10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)** | Secondary care under advice of stroke physician. |
| **10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)** | Only one 50mg vial of tenecteplase (0.25mg/kg, max dose 25mg) would ever be used in thrombolysis whereas the dose varies slightly more with alteplase with the available vial strengths (0.9mg/kg, max dose 90mg). Any patient that requires more than one vial of alteplase i.e., over 55kg, tenecteplase would be a cost saving. Therefore, there would be a cost saving on almost every patient treated. |

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| | Cost of Tenecteplase 50mg vial = £602<br>Cost of Alteplase 50mg vial = £518, 20mg vial = £311, 10mg vial £207. |
| **11. Do you expect the technology to provide clinically meaningful benefits compared with current care?** | Tenecteplase has been shown to be non-inferior to the current drug Alteplase. It may have a slightly improved side effect profile with fewer bleeding episodes.<br>The European Stroke Organisation (ESO) module working group, suggest favouring tenecteplase 0.25mg/kg over alteplase 0.9mg/kg for patients with acute ischaemic stroke of < 4.5hrs duration considering safety and efficacy data. |
| **11a. Do you expect the technology to increase length of life more than current care?** | No. |
| **11b. Do you expect the technology to increase health-related quality of life more than current care?** | A 40-min improvement in time from presentation to thrombectomy in transfer patients treated at an outside hospital was noted in one study after the transition to tenecteplase. This would have a significant impact on patient outcomes as for every 4-min delay from presentation to reperfusion, 1 of every 100 patients has a worse disability outcome (mRS increase by 1 or more). |
| **12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?** | The therapy might be more effective in patients who will need a thrombectomy procedure. |

## The use of the technology

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| **13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical** | Tenecteplase has been shown to be non-inferior to the current drug Alteplase. It may have a slightly improved side effect profile with fewer bleeding episodes. However, it is much easier to administer. It is given as an intravenous over a few seconds rather than as an infusion over an hour. One can be much more secure that a given patient has received their treatment. There are many more places where an infusion is prone to malfunction of failure. These extend from potential human error in setting the correct infusion rate to pump malfunction, line |

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| **implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)** | blockage or decannulation. Furthermore, there would be a shortening of time to completion of treatment in each patient of at least an hour when compared to the use of alteplase for the same indication. |
| **14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?** | For adults as fibrinolytic treatment in acute ischaemic stroke within 4.5 hours of onset of symptoms.<br><br>For adults with acute ischaemic stroke with large vessel occlusion eligible for mechanical thrombectomy.<br><br>Patients with acute ischaemic stroke otherwise eligible for treatment with thrombolysis should have their blood pressure reduced to below 185/110 mmHg before treatment. |
| **15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?** | No. |
| **16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?** | Tenecteplase is a single bolus thrombolytic agent with higher fibrin specificity and longer half-life than alteplase. Tenecteplase can be infused over 5 seconds versus alteplase which is infused over 60 minutes. Bolus delivery enables rapid clot exposure to high enzyme concentrations facilitating rapid fibrinolysis thereby achieving earlier vessel recanalization and reperfusion.<br>Tenecteplase has clear practical work-flow advantages over alteplase given its relative ease of preparation and administration. This translated into objective improvements in treatment times in three different non-randomized, real-world clinical studies. A 40-min improvement in time from presentation to thrombectomy in transfer patients treated at an outside hospital was noted in one study after the transition to tenecteplase. This would have a significant impact on patient outcomes as for every 4-min |

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| | delay from presentation to reperfusion, 1 of every 100 patients has a worse disability outcome (mRS increase by 1 or more). |
| **16a. Is the technology a 'step-change' in the management of the condition?** | Incremental change. |
| **16b. Does the use of the technology address any particular unmet need of the patient population?** | No. |
| **17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?** | There may be fewer side effects (bleeding) than the current treatment. |

## Sources of evidence

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| **18. Do the clinical trials on the technology reflect current UK clinical practice?** | Nine RCTs have compared tenecteplase with alteplase in people with acute ischaemic stroke (Haley et al, 2010; Parsons et al, 2012; Huang et al, 2015; Logallo et al, 2017; Campbell et al, 2018b; Bivard et al, 2022; Kvistad et al, 2022; Menon et al, 2022; Wang et al, 2023).<br><br>No single trial in unselected patients has demonstrated that tenecteplase leads to greater recovery than alteplase. A 2019 meta-analysis (Burgos & Saver, 2019) concluded that tenecteplase was non-inferior to alteplase but this was confounded by the significant contribution of the large NOR-TEST study which used a higher dose of 0.4 mg/kg and included a substantial proportion of people with stroke mimics (Logallo et al, 2017). A subsequent trial of 0.4 mg/kg tenecteplase in patients with moderate-severe ischaemic stroke showed this higher dose led to higher rates of intracerebral haemorrhage than alteplase (NOR-TEST 2, part A; (Kvistad et al, 2022)), and this dose is no longer recommended. Tenecteplase (0.25 mg/kg) delivered in an MSU setting (TASTE-A; (Bivard et al, 2022)) led to better |

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| | measures of imaging reperfusion than alteplase but the study was inadequately powered to test any difference in outcomes. |
| **18a. If not, how could the results be extrapolated to the UK setting?** | Tenecteplase would allow more rapid administration of the full thrombolysis dose. |
| **18b. What, in your view, are the most important outcomes, and were they measured in the trials?** | Tenecteplase is non-inferior to alteplase. It is easier to administer. Patients receive the full dose more rapidly. It is likely to be cheaper. |
| **18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?** | N/A |
| **18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?** | No. |
| **19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?** | No. |
| **20. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA264?** | Two large, randomised trials have demonstrated that tenecteplase 0.25 mg/kg is non-inferior to alteplase for excellent clinical outcome when delivered within 4.5 hours of stroke onset (Menon et al, 2022; Wang et al, 2023). In patients with proven large artery occlusion prior to planned thrombectomy tenecteplase (0.25 mg/kg) may be superior to alteplase when given within 4.5 hours of onset (Campbell et al, 2018b). |

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| **21. How do data on real-world experience compare with the trial data?** | Similar outcomes. The New Zealand (NZ) Central Region Stroke Network, serving 1.17 million catchment population, changed to tenecteplase for stroke thrombolysis in 2020 but was forced to revert to Alteplase in 2021 due to a sudden cessation of drug supply. Between January 2018 and December 2022, 1121 patients were treated with Alteplase and 286 with tenecteplase. Overall, patients treated with tenecteplase had greater odds of favorable outcome ordinal mRS and a shorter door-to-needle (DTN) time. This was a real-world study of unselected consecutively thrombolysed patients at tertiary, urban and non-urban secondary, and small rural hospitals and found no evidence of harm related to tenecteplase use compared with alteplase and overall improved patient outcomes, with fewer adverse events, and reduced treatment delays. |

**Topic-specific questions**

How clinically similar are tenecteplase and its comparators (alteplase)?

Are there likely to be any differences between the populations who would receive tenecteplase compared to those who would receive alteplase?

## Equality

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| **22a. Are there any potential equality issues that should be taken into account when considering this treatment?** | No. |
| **22b. Consider whether these issues are different from issues with current care and why.** | N/A. |

## Key messages

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| **23. In up to 5 bullet points, please summarise the key messages of your submission.** | • The European Stroke Organisation (ESO) module working group, suggest favouring tenecteplase 0.25mg/kg over alteplase 0.9mg/kg for patients with acute ischaemic stroke of < 4.5hrs duration considering safety and efficacy data.<br>• Tenecteplase is a single bolus thrombolytic agent with higher fibrin specificity and longer half-life than alteplase.<br>• Tenecteplase can be infused over 5 seconds versus alteplase which is infused over 60 minutes.<br>• Only one 50mg vial of tenecteplase (0.25mg/kg, max dose 25mg) would ever be used in thrombolysis whereas the dose varies slightly more with alteplase with the available vial strengths (0.9mg/kg, max dose 90mg). Any patient that requires more than one vial of alteplase i.e., over 55kg, tenecteplase would be a cost saving.<br>• A 40-min improvement in time from presentation to thrombectomy in transfer patients treated at an outside hospital was noted in one study after the transition to tenecteplase. |

Thank you for your time.

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# Cost Comparison Appraisal

## Tenecteplase for treating acute ischaemic stroke [ID6306]

## Questions for Clinical Experts

Thank you for agreeing to provide your input for this appraisal.

Your comments and feedback on the questions below are really valued. You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. To help provide insights, please use the questionnaire below.

**Please submit your response by 5pm on Thursday 6 June 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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**Part 1: About you**

| | |
|---|---|
| **1. Your name** | **Ajay Bhalla** |
| **2. Name of organisation** | [redacted] |
| **3. Job title or position** | [redacted] |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with acute ischaemic stroke?<br>☒ A specialist in the clinical evidence base for acute ischaemic stroke or technology?<br>☐ Other (please specify): |
| **5. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | Non applicable |

**Part 2: Questions for clinical experts**

| **1. Treatment administration**<br><br>Please describe any benefits of tenecteplase over alteplase in relation to treatment administration |
| --- |
| Due it's longer half-life than alteplase, tenecteplase has the advantage of being delivered as bolus rather than an infusion, as is the case for alteplase. This can result in easier administration which can also reduce the potential of medication errors, dose interruption and time delays. Administration of tenecteplase as a bolus has the added advantage in patients who are undergoing inter-hospital transfer for mechanical thrombectomy with reduction in time delays. Studies evaluating tenecteplase in real world practice have demonstrated time saving benefits such as reduction in door to needle times in thrombolysis as well as reduction in the door-in-door-out times for inter-hospital transfers with favourable safety profile (Warach SJ et al, 2023; Zhong CS et al, 2021).<br><br>Warach SJ, Ranta A, Kim J et al. Symptomatic intracranial haemorrhage with tenecteplase vs alteplase in patients with acute ischaemic stroke: the comparative effectiveness of routine tenecteplase vs alteplase in acute ischaemic stroke. (CERTAIN) collaboration. *JAMA Neurol.* 2023;80(7):732-738. doi:10.1001/jamaneurol.2023.1449<br><br>Zhong CS, Beharry J, Salazar D et al. Routine use of Tenecteplase for thrombolysis in acute ischaemic stroke. Stroke. 2021 Mar;52(3):1087-1090. doi: 10.1161/STROKEAHA.120.030859.<br><br>[Please provide your answer here. The text box will expand as you type.] |

| |
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| **2. Acquisition costs**<br><br>Alteplase is given at a weight-based dose of 0.9 mg/kg, with a maximum dose of 90 mg for people with a body weight of 100 kg or over. The economic model applies weight-based dosing only for the IV administration (0.81 mg/kg) and assumes that the full 10 mg is always used for the bolus dose (rather than 0.09 mg/kg). Does this align with clinical practice?<br><br>Alteplase is available in 10 mg, 20 mg, and 50 mg vials (these are not linearly priced). The company assumes that the cheapest combination of vials is used to give alteplase, even if this requires more product being wasted. There is no vial sharing for alteplase. Do these assumptions align with clinical practice? |
| The recommended dose of alteplase is 0.9 mg/kg body weight (up to a maximum of 90 mg), with 10% given as an initial bolus over 1 minute and the remainder infused over 60 minutes.<br><br>In clinical practice, the 50 mg vial is usually used in the first instance.<br><br>[Please provide your answer here. The text box will expand as you type.] |
| **3. Uncaptured benefits** |

The External Assessment Group (EAG) considered additional practical benefits for treatment with tenecteplase that are not captured in the economic model, which include:

- Potentially a shorter time for a doctor to be present for administration.
- No need for a pump for administration or setting up a syringe driver.
- No need for an escort for people requiring transport in an ambulance. A professional organisation notes that UK practice is for people to have IV thrombolysis at their local hospital with an urgent transfer to the closest neuroscience centre for thrombectomy. This can require nurses to go in the ambulance to facilitate transfer or, more often, a delay to transfer for administration to be completed.
- Only 1 vial size is needed. Some hospitals do not have access to all vial sizes for alteplase, which would increase wastage.
- Reduction in the proportion of people needing a thrombectomy, with its associated costs.

Do you agree with the uncaptured benefits listed? Are there any other practical benefits to consider?

Other potential practical benefits include:

1) Saving training costs for health professionals (using one hour alteplase infusion)
2) Potential cost savings in reducing time metrics associated with improved outcome such as reduced door to needle time and door-in-door-out times

3) Bolus delivery has practical advantages in reducing medication errors and workload for health staff

[Please provide your answer here. The text box will expand as you type.]

Thank you for your time.

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# Cost Comparison Appraisal

## Tenecteplase for treating acute ischaemic stroke [ID6306]

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**Part 1: About you**

| | |
|---|---|
| **1. Your name** | **Keith W Muir** |
| **2. Name of organisation** | [redacted] |
| **3. Job title or position** | [redacted] |
| **4. Are you (please tick all that apply)** | ☒ An employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ A specialist in the treatment of people with acute ischaemic stroke?<br>☒ A specialist in the clinical evidence base for acute ischaemic stroke or technology?<br>☐ Other (please specify): |
| **5. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.** | None |

**Part 2: Questions for clinical experts**

| **1. Treatment administration**<br><br>Please describe any benefits of tenecteplase over alteplase in relation to treatment administration |
| --- |
| Tenecteplase is administered as a single intravenous bolus.<br><br>Alteplase is administered as an intravenous bolus of 10% of the dose followed by a 1 hour infusion of the remaining 90%. This requires a syringe driver for delivery. Given the pharmacokinetics of alteplase, no or minimal delay between bolus and 1 hour infusion is necessary to maintain thrombolytic efficacy, but the need for infusion preparation, additional equipment, and (frequently) movement between hospital areas, has commonly led to delays in infusion initiation. Infusion interruption during transfer is also a concern especially relevant to thrombectomy-eligible patients.<br><br>Observational data from regions that have adopted tenecteplase report better feasibility of administration in a scanner setting and reduced door-to-needle time (eg New Zealand, France, Texas). |
| **2. Acquisition costs** |

Alteplase is given at a weight-based dose of 0.9 mg/kg, with a maximum dose of 90 mg for people with a body weight of 100 kg or over. The economic model applies weight-based dosing only for the IV administration (0.81 mg/kg) and assumes that the full 10 mg is always used for the bolus dose (rather than 0.09 mg/kg). Does this align with clinical practice?

Alteplase is available in 10 mg, 20 mg, and 50 mg vials (these are not linearly priced). The company assumes that the cheapest combination of vials is used to give alteplase, even if this requires more product being wasted. There is no vial sharing for alteplase. Do these assumptions align with clinical practice?

In my experience alteplase is made up according to total dose based on body weight, most often 2 x 50mg vials (sometimes 50mg+20mg for low body weight patients). 10% of the dose is drawn up for the bolus and the remainder for the infusion from these two vials. I don't recall ever using a 10mg vial for bolus dosing.

**3. Uncaptured benefits**

The External Assessment Group (EAG) considered additional practical benefits for treatment with tenecteplase that are not captured in the economic model, which include:

- Potentially a shorter time for a doctor to be present for administration.
- No need for a pump for administration or setting up a syringe driver.

- No need for an escort for people requiring transport in an ambulance. A professional organisation notes that UK practice is for people to have IV thrombolysis at their local hospital with an urgent transfer to the closest neuroscience centre for thrombectomy. This can require nurses to go in the ambulance to facilitate transfer or, more often, a delay to transfer for administration to be completed.
- Only 1 vial size is needed. Some hospitals do not have access to all vial sizes for alteplase, which would increase wastage.
- Reduction in the proportion of people needing a thrombectomy, with its associated costs.

Do you agree with the uncaptured benefits listed? Are there any other practical benefits to consider?

Yes, these are correct, with the exception of uncertainty around a reduced need for thrombectomy, which was seen in one trial (EXTEND-IA TNK from Australia and New Zealand) but has not been confirmed in other trials to date (eg AcT from Canada and ATTEST-2 saw no difference in thrombectomy use in tenecteplase patients with large vessel occlusion).

In addition, reduced door to needle time and shortened workflow has been observed in several regions (best documented in New Zealand). This effect is plausible given simpler preparation and administration, including easier options to deliver the bolus in the scanning room. New Zealand reported 9 minute reduction in median door to needle times (Ranta et al Eur Stroke J 2023;8:942-6) and 67 minute median reduction in door to groin time for those undergoing thrombectomy. These effects were specific to tenecteplase since New Zealand experienced supply issues with tenecteplase and therefore described workflow in periods of different thrombolytic availability (alteplase, then tenecteplase, then alteplase again), and workflow times returned to baseline when alteplase had to be re-adopted.

Thank you for your time.

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# Tenecteplase for treating acute ischaemic stroke [ID6306]

## A Cost Comparison Appraisal


| | |
|---|---|
| **Produced by** | Peninsula Technology Assessment Group (PenTAG)<br>University of Exeter Medical School |
| **Authors** | **Alex Allen**, Research Fellow[1]<br>**Alan Lovell**, Research Fellow[1]<br>**Sajid Alam**, Stroke Medicine Consultant[2]<br>**Ahamad Hassan**, Consultant Neurologist and Stroke Physician[3]<br>**Dawn Lee**, Associate Professor[1]<br>[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter<br>[2] East Suffolk and North Essex NHS Foundation Trust, Colchester<br>[3] Leeds Teaching Hospitals NHS Trust, Leeds |
| **Correspondence to** | Alex Allen<br>3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; a.allen9@exeter.ac.uk |
| **Date completed** | 10/05/2024 |
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| **Declared competing interests of the authors** | Authors have no competing interests to declare. |
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**Author contributions**

| | |
|---|---|
| *Alex Allen* | Lead for EAG's critical appraisal of the clinical evidence. Writing and editorial input. |
| *Alan Lovell* | Lead for EAG's critical appraisal of the search strategy. Writing and editorial input. Project manager. |
| *Sajid Alam* | Expert clinical advice to the EAG about ischaemic stroke and its treatment |
| *Ahamad Hassan* | Expert clinical advice to the EAG about ischaemic stroke and its treatment |
| *Dawn Lee* | Project director. Lead for EAG's critical appraisal of the economic evidence. Writing and editorial input. Guarantor of the report. |

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# Abbreviations

| | |
|---|---|
| ABN | Association of British Neurologists |
| AE | adverse event |
| AIS | acute ischaemic stroke |
| BIASP | The British Irish Association of Stroke Physicians |
| CDSR | Cochrane Database of Systematic Reviews |
| CEAC | cost-effectiveness acceptability curve |
| CI | confidence interval |
| CS | company submission |
| CT | computed tomography |
| EQ-5D | EuroQol five dimension |
| EQ-VAS | EuroQol Visual Analogue Scale |
| EAG | External Assessment Group |
| ED | Emergency department |
| HRQL | Health-related quality of life |
| HSE | Health Survey for England |
| HTA | Health technology assessment |
| ICH | intracerebral haemorrhage |
| ICTRP | International Clinical Trials Registry Platform |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| IQR | interquartile range |
| ITT | intention-to-treat |
| IV | intravenous |
| MRI | magnetic resonance imaging |
| mRS | modified Rankin Scale |
| N/A | not applicable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| NIHSS | National Institutes of Health Stroke Scale |
| N/R | not reported |
| PRISMA | Preferred Reporting Items for Systematic reviews and Meta-Analyses |
| RCT | randomised controlled trial |

| | |
|---|---|
| RoB | risk of bias |
| SLR | systematic literature review |
| SSNAP | Sentinel Stroke National Audit Programme |
| TIMI | Thrombolysis in Myocardial Infarction |
| vs | versus |
| UK | United Kingdom |

# 1. SUMMARY OF THE EAG'S VIEW OF THE COMPANY'S COST COMPARISON CASE

## 1.1. Similarity of effectiveness and safety of tenecteplase relative to alteplase

The EAG agreed that tenecteplase was non-inferior and equally safe in comparison with alteplase for thrombolytic treatment of acute ischaemic stroke (AIS) within 4.5 hours from when patients were last known to be well.

## 1.2. Similarity of costs across interventions

The EAG agreed that for the cohort expected to be treated tenecteplase was cheaper than alteplase on the basis of drug costs alone.

## 1.3. Areas of uncertainty

Overall, there is little uncertainty that tenecteplase is of at least similar effectiveness and safety as, and cheaper than, alteplase. In relation to the clinical data, the EAG noted three areas of minor uncertainty:

- ATTEST-2,[1,2] the most relevant trial to the UK, had not yet been published. The results presented were therefore preliminary and subject to change following database lock.
- There were seven relevant RCTs to this assessment. The non-inferiority of tenecteplase versus alteplase was assessed individually for each. If a meta-analysis were undertaken, then it could have further improved the precision of the non-inferiority assessment.
- No EQ-5D-5L utility score was presented, and so it was unclear how a number of small benefits for alteplase over tenecteplase would manifest across all five dimensions.

[redacted]. No data is available on the mean weight of people expected to be treated with tenecteplase in clinical practice. However, the population mean weight would need to be implausibly low for tenecteplase to no longer be cheaper ([redacted]). There may be other benefits, as noted in Section 4.1.4, that are not included in the economic analysis, which might result in a small additional reduction in costs.

# 2. CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The company submission (CS) assessed the clinical and cost effectiveness of tenecteplase within its expected marketing authorisation for fibrinolytic treatment of acute ischaemic stroke. A summary of the decision problem for this appraisal, and the EAG's appraisal of how the CS addresses it, is shown in Table 1.

The EAG noted one inconsistency between the stated decision problem addressed in the CS and the content of the CS. The final scope issued by NICE detailed seven outcome measures to be considered and this included neurological deficit. Two pivotal trials, AcT and EXTEND-IA TNK Part 1, were used to support the submission and the company stated in Table 5 in Document B that all seven outcomes in the final scope issued by NICE, including neurological deficit, were reported in the AcT trial. The EAG's clinical experts explained that neurological deficit could be measured using the National Institutes of Health Stroke Scale (NIHSS). However, in their practices, the NIHSS was not routinely measured at an appropriate time point. Instead, a person's recovery from stroke is evaluated though functional outcomes that are understood to be correlated with their neurological deficit. In the AcT trial there was no measurement of neurological deficit, and the efficacy outcomes were oriented around functional recovery assessed through the modified Rankin scale (mRS). Given that the outcomes measured in the trial reflected UK practice and given the understood correlation of functional outcomes with neurological deficit, the EAG was not concerned that this omission impacted on the cost effectiveness estimates of tenecteplase versus alteplase.

The EAG recognised that neurological deficit was measured and reported very soon after treatment (up to 72 hours) in the EXTEND-IA TNK Part 1 trial as "early neurological improvement". The EAG's clinical experts explained that early neurological improvement could be seen in a subgroup of people who arrived soon after their stroke onset, and who have not sustained any damage. Once the artery was opened, they immediately get much better. There was a link between this improvement and mRS score at three months but the EAG's experts noted that many benefits of thrombolysis will be seen after 72 hours, and as such, they cautioned against assessing longer term efficacy via early neurological improvement.

**Table 1: Summary of decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| Population | People with acute ischaemic stroke who can have thrombolytic treatment | Adults for the thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well and after exclusion of intracranial haemorrhage | As per marketing authorisation | N/A |
| Intervention | Tenecteplase | As per final scope | N/A | The intervention used in the pivotal trials was tenecteplase (0.25 mg/kg to a maximum of 25 mg) and was administered as a single intravenous bolus over approximately 10 seconds. |
| Comparator(s) | Other established clinical management without tenecteplase including:<br>• Alteplase | As per final scope | N/A | The comparator in the pivotal trials was alteplase (0.9 mg/kg to a maximum of 90 mg) with 10% of the total dose administered as an initial IV bolus, immediately followed by the remainder of the total dose infused intravenously over 60 minutes. |
| Outcomes | The outcome measures to be considered include:<br>• Disability or change in daily activities status | As per final scope | N/A | The EAG noted that neurological deficit was not an outcome in the AcT trial but was measured at 72 hours in the EXTEND-IA TNK Part 1 as “early neurological |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | • Functional recovery<br>• Neurological deficit<br>• Mortality<br>• Length of hospital stay<br>• Adverse effects of treatment, including bleeding events<br>• Health-related quality of life | | | improvement". Given that the outcomes measures in the trials reflected NHS practice and the understood correlation of functional outcomes with neurological deficit, the EAG does not consider this to be an area of weakness. |
| Economic analysis | The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.<br>If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out.<br>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or | Tenecteplase has demonstrated similar clinical efficacy to alteplase at lower costs. Hence, a cost-comparison model has been developed. | Compared with alteplase, tenecteplase is associated with non-inferior efficacy and equivalent safety outcomes. Tenecteplase is also associated with treatment cost savings and time saved in administration.<br>The evidence on efficacy and safety for this submission is based on two clinical trials, AcT1, 2 and EXTEND-IA TNK Part 1.3, 4<br>**AcT**<br>• In patients with AIS presenting within 4.5 hours of stroke symptom onset, tenecteplase demonstrated a clinically relevant non-inferiority to alteplase for the primary outcome of excellent functional outcome (measured as mRS score 0–1) at 90–120 | The economic case submitted is based solely on lower drug costs. The company assume the same administration costs for both treatments which is in line with clinical expert advice received by the EAG. |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | outcomes between the technologies being compared.<br><br>Costs will be considered from an NHS and Personal Social Services perspective. | | days. The direction of the effect favoured tenecteplase; however, this was not statistically significant.<br><br>• These results were consistent across all pre-specified subgroups, including: age (< 80 vs ≥ 80 years), sex, baseline stroke severity, symptom onset-to-needle time, large vessel occlusion, type of enrolling centre, and source registry for both ITT and per-protocol populations.<br><br>• There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage, extracranial bleeding, or 90-day mortality.<br><br>**EXTEND-IA TNK Part 1**<br><br>• In patients with AIS presenting within 4.5 hours of stroke symptom onset, tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome (measured as mRS score at 90 days) compared with alteplase. | |

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope | EAG comment |
|---|---|---|---|---|
| | | | • There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage or 90-day mortality. | |
| Subgroups | If the evidence allows, the following subgroup will be considered:<br>• Subgroups by time to treatment (0 to 3 hours and 3 to 4.5 hours) | Clinical evidence presented for this subgroup, but not cost-effectiveness evidence | Evidence from two large, well-conducted randomized controlled trials demonstrate that the results of tenecteplase treatment versus alteplase are applicable to the whole AIS target population (Subgroup Analysis, Appendix E). Hence, subgroup analyses including the one suggested in the final scope are not justified. | The clinical evidence presented was appropriate. There would not be any expectation of differences in costs for the subgroups. |
| Special considerations including issues related to equity or equality | Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorization granted by the regulator. | N/A | N/A | N/A |

Abbreviations: AIS, acute ischaemic stroke; CS, Company submission; EAG, External Assessment Group; mg/kg, mRs, modified Rankin scale; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; SLR, systematic literature review.

# 3. SUMMARY OF THE EAG'S CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

## 3.1. Systematic literature review conducted by the company

The company undertook a global systematic literature review (SLR) to identify the current available evidence on the clinical efficacy and safety of tenecteplase and alteplase administered to people with acute ischaemic stroke (AIS) within the first 4.5 hours of symptom onset. An overview of the SLR methods used by the company and a summary of the EAG appraisal of these is shown in Table 2.

The SLR inclusion criteria presented in Table 6 (Appendix D.1.2) were appropriate to identify evidence relevant to the decision problem. However, they were broader than the decision problem outlined in the NICE final scope. The interventions included were either tenecteplase with or without thrombectomy or alteplase with or without thrombectomy. The comparators were alteplase with or without thrombectomy, placebo or standard of care, or thrombectomy alone. If the company followed these inclusion criteria, then studies irrelevant to the decision problem – for example comparing alteplase to placebo – would be eligible for inclusion. The EAG reiterate that the only comparison relevant to the decision problem is tenecteplase with or without thrombectomy versus alteplase with or without thrombectomy.

The SLR also included controlled trials (non-RCTs) or non-comparative (single-arm) trials in addition to randomised controlled trials (RCTs). Given there are a number of RCTs comparing tenecteplase to alteplase it was unnecessary to include uncontrolled trials (non-RCTs) or non-comparative (single-arm) trials in the SLR.

Initial screening was undertaken in-line with the inclusion criteria stated. The company state in Section D.1.2 that 27 unique trials were included in the full data synthesis, and six trial registry records reporting six ongoing trials were included in a summary data synthesis (as results of these trials were not yet published at time of review). However, no full data synthesis or summary data synthesis were presented in the CS. Instead, the company hand selected eligible trials to be included and excluded using unknown criteria, meaning that relevant trials were excluded from the SLR. This led to two trials, AcT and EXTEND-IA TNK Part 1, being included in the SLR and 25 trials being excluded.

The EAG noted that four of the excluded trials were comparisons of tenecteplase 0.25 mg/kg to alteplase 0.9 mg/kg in an AIS population:

- Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) (NCT01472926)[3]
- Tenecteplase versus Alteplase for Acute Ischaemic Stroke (TAAIS) Trial (ACTRN12608000466347)[4]
- Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance (TASTEa) (NCT04071613)[5]
- Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events (TRACE) (NCT04676659)[6]

The non-inferiority of tenecteplase to alteplase was evaluated in these relevant trials at the clarification stage, in response to a question from the EAG (Question A2).

In Section D.3. the company state that the tool used for the quality assessment of the two included RCTs was the Cochrane Risk of Bias tool. No reference was provided to the specific tool, and it was unclear whether the original Cochrane Risk of Bias tool (2011)[7] or the Risk of Bias 2 (RoB 2) tool (2019)[8] was used. In Table 8 (Appendix D), the company present a summary of risk of bias assessments for the two studies, answering yes or no within the seven domains assessed. The Cochrane Handbook states that all judgements of risk of bias in the 'Risk of bias' tool must be supported by a succinct summary of the evidence or rationale underlying the judgement to ensure transparency in how these judgements are reached.[9] The company did not present any reasoning, and this limited the transparency of their judgements.

**Table 2: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem**

| Systematic review step | Section of CS in which methods are reported | EAG assessment of robustness of methods |
|---|---|---|
| Searches | Appendix D.1 and G.2 | The company conducted SLRs for clinical and economic evidence in MEDLINE, Embase, Cochrane CENTRAL, Cochrane CDSR, Clinicaltrials.gov, International Clinical Trials Registry Platform (ICTRP), EconLit, and the International Network of Agencies for Health Technology Assessment (INAHTA) database. The search terms used (including key words and indexing terms) were |

| Systematic review step | Section of CS in which methods are reported | EAG assessment of robustness of methods |
|---|---|---|
| | | reasonable, given the cost comparison structure of the submission. There economic review was registered in PROSPERO.<br>There were some transcription errors in the search strategy and mistakes in the PRISMA diagrams, but these were clarified and corrected during clarification. The EAG was satisfied that all the key relevant literature was likely to have been retrieved by the search. |
| Inclusion criteria | Table 6 in Appendix D.1.2 | The inclusion criteria were appropriate to identify evidence relevant to the decision problem. However, as noted they were overly broad and led to studies that were not relevant to the decision problem being included in the SLR. |
| Screening | Appendix D.1.2 | Initial screening was undertaken in-line with the inclusion criteria presented in Table 6 (Appendix D.1.2). The company then hand selected eligible trials to be in and out using unknown criteria, meaning that relevant trials were excluded from the SLR. The EAG identified four relevant RCTs that were excluded and requested clarification from the company (additional details were then supplied in response to Question A2). |
| Data extraction | Appendix D.1.2 | The EAG was satisfied with the data extraction process as detailed in Appendix D. |
| Tool for quality assessment of included study or studies | Appendix D.3. A summary of risk of bias assessments was presented in Table 8 (Appendix D). | The company stated that the tool used for the quality assessment of the two included RCTs was the Cochrane Risk of Bias tool. No reference was provided to the specific tool used and it was unclear whether the original Cochrane Risk of Bias tool (2011)[7] or the Risk of Bias 2 (RoB 2) tool (2019)[8] was used. In the summary of risk of bias assessments (Table 8, Appendix D), the company does not offer any specific reasoning why each trial was, or was not, adequate under each of the seven domains assessed. This lack of transparency limited the EAG's ability to critique of the risk of bias assessment presented. |
| Evidence synthesis | NR | No statement was made in the SLR methods on the evidence synthesis planned. The company presented a narrative synthesis of efficacy and safety outcomes from the two included trials in Section B.3.6. of the CS. The company did not offer any reasoning for why a meta-analysis was not presented, but the EAG accepted that the population recruited to the EXTEND-IA TNK Part 1 trial were more severely affected than the population recruited to AcT trial. |

Abbreviations: CS, Company submission; EAG, External Assessment Group; SLR, systematic literature review.

## 3.2. Overview of clinical evidence submitted by the company

The CS primarily comprised two trials, AcT[10] and EXTEND-IA TNK Part 1, and safety data from the ATTEST trial[11] were presented in Appendix F. The company also assessed the non-inferiority of tenecteplase to alteplase in five relevant trials, ATTEST,[11] ATTEST-2,[1,2] TAAIS,[12] TASTE-A,[13] and TRACE[14] at the clarification stage (questions A1 and A2). All the studies relevant to the decision problem were investigator initiated. An overview of these studies is provided in Table 3, below.

**Table 3: Clinical evidence included in the CS and the clarification stage**

| Study name | Study type/design | Population | Intervention | Comparator |
|---|---|---|---|---|
| AcT[10] (NCT03889249)[15] | Phase III, open-label, multicentre, RCT | Adults presenting with AIS within 4.5 hours of onset | Tenecteplase (n=816) | Alteplase (n=784) |
| ATTEST[11] (NCT01472926)[3] | Phase II, open-label, UK single-centre, RCT | Adults presenting with AIS within 4.5 hours of onset | Tenecteplase (n=52) | Alteplase (n=52) |
| ATTEST-2[1,2] (NCT02814409)[16] | Ongoing, phase III, open-label, UK multicentre, RCT | Adults presenting with AIS within 4.5 hours of onset | Tenecteplase (n=927) | Alteplase (n=931) |
| EXTEND-IA TNK Part 1[17] (NCT02388061)[18] | Phase II, open-label, multicentre, RCT | Adults presenting with AIS within 4.5 hours of onset | Tenecteplase (n=101) | Alteplase (n=101) |
| TAAIS[12] (ACTRN12608000466347)[4] | Phase IIb, open-label, multicentre, RCT | Adults presenting with AIS within 6 hours of onset | Tenecteplase (n=25) | Alteplase (n=25) |
| TASTE-A[13] (NCT04071613)[5] | Phase II, open-label, multicentre, RCT | Adults presenting with AIS in a mobile stroke unit within 4.5 hours of onset | Tenecteplase (n=55) | Alteplase (n=49) |
| TRACE[14] (NCT04676659)[6] | Phase II, open-label, multicentre, RCT | Adults presenting with AIS within 3 hours of onset. NIHSS 4-25 | Tenecteplase (n=57) | Alteplase (n=59) |

Abbreviations: AIS, acute ischaemic stroke; CS, company submission; RCT, randomised controlled trial, IV, intravenous; NIHSS, National Institutes of Health Stroke Scale.

## 3.3. Methodology of the included studies submitted by the company

A comparative overview of the methods used in the included trials submitted by the company is provided in Table 4. AcT was a phase III, investigator-initiated, open-label, RCT and EXTEND-IA TNK Part 1 was a phase II, investigator-initiated, open-label, RCT. The smaller trials that were assessed at the clarification stage (ATTEST, TAAIS, TASTE-A, and TRACE) were not included by the company in the CS, and as such, have not been included in this section. However, ATTEST-2 was a large ongoing Phase III, investigator-initiated, multicentre, RCT being conducted in the UK. The company did not include this trial in the CS but provided preliminary results from the trial at the clarification stage (Question A1). Given the size and location of the study, the EAG considered it was important for it to be included in this analysis and have formally included it alongside the pivotal trials here.

The company's two pivotal trials were not UK-based. AcT took place across 22 centres in Canada and EXTEND-IA TNK Part 1 in 12 centres in Australia and one in New Zealand. The EAG's clinical experts noted, in relation to stroke treatment in Canda, that stroke was an emergency and people would not be waiting to be taken to a private hospital. Therefore, treatment would not vary by a person's socio-economic or ethnic background, and they reasoned that this was an indicator that acute stroke care provided in Canada was reflective of the care provided by the NHS in the UK. The healthcare system in Australia is Medicare – a similar system to the NHS – which offers equivalent acute treatment of stroke to that found in the UK. However, the EAG's clinical experts cautioned that a key factor to stroke outcome is the time taken from symptom onset to needle time (thrombolysis) and that this may differ in Canada, Australia, or New Zealand, compared to the UK. However, the ATTEST-2 trial was based in the UK and thus offered an important UK perspective to this submission, and allayed some EAG concerns over the relevance of the pivotal trials to the UK.

All three trials recruited adults with ischaemic stroke within 4.5 hours of onset. Sixteen-hundred people were recruited to AcT, 23 withdrew consent, and 1577 people made up the intention-to-treat (ITT) population. The baseline characteristics and disease characteristics for AcT were presented in Table 6 in Document B. The EAG's clinical experts stated that the study included people with a range of stroke severities. This could be seen in the occlusion site and the baseline NIHSS score categories. Across the study, 619 (39.5%) participants had a NIHSS score of less than 8, 503 (32.1%) had a NIHSS score of 8 to 15, and 447 (28.4%) had an NIHSS score of more than 15. The median (IQR) NIHSS score was 9 (6-16) in the tenecteplase

arm and 10 (6-17) in the alteplase arm. The EAG's clinical experts considered the participants reasonably representative to their current UK practice.

EXTEND-IA TNK Part 1 recruited 202 people with AIS who had a large vessel occlusion of the internal carotid, middle cerebral or basilar artery and were eligible to receive endovascular thrombectomy. The baseline characteristics and disease characteristics of the participants were presented in Table 7 in Document B. The median (IQR) NIHSS score in the trial was 17 (12-22) and the EAG's clinical experts stated that this is what would be expected in a more severe population who have had a large artery occlusion and were on a pathway to receive a thrombectomy.

As of 06 October 2023, ATTEST-2 recruited [redacted] across [redacted] in the UK. The baseline characteristics and disease characteristics for ATTEST-2 were presented in Table 1 in the clarification response (Question A1). The EAG understood the population recruited to be representative of current UK practice.

The intervention and comparator for all three trials were IV tenecteplase (0.25 mg/kg body weight, up to 25 mg) versus IV alteplase (0.9 mg/kg body weight, up to 90 mg). The treatment allocation was open label and the trials state that due to the time sensitive nature of acute stroke treatment, masking the enrolling health personnel and participants to treatment allocation was not practical.

In the AcT and EXTEND-IA TNK Part 1 trials, outcome assessments at 90–120 days after randomisation and treatment were done using centralised telephone interviews by trial personnel masked to treatment allocation. We do not have detailed descriptions of the methods used in ATTEST-2, but we understand it also used a blinded end-point design.

All three trials assessed functional recovery through the modified Rankin scale (mRS) score at 90 days (EXTEND-IA TNK Part 1 and ATTEST-2) or 90 to 120 days (AcT). The AcT trial undertook seven pre-planned subgroup analyses using this outcome. The primary outcome for EXTEND-IA TNK Part 1 trial was reperfusion at the initial angiographic assessment. Both the EXTEND-IA TNK Part 1 trial, and the ATTEST-2 trial, reported outcomes linked to early neurological improvement. The AcT trial also measured quality of life using EQ-5D and EQ-VAS at 90 days.

**Table 4: Comparative summary of trial methodology**

| Study | AcT[10] | ATTEST-2[1,2] | EXTEND-IA TNK Part 1[17] |
|---|---|---|---|
| Location | 22 stroke centres in Canada | [redacted] | 12 centres in Australia and one in New Zealand |
| Trial design | Phase III, investigator-initiated, open-label, RCT | Phase III, investigator-initiated, open-label, RCT | Phase II, investigator-initiated, open-label, RCT |
| Eligibility criteria | • Adults with a AIS causing disabling neurological deficit within 4.5 hours of onset<br>• Eligible for thrombolysis as per Canadian guidelines | • Adults presenting with AIS within 4.5 hours of onset<br>• Independent prior to the stroke (estimated modified Rankin Scale 0-1)<br>• Eligible for intravenous thrombolysis | • Adults presenting with AIS within 4.5 hours of onset<br>• With large vessel occlusion of the internal carotid, middle cerebral or basilar artery<br>• Eligible to undergo intravenous thrombolysis and endovascular thrombectomy |
| Interventions evaluated | IV tenecteplase (0.25 mg/kg body weight up to 25 mg)<br>n=816 | IV tenecteplase (0.25 mg/kg body weight up to 25 mg)<br>[redacted] | IV tenecteplase (0.25 mg/kg body weight up to 25 mg)<br>n=101 |
| Concomitant medication | IV alteplase (0.9 mg/kg body weight up to 90 mg)<br>n=784 | IV alteplase (0.9 mg/kg body weight up to 90 mg)<br>[redacted] | IV alteplase (0.9 mg/kg body weight up to 90 mg)<br>n=101 |
| Primary outcome | modified Rankin scale (mRS) score 0–1 at 90–120 days | [redacted] | Greater than 50% reperfusion at initial angiographic assessment |
| Key secondary outcomes | • mRS score 0–2 at 90–120 days<br>• Actual mRS score at 90–120 days<br>• Return to baseline function<br>• Length of hospital stay | [redacted] | • mRS of 0 to 2 or no change from baseline at 90 days<br>• mRS of 0 to 1 or no change from baseline at 90 days<br>• Early neurological improvement [a] |
| HRQL outcomes | • EQ-VAS at 90 days<br>• EQ-5D – mobility at 90 days | [redacted] | Not measured |

| Study | AcT[10] | ATTEST-2[1,2] | EXTEND-IA TNK Part 1[17] |
|---|---|---|---|
| | • EQ-5D – self care at 90 days<br>• EQ-5D – usual task at 90 days<br>• EQ-5D – pain at 90 days<br>• EQ-5D - anxiety at 90 days | | |
| Pre-planned subgroups | • Age (< 80 vs ≥ 80 years)<br>• Sex<br>• Baseline stroke severity<br>• Symptom onset-to-needle time<br>• Large vessel occlusion<br>• Type of enrolling centre<br>• Source registry | [redacted] | Not reported/measured |

Abbreviations: AIS, acute iscaemic stroke; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; IV, intravenous; RCT, randomised controlled trial.

Notes:

[a] 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.

[b] This comprised three outcomes: NIHSS score at 24 hours, NIHSS change from admission at 24 hours, early major NIHSS improvement (not defined) at 24 hours, n (%).

### 3.3.1. Non-inferiority margins

All three trials were designed to test for non-inferiority of tenecteplase to alteplase, and as such, formulated non-inferiority margins prior to conducting the trial.

In the AcT trial,[10] non-inferiority would be established if the lower boundary of the 95% confidence interval of the unadjusted percentage difference in participants obtaining the primary outcome (an mRS score of 0–1) in the tenecteplase versus alteplase groups was greater than -5%. This was chosen in relation to a meta-analysis of alteplase versus placebo or control treatment presented in Emberson et al (2014).[19] It was not clear to the EAG, from either the paper reporting the AcT trial or from the reporting in the CS, exactly how the non-inferiority margin was formulated using the analysis presented in Emberson (2014).

The non-inferiority margin for the EXTEND-IA TNK Part 1 was based on a meta-analysis of three trials comparing alteplase to placebo for AIS. In EXTEND-IA,[20] SWIFT PRIME,[21] and ESCAPE[22] trials, 19 of 253 participants (7.5%; 95% CI, 4.6 to 11.5) who received alteplase had reperfusion at the initial angiographic assessment. 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%).Therefore, noninferiority would be established if the lower boundary of the 95% confidence interval of the difference in the percentages of participants with substantial reperfusion at the initial angiographic assessment in the tenecteplase group versus the alteplase group was greater than -2.3%.

The ATTEST-2 trial reported pre-specified non-inferiority margins for the shift analysis of mRS score at 90 days to be an odds ratio of [redacted]. A non-inferiority margin was also pre-specified for the mRS score of 0–1 at 90 days outcome. In line with the AcT analysis, non-inferiority would be established if the lower boundary of the 95% CI of the percentage difference in participants obtaining the outcome in the tenecteplase versus alteplase groups was greater than -5%.

### 3.3.2. Critical appraisal

No quality assessment was presented for the ATTEST-2 trial as the trial was ongoing and no detailed publications of the methods were available to the company or the EAG. Quality assessment of the AcT and EXTEND-IA TNK part 1 trials was presented in Table 8 in Appendix D.3. of the CS.

As stated in Section 3.1, the company answered yes or no for each of seven domains of bias and did not provide any reasoning on how their risk of bias judgments were made. Thus, the

EAG were unable to fully critique these judgments. The company assessed that AcT was not adequate for two of seven domains of bias, while EXTEND-IA TNK Part 1 was not adequate for one of seven domains of bias.

The company evaluated that both pivotal trials were not adequate in relation to Domain 4: “Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?” The EAG consider the company were reflecting on the open-label treatment allocation in both trials when making this judgment and agree with their assessment. Blinding of participants was especially important where there were subjective outcomes. The modified Rankin scale (mRS) score, and EQ-5D and EQ-VAS in the AcT trial, were outcomes assessed over the phone by a blinded assessor, but they made this judgement based on input from the trial participant who was not blinded to the treatment they received. Similarly, all assessments in the EXTEND-IA TNK part 1 trial were performed by people who were blinded to the treatment assignment. This included mRS score and early neurological improvement, both of which rely on input from the unblinded participant. The EAG were concerned that participants may have offered a more positive view of their health state if they had been randomised to tenecteplase. Participants were aware tenecteplase was the newer treatment and it was delivered in a bolus over 10 seconds and, unlike alteplase, did not require infusion for an hour. Given the potential influence an unblinded participant may have had over key outcomes in the trials, the EAG had some concerns over risk of bias related to Domain 4.

The second domain for which AcT was not deemed adequate was Domain 6: “Is there any evidence to suggest that the authors measured more outcomes than they reported?” The published protocol for AcT stated that the primary outcome was the mRS score at 90 to 120 days and that quality of life and safety outcomes would also be measured.[23] These outcomes were measured and presented in the CS, and it was unclear to the EAG what evidence suggested more outcomes were measured than reported. The EAG would have been better able to critique the company’s assessment of Domain 6 if they had provided their reasoning.

The EAG also noted that there were unexpected imbalances in dropouts between groups (Domain 5) in the AcT trial for the health-related quality of life (HRQL) outcomes. In Table 11 (Document B), the HRQL outcome data was presented and 20% of data were missing for the EQ-VAS outcome and 18.3% were missing for the EQ-5D-5L outcomes. However, the total number of participants analysed was presented, and it was unclear what proportion was missing

from each treatment arm, and whether a single arm was disproportionately represented in the analysis.

The EAG agree with the company that the trials were adequate in terms of random allocation (Domain 1), allocation concealment (Domain 2), similarity of groups at outset (Domain 3), and intention to treat analysis (Domain 7).

The company concluded that both trials were at low risk of bias. However, due to the lack of blinding of participants and their potential bias on the scoring of subjective outcomes, the EAG has some concerns over both studies for those outcomes and the resulting bias would favour tenecteplase. In addition, there was a high proportion of missing data for the HRQL outcomes in the AcT trial and it was not reported whether similar proportions were missing in each treatment arm. Given these concerns, the EAG consider the EQ-5D and EQ-VAS outcomes reported in AcT to be at a high risk of bias, with the resulting bias favouring tenecteplase.

## 3.4. Clinical effectiveness of tenecteplase

Evidence relevant to the decision problem, with reference to the non-inferiority margins used, was presented separately for the AcT trial and the EXTEND-IA TNK Part 1 trial. The company did not undertake formal meta-analysis of outcomes but presented “a qualitative overview of key efficacy and safety outcomes from both trials” in Table 14 in Section B.3.8. of the CS. At the clarification stage (Question A1), the company provided evidence from the large, ongoing, UK trial, ATTEST-2 with reference to the non-inferiority margins developed for the trial. Also at the clarification stage (Question A2), the company provided an assessment of ATTEST, TAAIS, TASTE-A, TRACE, using where possible, the non-inferiority margins established in AcT and the EXTEND-IA TNK Part 1 trials.

### 3.4.1. AcT clinical effectiveness results

#### 3.4.1.1. Primary and secondary endpoints

The efficacy results were presented for the ITT population (Table 5), which included 1,577 participants who were randomised and did not withdraw consent. Within the ITT population, 806 participants were randomized to tenecteplase and 771 participants were randomized to alteplase.

The primary outcome (mRS score of 0–1 after 90 to 120 days) occurred in 296 (36.9%) of 802 participants assigned to tenecteplase and 266 (34.8%) of 765 participants assigned to alteplase.

The unadjusted risk difference (95% CI) was 2.1% (-2.6, 6.9). The lower bound 95% CI of the difference in primary outcome rate (-2.6%) was greater than -5%, thus meeting the pre-specified non-inferiority margin.

The EAG also noted that a higher proportion of people in the tenecteplase arm had an mRS score 0–2 at 90–120 days and a higher proportion had a return to baseline function. Median (IQR) actual mRS score at 90–120 days and mean (95% CI) length of hospital stay were similar between the treatment arms.

The company presented subgroup analysis for the primary outcome in Appendix E of the CS. The EAG was not concerned that tenecteplase was inferior to alteplase for any of the subgroups analysed. It was notable that AcT found a numerical benefit for tenecteplase over alteplase in stroke onset to needle time at both timepoints (≤ 180 minutes and > 180 minutes).

**Table 5: Summary of primary and secondary efficacy endpoints specific to the decision problem from the AcT trial (adapted from table 10, Document B)**

| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of effect | Estimate (95% CI) |
|---|---|---|---|---|
| mRS score 0–1 at 90–120 days (n = 1,567), n (%) | 296/802 (36.9) | 266/765 (34.8) | Unadjusted risk difference | 2.1% (2.6, 6.9) |
| | | | Risk ratio (adjusted[a]) | 1.1 (1.0, 1.2) |
| mRS score 0–2 at 90–120 days (n = 1,567), n (%) | 452/802 (56.4) | 425/765 (55.6) | Difference in proportion (unadjusted) | 0.8 (-4.1, 5.7) |
| | | | Risk ratio (adjusted[a]) | 1.0 (1.0, 1.1) |
| Actual mRS score at 90–120 days (n = 1,567), median (IQR) | 2 (1, 4) | 2 (1, 4) | Difference in medians | 0 |
| | | | Odds ratio (adjusted[a]) | 0.9 (0.8, 1.1) |
| Return to baseline function (n = 1,454), n (%) | 219/740 (29.6) | 199/714 (27.9) | Difference in proportion (unadjusted) | 1.7 (-2.9, 6.4) |
| | | | Risk ratio (adjusted[a]) | 1.1 (0.9, 1.2) |
| Length of hospital stay (n = 1,479), mean (95% CI) | 5 (2, 11) | 5 (3, 11) | Difference in proportion (unadjusted) | 0 |
| | | | Risk ratio (adjusted[a]) | 1.0 (0.9, 1.1) |

Abbreviations: CI, confidence interval; IQR, interquartile range; mRS, modified Rankin scale.

Note:

[a] Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time, and source registry as fixed-effects variables, and site as a random-effects variable.

### 3.4.1.2. HRQL outcomes

HRQL outcomes were measured at 90 days using both the EQ-VAS (n = 1,262) and EQ-5D-5L (n = 1,289) scales and are presented in Table 6.

There was a numerical benefit for tenecteplase over alteplase for EQ-VAS at 90 days. EQ-5D-5L outcomes were presented by dimension, with dimensions summarized on a one to five scale. with one indicating no problem and five indicating unable to/extreme problems. The medians (IQR) were identical for each treatment arm across all five dimensions, although there was a numerical benefit in the odds ratios presented for four domains (mobility, usual task, pain, and anxiety) for alteplase over tenecteplase. No EQ-5D-5L utility score was presented, so it was unclear how these small benefits for alteplase would manifest across all five dimensions.

**Table 6: HRQL outcomes measured in the ITT population of the AcT trial (adapted from table 11, Doc B)**

| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of effect | Estimate (95% CI) |
|---|---|---|---|---|
| EQ-VAS at 90 days (n = 1,262), mean (SD) | 70.5 (21.3) | 68.1 (22.6) | Difference in proportion (unadjusted) | 2.4 (-0.1, 4.8) |
| | | | Beta-coefficient [a] (adjusted[b]) | 2.1 (-0.3, 4.5) |
| EQ-5D – mobility at 90 days (n = [redacted]), median (IQR) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Odds ratio (adjusted[a]) | [redacted] |
| EQ-5D – self care at 90 days (n = [redacted]), median (IQR) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Odds ratio (adjusted[a]) | [redacted] |
| EQ-5D – usual task at 90 days (n = [redacted]), median (IQR) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Odds ratio (adjusted[a]) | [redacted] |
| EQ-5D – pain at 90 days (n = | [redacted] | [redacted] | Difference in medians | [redacted] |

| Outcomes | Tenecteplase group (n = 806) | Alteplase group (n = 771) | Measure of effect | Estimate (95% CI) |
|---|---|---|---|---|
| [redacted]), median (IQR) | | | Odds ratio (adjusted[a]) | [redacted] |
| EQ-5D - anxiety at 90 days (n = [redacted]), median (IQR) | [redacted] | [redacted] | Difference in medians | [redacted] |
| | | | Odds ratio (adjusted[a]) | [redacted] |

Abbreviations: CI, confidence interval; IQR, interquartile range.

Notes:

[a] Beta coefficients for categorical predictors, such as treatment, represents the change in the outcome variable when switching from one category of the predictor variable to another.

[b] Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time, and source registry as fixed-effects variables, and site as a random-effects variable.

### 3.4.2. EXTEND-IA TNK Part 1 clinical effectiveness results

From March 2015 to October 2017, 204 participants were enrolled, two excluded, and 101 participants were assigned to receive tenecteplase and 101 were assigned to receive alteplase. No participants were lost to follow-up.

The primary outcome (reperfusion of greater than 50% of the involved territory or an absence of retrievable thrombus at the time of the initial angiographic assessment) was observed in 22 patients (22%) who were randomized to tenecteplase, as compared with 10 (10%) who were randomized to alteplase. The incidence difference (95% CI) was 12% (2%, 21%) and did not cross the noninferiority margin of −2.3% (p=0.002 for noninferiority). This translated into an adjusted odds ratio (95% CI) of 2.6 (1.1, 5.9), which demonstrated a statistically significant benefit for tenecteplase over alteplase. Thrombectomy was not performed in people who met the primary outcome of reperfusion at the initial angiographic assessment, with the exception of one person in the tenecteplase group. This person had substantial reperfusion, but a residual thrombus, which was treated with thrombectomy.

There were numerical benefits for tenecteplase over alteplase for an mRS of 0 or 1 at 90 days, mRS of 0 to 2 at 90 days, and early neurological improvement.

**Table 7: Summary of primary and secondary efficacy endpoints specific to the decision problem from the EXTEND-IA TNK Part 1 trial (adapted from tables 12 and 13, Document B)**

| Outcomes | Tenecteplase group (n=101) | Alteplase group (n=101) | Measure of effect | Estimate (95% CI) | P value |
|---|---|---|---|---|---|
| Greater than 50% reperfusion at initial angiographic assessment, no. (%) [a] | 22 (22%) | 10 (10%) | Percentage difference | 12 (2, 21) | 0.002 (non-inferiority) |
| | | | Adjusted incidence ratio | 2.2 (1.1, 4.4) | 0.03 |
| | | | Adjusted odds ratio | 2.6 (1.1, 5.9) | 0.02 |
| mRS score at 90 days, median (IQR) [b] | 2 (0, 3) | 3 (1, 4) | Adjusted odds ratio | 1.7 (1.0–2.8) | 0.04 |
| mRS of 0 to 2 or no change from baseline at Day 90, no. (%) [c] | 65 (64%) | 52 (51%) | Adjusted incidence ratio | 1.2 (1.0, 1.5) | 0.06 |
| | | | Adjusted risk ratio | 1.8 (1.0, 3.4) | 0.06 |
| mRS of 0 or 1 or no change from baseline at Day 90, no. (%) [c] | 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 neurological improvement, no. (%) [c, d] | 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 |

Abbreviations: CI, confidence interval; IQR, interquartile range; mRS, modified Rankin scale.

Notes:

[a] Reperfusion > 50% to the involved territory or no retrievable thrombus. The analysis was adjusted for the site-of vessel occlusion strata. The P value for the difference is for non-inferiority, and the P values for the incidence ratio and odds ratio are for superiority.

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

[c] 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.

[d] Early neurological 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.

### 3.4.3. ATTEST-2 trial clinical effectiveness results

The company provided preliminary outcome data from the ongoing ATTEST-2 trial in response to clarification question A1. The data were provided by Professor Keith Muir, the Principal

Investigator of the ATTEST-2 trial. They presented a [redacted], and [redacted]. The trial found a [redacted] for [redacted] for the primary outcome, [redacted]. The adjusted odds ratio (95% CI) was [redacted] which [redacted] the pre-specified non-inferiority margin of [redacted]. The risk difference (95% CI) of [redacted] was [redacted] which [redacted] the pre-specified non-inferiority margin of [redacted]. The trial found a numerical benefit for [redacted] for [redacted]. The treatments were [redacted] for [redacted].

**Table 8: Summary of primary and secondary efficacy endpoints specific to the decision problem from the ATTEST-2 trial (adapted data presented in clarification question A1)**

| Outcomes | Tenecteplase group ([redacted]) | Alteplase group ([redacted]) | Measure of effect | Estimate (95% CI) | P value |
|---|---|---|---|---|---|
| [redacted] | N/A | N/A | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | | | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | N/R | N/R | N/R |
| [redacted] | [redacted] | [redacted] | N/R | N/R | N/R |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Abbreviations: CI, confidence interval; IQR, interquartile range; mRS, modified Rankin scale; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; N/R, not reported

Notes:

[redacted]

## 3.4.4. Assessment of non-inferiority using outcome data from the ATTEST, TAAIS, TASTE-A, and TRACE trials

At the clarification stage (question A2), the company provided as assessment of outcome data presented in four additional relevant RCTs, ATTEST, [11] TAAIS, [12] TASTE-A, [13] and TRACE, [14] using the non-inferiority margins developed for the AcT and EXTEND-IA TNK Part 1 trials.

### 3.4.4.1. Proportion of people who had a score of 0 or 1 on the mRS at 90 days, up to 120 days after randomization

Non-inferiority was met if the lower 95% confidence interval (CI) of the unadjusted difference in the proportion of patients who met the primary outcome between the tenecteplase and alteplase groups was more than -5%. The studies each found a benefit for tenecteplase over alteplase, but they were small, and the company did not undertake a meta-analysis. When taken individually there was substantial uncertainty linked to each estimate of effect and none of the trials met the non-inferiority margin.

**Table 9: Non-inferiority assessment of the ATTEST, TAAIS, TASTE-A, and TRACE trials using the inferiority margin developed for the AcT trial**

| Trial | Tenecteplase arm, n/N (%) | Alteplase arm, n/N (%) | Difference (95% CI) |
|---|---|---|---|
| ATTEST (NCT01472926) | 13/47 (28%) | 10/49 (20%) | 7.3 (-9.8, 24.3) |
| TAAIS (ACTRN12608000466347) | 18/25 (72%) | 10/25 (40%) | 32 (-6.0, 58.1) |
| TASTE-A (NCT04071613) | 23/55 (42%) | 20/49 (41% | 1 (-18.0, 20.0) |
| TRACE (NCT04676659) | 35/57 (64%) | 35/59 (59%) | 2.1 (-15.7, 19.9) |

Abbreviation: CI, confidence interval

### 3.4.4.2. Restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment

The EXTEND-IA TNK Part 1 trial established non-inferiority if the lower boundary of the two-sided 95% CI of the unadjusted 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 TASTE-A trial reported an outcome that was closely aligned to the outcome reported in the EXTEND-IA TNK Part 1 trial. They found a very similar effect between treatment arms, but the study was too small to find a precise estimate of effect and establish non-inferiority by the −2.3 percentage points margin.

The TAAIS trial found a statistically significant benefit for tenecteplase over alteplase in percent reperfusion at 24 hours. The ATTEST trial found a numerical benefit for alteplase over tenecteplase in recanalisation at 24-48 hours (evaluated using the Thrombolysis in Myocardial Infarction (TIMI) flow grade). The TRACE trial did not report a reperfusion outcome.

It is unclear to the EAG from these data whether tenecteplase is non-inferior to alteplase for reperfusion at the initial angiographic assessment. However, as noted in Section 3.4.4.1, these are small studies and are underpowered to offer a reliable estimate of non-inferiority of tenecteplase to alteplase. The outcomes reported were too heterogenous for meta-analysis and individually offered a contrasting picture of tenecteplase versus alteplase in early reperfusion. Given the results of the EXTEND-IA TNK Part 1 trial and those presented from the smaller RCTs, on the balance of probabilities, the EAG considered it likely that tenecteplase was non-inferior to alteplase for early reperfusion. However, the outcome data supporting this conclusion were inconsistent.

**Table 10: Non-inferiority assessment of the ATTEST, TAAIS, TASTE-A, and TRACE trials using the inferiority margin developed for the EXTEND-IA TNK Part 1 trial**

| Trial | Outcome reported | Tenecteplase arm, n/N (%) | Alteplase arm, n/N (%) | Difference (95% CI) |
|---|---|---|---|---|
| ATTEST (NCT01472926) | Recanalisation at 24-48 hours (TIMI grade 2-3[a]) | 21/32 (66%) | 26/35 (74%) | -8.7 (-30.6, 13.3) |
| TAAIS (ACTRN12608000466347) | Median (range) percent reperfusion at 24 hours | n=25<br>100% (5.8, 100) | n=25<br>61.4% (-5.3, 100) | Adjusted p value vs alteplase: p < 0.001 |
| TASTE-A (NCT04071613) | 50% reperfusion between ED CT perfusion and 24-hour perfusion imaging (MRI) | 33/35 (94%) | 34/35 (97%) | -2.9 (-12.3, 6.6) |

| Trial | Outcome reported | Tenecteplase arm, n/N (%) | Alteplase arm, n/N (%) | Difference (95% CI) |
|---|---|---|---|---|
| TRACE (NCT04676659) | No reperfusion data reported | n/a | n/a | n/a |

Abbreviations: CI, confidence interval; CT, computed tomography; ED, emergency department.

Notes:

[a] Thrombolysis in myocardial infarction (TIMI) flow-grading system classifies successful reperfusion after thrombolysis as either grade 2 (partial) or grade 3 (complete) flow.

## 3.5. Safety of tenecteplase

### 3.5.1. Safety in the AcT trial

A summary of safety outcomes in the AcT trial was presented in Table 15 (Document B). The EAG's clinical experts concluded that the trials were well matched for safety outcomes and adverse events. They noted that a key safety outcome was symptomatic intracerebral haemorrhage (ICH). This was experienced by 27 (3.4%) of participants in the tenecteplase arm and 24 (3.2%) of participants in the alteplase arm.

The company presented subgroup analysis of death up to Day 90 in Appendix E of the CS. There was a statistically significantly fewer deaths in the tenecteplase arm in people with an NIHSS score of less than 8 at baseline, and a statistically significantly fewer deaths in the alteplase arm in people with an NIHSS score of 8 to 15 at baseline. It was notable that the treatments were found to have equivalent mortality in people with an NIHSS score of more than 15. The EAG's clinical experts were unaware of any plausible reason why safety would vary across these subgroups. They agreed that the study was underpowered to offer a reliable estimate of mortality across three subgroups.

### 3.5.2. Safety in the EXTEND-IA TNK Part 1 trial

Only three safety outcomes in the EXTEND-IA TNK Part 1 trial were presented in the CS (Table 16, Document B). Similar numbers of participants in each arm experienced symptomatic intracerebral haemorrhage and parenchymal haematoma. There were 10 (10%) deaths in the tenecteplase arm and 18 (18%) deaths in the alteplase arm. This was a statistically significant effect with an adjusted risk ratio of 0.5 (95% CI: 0.3 to 1.0, p-value: 0.049). The EAG's clinical experts explained that this could be a meaningful mortality benefit of tenecteplase over alteplase for people who have experienced large artery occlusion and were eligible to undergo endovascular thrombectomy. They noted that it was hard to lower deaths in strokes, but that the

mortality benefit could reflect earlier reperfusion in the tenecteplase arm over the alteplase arm, which may have led to less damage to a person's brain.

### 3.5.3. Safety in the ATTEST-2 trial

The company provided preliminary safety data from the ongoing ATTEST-2 trial in response to clarification question A1. There were [redacted] between the treatment arms. There was a [redacted] of tenecteplase over alteplase for [redacted] ([redacted] versus [redacted], and a [redacted] for alteplase over tenecteplase for [redacted], ([redacted] versus [redacted].

### 3.5.4. Safety in the ATTEST trial

Adults with supratentorial ischaemic stroke within 4.5 hours of onset were recruited and randomly assigned (1:1) to receive tenecteplase 0.25 mg/kg (maximum 25 mg) or alteplase 0.9 mg/kg (maximum 90 mg). Safety data from this study was presented in Table 9 and Table 10 in Appendix F of the CS.

The study found a lower proportion of people in the tenecteplase arm (8 of 52, 15%) than the alteplase arm (14 of 51, 27%) experienced an ICH. It also detailed adverse events up to day 90 and found 22 (42%) of participants in the tenecteplase arm and 16 (31%) of participants in the alteplase arm experienced at least one serious adverse event.

The EAG's clinical experts noted that this was a small study and were not convinced that the differences in safety between treatment arms represented meaningful differences between tenecteplase and alteplase. They also noted that the larger AcT and EXTEND-IA TNK Part 1 trials found similar proportions in each treatment arm experienced an ICH or serious adverse events.

## 3.6. EAG conclusions on the clinical effectiveness of tenecteplase

Based on the above evidence, the EAG agreed that tenecteplase was non-inferior and equally safe to alteplase for thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well.

The submission used the two largest completed RCTs (AcT and EXTEND-IA TNK Part 1) and a large ongoing RCT (ATTEST-2) to support the submission. The AcT and EXTEND-IA TNK Part 1 trials did not have UK locations, but the ATTEST-2 trial took place in [redacted] across the UK. The trials were open label and the patients, carers and people delivering the interventions

were aware of the participant's assigned intervention during the trial. Trials lacking blinding on participants and health care providers are understood to significantly exaggerate treatment efficacy in subjective outcomes. Critical outcomes in this submission have subjective elements, such as the mRS score, EQ-5D/EQ-VAS, and early neurological improvement. The EAG considered this would favour tenecteplase as it was the newer treatment, could be administered over 10 seconds, and did not require IV infusion for an hour.

Results from the AcT, EXTEND-IA TNK Part 1, and ATTEST-2 trials found tenecteplase to be [redacted] to alteplase for their primary outcomes using the pre-specified non-inferiority margins. In addition, tenecteplase was [redacted] than alteplase for the functional outcomes measured using the mRS scale at 90 days in all seven studies assessed in this appraisal. Reporting of early reperfusion, EXTEND-IA TNK Part 1's primary outcome, was heterogenous and the smaller completed RCTs found conflicting results. However, on the balance of probabilities, the EAG considered it likely that tenecteplase was non-inferior to alteplase for early reperfusion.

The AcT trial assessed participants HRQL at 90 days. It did not find a statistically significant benefit for either treatment. There were numerical benefits for alteplase for four of the five EQ-5D domains, although no EQ-5D utility score was presented, so it was unclear how small benefits might manifest across all five dimensions. The EAG noted the high proportion of missing data for the EQ-5D (20.0%) and EQ-VAS (18.3%) outcomes and these outcomes were at a high risk of bias.

The company presented safety data for four trials: AcT, ATTEST, ATTEST-2 and EXTEND-IA TNK Part 1. The three large trials all found similar safety and AEs for each treatment, including adverse events of special interest such as intercranial haemorrhage. In the EXTEND-IA TNK Part 1 trial there was a statistically significant reduction in mortality in the tenecteplase arm than the alteplase arm. The EAG's clinical experts explained that this could be a meaningful mortality benefit of tenecteplase over alteplase for people who have experienced large artery occlusion and were eligible to undergo endovascular thrombectomy, i.e. people with bigger strokes. While they noted that it is hard to lower deaths in strokes, the mortality benefit could reflect earlier reperfusion in the tenecteplase arm over the alteplase arm, which may have led to less damage to a person's brain. However, the EAG understand this benefit was not reflected in the other included studies and it was unclear whether it was a consequence of recruiting a more severe population to the EXTEND-IA TNK Part 1 trial or whether it was a chance effect.

The professional organisation submissions highlighted two benefits of tenecteplase linked to the speed and ease of administration. Dr Fergus Doubal and Dr Michelle Dharmasiri, of the British and Irish Association of Stroke Physicians, stated that using a single bolus would substantially speed up transfer to neuroscience centres, improving outcomes in people after an AIS. Therefore, some of the benefits seen in the seven trials presented in this submission may have been due to faster movement down the care pathway. Dr Tom Hughes, of the Association of British Neurologists, stated that tenecteplase would be particularly useful in people who are restless or combative or who may be reluctant or unable to tolerate an IV infusion. It is unclear to the EAG what proportion of patients meet these criteria but there is potentially a real-world benefit linked to the speed and ease of administration.

# 4. SUMMARY OF THE EAG'S CRITIQUE OF THE COST-EFFECTIVENESS EVIDENCE SUBMITTED

## 4.1. Company's cost comparison analysis

### 4.1.1. Overview of cost comparison

The company have submitted a cost-effectiveness analysis, which they have modified by setting the effectiveness of the two drugs to be equal. The company assumed the same administration cost and adverse events for the two treatments in the base case – therefore, the only material difference included is the cost of the drugs. The EAG have therefore only verified calculations relating to drug costs, for if the Committee consider the assumption of similar effectiveness and safety to be satisfied then these are the only relevant costs.

Tenecteplase is used in an acute setting and therefore the model, appropriately, only considers the costs of administration during the acute time frame (first 72 hours after stroke onset).

There are no other cost categories identified by the EAG that would be expected to be different between the two treatments. There is not expected to be any impact on subsequent treatment choice.

### 4.1.2. Technology acquisition costs

Tenecteplase for acute ischemic stroke is given in a 25 mg vial at a price of [redacted]. Vial sharing is not possible, and the maximum single dose is 25 mg, meaning that the cost of one administration is fixed (Appendix C, CS). However, the 25 mg vial is not currently available. The analyses presented below are contingent on this availability, which is pending marketing authorization.

Alteplase is given at a weight-based dose of 0.9 mg/kg, with a maximum dose of 90 mg for patients with a body weight of 100 kg or over.[24] The economic model applies weight-based dosing only for the IV administration (0.81 mg/kg) and assumes that the full 10 mg is always used for the bolus dose (rather than 0.09 mg/kg). This does not align with clinical practice; experts consulted by the EAG stated they would use any remainder from vials that were opened towards the infusion.

Alteplase is available in 10, 20 and 50 mg vials. These are not linearly priced. The cost for each of the vial sizes is £172.80, £259.20 and £432.00, respectively. No patient access scheme

applies. The company assume the cheapest combination of vials is used to give alteplase, even if this requires more product being wasted, which would appear reasonable. The EAG were, however, informed that not all hospitals have access to all vial sizes, which may increase the cost of alteplase in those hospitals.

The company assume no vial sharing is possible for alteplase. They used method of moments, assuming a normal distribution and a mean weight of 78.9kg and an SD of 7.89, based on the mean weight in the overall UK population from HSE of 85.1 kg for males and 71.8 kg for females, and a split of 53.6% males and 46.4% females, derived from data from the SSNAP on stroke patients admitted to and/or discharged from hospital between April 2022 and March 2023.[25,26] The proportion of males is similar to that observed across the ATTEST-2, AcT and EXTEND-IA TNK Part 1 trials ([redacted] 52.1%, 54.5%, respectively).

In the AcT trial the mean (standard deviation) weight was [redacted] kg (SD [redacted]) in the tenecteplase group and [redacted] kg (SD [redacted]) in the alteplase group, which is consistent with the weight calculated. Data on mean weight are not available for EXTEND-IA TNK or ATTEST-2.

Clinical experts consulted by the EAG considered that the mean weight used by the company may be a little light, as stroke patients are more likely to be overweight. Increasing the assumed mean weight increases the cost of alteplase (but not tenecteplase) and therefore makes use of tenecteplase even more cost saving. The EAG also explored the impact of using a lognormal distribution instead and found it made little difference to the results.

Clinical experts consulted by the EAG stated that they are not able to share vials of alteplase across patients.

### 4.1.3. Administration and monitoring costs

The EAG heard from clinical experts that there was unlikely to be a cost saving from the reduced administration time as patients receiving both treatments would still need monitoring every 15 minutes.

### 4.1.4. Other impacts

Based on consultation with clinical experts and professional organization submissions from the ABN, BIASP and St Georges, the EAG consider that there may be additional practical benefits to treatment with tenecteplase, which are not captured in the economic analysis. These could reduce delays or the need for additional interventions in practice. They include:

- Potentially shorter time for a doctor to be present for administration. This can be a problem out of hours, although there was disagreement amongst experts as to whether tenecteplase could be administered without a doctor present.
- No need to find a pump for administration or set up a syringe driver.
- No need for an escort for patients requiring transport in an ambulance. This is a particular benefit as the BIASP note in their submission that UK practice is for patients to receive IV thrombolysis at their local hospital with an urgent transfer to the closest neuroscience centre for thrombectomy. This can require nurses to go in the ambulance to facilitate transfer or, more often, a delay to transfer for administration to be completed.
- Only one vial size required. Some hospitals do not have access to all vial sizes for alteplase, which would increase wastage.
- Reduction in the proportion of patients requiring a thrombectomy, with its associated costs (including stent retrievers which, based upon a 2018 briefing, cost £1,900 - £,5000).[27,28] Based upon EXTEND-IA TNK Part 1, which looked specifically at this sub-population, a difference of 11% was observed in patients treated with thrombectomy (as previously noted, all patients except one meeting the primary endpoint did not require thrombectomy). [redacted]. Given that around 10-20% of the patient population would be considered for thrombectomy, we would expect a cost saving of around £20 - £110 for the overall population.

### 4.1.5. Company results

Based upon the company's analysis, tenecteplase is expected to be cost saving purely due to the reduction in drug costs. The total cost of alteplase on this basis is calculated as £867.72, of which 41% is the cost of wastage. This compares to [redacted] for tenecteplase.

Within the EAG's analysis (which assumes that the bolus and infusion dose are drawn from the same set of vials) the cost of alteplase is £782.08. In fact, the cost without including wastage, based upon the mean weight used in the company analysis, is £613.69 [redacted].

## 4.2. EAG conclusion on the company's cost comparison

The EAG consider that tenecteplase is likely to be cheaper than alteplase on the basis of drug costs alone. There may be other benefits, which are not included in the economic analysis, which might result in a small additional reduction in costs.

# 5. EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

## 5.1. Strengths

### 5.1.1. Clinical evidence

The two pivotal trials presented in the CS consistently found tenecteplase to be non-inferior and, in many cases, numerically superior to alteplase for thrombolytic treatment of AIS within 4.5 hours from when patients were last known to be well. At the clarification stage, this was supported by preliminary results from a large ongoing UK trial and the published results of four smaller completed RCTs.

### 5.1.2. Economic evidence

Administration, adverse event, and other resource use costs are expected to be similar for both treatments, which leads to a simple cost comparison based upon drug costs alone. Based upon the 25 mg vial, which is yet to be launched, tenecteplase is expected to be [redacted] cheaper than alteplase. [redacted].

## 5.2. Weaknesses and areas of uncertainty

### 5.2.1. Clinical evidence

The EAG noted three areas of minor uncertainty:

- ATTEST-2,[1,2] the most relevant trial to the UK, had not been published yet. Therefore, the results presented were preliminary and subject to change following database lock.
- There were seven relevant RCTs to this assessment. The non-inferiority of tenecteplase versus alteplase was assessed individually for each. If a meta-analysis were undertaken, then it could have further improved the precision of the non-inferiority assessment.
- No EQ-5D-5L utility score was presented, and so it was unclear how a number of small benefits for alteplase over tenecteplase would manifest across all five dimensions.

### 5.2.2. Economic evidence

[redacted].

No data is available on the mean weight of patients expected to be treated with tenecteplase in clinical practice. The data provided, calculated based upon mean weights from HSE and male / female split from SSNAP, did however align with the available weight data from the AcT trial. The population mean weight would need to be implausibly low for tenecteplase to no longer be cheaper ([redacted]).

There may be other benefits, as noted in Section 4.1.4, that are not included in the economic analysis, which might result in a small additional reduction in costs.

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**Single Technology Appraisal**

**Tenecteplase for treating acute ischaemic stroke [ID6306]**

**EAG report – factual accuracy check and confidential information check**

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 21 May** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

**Issue 1** Critique of Screening Methods

| Description of problem | Description of proposed amendment | Justification for amendment | EAG response |
|---|---|---|---|
| In Table 2 on Page 16, where the EAG provides their assessment of the robustness of methods, it states “The EAG identified four relevant RCTs that were excluded without reason.”. | Suggest alternate wording is used as this inaccurately portrays that we have excluded trials without reason. Table 7 in the Appendix has a column called “Reason for exclusion from submission” where it can be season the reason for the four trials original exclusion:<br><br>ATTEST –“Small, single-centre study”<br><br>TTAIS – “Small study, only 25 patients treated with 0.25 mg/kg tenecteplase, other doses not relevant to clinical practice”<br><br>TASTEa – “Small study, only 49 patients treated with 0.25mg/kg tenecteplase, in a mobile stroke unit which is not relevant to UK clinical practice.”<br><br>TRACE – “Chinese population only, only 57 patients treated with 0.25 mg/kg tenecteplase, other doses not relevant to clinical practice” | Table 7 in the Doc B Appendices (Section D.1.2) provides an overview of the trials identified during the SLR and a column is included which provides reasoning behind exclusion for all excluded trials from the submission. | Thank you for the comment. The EAG recognise reasons for the exclusions were presented and has removed the phrase “without reason” from three places in the report. However, the broad critique has been retained as they were excluded using unknown criteria. |

| **Location of incorrect marking** | **Description of incorrect marking** | **Amended marking** | |
|---|---|---|---|
| Page 29 states, “They presented a [redacted], and to [redacted].” | We suggest that “[redacted]” also needs confidential marking.<br><br>This is unpublished data that is not owned by the company, therefore should also be marked confidential to ensure complete confidentiality is kept for the presentation of these results. | They presented a [redacted], and [redacted].” | Thank you for the correction. The marking has been updated in line with the suggestion. |

(Please add further lines to the table as necessary)