Tenecteplase for treating acute ischaemic stroke [ID6306]

A Cost Comparison Appraisal

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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Alex Allen	Lead for EAG's critical appraisal of the clinical evidence. Writing and editorial input.
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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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Table of Contents

List of tables

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: • 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: • 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 • Neurological deficit • Mortality • Length of hospital stay • Adverse effects of treatment, including bleeding events • 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. 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. 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. 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 **AcT** • 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. 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. • 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. • There were no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage, extracranial bleeding, or 90-day mortality. **EXTEND-IA TNK Part 1** • 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: • 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. 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 • Eligible for thrombolysis as per Canadian guidelines	• Adults presenting with AIS within 4.5 hours of onset • Independent prior to the stroke (estimated modified Rankin Scale 0-1) • Eligible for intravenous thrombolysis	• Adults presenting with AIS within 4.5 hours of onset • With large vessel occlusion of the internal carotid, middle cerebral or basilar artery • Eligible to undergo intravenous thrombolysis and endovascular thrombectomy
Interventions evaluated	IV tenecteplase (0.25 mg/kg body weight up to 25 mg) n=816	IV tenecteplase (0.25 mg/kg body weight up to 25 mg) [redacted]	IV tenecteplase (0.25 mg/kg body weight up to 25 mg) n=101
Concomitant medication	IV alteplase (0.9 mg/kg body weight up to 90 mg) n=784	IV alteplase (0.9 mg/kg body weight up to 90 mg) [redacted]	IV alteplase (0.9 mg/kg body weight up to 90 mg) 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 • Actual mRS score at 90–120 days • Return to baseline function • Length of hospital stay	[redacted]	• mRS of 0 to 2 or no change from baseline at 90 days • mRS of 0 to 1 or no change from baseline at 90 days • Early neurological improvement [a]
HRQL outcomes	• EQ-VAS at 90 days • 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 • EQ-5D – usual task at 90 days • EQ-5D – pain at 90 days • EQ-5D - anxiety at 90 days		
Pre-planned subgroups	• Age (< 80 vs ≥ 80 years) • Sex • Baseline stroke severity • Symptom onset-to-needle time • Large vessel occlusion • Type of enrolling centre • 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=25 100% (5.8, 100)	n=25 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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