NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# April 2023

## Tenecteplase for treating acute ischaemic stroke

| Company/Developer | Boehringer Ingelheim Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 36178 | NICE TSID: 11871 | UKPS ID: 668321 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development.

## Summary

Tenecteplase is in clinical development for acute ischaemic stroke in adults. Acute ischaemic stroke is caused by clots blocking blood vessels, which cuts off the blood supply to parts of the brain. Without blood supply, brain cells can be damaged or destroyed due to lack of oxygen and nutrients. Symptoms include numbness or weakness of the face, arm or leg on one side of the body, and often problems with speech and swallowing. The risk of stroke is increased by factors including age, high blood pressure, atrial fibrillation, diabetes mellitus type 2 and high cholesterol. Treatments to restore blood flow to the brain include alteplase, which dissolves blood clots; or thrombectomy, where large blood clots are removed mechanically. Both of these treatments require rapid administration after the stroke to be effective.

Tenecteplase is an enzyme used to break down blood clots, by binding to the protein chains and breaking down the mesh that forms the clot. It is administered directly into a vein. If licensed, tenecteplase would offer an additional treatment option, requiring only one injection, for patients with acute ischaemic stroke.

## Proposed Indication

Thrombolytic treatment of acute ischaemic stroke in adults.[1]

## Technology

### Description

Tenecteplase (Metalyse) is a recombinant fibrin-specific plasminogen activator derived from native t-PA by modifications at three sites of the protein structure. It binds to the fibrin component of the thrombus (blood clot) and selectively converts thrombus-bound plasminogen to plasmin, which degrades the fibrin matrix of the thrombus. Tenecteplase has a higher fibrin specificity and greater resistance to inactivation by its endogenous inhibitor (PAI-1) compared to native t-PA.[2]

Tenecteplase is currently in clinical development for the treatment of acute ischaemic stroke. In the phase III clinical trial (ATTEST2, NCT02814409) adult patients are given tenecteplase 0.25 mg/kg administered as a single rapid intravenous bolus.[1]

### Key Innovation

Intravenous (IV) thrombolysis with currently available plasminogen activator significantly increases the probability of a favourable outcome, but dosage and administration have remained unchanged since 1995. There is potentially substantial benefit from newer IV thrombolytic agents due to improved pharmacological characteristics. Data from previous small studies suggest that tenecteplase is potentially superior to other plasminogen activators, having better safety and efficacy, simpler administration requiring a single bolus injection, and lower cost.[3,4]

Tenecteplase arose from mutagenesis studies, which produced a variant of currently available plasminogen activator with 14-fold greater fibrin specificity, 10-fold greater conservation of fibrinogen, 80-fold increased resistance to plasminogen activator inhibitor-1 activity, more rapid thrombolysis and reduced plasma clearance, as well as a longer plasma half-life that could achieve thrombolysis as a single bolus injection.[5]

If licenced, tenecteplase will provide an additional treatment option for patients with acute ischaemic stroke.

### Regulatory & Development Status

Tenecteplase currently has Marketing Authorisation in the EU/UK for the thrombolytic treatment of myocardial infarction with persistent ST elevation or recent left bundle branch block within 6 hours after the onset of acute myocardial infarction symptoms.[2]

Tenecteplase is also in phase II/III clinical development for the treatment of:[6]

- Central retinal artery occlusion
- Cerebrovascular Disorders
- Basilar Artery Occlusion
- ST Elevation Myocardial Infarction

## Patient Group

### Disease Area and Clinical Need

A stroke is a serious, life-threatening medical emergency that occurs when the blood supply to part of the brain is cut off.[7] There are two main types of stroke: ischaemic and haemorrhagic. Ischaemic stroke, which accounts for 85% of all cases, is caused by a clot blocking the blood supply to parts of the brain.[7] Symptoms include numbness or weakness of the face, arm or leg on one side of the body, and often problems with speech and swallowing.[8] The risk of stroke is increased by factors including age, high blood pressure, atrial fibrillation, diabetes mellitus type 2 and high cholesterol.[7] Other risk factors include a personal or family history of stroke, gender, race and ethnicity, and brain aneurysms or arteriovenous malformations, and behavioural factors (smoking, alcohol intake, poor diet, and low physical activity).[9,10]

Stroke is one of the leading causes of death in the UK, accounting for about 75% of deaths from cerebrovascular diseases. There are approximately 100,000 people who have strokes in the UK each year.[11] It is projected that the overall costs of stroke in the UK for those aged 45 years and over will rise from £25.6 billion in 2015 to £42.6 billion in 2025 and £75.2 billion in 2035, an increase of 195% over 20 years. In addition, it is projected the annual NHS cost of stroke will increase from £3.4 billion in 2015 to £6.9 billion in 2025 and £10.2 billion in 2035.[12] In 2015, the average societal cost of ischaemic stroke per person was £44,231 in the first 12 months after stroke (cost of incident stroke), plus £24,381 in subsequent years (cost of prevalent stroke).[9] In England, in 2021-22 there were 161,142 finished consultant episodes (FCE) for cerebral infarction (ICD-10 code: I63) resulting in 77,844 hospital admissions, 1,239,898 FCE bed days and 282 day cases.[13]

### Recommended Treatment Options

Acute ischaemic stroke management aims to restore blood flow to the brain and involves thrombolysis with alteplase, which dissolves blood clots. Treatment effect is time-dependent: alteplase is most effective if administered as early as possible and within 4.5 hours of the onset of stroke symptoms. It must only be given once an intracranial haemorrhage has been ruled out by appropriate imaging. [14,15]

## Clinical Trial Information

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| Trial | **ATTEST 2;** NCT02814409; Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis a phase 3 open-label Randomized Placebo Controlled Trial of Tenecteplase in participants with acute ischaemic stroke<br>**Phase III:** recruiting<br>**Location:** UK<br>**Primary completion date:** August 2019 |
| Trial Design | Randomised, parallel assignment, open label |
| Population | N = 1870 (estimated); male or non-pregnant female ≥ 18 years of age, < 4.5h after symptom onset, eligible for intravenous thrombolysis, independent prior to the stroke (estimated modified Rankin Scale 0-1). |
| Intervention(s) | Tenecteplase 0.25mg/kg administered as a single rapid IV bolus (maximum dose 25mg) |
| Comparator(s) | Alteplase 0.9 mg/kg with 10% of the total dose administered as an initial IV bolus and remaining 90% of the total dose administered as an IV infusion over 1 hour (maximum dose 90mg) |

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| Outcome(s) | Primary outcome measures: modified Rankin Scale (Time frame: Day 90 [+/- 7])<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | **AcT;** NCT03889249; Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke<br>**Phase III:** active, not recruiting<br>**Location:** Canada<br>**Primary completion date:** April 2022 |
| Trial Design | Randomised, parallel assignment, single-blinded |
| Population | N = 1600 (actual); adults, < 4.5h after symptom onset, eligible for IV thrombolysis. |
| Intervention(s) | Tenecteplase 0.25mg/kg administered over 10-20 seconds as a single rapid IV bolus (maximum dose 25mg) |
| Comparator(s) | Alteplase 0.9 mg/kg with 10% of the total dose administered as an initial IV bolus and remaining 90% of the total dose administered as an IV infusion over 1 hour (maximum dose 90mg) |
| Outcome(s) | Primary outcome measures: modified Rankin Scale (Time frame: 90-120 days)<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | As of data cut-off (Jan 21, 2022), 296 (36.9%) of 802 patients in the tenecteplase group and 266 (34.8%) of 765 in the alteplase group had an mRS score of 0–1 at 90–120 days (unadjusted risk difference 2.1% [95% CI – 2·6 to 6·9], meeting the prespecified non-inferiority threshold).[16] |
| Results (safety) | In safety analyses, 27 (3.4%) of 800 patients in the tenecteplase group and 24 (3.2%) of 763 in the alteplase group had 24 h symptomatic intracerebral haemorrhage and 122 (15.3%) of 796 and 117 (15.4%) of 763 died within 90 days of starting treatment.[16] |

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| Trial | **EXTEND-IA TNK;** NCT02388061; Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke<br>**Phase II:** completed<br>**Locations:** Australia and New Zealand<br>**Primary completion date:** October 2017 |
| Trial Design | Randomized, parallel assignment, open label |
| Population | N = 202 (actual); adults, < 4.5h after symptom onset, eligible for IV thrombolysis. |

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| Intervention(s) | Tenecteplase 0.25mg/kg administered over approximately 10 seconds as a single rapid intravenous bolus (maximum dose 25mg) |
| Comparator(s) | IV tissue plasminogen activator at the standard licensed dose of 0.9 mg/kg up to a maximum of 90mg, 10% as bolus and the remainder over 1 hour. |
| Outcome(s) | Primary outcome measures: proportion of patients with substantial angiographic reperfusion score of 2b/3 (restoration of blood flow to >50% of the affected arterial territory) or absence of retrievable thrombus at initial angiogram (Time frame: Initial angiogram day 0) |
| Results (efficacy) | The primary outcome occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (incidence difference, 12 percentage points; 95% confidence interval (CI), 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=0.002 for noninferiority; P=0.03 for superiority). Tenecteplase resulted in a better 90-day functional outcome than alteplase (median modified Rankin scale score, 2 vs. 3; common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04).[17] |
| Results (safety) | Symptomatic intracerebral haemorrhage occurred in 1% of the patients in each group.[17] |

## Estimated Cost

Tenecteplase is already marketed in the UK; the NHS indicative price for 10,000 unit powder and solvent for solution for injection vial is £602.70.[18]

## Relevant Guidance

### NICE Guidance

- NICE technology guidance. Alteplase for treating acute ischaemic stroke (TA264). September 2012.
- NICE guidance. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (NG128). May 2019.
- NICE quality standard. Stroke in adults (QS2). April 2016.
- NICE interventional procedure guidance. Mechanical clot retrieval for treating acute ischaemic stroke (IPG548). February 2016.

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Service Specifications: Specialised Vascular Services (Adults). 170004/S.
- NHS England. Clinical Commissioning Policy: Mechanical thrombectomy for acute ischaemic stroke (all ages). 170033P. March 2018.

### Other Guidance

- Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke for the UK and Ireland. 2023.[19]

- Berge E, Whiteley W, Audebert H, De Marchis, GM, Fonseca AC, Padiglioni C, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. 2021.[20]
- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. 2018.[21]

## Additional Information

## References

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