NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# January 2023

## Invimestrocel for Acute ischaemic stroke

| Company/Developer | Athersys Inc |
|---|---|

☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 7134 | NICE TSID: 10190 | UKPS ID: N/A |
|---|---|---|

## Licensing and Market Availability Plans

Currently in phase II and III clinical development

## Summary

Invimestrocel is in clinical development for the treatment of acute ischaemic stroke within 18-36 hours of onset. Ischaemic stroke is the most common type of stroke. It happens when a blood vessel is blocked by a blood clot, cutting off blood flow to part of the brain (ischaemia). Without blood supply, brain cells can be damaged or destroyed due to lack of oxygen. Symptoms may include numbness or weakness on one side of the body and problems with balance, speech and swallowing. Symptoms may range from mild, through to severe strokes that can lead to long-term disability, coma and death. While there are some treatments available for ischemic stroke, patients must receive these treatments within only a few hours of having a stroke.

Invimestrocel is developed from a special class of stem cells obtained from healthy adult bone marrow. These cells may be intravenously administered without tissue matching or immune suppression, and results show they are capable of reducing inflammation, protecting damaged or injured tissue, and enhancing the formation of new blood vessels in regions of ischaemic injury. If licenced, invimestrocel may provide a wider time window for treatment of ischemic stroke, allowing treatment for a greater number of patients, and with more substantial long-term recovery.

## Proposed Indication

Treatment of acute ischemic stroke (AIS) within 18-36 hours of onset.[1-3]

# Technology

## Description

Invimestrocel (MultiStem) cells) is a distinct subpopulation of adherent bone marrow cells that are easily expandable to generate sufficient quantities for intravenous delivery and have shown efficacy in animal models of ischaemic stroke. When administered intravenously, invimestrocel downregulates immune activation and inflammatory responses while upregulating neurogenesis. Reduction in spleen size that occurs following stroke is prevented by invimestrocel administration consistent with immune modulation as an important mechanism of action of these cells.[4]

Invimestrocel is currently in clinical development for the treatment of AIS within 18-36 hours of onset. In the phase III clinical trial (NCT03545607; MASTERS-2), patients will receive a single intravenous (IV) infusion containing 1.2 billion cells of invimestrocel 18-36 hours after an AIS.[1-3]

## Key Innovation

Ischaemic stroke remains a leading cause of death and disability.[4] While there are some treatments available for ischemic stroke, patients must receive these treatments within only a few hours of having a stroke. Unfortunately, only a modest percentage of stroke patients arrive at the hospital in time to receive these treatments. Invimestrocel cell therapy for the treatment of ischemic stroke may be delivered to a patient up to 36 hours after the stroke. This opens up the time window for treatment, allowing up to 90-95% of the stroke patients to be eligible to receive treatment.[5]

Invimestrocel for AIS may meet the criteria for an advanced therapy medicinal product (ATMP) classification by the European Medicines Agency (EMA). The scientific recommendation for an ATMP classification is issued by the EMA's Committee for Advanced Therapies (CAT).

## Regulatory & Development Status

Invimestrocel is not currently licensed for any indication in the EU/UK.

Invimestrocel is in phase II and III clinical trials for the following idications:[6]

- acute respiratory distress syndrome
- acute myocardial infarction
- trauma induced Multiple Organ Failure/Systemic Inflammatory Response Syndrome
- ulcerative colitis

# Patient Group

## Disease Area and Clinical Need

A stroke is a serious, life-threatening medical condition that occurs when the blood supply to part of the brain is cut off.[7] There are three main types of stroke: ischaemic stroke, haemorrhagic stroke, and transient ischaemic attack (TIA). Ischaemic stroke is caused by blockages which cut off the blood supply to parts of the brain and this is the most common type of stroke.[8] Stroke is most commonly manifested by focal neurological deficits such as numbness or weakness of the face, arm or leg on one side of the body, and often problems with speech and swallowing.[9,10] Certain conditions increase the risk of having a stroke

including high blood pressure (hypertension), high cholesterol, atrial fibrillation, and diabetes.[7] Other risk factors may include smoking, age and gender, race and ethnicity, a personal or family history of stroke or TIA, and brain aneurysms or arteriovenous malformations.[11]

Stroke is one of the leading causes of death in the UK. There are 100,000 people who have strokes in the UK each year. Stroke accounts for roughly 75% of deaths from cerebrovascular diseases.[12] In 2015, the average societal cost of stroke per person was £45,409 in the first 12 months after stroke (cost of incident stroke), plus £24,778 in subsequent years (cost of prevalent stroke). It is projected that the overall costs of stroke in the UK for those aged 45 years and over will rise from £26 billion in 2015 to £43 billion in 2025 and £75 billion in 2035, an increase of 194% over 20 years.[13] 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 and 1,239,898 FCE bed days.[14]

## Recommended Treatment Options

Treating ischaemic strokes involve a combination of medications to treat the condition and prevent it happening again. Some of these medications need to be taken immediately and only for a short time, while others may only be started once the stroke has been treated and may need to be taken long term.[15]

The pharmacological treatment recommendations for people with AIS include:[16]

- Alteplase
- Aspirin and anticoagulant treatment

## Clinical Trial Information

| | |
|---|---|
| Trial | NCT03545607; **MASTERS-2;** MultiStem Administration for Stroke Treatment and Enhanced Recovery Study<br>**Phase III -** Recruiting<br>**Location(s):** US and Taiwan<br>**Primary completion date:** September 2022 |
| Trial Design | Randomised, parallel assignment, quadruple-blinded |
| Population | N=300 (estimated); subjects ≥18 years of age with ischaemic stroke involving cerebral cortex; occurrence of moderate to moderately severe stroke with a persistent neurologic deficit |
| Intervention(s) | Invimestrocel (1.2 billion cells) (IV) |
| Comparator(s) | Matched placebo |
| Outcome(s) | **Primary outcome measure:**<br><br>Assessment of disability by examining the distribution of modified Rankin Scale (mRS) scores [scale range = 0 to 6] evaluated by shift analysis [Time frame: 90 days]<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | - |

| | |
|---|---|
| Results (safety) | - |

| | |
|---|---|
| Trial | NCT02961504; **TREASURE;** Placebo-Controlled, Double-Blind, Phase 2/3 Efficacy and Safety Trial of HLCM051 (MultiStem®) in Patients With Ischemic Stroke<br>**Phase II & III –** Completed<br>**Location(s):** Japan<br>**Primary completion date:** March 2021 |
| Trial Design | Randomized, parallel assignment, double-blind |
| Population | N= 206; subjects aged 20 years and older with a clinical diagnosis of cerebral cortical ischaemic stroke; occurrence of ischaemic stroke with clear motor or speech deficit; onset of ischaemic stroke within 18 to 36 hours |
| Intervention(s) | A single dose of 1.2 billion invimestrocel cells to be intravenously administered |
| Comparator(s) | Matched placebo |
| Outcome(s) | **Primary outcome measures:**<br><br>Proportion of subjects with an excellent outcome defined by the functional assessments [Time frame: Day 90]<br><br>Comparison between the HLCM051 and the placebo groups in key adverse events [Time frame: Day 90]<br><br>See trial record for full list of other outcomes |
| Results (efficacy) | The primary endpoint, Excellent Outcome at 90 days, did not reach statistical significance in this trial. Improvement in pre-specified measures of functional "independence" and good outcomes, such as mRS ≤2, Barthel Index ≤95 and Global Recovery associated with invimestrocel treatment.[17] |
| Results (safety) | No material differences in safety outcomes, including mortality and life-threatening adverse events between the treatment and placebo groups.[17] |

| | |
|---|---|
| Trial | NCT01436487; Double-Blind, Randomized, Placebo-Controlled Phase 2 Safety and Efficacy Trial of MultiStem® in Adults With Ischemic Stroke<br>**Phase II** – Completed<br>**Location(s):** UK & US<br>**Primary completion date:** December 2015 |
| Trial Design | Randomised, parallel assignment, quadruple-blinded |
| Population | N= 134 (actual); subjects aged 18 to 83 years with a clinical diagnosis of cortical cerebral ischaemic stroke; occurrence of a moderate to moderately severe stroke |
| Intervention(s) | A single dose of invimestrocel to be intravenously administered |

| | |
|---|---|
| Comparator(s) | Matched placebo |
| Outcome(s) | **Primary outcome measures:**<br><br>- Frequency of dose limiting adverse events [Time frame: 7 days]<br>- Stroke recovery based on global test analysis including modified Rankin Scale (mRS), NIHSS, and Barthel Index (BI) [Time frame: 90 days]<br><br>See trial record for dull list of other outcomes |
| Results (efficacy) | There was no difference between the multipotent adult progenitor cell group and placebo groups in global stroke recovery at day 90 (odds ratio 1.08 [95% CI 0.55-2.09], p=0.83)[18] |
| Results (safety) | There were no dose-limiting toxicity events in either group. There were no infusional or allergic reactions and no difference in treatment-emergent adverse events between the groups.[18] |

## Estimated Cost

The cost of invimestrocel is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE technology guidance. Alteplase for treating acute ischaemic stroke (TA264). September 2012.
- NICE clinical 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

- 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. stroke. 2018.[19]
- Royal College of Physicians. National clinical guideline for stroke. 2016.[20]

- Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline (SIGN 118). June 2010.[21]

## Additional Information

Athersys Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## References

1 ClinicalTrials.gov. *Treatment Evaluation of Acute Stroke for Using in Regenerative Cell Elements (TREASURE). Trial ID: NCT02961504*. 2016. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02961504 [Accessed 1 December 2022].

2 ClinicalTrials.gov. *Study to Examine the Effects of MultiStem in Ischemic Stroke. Trial ID: NCT01436487*. 2016. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT01436487 [Accessed 1 December 2022].

3 ClinicalTrials.gov. *MultiStem® Administration for Stroke Treatment and Enhanced Recovery Study (MASTERS-2). Trial ID: NCT03545607*. 2018. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03545607 [Accessed 1 December 2022].

4 Kenmuir CL, Wechsler LR. Update on cell therapy for stroke. *Stroke and Vascular Neurology*. 2017;2(2). Available from: http://dx.doi.org/10.1136/svn-2017-000070.

5 Athersys Inc. *Ischemic Stroke*. Available from: https://www.athersys.com/multistem-therapy/clinical-trials/ischemic-stroke/default.aspx [Accessed 1 December 2022].

6 ClinicalTrials.gov. *MultiStem | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?term=MultiStem&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 1 December 2022].

7 National Health Services (NHS). *Overview-Stroke*. Available from: https://www.nhs.uk/conditions/stroke/ [Accessed 1 December 2022].

8 Stroke Association. *Types of Stroke*. Available from: https://www.stroke.org.uk/what-is-stroke/types-of-stroke [Accessed 2 December 2022].

9 Khandelwal P, Yavagal DR, Sacco RL. Acute ischemic stroke intervention. *Journal of the American College of Cardiology*. 2016;67(22):2631-44. https://doi.org/10.1016/j.jacc.2016.03.555.

10 National Institute for Health and Care Excellence (NICE). *Mechanical clot retrieval for treating acute ischaemic stroke*. 2016. Available from: https://www.nice.org.uk/guidance/ipg548/resources/mechanical-clot-retrieval-for-treating-acute-ischaemic-stroke-pdf-1899871933511365 [Accessed 5 December 2022].

11 National Heart Lung and Blood Institute (NIH). *Stroke-Causes and Risk Factors*. 2022. Available from: https://www.nhlbi.nih.gov/health/stroke/causes [Accessed 5 December 2022].

12 Stroke Association. *Stroke statistics*. 2022. Available from: https://www.stroke.org.uk/what-is-stroke/stroke-statistics [Accessed 5 December 2022].

13 Stroke Association. *Current, future and avoidable costs of stroke in the UK*. 2017. Available from: https://www.stroke.org.uk/sites/default/files/costs_of_stroke_in_the_uk_report_-executive_summary_part_2.pdf [Accessed 5 December 2022].

14 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 5 December 2022].

15 National Health Services (NHS). *Treatment-Stroke*. Available from: https://www.nhs.uk/conditions/stroke/treatment/ [Accessed 5 December 2022].

16 National Institute for Health and Care Excellence (NICE). *Stroke and transient ischaemic attack in over 16s: diagnosis and initial management*. 2019. Available from: https://www.nice.org.uk/guidance/ng128/chapter/Recommendations#initial-management-of-suspected-and-confirmed-tia [Accessed 5 December 2022].

17 Business Wire. *Athersys Announces That Its Partner, HEALIOS K.K., Reported Topline Data From the TREASURE MultiStem Ischemic Stroke Study*. 2022. Available from: https://www.businesswire.com/news/home/20220520005089/en [Accessed 9 December 2022].

18 Hess DC, Wechsler LR, Clark WM, Savitz SI, Ford GA, Chiu D, et al. Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet Neurology*. 2017;16(5):360-8. https://doi.org/10.1016/s1474-4422(17)30046-7.

19 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. *stroke*. 2018;49(3):e46-e99. https://www.bmc.org/sites/default/files/Patient_Care/Specialty_Care/Stroke_and_Cerebrovascular_Center/Medical_Professionals/Protocols/2018%20AHA%20Ischemic%20Stroke%20Guideline%20Update%202018.pdf

20 Royal College of Physicians. *National clinical guideline for stroke*. 2016. Available from: https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx [Accessed 9 December 2022].

21 Scottish Intercollegiate Guidelines Network (SIGN). *Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline*. 2010. Available from: https://www.sign.ac.uk/media/1056/sign118.pdf [Accessed 5 December 2022].

***NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.***