POSITIVE RESULTS IN KEY IND ENABLING STUDIES CONFIRMS COMPETITIVE POSITION OF ARG-007

Highlights:

- *Argenica has generated positive results in a number of key safety studies required by the US Food & Drug Administration (FDA) for inclusion in the Company's Investigational New Drug (IND) Application, which is due for submission by the end of 2024.*
- *The in vivo micronucleus study in rats confirmed ARG-007* ***does not impact genetic material****, and a high maximum tolerated dose of 17.5 mg/kg was achieved, well above the therapeutic dose used in the current Phase 2 acute ischaemic stroke (AIS) clinical trial.*
- *At the request of the FDA, Argenica undertook a further study on the impact of ARG-007 on standard of care drug tissue plasminogen activator (tPA). The study, utilising human blood clot, confirmed* ***ARG-007 did not impact the clot dissolving activity of tPA****, indicating ARG-007 can be used with the standard of care tPA therapy.*
- *The glutamate receptor recycling study confirmed* ***ARG-007 does not permanently downregulate receptors*** *responsible for calcium influx,* ***suggesting the drug mechanism of action will not cause neurotoxicity****.*
- *The data further demonstrates that ARG-007 has a* ***unique mechanism of action and pharmacological benefits*** *compared to competitor drugs.*
- *Argenica's current Phase 2 clinical trial in AIS patients is progressing well, with no safety issues identified to date and sufficient funding to complete the trial.*

Perth, Australia; 25 September 2024 - Argenica Therapeutics Limited (ASX: AGN) ("Argenica" or the "Company"), a biotechnology company developing novel therapeutics to reduce brain tissue death after stroke and other neurological conditions, is pleased to announce the completion of key safety studies required to be included in Argenica's IND application.

An IND application is a request made by a clinical sponsor to obtain authorisation from the FDA to administer an experimental drug to humans in clinical trials. Accordingly, obtaining authorisation and opening an IND will enable Argenica to do later stage clinical trials in AIS patients in the US.

The first IND enabling study, known as an *in vivo* micronucleus assay, is designed to evaluate the potential of a substance (e.g., a drug, chemical, or other compound) to cause genetic damage in bone marrow or peripheral blood cells of animals, in this case rats.

The formation of micronuclei is indicative of chromosomal breakage or mis-segregation during cell division, which can lead to mutations, carcinogenesis, or other genetic disorders. This study confirmed **ARG-007 has no impact on genetic material** up to the determined maximum tolerated dose of 17.5 mg/kg. This study is a key safety assessment required by the FDA when submitting an IND application.

The second study was conducted to determine whether ARG-007 interacts with the ability of the current standard of care drug, tissue plasminogen activator (tPA), to dissolve clots. This was specifically requested by the FDA via the Company's pre-IND meeting. The study was conducted utilising a human blood clot. The study showed that when ARG-007 was administered with tPA, **ARG-007 had no impact on the ability of tPA to dissolve the clot**. Regulatory authorities must ensure that any experimental drug does not have an impact on the efficacy of a current standard of care drug, including tPA used to treat AIS patients. By confirming ARG-007 does not impact the ability for tPA to dissolve human blood clots, this study provides evidence that ARG-007 could be administered alongside tPA in an emergency department setting.

The third study examined the recycling/recovery of neuronal glutamate receptors after treatment of neuronal cultures with ARG-007 by assessing the sensitivity of neurons to glutamate excitotoxicity over an extended time duration. This study revealed that significant neuroprotection from a single dose of ARG-007 lasted out to 12 hours, post 12 hours the neuroprotective effect dropped away. Neuroprotection was again restored when an additional dose was given post 12 hours. This indicates that after 12 hours the glutamate receptors return to normal function enabling neuronal signal transmission. This is an important safety consideration, because drugs that permanently block glutamate receptors have severe neurotoxic side effects. **This study indicates that ARG-007 does not permanently block glutamate receptors,** and therefore ARG-007 presents as an ideal drug candidate for acute neurological indications including ischaemic stroke where receptors are only required to be down regulated for a limited period of time to safeguard against stroke induced excitotoxicity prior to the blood flow being restored.

In addition to adding to the IND enabling safety profile of ARG-007, the results of these new studies taken together with previously confirmed data, demonstrate that ARG-007 has a number of key benefits over competitor drugs, including:

- Given ARG-007 is a D-isomer peptide it is resistant to proteolytic degradation and therefore is not readily degraded in the body, this was confirmed in Argenica's Phase 1 clinical trial showing a 12–15-hour half-life.[1]

[1] ASX Announcement dated 15 May 2023 – Final Phase 1 Clinical Trial Report Confirms Argencia Successfully Passes Critical Milestone

- The long half-life indicates prolonged efficacy at the effect site, which is an important requirement for acute conditions including ischaemic stroke.
- Given ARG-007 is resistant to proteolytic degradation it is not degraded by standard of care clot dissolving drugs, meaning it can be administered easily in a clinical setting with current standard of care drugs.[2]
- The short 10-minute IV infusion administration of the drug means that it does not impact clinical workflow, in particular the administration is completed prior to performing the standard of care thrombectomy procedure therefore not impacting IV delivery of drugs required during this procedure.
- ARG-007 works on multiple mechanisms of action[3], not only downregulating NMDA receptors, to achieve maximum neuroprotection, but importantly only for a period of 12 hours, meaning no safety issues are associated with permanent downregulation of glutamate receptors, which are required for normal neuronal signalling.
- ARG-007's superior stability means it is not genotoxic as confirmed in both *in vitro* and *in vivo* micronucleus assays, as stated above.

Dr Liz Dallimore, **Managing Director of Argenica**, stated "*The results generated from these studies not only supports our IND application to the FDA, but also provide further confirmation that ARG-007 has a unique mechanism of action and pharmacological profile which lends itself to being an ideal therapy in acute ischaemic stroke. We are working with our FDA regulatory consultants to compile the documentation required for our IND application, and with the completion of these studies, the Company is now well positioned to submit the IND application to the FDA by the end of this calendar year.*"

Argenica is currently drafting its IND submission, which is anticipated to be submitted to the FDA by the end of calendar year 2024. Once Argenica has an open IND with the FDA it will allow the Company to complete later stage clinical trials in the US following the completion of the current Phase 2 clinical trial. Argenica is fully funded to complete the Phase 2 clinical trial, which is progressing well with no safety issues identified to date.

This announcement has been approved for release by the Board of Argenica.

For more information please contact: info@argenica.com.au

[2] Meloni BP, Blacker DJ, Edwards AB, Knuckey NW. Impact of poly-arginine peptides R18D and R18 on alteplase and tenecteplase thrombolysis in vitro, and neuroprotective stability to proteolysis. J Thromb Thrombolysis. 2022 Jul;54(1):172-182.

[3] MacDougall G, Anderton RS, Trimble A, Mastaglia FL, Knuckey NW, Meloni BP. Poly-arginine-18 (R18) Confers Neuroprotection through Glutamate Receptor Modulation, Intracellular Calcium Reduction, and Preservation of Mitochondrial Function. Molecules. 2020 Jun 29;25(13):2977.

ABOUT ARGENICA

Argenica (ASX: AGN) is developing novel therapeutics to reduce brain tissue death after stroke and other types of brain injury and neurodegenerative diseases to improve patient outcomes. Our lead neuroprotective peptide candidate, ARG-007, has been successfully demonstrated to improve outcomes in pre-clinical stroke models, traumatic brain injury (TBI) and hypoxic ischaemic encephalopathy (HIE). The Company has recently completed a Phase 1 clinical trial in healthy human volunteers to assess the safety and tolerability of a single dose of ARG-007. Argenica is now conducting a Phase 2 clinical trial in ischaemic stroke patients, as well as continuing to generate preclinical data in other neurological conditions.