POSITIVE PRECLINICAL DATA FOR ARG-007 NEUROPROTECTION IN HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

Highlights:

- *ARG-007 shown to offer neuroprotection for late pre-term hypoxic-ischaemic encephalopathy (HIE), providing further evidence that the technology could have greater applications beyond stroke.*
- *HIE is a type of brain dysfunction that occurs when the brain doesn't receive enough oxygen or blood flow for a period of time. It is one of the most serious birth complications for infants.*
- *In an animal model of late pre-term HIE, ARG-007 reduced the volume of brain tissue death by 50% compared to groups which received a placebo saline injection.*
- *Importantly, ARG-007 reduced the volume of brain tissue death by 40% compared to hypothermia. Hypothermia is the current standard of care and the only approved treatment to improve neurological outcomes of HIE for late pre-term and term infants.*
- *Reducing brain tissue death caused by HIE could make a significant difference to an infants' clinical outcome. It could mean the difference of walking, talking and thinking normally or being disabled for life.*
- *Findings from the study are currently being prepared for publication in a scientific journal and will become the foundation for additional efficacy studies of ARG-007 in additional animal models of HIE.*

Perth, Australia; 3 November 2021 - Argenica Therapeutics Limited (ASX: AGN) ("Argenica" or the "Company"), a biotechnology company developing novel therapeutics to reduce brain tissue death after stroke and other types of brain injury, is pleased to share positive efficacy results from a preclinical study of ARG-007 in a late pre-term animal model of hypoxic-ischaemic encephalopathy (HIE); also referred to as perinatal asphyxia or perinatal hypoxia-ischaemia.

HIE is a type of brain damage that occurs when the brain does not receive enough oxygen or blood flow for a period of time. Although adults can experience HIE, it most commonly occurs as the result of an oxygen-depriving event during or around the time of birth.[1] HIE is one of

[1] https://hiehelpcenter.org/medical/causes-risk-factors/

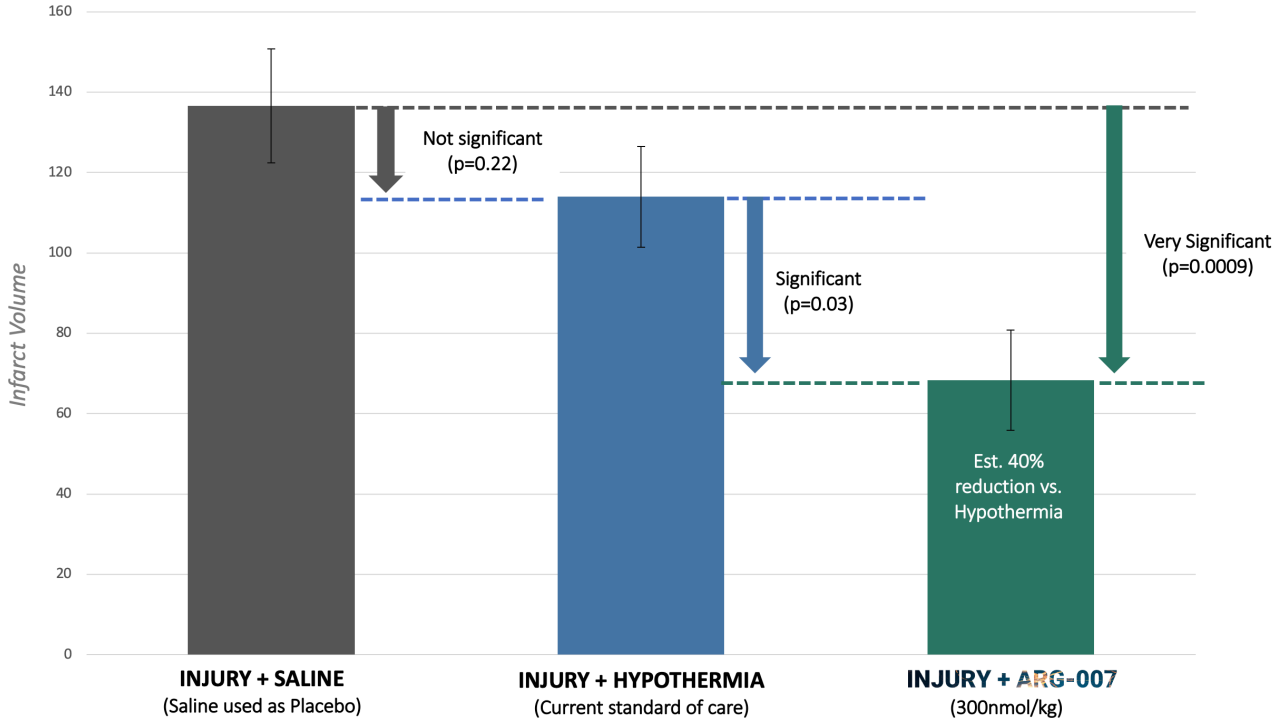
the most serious birth complications affecting full term infants.[2] HIE affects around 2.5 per 1000 live births in developed countries[3].

The study, undertaken at the Perron Institute for Neurological and Translational Science (Perron Institute), aimed to explore the neuroprotective properties of ARG-007 when administered immediately following hypoxia-ischaemia in an animal model equivalent to late pre-term infants (34 to 37 weeks gestation).

The results showed that ARG-007 very significantly reduced the volume of brain tissue death (infarct volume) for HIE compared to the control group which received a saline injection instead of ARG-007. The study also assessed the comparative neuroprotection of ARG-007 versus hypothermia, which is currently the only treatment available which improves neurological outcomes for late pre-term and term infants with HIE (current standard of care). Compared with hypothermia, ARG-007 also showed a significant reduction in the infarct volume.

The percentage reduction in infarct volume for ARG-007 treated animals was 50% (300 nmol/kg dose of ARG-007, see Figure 1) compared to the control group, and close to 40% compared to the hypothermia treated group (300 nmol/kg dose of ARG-007, see Figure 1).

ARG-007 significantly reduced the volume of brain tissue death (infarct volume) for HIE



[2] Schiariti V, Klassen AF, Hoube JS, et al. Perinatal characteristics and parents' perspective of health status of NICU graduates born at term. *J Perinatol.* 2008;28:368–376.
[3] Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol. 2008; 199(6):587-95.

Figure 1. Infarct volume (mm^3) in control (injury + saline) animals and treatment animals. Following injury (ischaemia-hypoxia), treatment animals received either hypothermia or ARG-007 (300 nmol/kg). Following treatment, the hypothermia treated group showed a small reduction in infarct volume (not statistically significant), whereas the ARG-007 treated group showed a significantly greater reduction in infarct volume (50% reduction). In addition, the ARG-007 treated group showed a significantly greater reduction in infarct volume than the hypothermia treated group (~40% reduction).

Argenica's CEO, Dr Liz Dallimore said: "This preclinical data further confirms the neuroprotective capability of ARG-007 in infant HIE, which is extremely encouraging. We now have a number of positive preclinical rodent models in HIE confirming the efficacy of ARG-007 to significantly protect brain cells from injury. This data is important because it shows that ARG-007 may have a greater application moving forward than just in the area of stoke patients. This is a very exciting development for the Company and we look forward to continuing to work with the Perron Institute to progress this application of ARG-007 in further studies."

Further information on HIE and the study is outlined is included as Appendix A.

NEXT STEPS

Following this positive data, Argenica will now look to progress further animal efficacy studies of ARG-007 in term animal models of HIE. Should these studies also show neuroprotective efficacy of ARG-007, Argenica will look to establish a clinical program of development for ARG-007 in HIE in human infants.

This study is currently being prepared for publication in a scientific journal.

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

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

ABOUT ARGENICA

Argenica (ASX: AGN) is developing novel therapeutics to reduce brain tissue death after stroke and improve patient outcomes. Our lead neuroprotective peptide candidate, ARG-007 has been successfully demonstrated to improve outcomes in pre-clinical stroke models and is in the process of being verified for its safety and toxicity before commencing Phase 1 clinical trials in humans. The aim is for our therapeutic to be administered by first responders to protect brain tissue against damage during a stroke with further potential to enhance recovery once a stroke has taken place.

ABOUT THE PERRON INSTITUTE

The Perron Institute for Neurological and Translational Science is Western Australia's longest established medical research institute. The Perron Institute undertakes cutting edge research on a broad spectrum of conditions including stroke, Parkinson's, motor neurone disease, muscular dystrophy, myositis and multiple sclerosis.

One of Perron Institute's special strengths is the connection between the Institute's laboratory research and its 21 specialist clinics. This multidisciplinary approach enables us to translate research outcomes into treatments aimed at providing a better quality of life for millions of people around the world who suffer with devastating neurological conditions.

APPENDIX A

Further Study & HIE Information

This study was undertaken by Dr Adam Edwards and Prof Bruno Meloni (Argenica's CSO) at the Perron Institute to determine the efficacy of ARG-007 in reducing neuronal cell death in the brain following hypoxic-ischaemic encephalopathy (HIE) in an established late pre-term animal model, equivalent to 34 to 37 weeks gestation in humans. The study compared the efficacy of ARG-007 against standard of care hypothermia treatment which is used in late pre-term and term infants to protect brain cells.

In newborn infants, HIE is one of the most serious complications affecting pre-term (less than 37 weeks gestation) and term (greater than 37 weeks gestation) infants, affecting around 2.5 per 1000 live births in developed countries[4].

HIE occurs when the brain does not receive enough oxygen or blood flow for a period of time. Perinatal hypoxia-ischaemia, also referred to as perinatal asphyxia, may occur at any time prior to labour, during labour and delivery, or immediately following delivery. The resultant HIE and damage to brain cells begins when cerebral blood flow and oxygen delivery to the brain is impaired. This initial injury that is caused due to a loss of oxygen supply, is followed by progressive brain cell death due to excitotoxicity, oxidative stress and inflammation[5,6]. The physiological effects resulting from the interruption to blood flow and/or oxygen in the brain can vary greatly depending on the length of time the disruption occurs as well as the location

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[4] Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE. A systematic review of the role of intrapartum hypoxia ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol. 2008; 199(6):587-95.
[5] Leonardo CC, Pennypacker KR. Neuroinflammation and MMPs: potential therapeutic targets in neonatal hypoxic-ischemic injury. *J Neuroinflammation* (2009) 6:13
[6] Thornton C, Hagberg H. Role of mitochondria in apoptotic and necroptotic cell death in the developing brain. *Clin Chim Acta* (2015) 451:35–8

of the disruption. Some children may only display mild effects whilst others will have severe permanent disability including cerebral palsy, cognitive impairment, or developmental delay.

Clinically, treatment to reduce brain injury for HIE is very limited. For late pre-term and term babies treatment predominately consists of exposing babies to moderate hypothermia (32 – 34°C for 72h) as a way of providing neuroprotection. Whilst this treatment may be well tolerated and safe for term babies, in 31-55% of babies the treatment has been shown to be ineffective at providing improved neurological outcomes[7]. Further, its use in earlier pre-term infants is associated with increased mortality and adverse effects and therefore it is not used for these babies.

Given the demonstrated efficacy of ARG-007 in several preclinical stroke models, the present study examined the efficacy of ARG-007 in a term neonatal animal model of HIE compared to exposure to hypothermia. This study builds on the previous preclinical studies supporting the use of ARG-007 as a treatment for perinatal HIE[8,9].

Methods

A model of HIE in perinatal rats (P7, equivalent to late pre-term infants) was used in this study in which blood flow to the brain from the right common and right internal carotid arteries were occluded, and animals were subsequently subjected to hypoxia (detailed methodology previously reported[10]). Immediately following hypoxia animals received either a dose of ARG-007 (100 or 300 nmol/kg) or a dose of saline, and were exposed to hypothermia (33.5°C for 2 hours) or normothermia (37°C).

Animals were assessed for total infarct volume (area of neuronal cell death), and data is expressed as infarct volume in mm^3 (Figure 1) or as a percentage of infarct volume compared to whole brain (minus cerebellum) (Figure 2).

Results

Results from both the 100 nmol/kg and 300 nmol/kg ARG-007 dose treatment groups showed significant reduction in infarct volumes following administration compared to control (saline)

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[7] Shankaran S. Therapeutic hypothermia for neonatal encephalopathy. Curr Treat Options Neurol. 2012;14(6):608–19

[8] Edwards, A. B., Cross, J. L., Anderton, R. S., Knuckey, N. W., & Meloni, B. P. (2018). Poly-arginine R18 and R18D (D-enantiomer) peptides reduce infarct volume and improves behavioural outcomes following perinatal hypoxic-ischaemic encephalopathy in the P7 rat. *Molecular brain*, *11*(1), 8.)

[9] Edwards, A. B., Anderton, R. S., Knuckey, N. W., & Meloni, B. P. (2018). Assessment of therapeutic window for poly-arginine-18D (R18D) in a P7 rat model of perinatal hypoxic-ischaemic encephalopathy. *Journal of neuroscience research*, *96*(11), 1816–1826.

[10] Edwards, A.B., Feindel, K.W., Cross, J.L., Anderton, R.S., Clark, V.W., Knuckey, N.W., Meloni, B.P. (2017). Modification to the Rice-Vannucci perinatal hypoxic-ischaemic encephalopathy model in the P7 rat improves the reliability of cerebral infarct development after 48 hours. *Journal of neuroscience methods*, 288, 62-71.

animals, with the 300 nmol/kg dose being slightly more effective, although the difference is not statistically significant. Furthermore, it was found that hypothermia alone did not significantly reduce infarct volume compared to control (saline) animals (Figure 2).

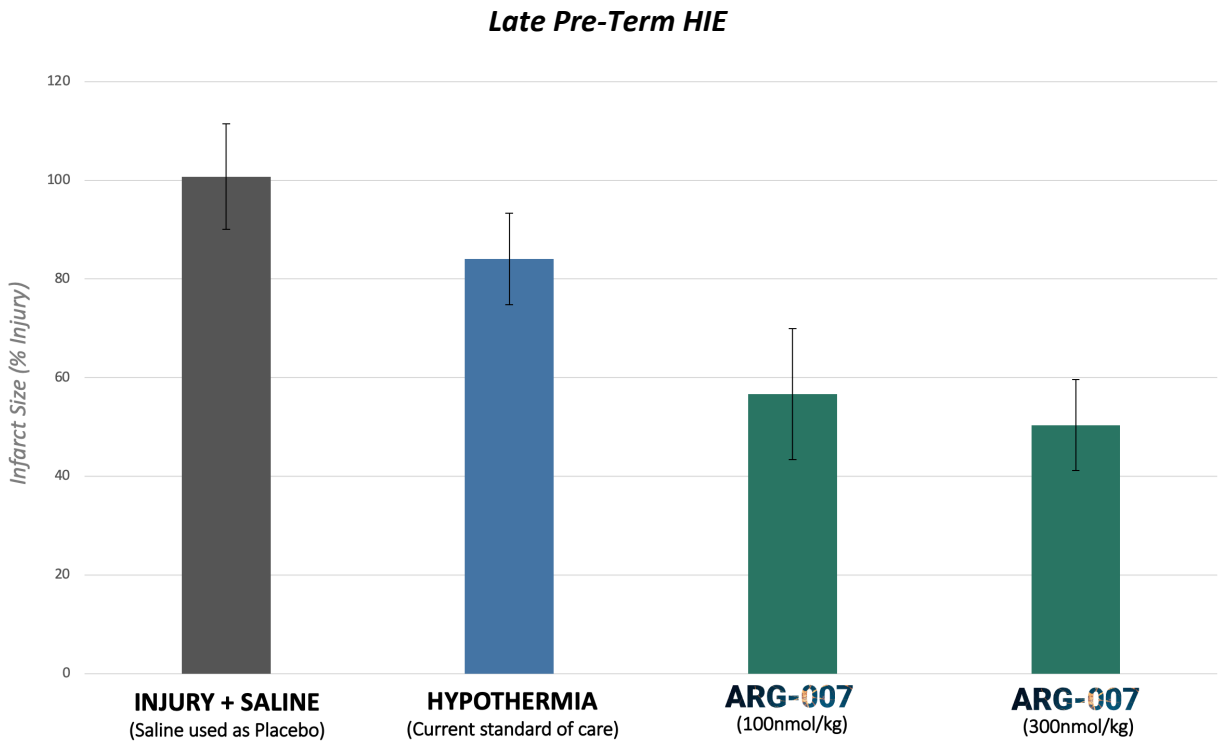

Figure 2. Infarct size as a percentage of the total infarct volume seen in the control (injury + saline) group. A non-statistically significant reduction is seen in animals treated with hypothermia. A statistically significant decrease in the percentage of infarct size compared to the control group is seen in both the 100 and 300 nmol/kg doses of ARG-007.

To determine if there were any benefits to combining hypothermia and ARG-007 treatments, the ARG-007 treatment groups were also exposed to hypothermia treatment. The addition of hypothermia to ARG-007 treatment groups showed no significant reduction in infarct size compared to the ARG-007 treatment groups that were not exposed to hypothermia (data not shown).

Conclusion

ARG-007 significantly reduces infarct volume following HIE in a preclinical late pre-term animal model. The significant reduction in neuronal cell death following a single dose of ARG-007 provides Argenica with additional data to continue to progress the development of ARG-007 as a therapeutic for HIE in pre-term and term babies.