FURTHER POSITIVE PRECLINICAL RESULTS FOR ARG-007 IN HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

Highlights:

- *ARG-007 shown to offer neuroprotection in a **full-term-equivalent** animal model of hypoxic-ischaemic encephalopathy (HIE), providing further evidence of the efficacy of the drug in HIE.*
- *HIE is one of the most serious birth complications affecting full-term infants, affecting around 2.5 per 1,000 live births in developed countries.*
- *Data shows a single dose of 300 nmol/kg ARG-007 reduces the volume of brain tissue death (infarct) by **86%** compared with saline control.*
- *Argenica will now look to engage a specialist paediatric clinical research facility to establish a clinical development program for ARG-007 in human infants with HIE.*

Perth, Australia; 29 September 2022 - 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 term-equivalent 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 supply 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 the most serious birth complications affecting full-term infants[2], and can result in life-long disabilities such as cerebral palsy. HIE affects around 2.5 per 1,000 live births in developed countries[3].

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

Previously (ASX Announcement 3 November 2021) the Company provided positive preclinical data in a **late pre-term** animal model of HIE (34 – 37 weeks gestation) where ARG-007 was shown to reduce the volume of brain tissue death by 50% compared to groups which received a placebo saline injection or 40% when compared to the current standard of care (hypothermia).

The latest study, undertaken at the Perron Institute for Neurological and Translational Science (Perron Institute) and led by Dr Adam Edwards and Argenica's Chief Scientific Officer Prof Bruno Meloni, examined the neuroprotective properties of ARG-007 when administered immediately following hypoxia-ischaemia in an animal model equivalent to **term infants** (37 - 40 weeks gestation).

ARG-007 significantly reduced the volume of brain tissue death (infarct volume) in a term-equivalent model of HIE

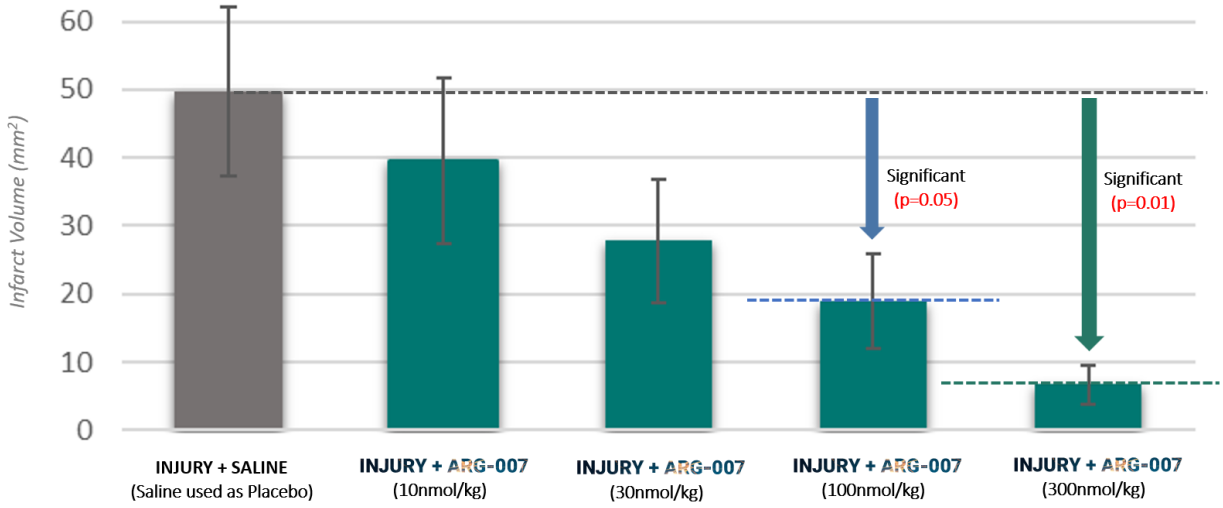

Figure 1. Infarct volume (mm^3) in control (injury + saline) animals and treatment (ARG-007) animals. Following injury (ischaemia-hypoxia), treatment animals received ARG-007 at varying doses (nmol/kg). Following treatment, the 100 nmol/kg and 300 nmol/kg ARG-007 treated groups showed significantly greater reduction in infarct volume compared with the saline control group.

The results demonstrated that ARG-007 significantly reduced the volume of brain tissue death (infarct volume) when examined at 48 hours post injury compared with the control group which received a saline injection instead of ARG-007. This reduction was dose dependent, with higher doses showing greater infarct reduction. The percentage reduction in infarct volume with ARG-007 treatment was **86%** at the 300 nmol/kg dose (see Figure 1) compared with the saline control group. A significant reduction (62%) was also seen with the 100 nmol/kg dose of ARG-007.

Argenica's CEO, Dr Liz Dallimore said: "We are incredibly excited about the results from this study. This preclinical research on the neuroprotective capability of ARG-007 in a term model of infant HIE further expands our preclinical data package for ARG-007 as a potential treatment for this devastating condition. Confirming ARG-007 works in a term animal model of HIE strengthens our position to potentially be able to successfully move ARG-007 into clinical trials in human infants who have been exposed to an ischaemic injury prior to, during or immediately after birth. Assuming the Company's upcoming Phase I trial for ARG-007 is successful, we look forward to progressing ARG-007 into infants for HIE."

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

NEXT STEPS

Argenica will now look to engage a specialist paediatric clinical research facility to establish a clinical program for the development of ARG-007 in human infants for HIE.

This study will be prepared for publication in a scientific journal.

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

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ABOUT ARGENICA

Argenica (ASX: AGN) is developing novel therapeutics to reduce brain tissue death after neurological injuries and improve patient outcomes. Our lead neuroprotective peptide candidate, ARG-007 has been successfully demonstrated to improve outcomes in preclinical stroke and HIE models and will shortly commence a Phase 1 clinical trial in healthy human volunteers to test its safety and tolerability. The aim is for our therapeutic to be administered by first responders to protect brain tissue against damage during a stroke and other types of brain injury, including HIE, with further potential to enhance recovery once a brain injury 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 term animal model, equivalent to 37 to 40 weeks gestation in humans. The study compared the efficacy of ARG-007 against a saline control.

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 the brain begins when cerebral blood flow and oxygen delivery to the brain is impaired. This initial injury that is caused due to a lack 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 depending on the length of time the disruption occurs as well as the location 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 limited. For late pre-term and term babies treatment predominately consists of inducing moderate hypothermia (33.5°C for 72h) as a way of providing neuroprotection. However, in 31 - 55% of babies, the treatment with hypothermia is ineffective at providing improved neurological outcomes[7].

Given the demonstrated efficacy of ARG-007 in a late pre-term model of HIE, the present study examined the efficacy of ARG-007 in a term-equivalent perinatal animal model of HIE compared to a saline control. This study builds on the previous preclinical studies supporting

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

the use of ARG-007 as a treatment for perinatal HIE[8,9] and provides further supporting efficacy data to move the treatment towards clinical trials.

Methods

A model of HIE in perinatal rats (10-day-old, equivalent to human term infants with respect to brain development) was used in this study in which blood flow to the brain was blocked by occluding the right common and right internal carotid arteries and subjecting animals to a period of hypoxia (detailed methodology previously reported[10]). Immediately following hypoxia animals received either a dose of ARG-007 (10, 30, 100 or 300 nmol/kg) or a dose of saline.

Animals were assessed for total infarct volume (area of neuronal cell death) 48 hours following injury and treatment. The data is expressed as infarct volume in mm^3 (Figure 1). All injury was measured on apparent diffusion coefficient (ADC) scans captured via magnetic resonance imaging (MRI).

Statistics for the data were performed in Prism with an ANOVA + Fisher's post hoc analysis.

Results

A dose-dependent response following administration of ARG-007 from 10 – 300 nmol/kg was observed, with reduction in infarct volume notable at the 30, 100, and 300 nmol/kg doses (Figure 1). Results from both the 100 nmol/kg and 300 nmol/kg ARG-007 dose treatment groups showed significant reductions ($p = 0.05$ and $p = 0.01$, respectively) in infarct volumes following administration compared to control (saline) animals.

Conclusion

Doses of both 100 nmol/kg and 300 nmol/kg of ARG-007 significantly reduce infarct volume following HIE in a preclinical term animal model, equivalent to 37 to 40 weeks gestation in humans. The significant reduction in brain injury following a single dose of ARG-007 provides Argenica with additional data to continue to progress the development of ARG-007 as a potential therapeutic for HIE in term human babies.

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[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.