ASX ANNOUNCEMENT

UPDATED - ARG-007 SHOWS SIGNIFICANT NEUROPROTECTION IN MAIN TRAUMATIC BRAIN INJURY STUDY

Perth, Australia; 4 FEBRUARY 2025 - Argenica Therapeutics Limited (ASX: AGN) ("Argenica" or the "Company") releases the following updated announcement to correct a typo in each of the legends to figures 1 and 2.

Authorised for release by the Managing Director and Company Secretary.

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 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 completed a Phase 1 clinical trial in healthy human volunteers to assess the safety and tolerability of a single dose of ARG-007. Argenica has now initiated a Phase 2 clinical trial in acute ischaemic stroke patients, as well as continuing to generate preclinical data in other neurological conditions.

ARG-007 SHOWS SIGNIFICANT NEUROPROTECTION IN MAIN TRAUMATIC BRAIN INJURY STUDY

Highlights:

- *ARG-007* ***significantly reduced damage to brain cells*** *caused by moderate traumatic brain injury (TBI) as assessed in a larger preclinical rat study measuring axonal injury and neuroinflammation following TBI.*

- *Damage to brain cells was assessed by measuring key markers of axonal injury and neuroinflammation following moderate TBI. Importantly, the biomarker levels of axonal injury and neuroinflammation following* ***ARG-007 treatment were equivalent to non-injured animals, suggesting ARG-007 prevents damage following TBI.***

- *Axonal injury and neuroinflammation play crucial roles in determining outcomes following TBI. They contribute significantly to many of the acute and chronic consequences of TBI, making them important targets for therapeutic intervention.*

- *ARG-007 treated animals also showed several signs of improvement* ***in a motor function test and a behavioural test and a significant*** *reduction in weight loss.*

- *This data verifies the data generated from the previous pilot study in rats*[1] *and pilot study in ferrets*[2]*, to confirm the* ***extensive neuroprotective effect of ARG-007*** *in moderate TBI in* ***multiple preclinical studies****.*

Perth, Australia; 4 February 2025 - Argenica Therapeutics Limited (ASX: AGN) ("Argenica" or the "Company"), a biotechnology company developing novel therapeutics to reduce brain tissue death after brain injury, is pleased to announce significant results from a larger preclinical study assessing the efficacy of ARG-007 in a rat model of moderate traumatic brain injury (TBI), suggesting ARG-007 can prevent axonal injury and neuroinflammation which significantly contribute to the acute and chronic consequences of TBI.

[1] ASX Announcement dated 22 June 2023, "ARG-007 protects brain cells in moderate traumatic brain injury model".
[2] ASX Announcement dated15 May 2024, "ARG-007 significantly reduces effects of traumatic brain injury in preclinical study."

This study expands on Argenica's previously announced rat pilot study in moderate TBI[3], and again was undertaken in the laboratory of Prof Lindy Fitzgerald at Curtin University and the Perron Institute for Neurological and Translational Sciences. The study assessed the therapeutic potential of ARG-007 in reducing axonal injury and neuroinflammation seen following moderate TBI and resulting behavioural outcomes. The aim was to confirm the results of the pilot study and ensure that the therapeutic effect of ARG-007 could be replicated multiple times in preclinical studies. The study was conducted in a well-characterised, impact-acceleration rat model of moderate TBI that results in diffuse injury to brain cells, mimicking an injury sustained during a moderate TBI such as from a fall or in a motor vehicle accident.

ARG-007 was found to protect brain cells in the injured brain by significantly reducing axonal injury following TBI, as measured by key axonal injury biomarkers neurofilament heavy protein (NF-H) and amyloid precursor protein (APP). The level of both NF-H and APP protein in ARG-007 treated animals was equivalent to animals that had not received a TBI (i.e. the same as the non-injured sham controls) as shown in Figure 1.

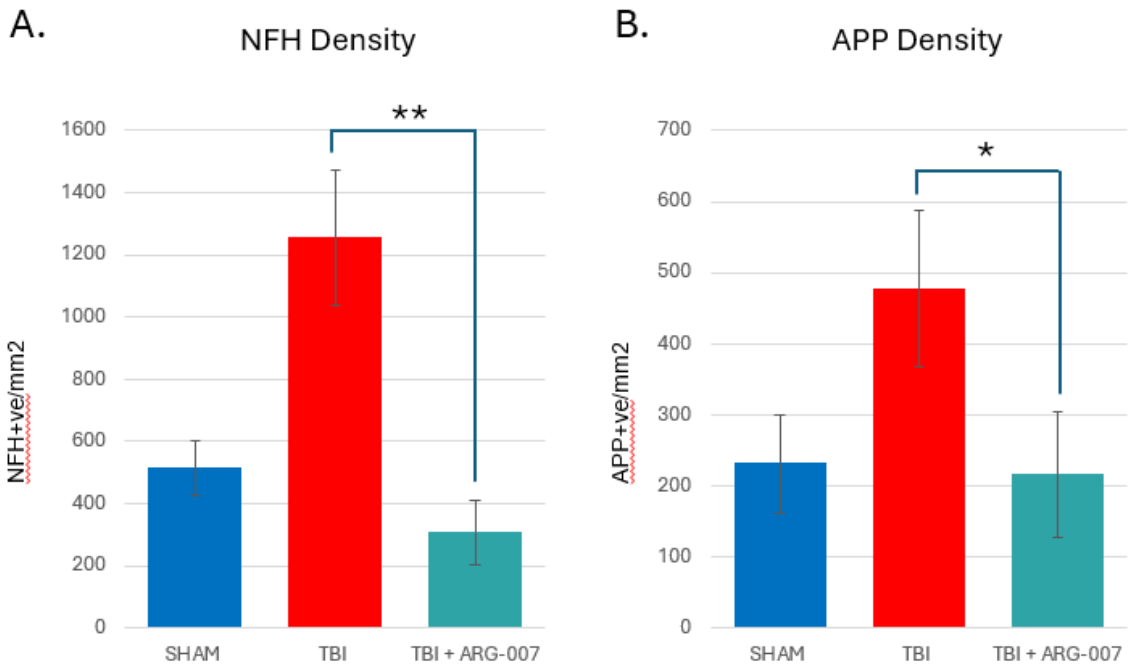

Figure 1. (A) ARG-007 protected brain cell axons in the pyramidal tract in the brain from injury as shown by a significant reduction in NF-H density (p = < 0.01), and (B) ARG-007 significantly protected brain cells from neurodegeneration following TBI as shown by a significant reduction in APP density (*p = < 0.05). Both protein levels were reduced to non-injury (sham) controls.**

In this main study, it was decided to also measure plasma concentrations of neurofilament light (NF-L), as this has emerged as a promising biomarker for TBI in humans. NF-L is a

[3] ASX Announcement dated 22 June 2023, "ARG-007 protects brain cells in moderate traumatic brain injury model".

neuronal cytoskeletal protein that provides structural axonal support and facilitates neurotransmission. NF-L levels are significantly elevated in TBI patients compared to non-injured patients[4] and levels of NF-L in the blood is now a widely used biomarker for measuring axonal injury and is a good predictor of clinical outcomes following TBI[5]. This study showed ARG-007 prevented the acute increase of NF-L in the blood following TBI (Figure 2A), suggesting the maintenance of axonal integrity in injured brain cells following ARG-007 treatment.

Further, ARG-007 was shown to significantly reduce inflammation in the brain, confirming results from the pilot study, with levels of a key neuroinflammation market, Iba1, reduced to non-injured (sham) control levels (Figure 2B). The biomarker Iba1 is a marker for microglial activation and neuroinflammation and increased Iba1 expression in the pyramidal tract indicates ongoing neuroinflammation and microglial activation in the brain. This neuroinflammation in the brain following TBI can be a significant cause of secondary brain injury which can last far beyond the acute phase of the initial injury.

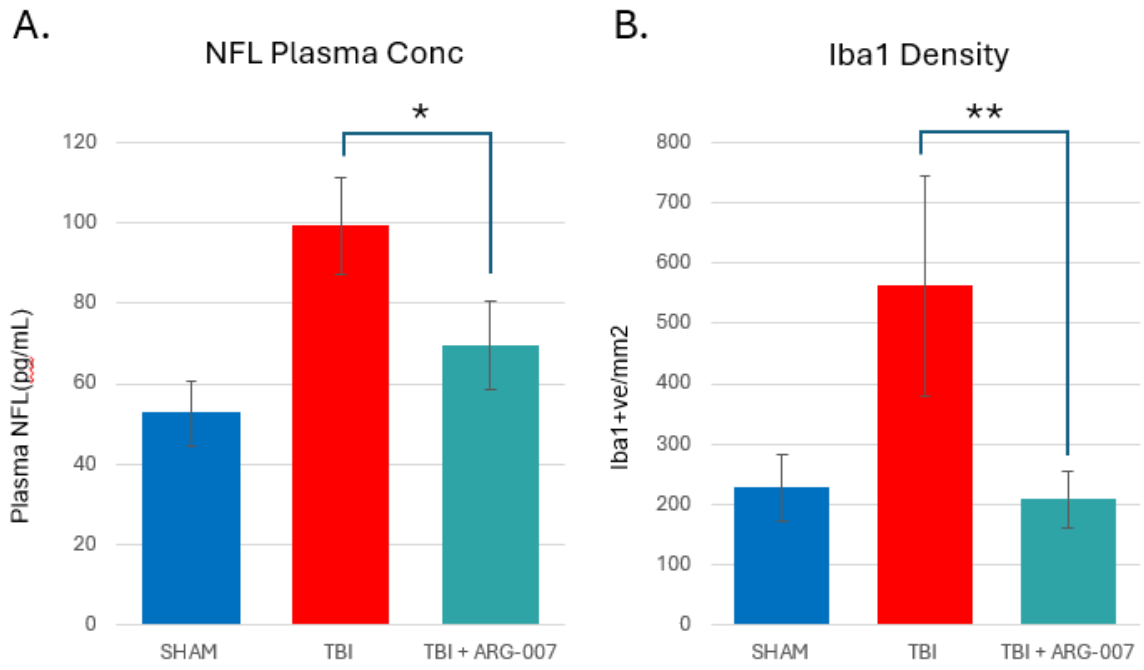

Figure 2. (A) ARG-007 reduced plasma NF-L acutely following moderate TBI as shown by a significant reduction in NF-L plasma concentration at day 1 (*p = < 0.01), and (B) ARG-007 significantly reduced Iba1 density in the pyramidal tract following TBI (p = < 0.05). Iab1 levels were reduced to Sham or non-injury control levels.**

Importantly, the reduction in protein and neuroinflammation levels in ARG-007 treated animals was also associated with a significant reduction in weight loss that often results from TBI.

[4] Shahim P, Politis A, van der Merwe A, Moore B, Chou YY, Pham DL, Butman JA, Diaz-Arrastia R, Gill JM, Brody DL, Zetterberg H, Blennow K, Chan L. Neurofilament light as a biomarker in traumatic brain injury. Neurology. 2020 Aug 11;95(6):e610-e622.

[5] Shahim, P., Gren, M., Liman, V. *et al.* Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. *Sci Rep* **6**, 36791 (2016)

Dr Liz Dallimore, Managing Director, said: "We are extremely pleased with the results from this larger preclinical study in a moderate TBI animal model. The study confirms previously generated data, indicating that ARG-007 consistently reduces axonal injury and neuroinflammation following TBI, and encouragingly to levels similar to non-injured animals. We will continue to progress further larger animal studies in TBI to ensure rigorous scientific validation of ARG-007 in TBI as a therapeutic target".

An overview of the study is provided in Appendix 1.

NEXT STEPS

Argenica will continue to work with its Cooperative Research Centre Projects (CRC-P) partners the University of Adelaide and Curtin University to finalise a larger preclinical studies assessing the efficacy of ARG-007 in moderate TBI in ferrets, as well and repeated dosing following multiple mild-TBIs in rats.

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

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APPENDIX 1

STUDY OVERVIEW

Background

Every year, over 69 million people in the world sustain a traumatic brain injury (TBI). Most of these people suffer ongoing neurological dysfunction, including motor and cognitive problems. In addition to primary tissue damage, TBI causes secondary degeneration of initially spared tissue around the primary damage. Secondary degeneration can lead to ongoing damage to brain cells, ultimately manifesting as neurological deficits. Despite the clinical demand, neuroprotective pharmacological agents targeting axonal injury and secondary degeneration are lacking for TBI.

Diffuse axonal injury following TBI results from the rapid acceleration and deceleration forces caused by the impact, causing deformation of brain tissue through shearing forces and stretching. When brain cells stretch over each other it gives rise to widespread damage throughout the cerebral hemispheres, corpus callosum, and brain stem. This stretching of neurons causes intra-axonal changes through specific protein accumulation and neuroinflammation leading to neurodegeneration[6].

ARG-007, a novel neuroprotective peptide being developed by Argenica, has previously shown preclinical efficacy in moderate TBI in both a pilot rat and ferret study[1,2]. The overarching hypothesis of this study is that data can be replicated to prove ARG-007 mitigates neural death, white matter injury, related cellular pathologies, and functional deficits following TBI. Further, given ARG-007 showed positive results in previous rat and ferret pilot studies, this study increased animal numbers to ensure the results of the pilot study could be replicated and ensure scientific rigour to the preclinical assessment of ARG-007 as a potential therapy for moderate TBI.

Aims

This study assessed the therapeutic potential of ARG-007 in protecting brain cells from injury and neuroinflammation, and resulting behavioural function, following moderate TBI, and build on data generated in the previously conducted pilot study. An impact-acceleration rat model of moderate TBI that induces diffuse axonal injury was used to model white matter damage, as seen after falls and motor vehicle accidents.

Animal Groups

The animal groups are defined as Sham (non-injured), TBI or TBI+ARG-007.

[6] Plummer S, Van den Heuvel C, Thornton E, Corrigan F, Cappai R. The Neuroprotective Properties of the Amyloid Precursor Protein Following Traumatic Brain Injury. Aging Dis. 2016 Mar 15;7(2):163-79.

The Sham animals did not sustain a TBI injury but were given an intravenous (IV) administration of saline. The TBI animals did sustain an injury and were given an IV dose of saline 30 minutes post injury. The TBI+ARG-007 animals did sustain an injury and were given an IV dose of 3 mg/kg dose of ARG-007 30 minutes post injury.

STUDY RESULTS HIGHLIGHTS

ARG-007 significantly reduces accumulation of neurodegenerative proteins NFH and APP days after moderate TBI

A single administered dose of ARG-007 at 30 minutes post-injury prevented the accumulation of both neurofilament heavy protein (NFH) and amyloid precursor protein (APP) in neurons, as assessed 11 days after injury, suggesting neuroprotection of brain cells and axons from ARG-007 following TBI. The level of NFH density correlates with the extent of diffuse axonal injury of neurons following TBI. The elevated density of APP following TBI is a marker for neurodegeneration, or brain cell death.

Animals that sustained a TBI treated with saline vehicle displayed an increased density of NFH in the pyramidal tract of the pons, which is an important pathway responsible for voluntary motor movement (Figure 1A & 3A). Encouragingly, ARG-007 reduced the density of NFH to saline-treated sham control levels (i.e., animals that were not injured; Figure 1). In addition, ARG-007 treatment attenuated APP density compared to TBI saline control animal levels (Figure 2B & 3B).

APP and neurofilaments are key proteins for axonal transport and cytoskeletal structural integrity, respectively[7]. Following TBI, hyper-phosphorylation can cause damaged APP and neurofilaments to aggregate, leading to prolonged microglia activation, Wallerian degeneration (degeneration of axons distal to the primary injury site) and inefficient or aberrant neurotransmission[8],[9]. In the pilot study, TBI increased the density of NF-H immunoreactivity in the pyramidal tract of the brainstem, but not in the cerebellum and corpus callosum, indicating that, in this model of moderate TBI, diffuse axonal damage is most prominent in the brainstem on day 11. Neuronal pathology was therefore only assessed in the brainstem on day 11, using markers of axonal transport disruption (APP) and damage to major components of neurofilaments (NF-H and NF-L). The use of different markers of axonal and cytoskeletal injury allows capture of the different phenotypes of axonal damage, as axons of different calibre and structure can respond differently to TBI mechanical forces[7].

NF-H accumulation in the pyramidal tract has been reported in the severe version of the impact acceleration TBI model[10]. Consistent with this, NF-H accumulated in the pyramidal

[7] Krieg JL, Leonard A V., Turner RJ, Corrigan F. Identifying the Phenotypes of Diffuse Axonal Injury Following Traumatic Brain Injury. Brain Sciences 2023, Vol 13, Page 1607 [Internet]. 2023 Nov 20

[8] Blennow K, Hardy J, Zetterberg H. The Neuropathology and Neurobiology of Traumatic Brain Injury. Neuron. 2012 Dec 6;76(5):886–99

[9] Devarakonda SS, Basha S, Pithakumar A, L B T, Mukunda DC, Rodrigues J, et al. Molecular mechanisms of neurofilament alterations and its application in assessing neurodegenerative disorders. Ageing Res Rev. 2024 Dec 1;102:102566.

[10] Hellewell SC, Yan EB, Agyapomaa DA, Bye N, Morganti-Kossmann MC. Post-traumatic hypoxia exacerbates brain tissue damage: Analysis of axonal injury and glial responses. J Neurotrauma [Internet]. 2010 Nov 1

tract following moderate TBI (Figure 1A), and ARG-007 prevented this accumulation, mirroring the findings of the pilot study.

TBI induced a notable increase in APP immunoreactivity relative to TBI injury only animals, and ARG-007 reduced APP immunoreactivity significantly. When considered together with the independent pilot study data, which showed the same pattern of APP change, this data suggests that ARG-007 mitigates axonal transport disruption following moderate TBI.

ARG-007 prevented the acute increase in plasma NF-L after moderate TBI

Blood NF-L concentration is a valuable biomarker for assessing axonal injury severity, progression, and response to therapeutic interventions following TBI[11,12,13]. TBI of all severities exhibit elevated circulating levels of NF-L, with more severe injuries resulting in greater NF-L levels[12]. In line with this, TBI increased plasma NF-L concentration on day 1 but not on day 11 post injury, demonstrating that, in this model of moderate TBI, NF-L increases acutely (day 1) and does not persist sub-acutely (day 11). Importantly, ARG-007 prevented the acute increase of NF-L in the blood following TBI (Figure 2A).

The mechanical forces from a TBI can shear, stretch or compress axons, leading to a breakdown of axonal cytoskeleton and extracellular release of NF-L in the interstitial fluid[14]. Diffuse axonal swelling and degradation can also lead to NF-L release. NF-L may subsequently enter the bloodstream through damaged blood-brain barrier or by first entering the cerebrospinal fluid then crossing into the blood via compromised meningeal lymphatic vessels.

ARG-007 prevented neuroinflammation in the pyramidal tract after moderate TBI

The increased immunoreactivity of the microglial marker, Iba1, in the pyramidal tract following TBI is likely a response to the concomitant increased in APP and NF-H pathology in the same region. As the resident immune cells of the brain, microglia play a critical role in phagocytosing and clearing TBI-associated cellular debris and proteins. However, the microglial response can be a 'double-edged sword' - critical for initial clearance and repair but potentially harmful if the pathology is excessive or prolonged[12]. Incomplete clearance of the pathological proteins may promote their extracellular accumulation, leading to a feed-forward cycle of protracted microglia activation, neuroinflammation and neuronal damage. The reduced I immunoreactivity of Iba1 in the pyramidal tract following treatment with ARG-007 indicated modulation of such damage-associated neuroinflammation.

[11] O'Brien WT, Spitz G, Xie B, Major BP, Mutimer S, Giesler LP, et al. Biomarkers of Neurobiologic Recovery in Adults With Sport-Related Concussion. JAMA Netw Open [Internet]. 2024 Jun 3

[12] Shahim P, Politis A, Van Der Merwe A, Moore B, Chou YY, Pham DL, et al. Neurofilament light as a biomarker in traumatic brain injury. Neurology. 2020 Aug 11;95(6):E610–22.

[13] O'Brien WT, Wright DK, van Emmerik ALJJ, Bain J, Brkljaca R, Christensen J, et al. Serum neurofilament light as a biomarker of vulnerability to a second mild traumatic brain injury. Translational Research. 2023 May 1;255:77–84.

[14] Gafson AR, Barthélemy NR, Bomont P, Carare RO, Durham HD, Julien JP, et al. Neurofilaments: neurobiological foundations for biomarker applications. Brain [Internet]. 2020 Jul 1

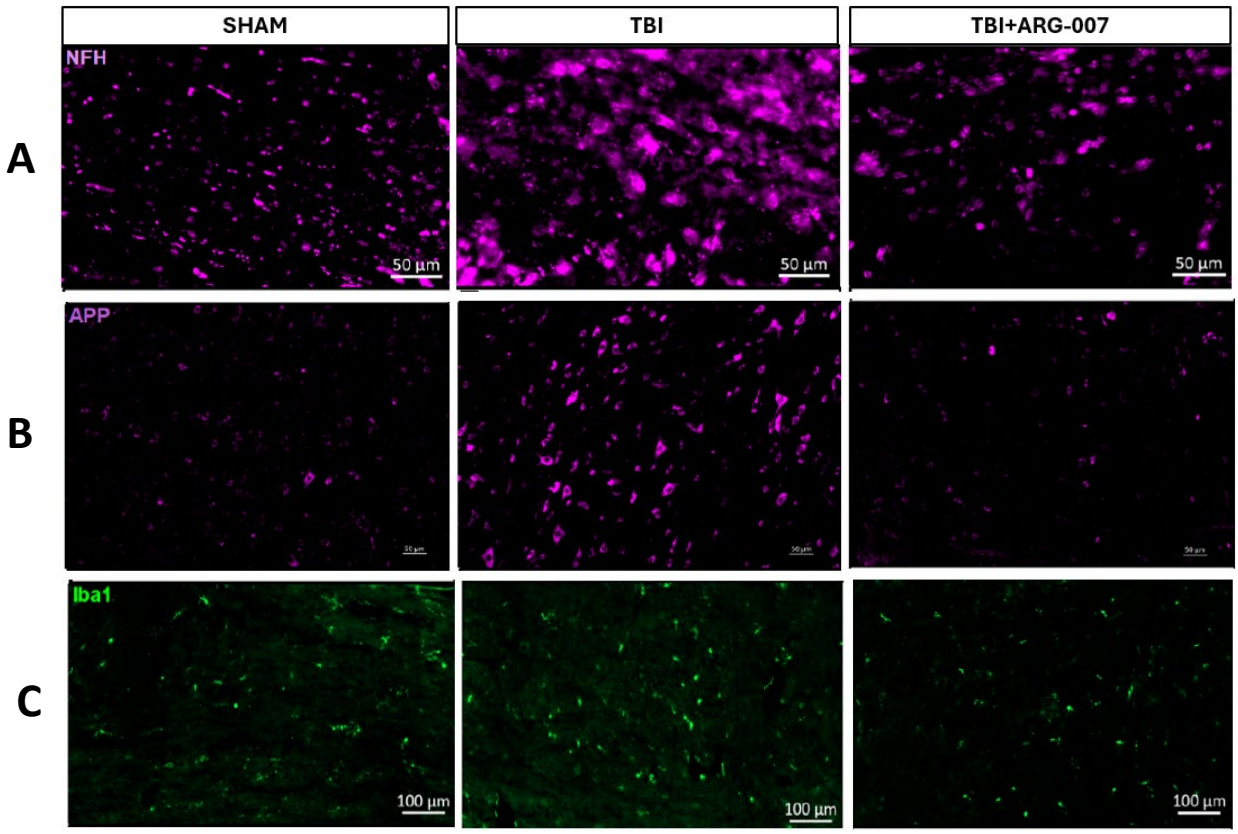

Figure 3. Histological sections show the immunoreactivity against NFH (row A), APP (row B) and Iba1 (row C) in the pyramidal tract of the brain in Sham animals, TBI animals with treatment, and TBI animals with ARG-007 treatment.

ARG-007 mitigated weight loss following moderate TBI

Moderate-severe TBI can cause weight loss[1,2], and post-injury weight loss has been associated with greater neurological deficit and mortality[2]. To determine the effect of moderate TBI on weight loss, the percentage of weight change relative to baseline (day 0) on each day post-injury was compared between rats treated with Sham + Saline and those treated with TBI + Saline (Figure 4A). Negative values indicate weight loss compared to pre-injury baseline weight, while positive values indicate weight gain.

To determine the effect of ARG-007 on TBI-induced weight loss, weight change was compared between rats treated with TBI + Saline and rats treated with TBI + ARG-007. There was a main statistically significant effect of drug treatment ($F(1, 26) = 5.422$; $p = 0.0279$) and effect of time since injury ($F(3.542, 91.77) = 56.36$; $p = 0.0001$). Posthoc comparisons at each timepoint showed that ARG-007-treated rats retained significantly more weight than their saline-treated counterparts at day 2 ($p = 0.0285$), day 3 ($p = 0.0263$), day 4 ($p = 0.0432$) and day 6 ($p = 0.0160$) post injury (Figure 4B). ARG-007-treated TBI rats regained their preinjury weight on day 6, whereas saline-treated TBI rats did not regain preinjury weight until day 8. Taken

together, these data suggest that TBI induced weight loss and ARG-007 increased the rate of weight recovery.

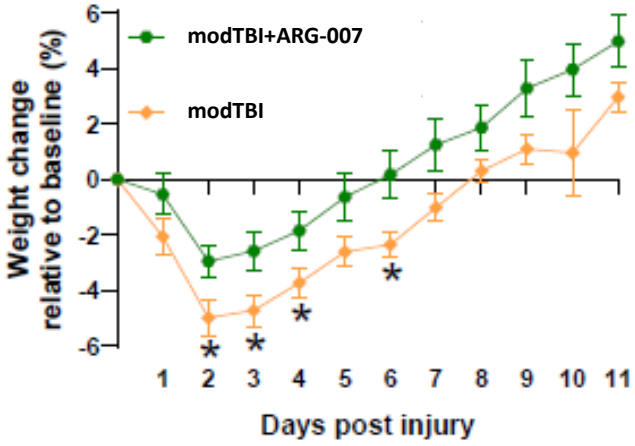

Figure 4. Line graphs show percentage of daily weight change relative to pre-injury baseline weight on day 0 across time. Weight changes between rats that received TBI + ARG-007 or TBI were compared to show effects of intravenous ARG-007. Negative values indicate weight loss compared to pre-injury baseline weight, while positive values indicate weight gain. * = p < 0.05. modTBI = moderate TBI

ARG-007 reduced motor dysfunction after moderate TBI

The Rotarod test examines body movement and sensorimotor coordination, which is impaired following TBI in rats. To determine whether TBI altered motor function, the percentage change in longest duration on the rotating rod relative to baseline (the average day -1 and day -2 pre-injury training performance for each rat) was compared between rats treated with Sham and those treated with TBI. TBI impaired performance on day 1 ($p = 0.0422$), but not on day 5 ($p = 0.8075$) or day 10 ($p = 0.4457$). However, ARG-007 prevented the reduction in motor performance on day 1 compared to saline treated TBI affected animals.

These data suggest that ARG-007 prevented acute motor deficit in the Rotarod task following moderate TBI.

CONCLUSIONS

Collectively, these data suggest that a single dose of ARG-007 administered IV and delivered 30 minutes after modetate TBI could be an effective treatment strategy for preserving normal motor coordination, systemic and histological neurofilament health, axonal transport and neuroinflammation, and for restoring normal body weight.