Public Announcement
ASX Code: 1AI

AI-116 for Dementia: Further Positive Pre-Clinical Results and PCT Patent Application Filing

Highlights:

- AI-116 significantly reduces glutamate-induced toxicity *in vitro*, exceeding that of existing FDA registered drug for dementia, Donepezil (originally marketed as Aricept);
- Relative cell viability increased by 53% for AI-116 versus 17% for Donepezil in the presence of elevated glutamate, which is associated with dementia and neurological disorders;
- RNA-sequencing identified genes associated with dementia that were uniquely modulated following treatment with AI-116;
- Algorae has filed an international Patent Cooperation Treaty (PCT) application to pursue patent protection for aspects of AI-116;
- Company commences clinical trial planning activities.

Melbourne, Australia, 31 July 2024: Algorae Pharmaceuticals Limited (Algorae or the Company) (ASX code: 1AI) is pleased to announce additional positive results from its pre-clinical program to assess AI-116.

AI-116 is Algorae's combination drug candidate comprising Donepezil, an acetylcholinesterase inhibitor (AChE inhibitor), and cannabidiol (CBD). AChE inhibitors are FDA registered first line treatments for Alzheimer's Disease and are also prescribed off-label for other neurodegenerative disorders and dementia. Algorae's goal is to develop and commercialise new therapeutics that improve upon current first line treatments for one or more forms of dementia.

Algorae has previously observed that AI-116 outperformed Donepezil *in vitro*, using a pre-clinical model of neuroprotection. A synergistic increase in neuroprotection was observed between the two active agents of AI-116, with their combined effect improving cell viability to a level 33% greater than what would be expected additively following exposure to amyloid β (Aβ) (**as detailed in Appendix 1**). Algorae has now completed additional preclinical assessments of glutamate toxicity. Elevated glutamate in neuroblastoma cells significantly contribute to the progression of dementia through mechanisms involving excitotoxicity, oxidative stress, neuroinflammation, synaptic dysfunction, and the interplay with Aβ and tau pathology. These processes are neurotoxic, ultimately resulting in cognitive decline and memory impairment.

In vitro assays compared cell viability in the presence of abnormal glutamate following treatment with AI-116. Relative to glutamate-only treated control cells, AI-116 restored a mean of 53% of total relative cell viability, which exceeded the effect of either CBD or Donepezil alone (**Figure 1**). These results demonstrate that AI-116 reduces glutamate-induced toxicity *in vitro*.

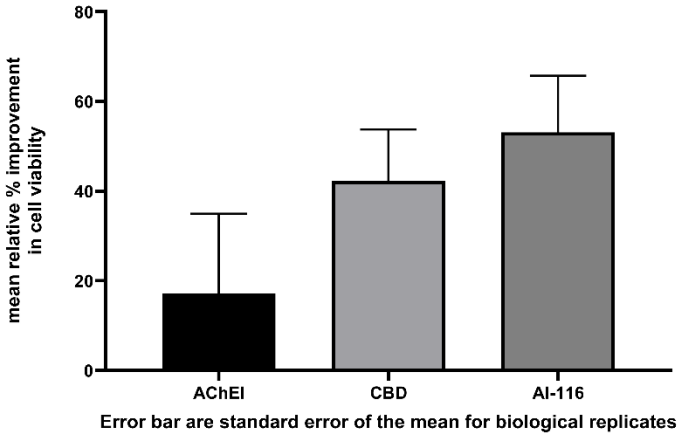

Figure 1. Average percentage increase in cell survival relative to glutamate treated control cells. Relative to the glutamate treated toxic control, Donepezil (represented as AChEI) alone restored a mean of 17% of total relative cell viability, CBD alone restored a mean of 42% of total relative cell viability and AI-116 at the optimal dosages restored a mean of 53% of total relative cell viability.

RNA sequencing was performed on samples obtained from SH-SY5Y neuroblastoma cells exposed to amyloid Aβ. RNA sequencing is a comprehensive, high-throughput technique, which Algorae has employed to investigate transcriptome changes following treatment with AI-116, Donepezil, or CBD.

AI-116 significantly modulated expression of key genes that are associated with one or more neurodegenerative disorders. When compared with genes modulated with CBD or Donepezil alone, at least 21 genes were identified as uniquely modulated following treatment with AI-116, including *APOE, ATN1, C19orf12, CFAP410, CTSD, DLG4, MT-TF, MT-TS1, NEK1, NIPA1, NOS2, NRXN1, TARDBP, CCDC88C, DNAH9, DTNBP1, ERCC8, HGSNAT, HTT, UBQLN4* and *UCHL1.*

This approach demonstrated that treatment with AI-116 can modulate the expression of genes associated with a range of neurodegenerative disorders and dementias, including Alzheimer's disease, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and traumatic brain injury, among others.

Taken together, these data provide further evidence of the neuroprotective effect of AI-116 following exposure to different neurotoxins (Aβ and elevated glutamate). Following these positive results, Algorae has commenced planning for a clinical trial to assess AI-116, including discussions with key opinion leaders in the fields of dementia and neurological disorders.

Furthermore, Algorae has filed an international patent application under the Patent Cooperation Treaty (PCT) (International (PCT) Application No. PCT/AU2024/050791) as part of its broader strategy to develop intellectual property assets that align with the Company's commercial interests. In particular, this application has been filed to provide Algorae with the opportunity to pursue patent protection for aspects AI-116 in a broad range of countries.

About Donepezil

Donepezil (i.e., Aricept) was registered by the US Food and Drug Administration (FDA) in 1996 for the symptomatic treatment of Alzheimer's disease, helping to improve cognitive function and quality of life for individuals with the condition. It has been prescribed off-label in the treatment of other neurodegenerative

disorders, such as Parkinson's disease, vascular dementia and dementia with Lewy bodies. It belongs to a class of drugs known as AChE inhibitors, which work by increasing the levels of acetylcholine, a neurotransmitter involved in memory and learning, in the brain. The market size for AChE inhibitors in 2024 is estimated to be US$21B and is driven by the rising prevalence of Alzheimer's disease[1].

This announcement has been approved by the Board of Directors of Algorae Pharmaceuticals Limited.

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For more information, please visit www.algoraepharma.com

Corporate and Media Enquiries
Mr Brad Dilkes - Director
P: +61 422 180 317
E: brad@algoraepharma.com

Reference: [1]Cholinesterase Inhibitors Market Analysis by Application (Alzheimer's Disease, Other Neurological Disorders), by Type of Drug (Donepezil, rivastigmine, galantamine), by Distribution Channel (Hospital Pharmacies, Retail Pharmacies and Drug Stores, Online Pharmacies) and by Region: Global Forecast, 2024 - 2033.

About Algorae Pharmaceuticals

Algorae is a pharmaceutical development company focussed on addressing unmet medical needs through the discovery and development of novel treatments. The Company has assembled a proficient R&D team and established collaborations with reputable academic institutions to advance its promising drug candidates, which include AI-116 for the treatment of neurodegenerative disorders and/or dementia, AI-168 for cardiovascular disease and NTCELL for Parkinson's disease.

Algorae intends to expand its therapeutic pipeline using a proprietary artificial intelligence (AI) drug discovery and development platform. Known as Algorae Operating System (AlgoraeOS), the AI platform leverages extensive medical and scientific databases from various disciplines within an advanced system at the intersection of AI and pharmaceutical research. By employing machine learning, deep learning, and neural networks, the aim of AlgoraeOS is to uncover synergistic drug combinations that lead to the development of novel and effective treatments for any medical condition, aligning with Algorae's commitment to address unmet medical needs. Algorae is listed and publicly traded on the Australian Stock Exchange (ASX: 1AI), providing investors an opportunity to participate in the Company's growth.

Appendix 1

In vitro assays were conducted to assess the therapeutic potential of AI-116 by comparing the viability of neuroblastoma cells in the presence of Aβ with varying exploratory doses of AI-116 against its individual constituents. The *in vitro* assays measured cell viability and drug synergy, which occurs when the effect of two drugs in combination is superior to the sum of their individual effects.

In these assays, neuroblastoma cells were concurrently treated with varying doses of CBD and Donepezil (annotated as AChEI) in the presence of Aβ. Cell viability was measured using the MTT assay. Improvement in cell viability was determined as a percentage increase in cell survival over cells treated with Aβ alone.

In the data reported below, the control arm of the *in vitro* study demonstrated high levels of toxicity when neuroblastoma cells are exposed to Aβ. Improvements in cell viability were observed with Donepezil or CBD alone but was substantially improved with the administration of the optimal fixed dose combination of AI-116 (**Figure 2**).

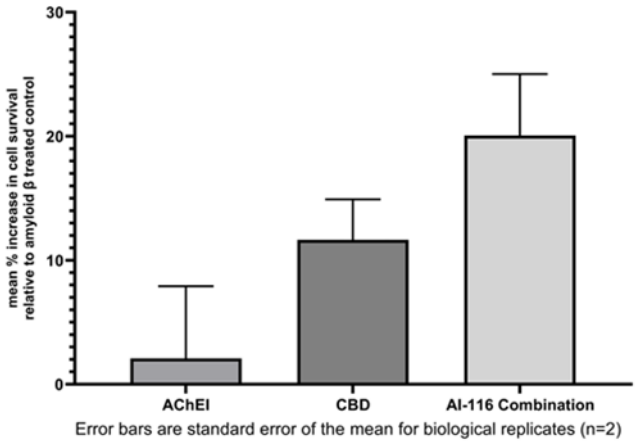

Figure 2. Average percentage increase in cell survival relative to Aβ treated control cells. Zero is the benchmark for Aβ effected cells with no treatments, whereby cell viability was 65.5%. Cell viability increased by 2.1% to 67.6% for Donepezil (represented as AChEI), by 11.6% to 77.1% for CBD and by 20.1% to 85.6% for AI-116.

Forward-looking Statements

This document may contain certain forward-looking statements, relating to Algorae's business, which can be identified by the use of forward-looking terminology such as "promising," "probable", "plans," "anticipated," "will," "project," "believe," "forecast," "expected," "estimated," "targeting," "aiming," "set to," "potential," "seeking to," "goal," "could provide," "intends," "is being developed," "could be," "on track," or similar expressions, or by express or implied discussions regarding potential filings or marketing approvals, or potential future sales of product candidates. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no assurance that any existing or future regulatory filings will satisfy the FDA's and other health authorities' requirements regarding any one or more product candidates, nor can there be any assurance that such product candidates will be approved by any health authorities for sale in any market or that they will reach any particular level of sales. In particular, management's expectations regarding the approval and commercialisation of the product candidates could be affected by, among other things, unexpected clinical trial results, including additional analysis of existing clinical data, and new clinical data; unexpected regulatory actions or delays, or government regulation generally; our ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; government, industry, and general public pricing pressures; and additional factors that involve significant risks and uncertainties about our products, product candidates, financial results and business prospects. Should one or more of these risks or uncertainties materialise, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated, or expected. Algorae is providing this information and does not assume any obligation to update any forward-looking statements contained in this document as a result of new information, future events or developments or otherwise.