Alterity Therapeutics Announces Positive ATH434 Phase 2 Trial Results in Multiple System Atrophy Led By Robust Clinical Efficacy

– Clinically Meaningful Benefit Observed at Both ATH434 Doses Studied –

– Achieved Statistical Significance with Up to 48% Slowing of Clinical Progression on UMSARS Rating Scale –

– Key MRI Biomarker Shows Iron Stabilization in MSA Affected Brain Regions –

– ATH434 Demonstrated a Favorable Safety Profile –

– Webcast Today at 11:00 a.m. AEDT (Sydney/Melbourne) / USA 4:00 p.m. PST, 7:00 p.m. EST –

MELBOURNE, AUSTRALIA AND SAN FRANCISCO, USA – 30 January 2025: Alterity Therapeutics (ASX: ATH, NASDAQ: ATHE) ("Alterity" or "the Company"), a biotechnology company dedicated to developing disease modifying treatments for neurodegenerative diseases, today announced positive topline results from the ATH434-201 randomized, double-blind, placebo-controlled Phase 2 clinical trial in patients with early-stage multiple system atrophy (MSA).

The topline data showed that ATH434 produced clinically and statistically significant improvement on the modified UMSARS Part I, a functional rating scale that assesses disability on activities of daily living affected in MSA[1]. On this important clinical measure, ATH434 demonstrated 48% slowing of clinical progression at the 50 mg dose (p=0.03)^ and 29% slowing of clinical progression at the 75 mg dose (p=0.2) at Week 52 when compared with placebo. The 75 mg dose group showed a 62% slowing of progression (p=0.05) at Week 26. In addition to the robust efficacy demonstrated on the UMSARS I, trends of improved motor performance were observed on the Parkinson's Plus rating scale[2] and overall benefit was shown on the Clinical Global Impression of Severity at the 50 mg dose (p=0.009).

Biomarkers were used to evaluate potential drug effect and target engagement. Regarding iron content by MRI, the 50 mg dose reduced iron accumulation in MSA affected brain regions (substantia nigra, putamen, and globus pallidus) and the 75 mg dose reduced iron accumulation in the globus pallidus. The reduced accumulation of iron was significant for the 50 mg dose group at 26 weeks (putamen, *P*=0.025) and approached statistical significance at 52 weeks (globus pallidus, *P*=0.08). Trends in preservation of brain volume were observed in the 50 mg and 75 mg groups relative to placebo at both 26 and 52 weeks of treatment.

"We are thrilled that ATH434 has demonstrated significant slowing of clinical progression and an excellent safety profile in this rare, rapidly progressive disease," said David Stamler, M.D., Chief

Executive Officer of Alterity. “Currently, there are no approved treatments that slow the progression of MSA and these results show that ATH434’s targeted iron engagement may truly have a disease modifying effect. The fact that we achieved statistical significance on the UMSARS is extremely meaningful because it assesses the functional areas affected in MSA and is the endpoint needed to support drug approval by the U.S. Food and Drug Administration (FDA). Based on the strength of these Phase 2 data, we look forward to engaging with the FDA as quickly as possible to discuss the path forward for accelerating the development of ATH434 given the tremendous unmet need for treating MSA. We are very grateful for the invaluable contributions of the study participants and the clinical sites who contributed to the study.”

Daniel Claassen, M.D., M.S., Professor of Neurology at Vanderbilt University Medical Center and Coordinating Investigator for the ATH434-201 Phase 2 study, commented “The findings from the study are compelling because ATH434 appears to have meaningfully slowed MSA progression and stabilized motor function. To date, no treatment has altered the progression of this devastating disease. The slowing of clinical progression in this study, particularly at 50 mg, is impressive. I look forward to continue working with Alterity to bring this therapy to patients, and I know the MSA community welcomes this exciting advancement.”

Dr. Stamler concluded, “We now have evidence that targeting excess labile iron in neurodegenerative disease can be achieved. By redistributing this reactive form of iron that contributes to disease pathogenesis, not only can we target α-synuclein aggregation, but we can also break the vicious cycle underlying disease progression. This has implications for developing disease modifying treatments for orphan diseases such as MSA and Friedreich’s ataxia as well as major neurodegenerative disorders such as Parkinson’s disease and Alzheimer’s disease.”

Webcast details

AUSTRALIA PARTICIPANTS:
Date: Thursday, 30 January 2025
Time: 11:00 a.m. AEDT (Sydney/Melbourne)

UNITED STATES PARTICIPANTS:
Date: Wednesday, 29 January 2025
Time: 4:00 p.m. Pacific Time
7:00 p.m. Eastern Time

Register for the Zoom webcast:
ATH434-201 Topline Results
Registration is required and dial in details will be sent directly upon registration.

ATH434-201 Topline Data Summary

The ATH434-201 Phase 2 clinical trial is a randomized, double-blind, placebo-controlled investigation of 12 months treatment with ATH434 in participants with early-stage MSA. The trial enrolled globally with 23 sites in six countries. The study evaluated the efficacy, safety and pharmacokinetics of ATH434 as well as the effect of ATH434 on neuroimaging and protein biomarkers. Wearable movement sensors were employed to evaluate motor activities in an outpatient setting. The study enrolled 77 adults who were randomly assigned to receive one of two dose levels of ATH434 (50mg or 75mg) or placebo. Treatment was administered orally twice-a-day (BID).

ATH434 Efficacy Results (n=61)

The principal efficacy analyses were performed on the modified Intent-to-Treat (mITT) population, which includes enrolled participants who received study drug and had at least one MRI evaluation for brain iron at six months. There were approximately 20 patients per arm in the mITT. Both clinical doses demonstrated improvement relative to placebo over 52 weeks, with the 50 mg dose showing a greater treatment effect. Additional analyses are ongoing to understand the differences between the two groups.

Key Biomarker Endpoint:

On the primary endpoint of iron content by MRI, ATH434 demonstrated reduced or stabilized iron content in key brain regions affected by MSA.

- Demonstrated target engagement of ATH434
- The 50 mg dose reduced iron accumulation in the substantia nigra, putamen, and globus pallidus
    - The reduced accumulation of iron was significant at 26 weeks (putamen, *P*=0.025) and approached statistical significance at 52 weeks (globus pallidus, *P*=0.08)
- The 75 mg dose reduced iron accumulation in the globus pallidus

Other biomarkers were used to evaluate potential drug effect and target engagement.

- Brain Volume: ATH434 demonstrated a trend in preserving brain volume as compared to placebo at both 50 mg and 75 mg dose levels, as assessed by the MSA atrophy index (MSA-AI)[3]
- NfL: The analysis of neurofilament light chain (NfL) levels in spinal fluid is ongoing

Key Clinical Endpoint: UMSARS Part I

The key secondary endpoint was defined as the change in the Unified MSA Rating Scale Part I (UMSARS I). UMSARS I is a functional rating scale that assesses disability and disease severity in MSA. It is the most meaningful endpoint in the trial, as it is the clinical endpoint of interest to support approval by regulatory authorities such as the FDA.

- Placebo treated patients declined by a mean of 4.5 points over 26 weeks and 8.2 points over 52 weeks
- The 50 mg dose declined by a mean of 4.3 points over 52 weeks, equivalent to a 48% slowing of clinical progression (p=0.03)
- The 75 mg dose declined by a mean of 5.8 points over 52 weeks, equivalent to a 29% slowing of clinical progression (p=0.2)
- The 75 mg dose declined by a mean of 1.8 points over 26 weeks equivalent to a 62% slowing of clinical progression (p=0.05)
- Both dose groups clearly separated from placebo.

Additional Secondary Endpoints:

Observed trends of improved motor performance support the efficacy of ATH434 in the clinical setting:

- Clinical Global Impression of Severity[4] (7-point scale, higher score worse)
    - Mean change at 50 mg: -0.81 (p=0.009)
    - Mean change at 75 mg: -0.18 (p=NS)
- Parkinson Plus total motor scale: Trends in both dose groups at 26 and 52 weeks with a clinical benefit apparent in multiple domains
- Increased activity on wearable sensors in both groups with increases in step count, bouts of walking, total walking time, and standing time
- Orthostatic Hypotension Symptom Assessment (patient rated) showed trends favoring benefit in both groups (p=0.13 at 50 mg)

ATH434 Safety Results (n=77)

The safety population includes all enrolled participants who received at least one dose of study drug. Overall, 26 participants received the 50 mg dose, 25 participants received the 75 mg dose, and 26 participants received placebo.

- ATH434 was well-tolerated with similar adverse event (AE) rates in ATH434 treatment groups and placebo
- Most AEs were mild to moderate in severity
- No serious adverse events (SAEs) related to ATH434 were reported
- Discontinuations for AEs were similar in the placebo (n=3) and 75 mg dose (n=5) groups and lowest at 50 mg (n=0). None of the AEs leading to discontinuation were related to treatment.

About ATH434

Alterity's lead candidate, ATH434, is an oral agent designed to inhibit the aggregation of pathological proteins implicated in neurodegeneration. ATH434 has been shown preclinically to reduce α-synuclein pathology and preserve neuronal function by restoring normal iron balance in the brain. As an iron chaperone, it has excellent potential to treat Parkinson's disease as well as various Parkinsonian disorders such as Multiple System Atrophy (MSA). ATH434 successfully completed Phase 1 studies demonstrating the agent is well tolerated and achieved brain levels comparable to efficacious levels in animal models of MSA. ATH434 recently announced positive results from the randomized, double-blind, placebo-controlled Phase 2 clinical trial in patients with early-stage MSA. A second Phase 2 open-label 2 Biomarker trial in patients with more advanced MSA is ongoing. ATH434 has been granted Orphan Drug Designation for the treatment of MSA by the U.S. FDA and the European Commission.

About Multiple System Atrophy

Multiple System Atrophy (MSA) is a rare, neurodegenerative disease characterized by failure of the autonomic nervous system and impaired movement. The symptoms reflect the progressive loss of function and death of different types of nerve cells in the brain and spinal cord. It is a rapidly progressive disease and causes profound disability. MSA is a Parkinsonian disorder characterized by a variable combination of slowed movement and/or rigidity, autonomic instability that affects involuntary functions such as blood pressure maintenance and bladder control, and impaired balance and/or coordination that predisposes to falls. A pathological hallmark of MSA is the accumulation of the protein α-synuclein within glia, the support cells of the central nervous system, and neuron loss in multiple brain regions. MSA affects at least 15,000 individuals in the U.S., and while some of the symptoms of MSA can be treated with medications, currently there are no drugs that are able to slow disease progression and there is no cure.[5]

About Alterity Therapeutics Limited

Alterity Therapeutics is a clinical stage biotechnology company dedicated to creating an alternate future for people living with neurodegenerative diseases. The Company's lead asset, ATH434, has the potential to treat various Parkinsonian disorders and is currently being evaluated in two Phase 2 clinical trials in Multiple System Atrophy. Alterity also has a broad drug discovery platform generating patentable chemical compounds to treat the underlying pathology of neurological diseases. The Company is based in Melbourne, Australia, and San Francisco, California, USA. For further information please visit the Company's web site at www.alteritytherapeutics.com.

Definitions and References

[1] Unified MSA Rating Scale, Part I (historical review). Domains assessed include speech, swallowing, handwriting, cutting food/handling utensils, dressing, hygiene, walking, falling, orthostatic symptoms, urinary function, sexual function and bowel function.

^ All p-values are uncorrected

[2] Natural History and Neuroprotection in Parkinson Plus Syndromes Parkinson's Plus Rating Scale, (NNIPPS-PPS)

[3] MSA Atrophy Index: This index measures the degree of atrophy relative to a normal population, with more negative values indicating greater atrophy

[4] Clinical Global Impression of Severity: a clinician assessment of the total picture of the subject including the impact of the illness on function and level of distress

[5] Multiple System Atrophy | National Institute of Neurological Disorders and Stroke (nih.gov)

Authorisation & Additional information

This announcement was authorized by David Stamler, CEO of Alterity Therapeutics Limited.

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Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements.

Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements are described in the sections titled "Risk Factors" in the Company's filings with the SEC, including its most recent Annual Report on Form 20-F as well as reports on Form 6-K, including, but not limited to the following: statements relating to the Company's drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company's drug development program, including, but not

limited to, ATH434, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company's drug components, including, but not limited to, ATH434, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company's drug compounds, including, but not limited to, ATH434, that could slow or prevent products coming to market, the uncertainty of obtaining patent protection for the Company's intellectual property or trade secrets, the uncertainty of successfully enforcing the Company's patent rights and the uncertainty of the Company freedom to operate.

Any forward-looking statement made by us in this press release is based only on information currently available to us and speaks only as of the date on which it is made. We undertake no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.