ASX Announcement I 6 March 2024

**AdAlta Limited (ASX:1AD)**

# AD-214 PHASE I EXTENSION STUDY ACHIEVES CRITICAL MILESTONE FOR PHASE II AND PARTNERING

## Safety, tolerability and bioavailability of target dose for Phase II clinical studies established; data package addressing key partnering questions complete

**Investment highlights**

- Phase I extension study of AD-214 tested the **target Phase II dose** of AD-214 in healthy volunteers
- Results positively answer key **partnering discussion** questions and support progressing AD-214 to **Phase II** clinical studies in Idiopathic Pulmonary Fibrosis (IPF)
- AD-214 was **well tolerated**, confirming and extending the excellent safety profile of the molecule
- AD-214 availability (pharmacokinetics – PK) and engagement with its target receptor (pharmacodynamics - PD) **was consistent** with prior studies and consistent across all four doses and all participants, increasing confidence in Phase II target dose selection
- Results also showed **no evidence** of antidrug antibody mediated or other effects that might detract from efficacy after extended use in diseases such as IPF
- **Results now being shared** with existing pipeline of potential partners with a view to progressing a licensing or asset financing transaction in the near term

**AdAlta Limited (ASX:1AD) ("AdAlta" or "the Company")** is pleased to announce key results from its Phase I extension study of lead asset AD-214 that positively answer questions being asked to date by pharma company partners, while establishing the safety and tolerability of the planned Phase II dose. AD-214 is being developed for fibrotic diseases including the debilitating and fatal disease, Idiopathic Pulmonary Fibrosis (IPF) and is now ready to progress to Phase II clinical studies.

**AdAlta CEO and Managing Director, Tim Oldham said:** "*With these excellent results, we believe we have answered in the best way possible the key clinical questions large pharma company partners have been asking about AD-214. With these questions answered, the molecule is now prepared for Phase II clinical studies, a significant milestone for AdAlta. We have already commenced the process of sharing these latest results with our potential partners with a view to progressing a licensing or asset financing transaction in the near term. Such a transaction would enable AD-214 to advance to Phase II clinical trials in Idiopathic Pulmonary Fibrosis to provide a new option for patients with this debilitating and fatal disease as well as providing a return on our investment to date*."

**Study was designed to assess safety and tolerability of planned Phase II doses of AD-214 and answer key questions for pharma partners**

AdAlta's Phase I extension study of AD-214 was conducted to evaluate the safety and tolerability of multiple intravenous (IV) 10 mg/kg doses in healthy volunteers. This is the dose planned for Phase II clinical studies and so the data is essential for both progressing to Phase II studies and for partnering.

All participants received four doses of AD-214. The first three were two weeks apart, as planned for the Phase II study. Interim results after these doses were reported in November 2023.

The fourth dose was 12 weeks after the third and designed to assess the effect, if any, of antidrug antibodies (ADAs) raised by the body against AD-214. ADAs are a common response to biologic drugs, but if present in significant concentrations they can reduce the effectiveness of a drug over time. Understanding the ADA profile of AD-214 is thus a key priority for potential pharmaceutical company partners.

**Top line study results support the safety, bioavailability and potential efficacy of the target Phase II dose of AD-214**

The key findings of the study to date are:

- AD-214 was well tolerated at 10 mg/kg intravenously (IV) every two weeks.
- The bioavailability and pharmacokinetics (PK) of AD-214 was consistent across all doses and with prior single dose studies.
- The pharmacodynamic (PD) activity of AD-214 as measured by transient changes in white blood cell counts was consistent across all doses and with prior single dose studies. Duration of receptor occupancy was consistent with prior studies and dosing simulations and supports dosing every two weeks.
- Antidrug antibodies (ADAs) were detected at low levels in all participants in the study but did not affect AD-214 PK or PD. This supports our hypothesis that the low levels of ADAs are unlikely to be of clinical safety or efficacy concern.

**AD-214 was well tolerated at 10 mg/kg intravenously (IV) every two weeks, establishing safety for Phase II**

Fewer adverse events were reported than in the prior Phase I study at lower doses and all were graded "minor" (the prior study reported some "moderate" adverse events). No infusions were interrupted. This confirms that AD-214 is well tolerated and establishes the safety profile necessary to advance this dose into Phase II clinical studies. All other clinical safety results, including liver function and blood chemistry, were within normal ranges.

**The pharmacokinetic (PK) and pharmacodynamic (PD) profiles of AD-214 were consistent across all participants and doses, supporting Phase II dose selection**

Pharmacokinetics (PK) measures the concentration of a drug (AD-214) in the blood over time. A minimum concentration is required for therapeutic effect and this should be consistently maintained over multiple doses. Key PK measures are maximum blood concentration and total exposure (concentration multiplied by time at that concentration). As shown in the Appendix, the maximum blood concentration of, and total exposure over time to, AD-214 was consistent across all participants and all doses.

Pharmacodynamics (PD) measures the immediate effect of a drug (AD-214) on its target biological system. While not the same as efficacy against disease, it is an important indicator that the drug retains its function in the body.

Blocking AD-214's biological target, known as CXCR4, results in short term increases in the number of white cells circulating in the blood. As shown in the Appendix, the magnitude of the increase observed was consistent with single dose studies, was the same for each participant and was the same for each dose. This shows that AD-214 is able to engage CXCR4 and modulate its biological effect in patients and can do so consistently across multiple doses.

Another PD marker is the duration of time that AD-214 can block the CXCR4 receptor. This is known as receptor occupancy (RO). Previously announced results (July 2023) determined the minimum levels of RO believed necessary to inhibit fibrotic processes. As previously announced (November 2023), the duration of CXCR4 RO by AD-214 was consistent across participants and across the first three doses and in line with prior single dose findings. The RO profile was also in line with that predicted by AdAlta's dose simulation models and sufficient to achieve these target minimum RO levels at all times between two weekly doses. RO results following the fourth dose continue to be evaluated.

Taken together, these results show that AD-214 can sustain levels of RO believed necessary for efficacy when administered at 10 mg/kg every two weeks, supporting the selection of this dose regimen for Phase II studies.

**Antidrug antibodies (ADAs) appear unlikely to be of concern to clinical safety or efficacy**

When the body's immune system recognises a therapeutic protein as "foreign", it may generate antibodies to clear the protein from the body as part of a normal immune response. These antibodies are known as antidrug antibodies (ADAs) since they are directed against the drug. These antibodies may result in reduced concentrations of the drug over time and/or its activity being reduced. It is very common for therapeutic proteins to generate ADAs and this does not necessarily prevent them being used clinically, however the objective of drug development is to minimize both the number and effect of ADAs. This is one reason why AdAlta's i-body® platform (which is used in AD-214) was developed using human protein templates that are less likely to trigger the production of ADAs.

ADAs were detected in all participants in this study. Consistent with results at lower doses, ADA levels induced by three AD-214 doses varied widely between participants and concentrations were generally low or very low when compared with some other protein therapeutics. The fourth dose of AD-214 was administered at the peak of previously observed ADA levels specifically to test the effect of these ADAs on PK, PD and safety.

The similarity of all PK and PD results after the first and fourth dose of AD-214 confirmed that recipients of AD-214 are not developing tolerance to the drug and that any antidrug antibodies are not impacting the availability or activity of AD-214 (which would otherwise reduce efficacy over time). This supports AdAlta's hypothesis that the low levels of ADAs are unlikely to be of clinical safety or efficacy concern.

**Top line study results complete key partnering and Phase II planning milestone**

AdAlta's plan is to evaluate 10 mg/kg intravenous doses of AD-214 every two weeks as treatment for IPF. Completion of the Phase I extension study completes the safety and dose selection data package to support progressing this dose regimen into Phase II clinical studies.

AdAlta is pursuing two parallel strategies to secure the necessary financing for Phase II clinical trials and to generate a return on its investment to date in AD-214:

1. Out-licensing of AD-214 to large biopharmaceutical companies who would then conduct Phase II and further studies.
2. Co-developing AD-214 in an asset specific investment vehicle managed by AdAlta and financed by third party strategic or financial investors.

Several potential partners have executed confidentiality agreements with AdAlta and are now receiving the full Phase I extension study results to enable them to complete their evaluation of AD-214. AdAlta will provide updates on these partnering discussions when binding commitments are in place.

For a video summary of this release and opportunity to engage in a virtual discussion see: https://investorhub.adalta.com.au/link/drLWGe

This ASX announcement has been authorised for release by the Board of AdAlta Limited (ASX:1AD).

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## Appendix

AdAlta's Phase I extension study of AD-214 evaluated the safety and tolerability of 10 mg/kg intravenous doses of AD-214 every two weeks (three doses) with a fourth dose given 12 weeks after the third to evaluate the impact of any ADAs on the availability (PK) and activity (PD) of AD-214. A total of 8 healthy volunteers participated with six receiving AD-214 and two receiving a placebo. This study followed a prior Phase I study testing single doses of AD-214 up to 20 mg/kg (44 participants, 32 received AD-214 and 12 received placebo) and multiple doses of AD-214 at 5 mg/kg (8 participants, 6 received AD-214 and 2 received placebo).

A key objective was to demonstrate that, at target Phase II doses of 10 mg/kg, AD-214 could maintain its availability and activity across multiple doses despite the possible presence of ADAs. The figures below indicate that this objective was achieved.

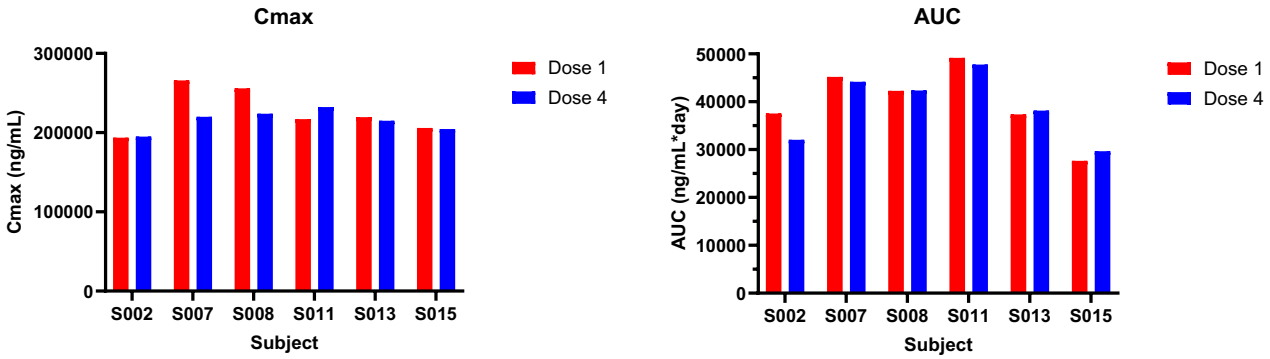


*Figure 1: PK profile of AD-214 after four doses is the same as after the first dose. PK was assessed by measuring the concentration of AD-214 in the blood over time. Every participant receiving AD-214 achieved the same maximum concentration of AD-214 (Cmax, left hand chart) and total exposure (concentration multiplied by time at that concentration or AUC, right hand chart) at dose four as at dose one, despite different levels of ADAs. Slight variations between doses for individual participants reflect experimental variability and were not correlated with ADA levels or any other measured parameter. Variations between participants are normal and expected. Analysis was conducted by AdAlta using raw study data and PKSolver. Placebo results not shown.*

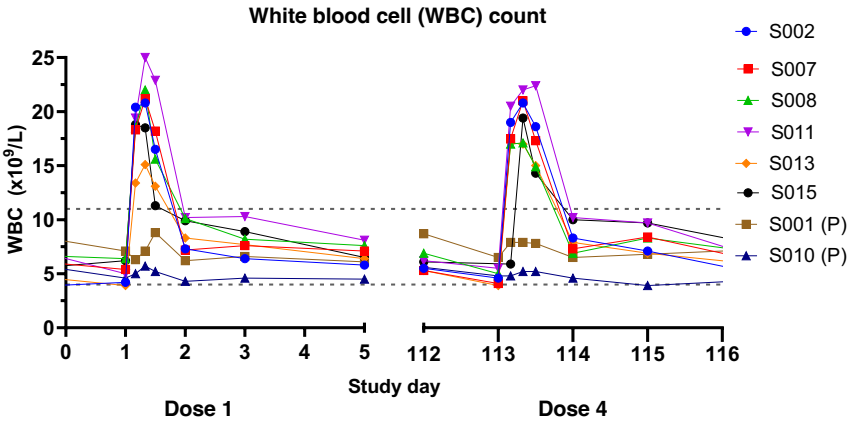


*Figure 2: PD profile of AD-214 after four doses is the same as after the first dose. PD was assessed by measuring the increase in white blood cells (WBC) circulating over time (chart above) and the level and duration of RO (data not shown). Every participant receiving AD-214 achieved the same maximum WBC count at dose four as at dose one, despite different levels of ADAs. No increase in WBC counts was observed in placebo recipients (marked P). Analysis was conducted by AdAlta using raw study data. Dotted lines show lower and upper limits of normal WBC levels in the absence of CXCR4 blocking.*

## About AdAlta Limited

AdAlta Limited is a clinical stage drug development company headquartered in Melbourne, Australia. The Company is using its proprietary i-body technology platform to solve challenging drug targeting problems and generate a promising new class of single domain antibody enabled protein and cell therapeutics with the potential to treat some of today's most challenging medical conditions.

The i-body technology mimics the shape and stability of a unique and versatile antigen binding domain that was discovered initially in sharks and then developed as a human protein. The result is a range of unique proteins capable of interacting with high selectivity, specificity and affinity with previously difficult to access targets such as G-protein coupled receptors (GPCRs) that are implicated in many serious diseases. i-bodies are the first fully human single domain antibody scaffold and the first based on the shark motif to reach clinical trials.

AdAlta is extending Phase I clinical studies for its lead i-body® enabled candidate, AD-214, that is being developed for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and other human fibrotic diseases for which current therapies are sub-optimal and there is a high unmet medical need. Preparation for Phase II clinical studies is also underway. AdAlta has a second target in discovery research, also in the field of fibrosis and inflammation.

The Company is also entering collaborative partnerships to advance the development of its i-body® platform. It has a collaboration with Carina Biotech to codevelop precision engineered, i-body® enabled CAR-T cell therapies (i-CAR-T) to bring new hope to patients with cancer. It has an agreement with GE Healthcare to co-develop i-bodies as diagnostic imaging agents (i-PET imaging) against Granzyme B, a biomarker of response to immuno-oncology drugs, a program now in preclinical development.

AdAlta's strategy is to maximise the products developed using its next generation i-body® platform by internally discovering and developing selected i-body enabled product candidates against GPCRs implicated in fibrosis, inflammation and cancer and partnering with other biopharmaceutical companies to develop product candidates against other classes of receptor, in other indications, and in other product formats.

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