19 July 2021

ASX Announcement

ADALTA MAPS PATHWAY TO AD-214 EFFICACY STUDIES IN IPF

Highlights/Key Points

- **AdAlta to progress inhaled version of AD-214 into efficacy studies for IPF**
- **Intravenous AD-214 successfully completes Phase I multidose cohort at 5 mg/kg with no dose limiting safety issues identified; progress to 10mg/kg approved by Human Research Ethics Committee**
- **Pre-clinical development of radiolabelled AD-214 complete, informs and supports early transition to direct lung delivery**
- **Totality of results to date provide clear pathway for future development of AD-214 for IPF via inhalation: a more convenient and cost-effective route**
- **Timelines to efficacy data in IPF patients largely unchanged**
- **Current Phase I program to conclude, having achieved key safety objectives, releasing cash and AD-214 drug substance to progress inhaled delivery studies for IPF patients**

A webinar to discuss these results will be held at 2pm AEST Monday, 19 July 2021.

MELBOURNE Australia, 19 July 2021: AdAlta Limited (ASX:1AD), the clinical stage biotechnology company developing novel therapeutic products from its i-body platform announces plans to develop an inhaled version of its first in class anti-fibrotic, AD-214, for Idiopathic Pulmonary Fibrosis (IPF) and other Interstitial Lung Diseases (ILDs).

AdAlta's Phase I clinical studies for the first cohort of healthy volunteers receiving multiple doses at 5 mg/kg via intravenous administration has been successfully completed. The supervising Human Research Ethics Committee (HREC) has granted approval to progress to the next, 10 mg/kg, cohort. The data suggests that the AD-214 molecule fully engages its target receptor in humans with no dose limiting safety issues. The pharmacokinetic and safety results were consistent with prior single dose results, with the exception of three moderate infusion related reactions (one placebo and two treated participants from a total of eight) linked to the formulation.

Separately, AdAlta has completed development of a radiolabelled version of AD-214 (RL-AD-214) to inform dose levels and optimal routes of administration for various fibrotic indications. Pre-clinical imaging studies identified that rapid liver distribution following intravenous administration is likely to significantly increase the dose of AD-214 required for therapeutic effect by this delivery route. Whilst no liver toxicity has been observed in any pre-clinical or clinical studies to date, delivery of AD-214 by inhalation directly to the site of fibrosis in IPF patients is expected to significantly reduce the required dose of the drug, deliver greater patient and clinician convenience, enhance cost effectiveness and diversify AdAlta's partnering options.

Importantly, AdAlta believes that it can develop the inhaled formulation within the current budget and without delaying the next clinical trial program. AdAlta has initiated

discussions with contract research organisations with expertise in inhaled drug delivery, access to approved delivery devices and with capability to execute preclinical inhalation studies. The AD-214 molecule remains unchanged, so existing drug substance manufacturing processes remain unchanged and safety data from our Phase 1 study supports the safety of the much lower systemic exposure likely via inhalation.

The next clinical trials are anticipated to be conducted in IPF patients (subject to regulatory approval and short bridging studies in healthy volunteers) and will comprise a program of inhalation safety, dose ranging and efficacy studies. The time to Phase II efficacy data is therefore largely unchanged relative to the intravenous route, but with a more convenient formulation.

Dr Tim Oldham, AdAlta's Chief Executive Officer, said: *"We have taken several invaluable findings away from both our AD-214 clinical study and the additional work undertaken with the radiolabelled version.*

AD-214 behaved as expected across all safety measures. We have also benefited with the radiolabelled AD-214 showing distribution and clearance via the liver to guide our move ahead with an inhaled version of the drug.

We are pleased to be able to respond quickly to these results and progress a preferred, inhaled formulation of AD-214 for IPF without delaying the next clinical trials in patients.

Inhalation will deliver AD-214 directly to the sites of fibrosis in IPF and ILDs with less drug required, significantly reducing the cost of goods. For treating respiratory diseases like IPF and ILDs, inhalation is also likely much more desirable for patients than intravenous infusions. Currently, IPF patients routinely inhale salbutamol and steroids for symptom relief and we are aware of clinician and patient interest in current clinical trials for inhaled pirfenidone, one of the two marketed drugs for IPF."

Further detail about these results can be found below.

AdAlta will host a Webinar to discuss these results at 2pm AEST Monday, 19 July 2021. Register here:

https://us02web.zoom.us/webinar/register/WN_CnMpEkOQT3qLSFRPKIa1Cg

Authorised for lodgement by:

Tim Oldham
CEO and Managing Director
July 2021

DETAILED RESULTS AND DISCUSSION

Phase I healthy volunteer clinical results

AD-214 targets a receptor called CXCR4. CXCR4 is a critical player in the development of fibrosis in many organs and the progression of many cancers. In healthy individuals it is expressed primarily on blood and immune system cells and organs where these cells reside (for example blood, bone marrow, spleen). It also becomes highly expressed in fibrotic tissue including in IPF and other ILDs.

The safety profile of intravenously administered AD-214 has been established in AdAlta's Phase I clinical trial of single and multiple doses in healthy volunteers. In March 2021, AdAlta announced the results of single ascending dose studies of AD-214 in healthy volunteers. These showed that AD-214 was well tolerated at single doses up to 20 mg/kg; clearly engaged the target receptor, called CXCR4; and was able to occupy the receptor (receptor occupancy) at high levels and for extended periods of time at 5-20 mg/kg.

AdAlta has now completed the first (5 mg/kg) multiple dose cohort and has received Human Research Ethics Committee (HREC) approval to progress to the next, 10 mg/kg, multiple dose cohort. Eight participants received three 5 mg/kg doses of AD-214 or placebo (6:2 ratio) at two weekly intervals.

The key Phase I healthy volunteer results are set out below.

Pharmacokinetics consistent across doses. The pharmacokinetic profile (concentration over time and total exposure) of AD-214 in blood plasma was consistent with that observed in the single dose studies and consistent across multiple doses indicating no drug induced tolerance or clearance occurred.

AD-214 binds to the CXCR4 receptor. The CXCR4 receptor was engaged in a manner consistent with the single dose results at 5 mg/kg. After two doses of AD-214, 100% receptor occupancy on circulating T cells was maintained for at least 24 hours. The detailed receptor occupancy profile to seven days was measured only for the third dose for which data is not yet available. The results continue to show binding of AD-214 to the CXCR4 receptor on immune cells long after it clears from the blood, supporting extended intervals between doses for therapeutic effect. This effect does not diminish with repeat dosing.

AD-214 influences CXCR4 receptor function. As expected, transient increases in white blood cell and blood stem cell counts and the natural ligand for CXCR4 were observed after each repeat dose, and were consistent with levels observed in single dose studies. These results confirmed again that AD-214 was able to engage the CXCR4 receptor.

Positive safety profile for AD-214 molecule. Safety findings reflected the single dose studies. Reported treatment related adverse events in the multiple dose cohort were mild (Grade 1) with the exception of three moderate (Grade 2) arising in placebo and treatment participants. Three participants (one receiving placebo, two receiving active drug) reported infusion related reactions (flushes, tingling sensations, musculoskeletal

pain) after more than one dose. In two cases (one placebo, one active drug), infusions were ended early. Symptoms resolved rapidly after the end of infusion.

The observation of these reactions in the placebo group indicate that they are related to the formulation rather than AD-214 itself. Such reactions are relatively common in novel drug development and are usually managed with treatment with antihistamines and hydrocortisone. The HREC approval to progress to 10 mg/kg included these standard management approaches.

There were no concerning immune responses or changes to vital signs or clinical or laboratory parameters associated with these infusion reactions, or in general. Anti-drug antibodies were detected in three of six participants receiving active drug and, as in the single dose study, were generally at low levels. The nature of these antidrug antibodies is still being characterised.

Pre-clinical imaging results

Separate to the Phase I safety studies of AD-214, AdAlta has now completed development of a radiolabelled version of AD-214 (RL-AD-214) for PET imaging. Pre-clinical development studies of RL-AD-214 in mice and non-human primates (NHPs) confirm that AD-214 has been successfully radiolabelled, enabling PET images to be obtained that show the distribution of AD-214 and other i-bodies *in vivo*.

The objective of this program was to enable the distribution of AD-214 in different organs to be determined to inform dose levels and optimal routes of administration for various fibrotic indications. This is important since it is straight forward to determine AD-214's engagement with CXCR4 receptors in the blood, but very difficult in fibrotic tissues without an imaging tool.

This program has demonstrated its value in defining dose and route of administration and achieved its initial objectives earlier than expected.

RL-AD-214 shows that AD-214 distributes to tissues containing high expressing CXCR4 cells. Mouse and NHP imaging and complementary radiochemistry distribution studies showed when very small doses of radiolabelled AD-214 were intravenously administered, part of the dose could be found on circulating blood cells and distributed in other tissues where these cells reside such as the spleen and bone marrow. High doses of un-labelled AD-214 co-administered with RL-AD-214 were able to block these signals, confirming that distribution of AD-214 to these cells and tissues was mediated by specific binding to CXCR4.

AD-214 also distributes rapidly to the liver. These same studies also showed that the majority of the intravenous RL-AD-214 dose rapidly distributes to the liver. This could only partly be blocked with un-labelled AD-214, indicating that the mechanism of liver distribution was partly specific binding to CXCR4 and predominantly non-specific and independent of CXCR4. There has been no evidence of any unusual liver function or toxicities in any pre-clinical toxicology or human clinical studies to date, suggesting that while the liver appears to be a substantial sink for much of the administered dose of AD-214, this does not appear to detract from the positive overall safety profile of AD-214. Additional studies in mice suggest that the site of distribution in the liver is not hepatocytes (which are responsible for the metabolic function of the liver), further supporting the safety profile.

Other i-bodies do not display liver distribution or clearance. The observed liver distribution or clearance of AD-214 so far appears unique to this i-body. AdAlta has radiolabelled two other i-bodies in the same format and formulation as AD-214 and these have not demonstrated any unusual tissue distribution. This suggests that the liver distribution is not mediated by either the i-body scaffold or the Fc-fusion domain used for half-life extension in AD-214 and is specific to the particular pattern of amino acids in the region of the i-body that makes it specific for CXCR4. Additional studies with other i-bodies and formats are underway to confirm this finding.

Rationale for inhalation pathway

AdAlta has been progressing development of AD-214 using intravenous administration because it was potentially the fastest pathway to demonstration of potential clinical efficacy in IPF in a Phase II clinical trial forecast to commence in 2023. Alternative routes of administration have been considered as part of the AD-214 development strategy outlined in March 2020. The benefits of alternatives to intravenous administration include greater convenience for patients and clinicians, potentially lower drug doses, lower add-on healthcare costs for administration and the ability to select different partners for each indication of AD-214.

The PET imaging results using RL-AD-214 suggest that, despite clear evidence of efficacy in pre-clinical IPF models and of CXCR4 engagement and safety in animals and humans, much of the administered dose of AD-214 will end up in the liver where it is unavailable to deliver its therapeutic effect. This means much higher doses of AD-214 would be required for therapeutic effect via intravenous administration. Inhaled administration for IPF, in addition to the advantages already listed, would deliver AD-214 directly to the anticipated primary location of action in the lungs, improving its bioavailability, with the reducing dosing requirements resulting in a significantly lower cost of goods, and a much less aggressive (and therefore less expensive) manufacturing improvement program.

Several IPF drug candidates have been formulated for inhaled administration and IPF patients routinely inhale salbutamol and steroids for symptom relief. Clinicians report significant interest in trials of inhaled pirfenidone, one of the two marketed drugs for IPF, due in part to the potential for reduced side effects associated with oral delivery. The technology to deliver biologic drugs via inhalation has advanced rapidly in recent years, particularly for lung active agents and there are now at least 21 inhaled biologics approved or that have reached clinical development.[1]

Progressing AD-214 into patient studies with inhaled formulation

Time to AD-214 resupply can be used to prepare an inhaled formulation. Lead times across the global biologics contract manufacturing industry have lengthened due to COVID-19 induced capacity constraints, and can be the rate limiting step to commencing follow-on clinical trials. AdAlta has taken steps to shorten this lead time and recently announced (1 July 2021) that it had secured a drug substance manufacturing slot at KBI Biopharma that will resupply AD-214 for an earliest next clinical study in the second half of 2023. Formulation changes for biologics are best introduced as early as possible in the clinical development process and the Company can now use the time

[1] AA Matthews *et al*, Developing inhaled protein therapeutics for lung diseases, Molecular Biomedicine, 2020, 1, 11; W Liang *et al*, Pulmonary delivery of biological drugs, Pharmaceutics 2020, 12, 1025.

until the next clinical trial to develop the preferred inhaled formulation without delaying this progression to patient studies.

Timeline to efficacy data in IPF is largely unaffected by inhalation approach. AdAlta is commencing immediately the bridging activities necessary to deliver AD-214 by inhalation and confirm inhaled AD-214 distribution, efficacy and toxicology. The Company has initiated discussions with contract research organisations with expertise in inhaled drug delivery, access to approved delivery devices and with capability to execute preclinical inhalation studies in relevant toxicology and efficacy models. Since the AD-214 molecule is unchanged, no changes to bulk drug manufacturing are required and existing intravenous safety data will remain supportive. Systemic dose levels achieved in the current Phase I exceed the likely systemic exposure via inhalation, so the necessary toxicology studies need only focus on local lung toxicity.

The next clinical trials are anticipated to be conducted in IPF patients (subject to regulatory approval and a short single dose bridging study in healthy volunteers) and will comprise a program of inhalation safety, dose ranging and efficacy studies. The time to Phase II efficacy data is therefore largely unchanged relative to the intravenous route, but with a more convenient formulation.

Cash and AD-214 drug substance saved by concluding current Phase I program now. The Company has determined that the Phase I program and development of RL-AD-214 have achieved their objectives. Notwithstanding HREC approval to proceed, AdAlta will conclude the current Phase I clinical studies once full data from the 5 mg/kg multiple dose cohort is available.

RL-AD-214 and PET imaging will remain important research tools. However, the previously planned Phase Ib study of AD-214 in patients, including PET imaging using RL-AD-214, will also not proceed. Plans to use imaging to show that AD-214 can bind to CXCR4 receptors in fibrotic tissue will now be realized by using RL-AD-214 and other imaging techniques to demonstrate AD-214 distribution in preclinical inhalation studies. In particular, RL-AD-214 may also be able demonstrate differences in AD-214 distribution between healthy and fibrotic tissue much more accurately (and cost effectively) in large animal models than in human studies and will be critical to rapidly optimizing dosing regimens.

Concluding these studies will release funds and AD-214 drug substance to bridge to the inhaled formulation.

Mechanism of liver distribution and clearance to be further investigated. A final advantage of the inhalation pathway is the potential to create a unique, indication specific formulation and presentation that would enable AD-214 to be partnered for lung fibrosis alone. Several other fibrosis indications are also amenable to non-systemic (or local, organ specific) routes of administration. Each alternate route of administration opens the opportunity for additional AD-214 partnerships, broadening the revenue generating potential of AD-214.

AdAlta will also continue to study the intravenous administration of AD-214. Deeper understanding of the mechanism of liver distribution and clearance following intravenous administration may also enable formulation changes that improve the availability of AD-214 when administered by this route, opening up further indication and partnering

options. Formulation changes may also reduce the infusion related reactions observed in the multiple dose studies of AD-214 and improve storage conditions.

Updated AD-214 milestones

The Phase I and PET imaging programs have delivered favourable AD-214 safety and target engagement data and important data, informing optimal routes of administration. The Company now has a clear path forward to patient and efficacy studies for AD-214.

AdAlta anticipates:

- Completing studies to confirm the distribution of inhaled AD-214 in healthy and disease model animals using PET and other imaging techniques by the first quarter of 2022. This is approximately when first images would have been available from the Phase Ib patient protocol.
- Completing studies to confirm efficacy of inhaled AD-214 in animal models in mid 2022. These may now also be correlated with imaging of AD-214 distribution, providing significantly more information than was possible with prior pre-clinical studies or in the Phase Ib protocol.
- Being able to commence inhaled clinical trials when AD-214 resupply is received from KBI Biopharma – in line with previous Phase II plans.

AdAlta's collaboration with GE Healthcare and plans to initiate discovery on two new targets before the end of 2021 remain unchanged, and on target.

Notes to Editors
About AdAlta

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 protein 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 has advanced its lead i-body candidate, AD-214, into clinical studies. AD-214 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.

The Company is also entering collaborative partnerships to advance the development of its i-body platform. It has an agreement with GE Healthcare to co-develop i-bodies as diagnostic imaging agents 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.

Further information can be found at: https://adalta.com.au

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