2 November 2022

ASX Announcement

AD-214 progress and priorities

Key points

- **Applications of AD-214 expanded; now include lung, kidney and eye fibrosis, and cancer, all major areas of unmet need with substantial commercial interest**
- **AdAlta to prioritise injectable delivery of AD-214 for lung, kidney or eye fibrosis for development; will partner to progress other applications**
- **Additional preclinical data expected for eye and kidney fibrosis in H1 2023, will guide indication for next fibrosis clinical trial**
- **Progress on manufacturing yield and formulation development enables continuation of intravenous (IV) delivery (lung and kidney fibrosis) and intravitreal (IVT) development (eye fibrosis)**
- **Inhaled delivery data available for potential lung fibrosis commercialisation partners**
- **Webinar to discuss results to be held on Wednesday 2 November from 3pm AEDT (Melbourne time)**

MELBOURNE Australia, 2 November 2022: AdAlta Limited (ASX:1AD), the clinical stage biotechnology company developing novel therapeutic products from its i-body platform provides an update on its lead program, AD-214, a first in class antifibrotic.

AdAlta has made substantial progress expanding the potential disease areas (indications) and routes of delivery for AD-214. Considering available manufacturing and toxicology study slots and return on investment, AdAlta is now progressing four strategic priorities for AD-214

1. Prioritise clinical development of AD-214 for lung, kidney and eye fibrosis. Pre-clinical data and partnering discussions over the next six months to guide final choice of indication for next clinical trial.
2. Progress injectable (intravenous/IV for lung, kidney fibrosis and intravitreal/IVT for eye fibrosis) routes of administration.
3. Continue investment in manufacturing and formulation improvement strategies.
4. Leverage progress in the development of an inhaled format of AD-214 for partnering for lung fibrosis.

AdAlta's CEO and Managing Director, Dr Tim Oldham said:

"In the interval between Phase I and Phase II trials of AD-214 we have made significant progress in expanding the value of this asset. We now have compelling preclinical data supporting efficacy in kidney fibrosis and have established that AD-214 can be delivered to the lungs via inhalation with mode of action evidence supportive of potential efficacy. We have an ongoing collaboration with University of Melbourne for eye fibrosis and a new collaboration with GPCR Therapeutics Inc to evaluate AD-214 in oncology. Importantly, we have also made progress identifying manufacturing and formulation improvements.

Taking into account the unmet needs in each disease area that AD-214 may address, levels of competition and the time and cost to develop each product option from here, we have elected to focus our own AD-214 efforts on injectable delivery for use in lung, kidney or eye fibrosis. We have secured manufacturing and toxicology bookings to prepare us for the next clinical trial in

2024. Other disease areas and routes of administration, including the inhaled version of AD-214 remain options available to future partners that can be progressed at low cost to AdAlta."

Several disease area opportunities – all with unmet need

To prioritise indications and routes of administration, AdAlta considered the unmet needs in each disease area and the competitive landscape. Also considered was the data, available or pending, supporting use of AD-214 in each indication, and the time and cost to progress each indication and route of administration to clinical proof of concept.

AdAlta has compelling pre-clinical data using the IV version of AD-214 in lung and kidney fibrosis. Like lung fibrosis, kidney fibrosis is an area of high unmet need with a less competitive landscape. Progress to Phase II proof of concept studies using the IV version is underpinned by previously completed Phase I studies and encouraging progress made identifying opportunities to increase manufacturing yields and reduce liver clearance.

Intravitreal (IVT) AD-214 could address an attractive, very underserved market in eye fibrosis with significant early stage partnering interest and a more favourable competitive landscape. Previous encouraging pre-clinical studies using the earlier version of the product, AD-114, are being replicated and extended using AD-214, with results due in the next six months.

IVT AD-214 (intravitreal) could be progressed separately to IV AD-214 (intravenous) through engagement with partners, or by AdAlta directly. It has the potential to achieve clinical proof of concept via Phase I studies.

Recent collaboration with GPCR Therapeutics for oncology

Oncology is now the largest therapeutic market globally. The application of CXCR4 antagonists such as AD-214 to treat cancer is attracting significant interest. The recently announced collaboration with GPCR Therapeutics, Inc represents a cost-effective way for AdAlta to progress an oncology pipeline.

Inhaled AD-214 – valuable data package for potential partners

AdAlta has now demonstrated the delivery of AD-214 via inhalation and the potential to reduce collagen deposition in cultured lung tissue. The additional time and cost to complete preclinical development and safety studies for IPF, coupled with the competitive clinical trial landscape has led the Company to focus resources on injectable formats and make the inhalation program available to lung fibrosis partners to progress.

Next steps

AD-214 milestones in the next six months now include:

- Commencement of manufacturing of AD-214 for extended-dose toxicology studies
- Additional pre-clinical results in eye and kidney fibrosis
- Further details on clinical program indication and design
- Continuation of partnering outreach for IV AD-214 in lung and kidney fibrosis

Webinar

Investors are invited to join a webinar to further discuss the AD-214 results and strategy on 2 November 2022 at 3pm AEDT (Melbourne time). Register at: https://us02web.zoom.us/webinar/register/WN_T_Dci-IXSQq1bQOavF78hg

After registering, investors will receive a confirmation email containing information about how to join the webinar.

Authorised for lodgement by:

Tim Oldham
CEO and Managing Director
November 2022

Additional information

Manufacturing sets earliest clinical timelines

In July 2021, AdAlta completed a Phase I clinical trial of intravenously administered AD-214 in healthy volunteers. AD-214 was well tolerated in single and multiple doses and demonstrated binding to its target, CXCR4, well beyond clearance from the blood. Lead times for supply of AD-214 meant that Good Manufacturing Practice (cGMP) grade AD-214 would not be available for further clinical trials until mid-2023 (subsequently extended to the end of 2023).

AD-214 pre-clinical program data establishes options in lung, kidney and eye fibrosis and oncology

In the period prior to the next availability of cGMP grade AD-214, AdAlta has progressed several initiatives to add value to AD-214 by diversifying indications (results have not previously been announced unless indicated):

- *Kidney fibrosis (IV administration)*: Kidney fibrosis is associated with many chronic kidney diseases (CKD) and as such represents an area of unmet need and significant commercial opportunity, The current pipeline for CKDs is dominated by immunosuppressives, immunomodulatory agents, anti-inflammatories, angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors with just 6 interventional clinical studies ongoing or about to commence in renal fibrosis.[1] In April 2022, AdAlta announced the publication of compelling preclinical data in a mouse model of kidney fibrosis for both AD-214 and AD-114 (the i-body which binds to CXCR4 and forms the active part of AD-214).
- *Eye fibrosis (IVT administration)*: Fibrosis is associated with many eye diseases, including wet Age-related Macular Degeneration (wet-AMD), the largest cause of blindness. Existing treatments eventually cease to work, and the resulting fibrosis contributes to progression and blindness. The current pipeline for eye diseases such as wet-AMD is dominated by new formulations of anti-VEGFs, other anti-angiogenics and anti-inflammatories with only two interventional clinical studies ongoing or about to commence in eye fibrosis.[2] AdAlta

[1] As at 7 October 2022 https://clinicaltrials.gov/ct2/results?cond=Renal+Fibrosis&recrs=b&recrs=a&age_v=&gndr=&type=Intr&rslt=&Search=Apply

[2] As at 7 October 2022 https://clinicaltrials.gov/ct2/results?cond=eye+fibrosis&term=&cntry=&state=&city=&dist=&Search=Search&recrs=a&recrs=b&type=Intr

has an established collaboration with the laboratory of Erica Fletcher, University of Melbourne. This group had previously demonstrated that AD-114 had anti-leakage and anti-fibrotic effects in the laser CNV mouse model of eye fibrosis. They have now demonstrated that AD-214 can be detected in the eye at least 30 days after injection and are replicating and extending the efficacy studies with AD-214 with results expected in the next six months.

- *Cancer (IV administration)*: CXCR4 has been implicated in 23 or more cancers and represents a natural indication extension for CXCR4 inhibitors such as AD-214. 22 interventional clinical studies of CXCR4 inhibitors in cancer are ongoing or about to commence.[3] To be competitive in this indication is likely to require a combination therapy approach. AdAlta has recently (announced October 2022) entered a collaboration with GPCR Therapeutics Inc, Korea, to evaluate use of CXCR4 i-bodies (including AD-214) in combination with beta blockers to improve cancer outcomes.

- *Lung fibrosis (IV or inhaled administration)*: Lung fibrosis, in the form or IPF and ILD, is progressive and fatal with poor treatment options today. There are 82 interventional clinical studies ongoing or about to commence.[4] Preclinical studies in the gold standard mouse bleomycin (BLM) model of lung fibrosis show efficacy of AD-214 when administered intravenously. AdAlta has now shown that inhaled AD-214 can be delivered to the smallest airways of the lungs in sheep treated with bleomycin and retained in the lungs. *In vitro* studies suggest that treatment of human lung tissue with AD-214 can modulate fibrosis processes. Given the substantial investments required for the next stages, the AdAlta Board believe this project is best progressed through commercial partnering.

AD-214 manufacturing and formulation program data establishes options in lung, kidney and eye fibrosis and oncology

In the period prior to the next availability of cGMP grade AD-214, AdAlta has progressed several initiatives to add value to AD-214 by improving manufacturing and routes of administration (results have not previously been announced unless indicated):

- *Inhaled formulation:* inhalation of AD-214 potentially offers a more patient convenient route of administration that would also bypass the known clearance of intravenous AD-214 via the liver, potentially reducing the dose required. AdAlta has successfully nebulised AD-214 in two commercially available, regulatory approved handheld nebulisers (announced December 2020) and made substantial progress identifying a formulation suitable for inhalation containing excipients already approved for inhalation that significantly reduces toxicology study requirements for future clinical studies. The formulation may also have use as an alternative IV formulation.

- *Manufacturing yield and flexibility*: Cell culture experiments have identified a strategy to substantially improve the yield of a key step in the manufacture of AD-214. While additional work is required to confirm the feasibility of this result, if successful it would substantially reduce the cost of producing AD-214 ahead of Phase III trials and improve future commercial margin opportunities. Changes to the manufacturing process are being implemented to enable rapid adoption of new formulations as they become available.

[3] As at 17 October 2022
https://clinicaltrials.gov/ct2/results?term=CXCR4&cond=Cancer&recrs=b&recrs=a&age_v=&gndr=&type=Intr&rslt=&Search=Apply
[4] As at 7 October 2022
https://clinicaltrials.gov/ct2/results?cond=Idiopathic+Pulmonary+Fibrosis&recrs=b&recrs=a&age_v=&gndr=&type=Intr&rslt=&Search=Apply

- *IV formulation*: Experiments with alternate diluents and buffers have identified a formulation and infusion strategy that may reduce the clearance of AD-214 via the liver, improving intravenous bioavailability. Confirmatory studies are under way.

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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 has completed Phase I clinical studies for its lead i-body 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. 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 co-develop 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.

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

For more information, please contact:

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