ASX Announcement/Press Release | 20 February 2024
AdAlta Limited (ASX:1AD)

Australia Biologics Festival Presentation

AdAlta Limited (ASX:1AD) ("AdAlta" or "the Company") is pleased to announce its participation in the Australia Biologics Festival to be held between 20 February and 21 February 2024 in Melbourne.

AdAlta CEO and Managing Director, Tim Oldham will be participating in two sessions:

- On 20 February 2024 at 9:00am AEDT in a leadership panel discussion titled "Current and future state of the Australian biologics market".
- On 21 February 2024 at 10:00am AEDT as an invited presenter on the topic of "Dose estimation and optimisation for a first in class antifibrotic" which will review the methods and rationale used for dose selection for Phase II studies of AD-214.

A copy of the presentation is attached.

The Australia Biologics Festival 2024 supports advancing biologics R&D, manufacturing, technology and innovation in Australian and New Zealand. More information and registration details can be found here: https://imapac.com/events/australia-biologics-festival/

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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.

For more information

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To learn more about AdAlta please visit: www.adalta.com.au

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

AdAlta

Dose estimation and optimization for a first-in-class anti-fibrotic therapeutic

Tim Oldham PhD
CEO and Managing Director
AdAlta Limited (ASX:1AD)
Australian Biologics Festival
20-21 February 2024

Disclaimer

Investment in AdAlta is subject to investment risk, including possible loss of income and capital invested. AdAlta does not guarantee any particular rate of return or performance, nor do they guarantee the repayment of capital.

This presentation is not an offer or invitation for subscription or purchase of or a recommendation of securities. It does not take into account the investment objectives, financial situation and particular needs of the investor. Before making any investment in AdAlta, the investor or prospective investor should consider whether such an investment is appropriate to their particular investment needs, objectives and financial circumstances and consult an investment advisor if necessary.

This presentation may contain forward-looking statements regarding the potential of the Company's projects and interests and the development and therapeutic potential of the company's research and development. Any statement describing a goal, expectation, intention or belief of the company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercialising drugs that are safe and effective for use as human therapeutics and the financing of such activities.

There is no guarantee that the Company's research and development projects and interests (where applicable) will receive regulatory approvals or prove to be commercially successful in the future. Actual results of further research could differ from those projected or detailed in this presentation. As a result, you are cautioned not to rely on forward-looking statements. Consideration should be given to these and other risks concerning research and development programs referred to in this presentation.

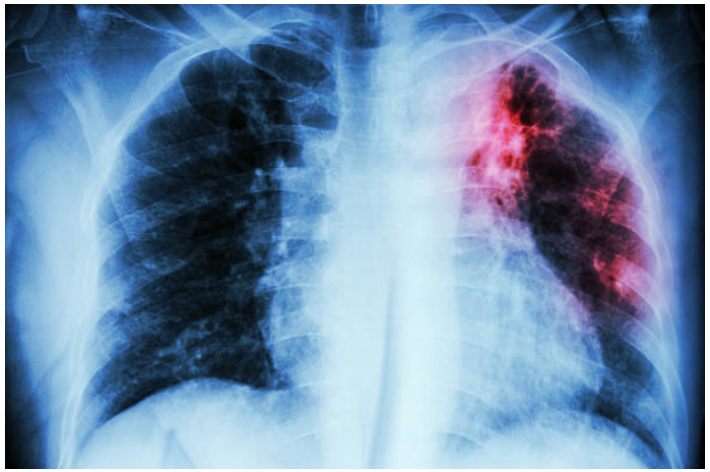
Summary

- AdAlta's i-body® platform: a powerful drug discovery tool for targets such as G-protein coupled receptors (GPCRs) where traditional antibody drugs struggle
- AdAlta's AD-214 targets the GPCR CXCR4 and has been specifically designed for the high unmet need in fibrotic diseases such as Idiopathic Pulmonary Fibrosis (IPF)
- AD-214's potential efficacy has been demonstrated using *in vitro, ex vivo* and animal models of fibrosis
- AD-214 shows extended CXCR4 receptor occupancy in toxicology and Phase I studies
- Dose finding is challenging in the absence of reliable biomarkers and limited CXCR4 expression in healthy volunteers
- ***AdAlta has recently used ex vivo models and PK/PD simulations to establish Phase II IV dosing at clinically convenient two weekly dosing schedules … and to demonstrate the feasibility of an enhanced weekly SC formulation to enhance patient convenience***

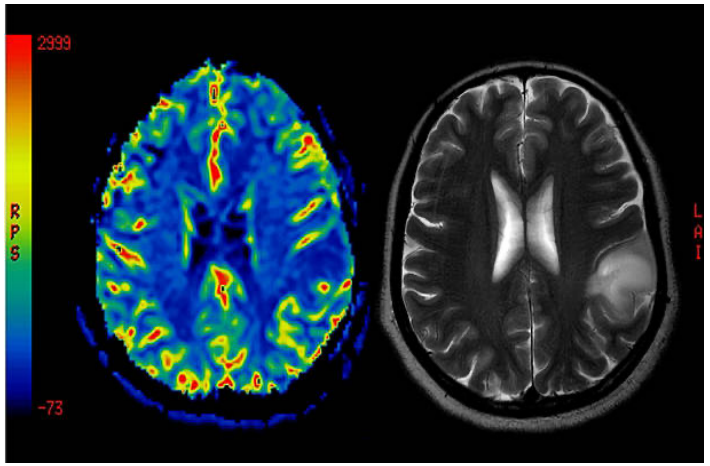
AdAlta (ASX:1AD) at a glance

AdAlta's i-body® platform is enabling a high-value product pipeline in two therapeutic areas of significant unmet medical need

i-body® discovery platform enables development of multiple, high value assets



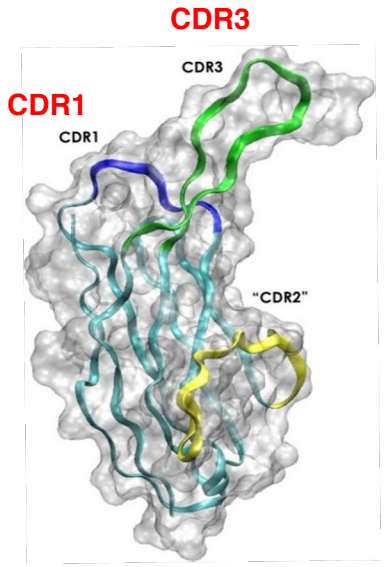
A wholly owned fibrosis and inflammation pipeline



A co-developed immuno-oncology pipeline

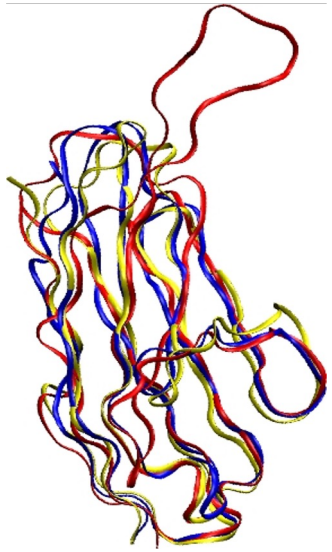
Invention of i-bodies

i-bodies mimic shark VNARs using a human NCAM domain 1 scaffold and randomized synthetic shark VNAR-like binding loops



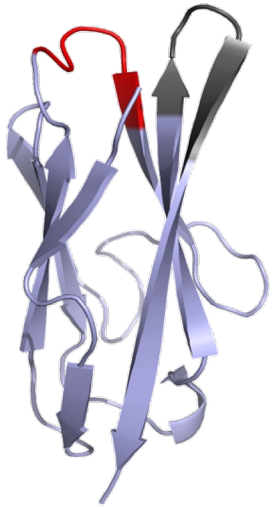
Shark VNAR

Basic research on unique shark immune system …



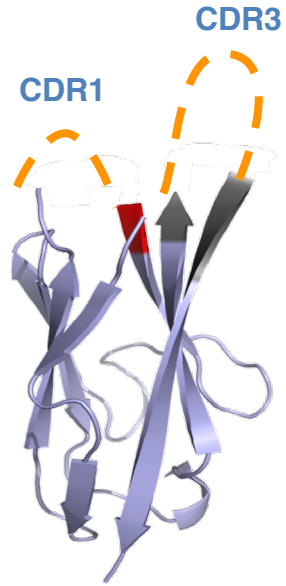
Ribbon overlay*

… led to discovery that the i-set family of human proteins have the same scaffold structure …



hNCAM Domain 1

… leading to the choice of human NCAM domain 1 for the current scaffold …



i-body® library

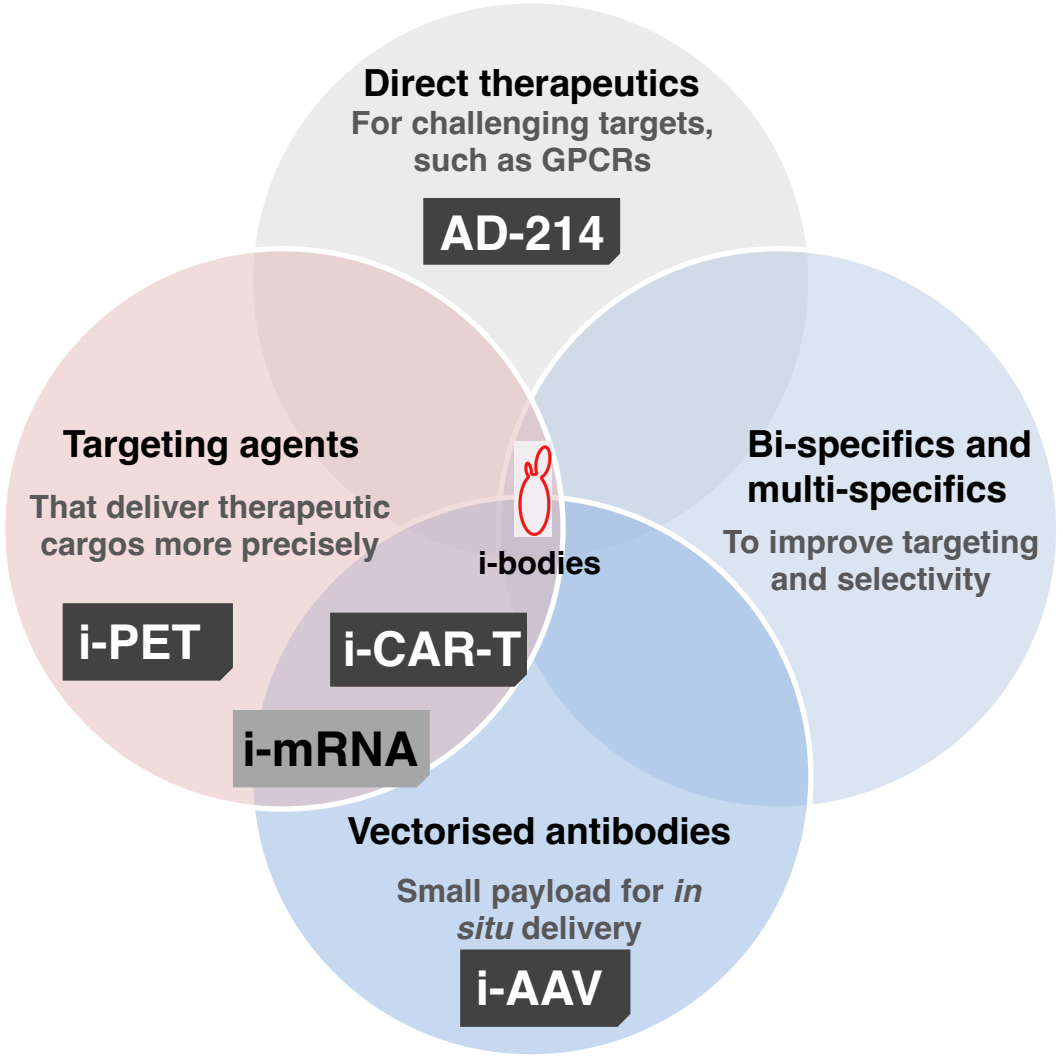
… and invention and patenting of i-bodies by adding randomized synthetic VNAR-like binding loops to NCAM-1

* Shark VNAR (red); human i-set immunoglobulins (yellow and blue)

An immensely powerful drug discovery platform applicable to multiple therapeutic formats

Current examples

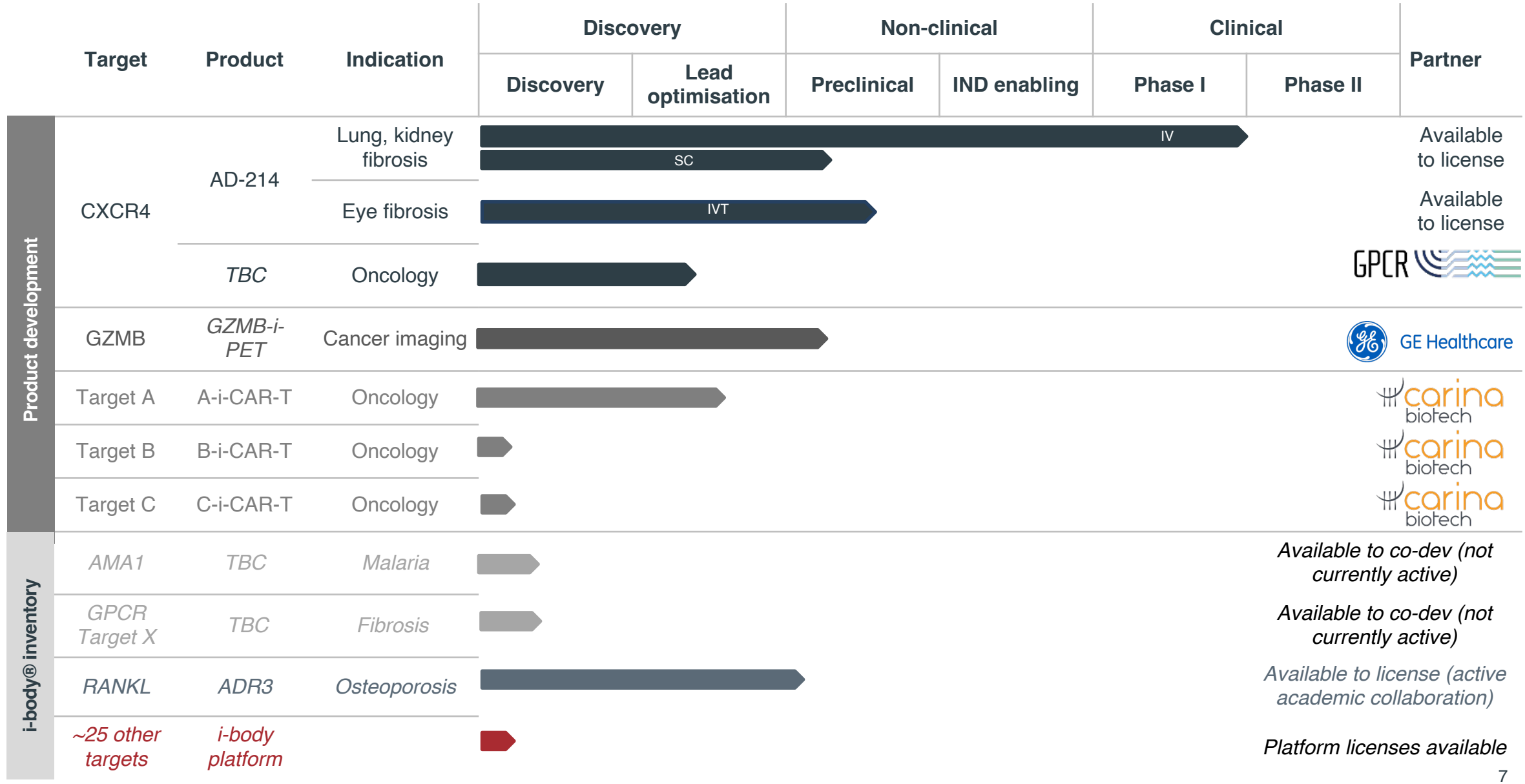
Future examples



Manufacturing and delivery

- Delivery and expression *ex vivo* and *in vivo* using viral vectors or DNA/RNA
- Efficient i-body® expression in bacterial fermentation systems
- Mammalian fermentation systems for more complex formats eg i-body-Fc-fusions
- Post synthesis chemical conjugation

AdAlta's pipeline so far: Five active assets plus growing i-body® inventory



Bill van Nierop: IPF survivor on the challenge of living with IPF

"… sadly I am one of a few who can actually relate to the lived experience with and without PF …"

"***You see our symptoms are basically an ongoing internal struggle to breathe freely*** … and it's invisible to all, including family, friends and the general community."

"I talked with a 60 something grandmother, who really enjoyed days looking after grandkids, but as disease progressed she found sometimes she needed to reduce the time a bit. You won't believe that her daughter in law suggested she would just bring them around less, 'you're always tired but you look really well', so I won't bother you as much. Shattering to the poor woman obviously, but again demonstrates the absolute lack of understanding of this debilitating disease. ***Looks well, so can't be too ill, except she's struggling to breathe and is on a journey with an inevitable end***."

Source: Bill van Nierop, https://www.facebook.com/kayakforlungs 28 September 2023

https://www.lonagkayakforlungs.com.au/

The need: better outcomes for Idiopathic Pulmonary Fibrosis (IPF) and other fibrotic diseases

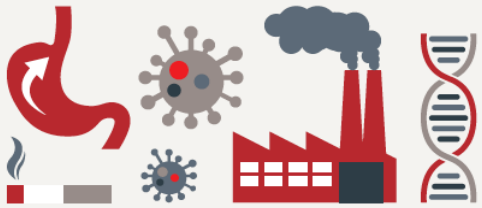
IPF incidence

>490,000 worldwide

50% of sufferers die within 3 – 5 years following diagnosis

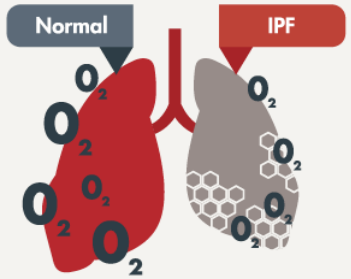
>100,000 pa

Causes



The cause is unknown but risk factors may include: smoking, environmental exposures, chronic viral infections, abnormal acid reflux and family history of the disease.

Pathology



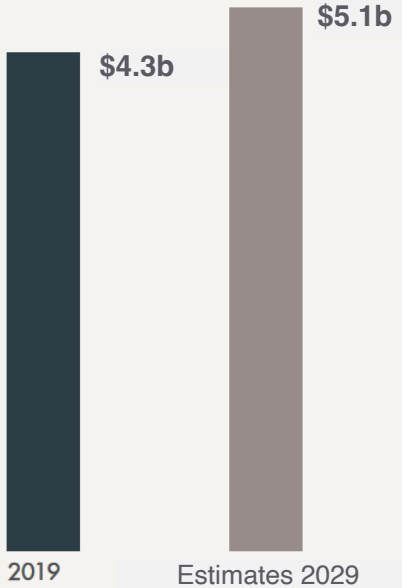
Resultant scarring/honeycombing in the lung restricts breathing and oxygen exchange.

Current IPF treatments

Pirfenidone — Roche

Nintedanib — Boehringer Ingelheim

Slow, but do not halt progression. Serious side effects limit compliance, tolerability



Source: GlobalData,[2] company financial reports, AdAlta analysis

45% of developed world deaths have a chronic fibrosis component

Every organ vulnerable:

- Lung (**US$4b**)
- Kidney **(US$10b)**
- Eye (**US$15b**)
- Cancer (**US$1b** each)[3]

New drivers of incidence

- "Long COVID"[1]
- Re-emergence of silicosis

[1] PM George, et al, "Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy", Lancet published online May 15, 2020.
[2] GlobalData, Idiopathic Pulmonary Fibrosis: Competitive Landscape, April 2023
[3] GlobaData, disease analysis reports

The value: Pharma companies are actively licensing IPF assets for significant value

Date	Licensor/target	Licensee/acquirer	Transaction	Upfront payment to licensor	Contingent milestones	Clinical Phase at transaction
Feb 23	Redx	Jounce Therapeutics	Acquisition#	**US$294m**	N/A	2
Jan 23	Daewoong	CSPC Pharmaceuticals (创新进中国)	China only license	**US$76m^**	US$336m	2
Aug-22	Kiniksa	Genentech, A Member of the Roche Group	License	**US$80m**	US$620m	2
Apr-20	Curzion Pharmaceuticals	Horizon	Acquisition*	**US$45m**	Not disclosed	2
Nov-19	Promedior	Roche	License	**US$390m**	US$1,000m	2
Nov-21	Blade Therapeutics	Biotech Acquisition Company	Acquisition#	**US$254m**	N/A	2 (Ready)
Nov-20	OncoArendi Therapeutics	Galápagos	License	**€25m**	€320m	2 (Ready)
Sep-21	Syndax	Icyte	License	**US$152m**	US$602m	2 (Ready)
Feb-21	泰德制药 Tide Pharmaceutical	Graviton Bioscience Corporation	License	**Not disclosed**	US$517.5m	1
Jul-19	bridgebio therapeutics	Boehringer Ingelheim	License	**€45m**	€1,100m	1
Oct-22	DJS antibodies	abbvie	Acquisition	**US$255m**	Not disclosed	Pre-clinical (+ platform)

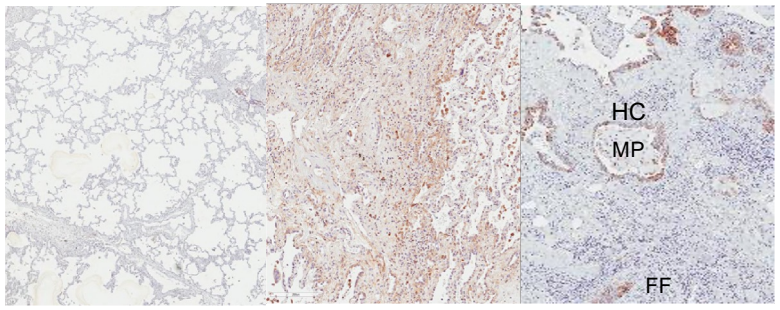
AD-214 almost Phase II ready

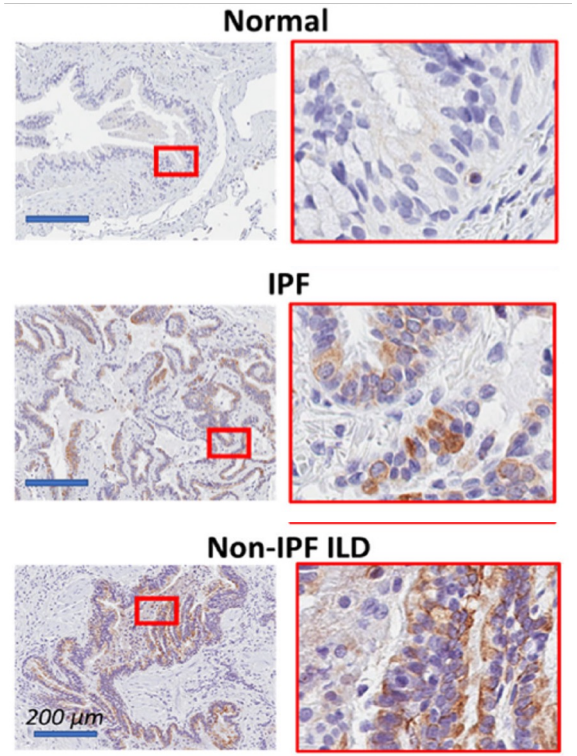
Source: Company press releases; * Lead indication was diffuse cutaneous systemic sclerosis which usually evolves into IPF; # Did not complete; ^ Includes development milestones

CXCR4 is an established GPCR target in fibrotic diseases

CXCR4 is a critical player in many **fibrotic indications** including lung, kidney, heart, eye, skin

Immunohistochemical analysis of lung IPF tissue showed expression of CXCR4 in human lung tissue from IPF and ILD patients with little staining in lung tissue from age-matched non-disease controls[1]





IPF – Idiopathic Pulmonary Fibrosis;
ILD – Interstitial Lung Disease;
HC – honeycomb cysts;
MP – mucus plugs,
FF – fibroblastic foci

CXCR4 imaging demonstrates strong CXCR4 expression correlated with areas of honeycombing in IPF

Changes in CXCR4 expression may be predictive of response to pirfenidone and may have a role in monitoring IPF disease progression[2]

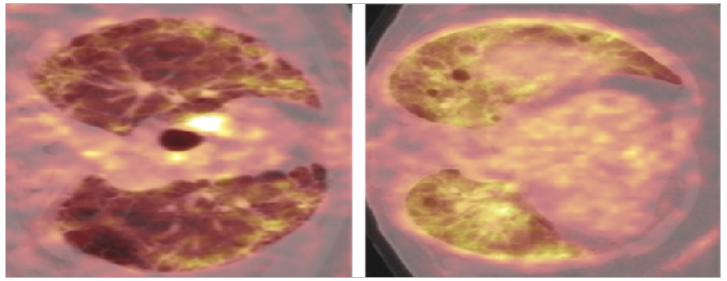
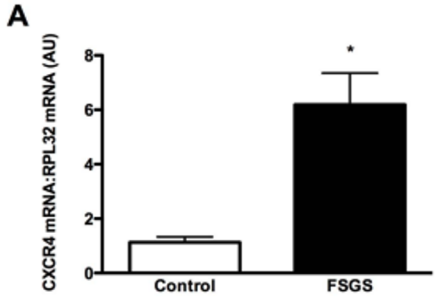


Figure 2. Baseline serial CXCR4 PET/CT scans of 2 patients with IPF

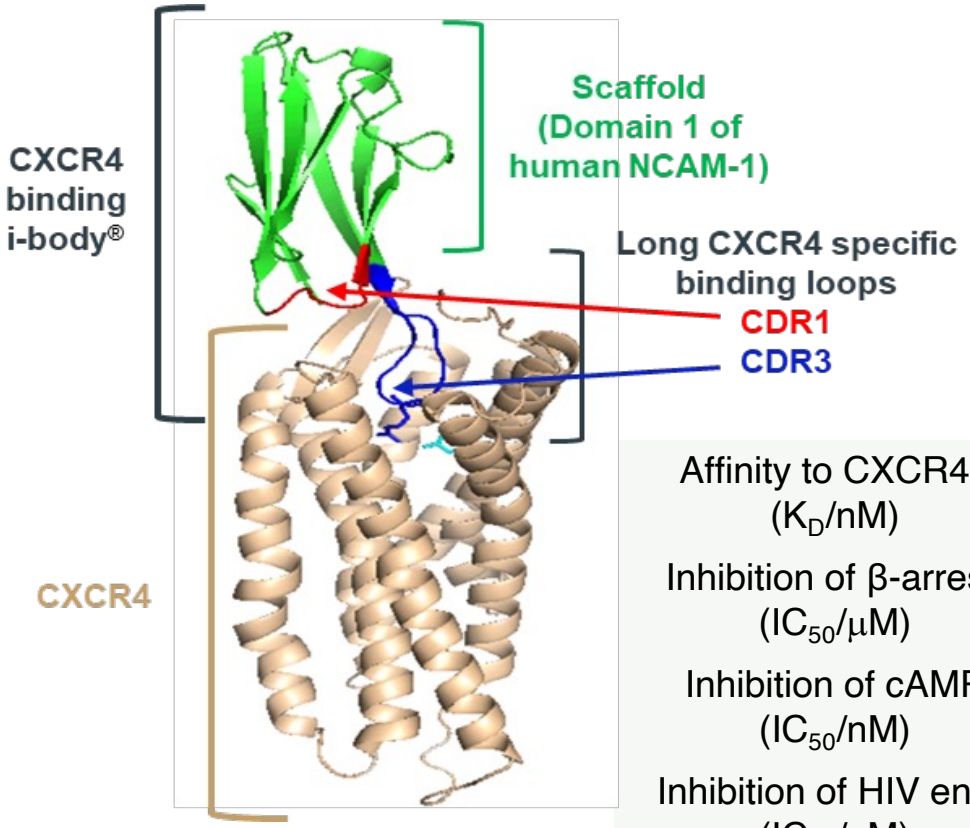
Real-time PCR for CXCR4 mRNA in kidney biopsies from patients with secondary FSGS and from non-disease live kidney donors (Control)[3]

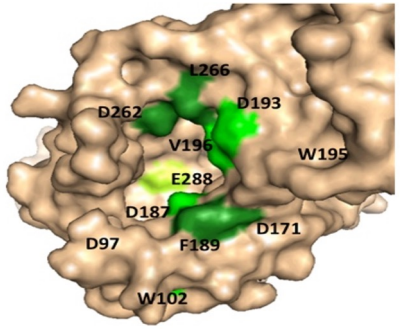
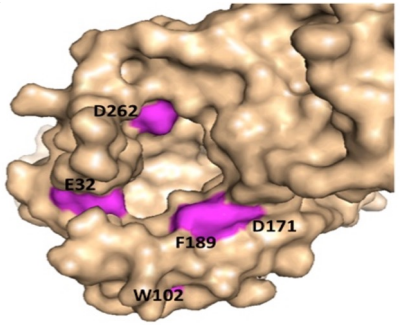
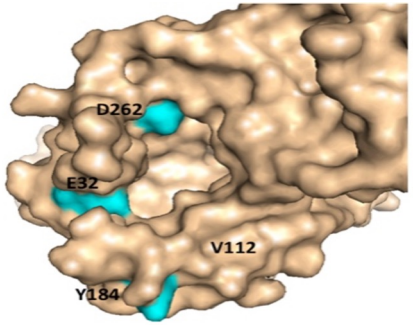


1. Griffiths et al 2018; Jaffar et al 2020
2. Prasse et al 2017
3. Chen et al 2014

AD-114 was selected as the lead candidate because of its optimal antifibrotic properties

CXCR4 i-bodies demonstrate differential pharmacology, allowing optimization of target interaction



	AD-114	AD-272	AD-523
			
Affinity to CXCR4 (K_D/nM)	4.2	1.8	9.2
Inhibition of β-arrestin (IC_{50}/μM)	1.18	1.38	2.94
Inhibition of cAMP (IC_{50}/nM)	99	300	225
Inhibition of HIV entry (IC_{50}/nM)	131	838	349
Attenuation of laser induced eye leakage and fibrosis[1]	YES	N/A	NO

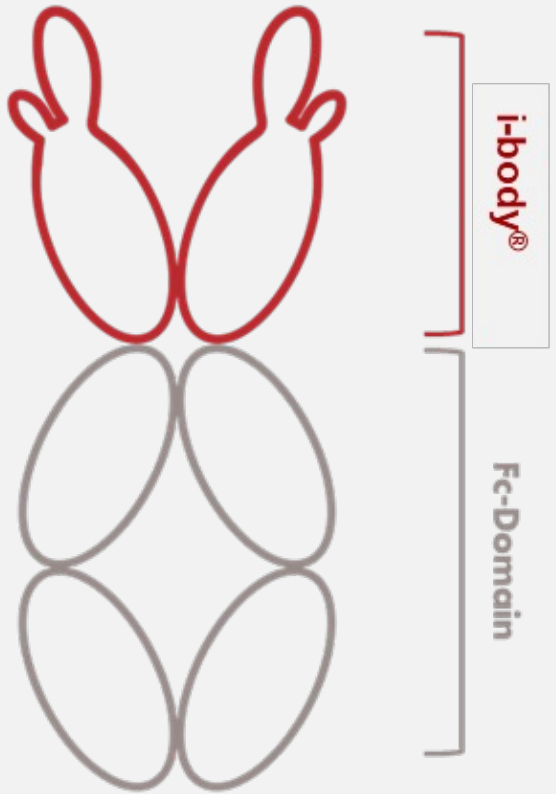
1. Fletcher et al 2021 (unpublished)

Drug candidate AD-214 is a dual AD-114 i-body-Fc fusion protein with optimized CXCR4 affinity and half-life

Therapeutic candidate

AD-214 CXCR4 antagonist

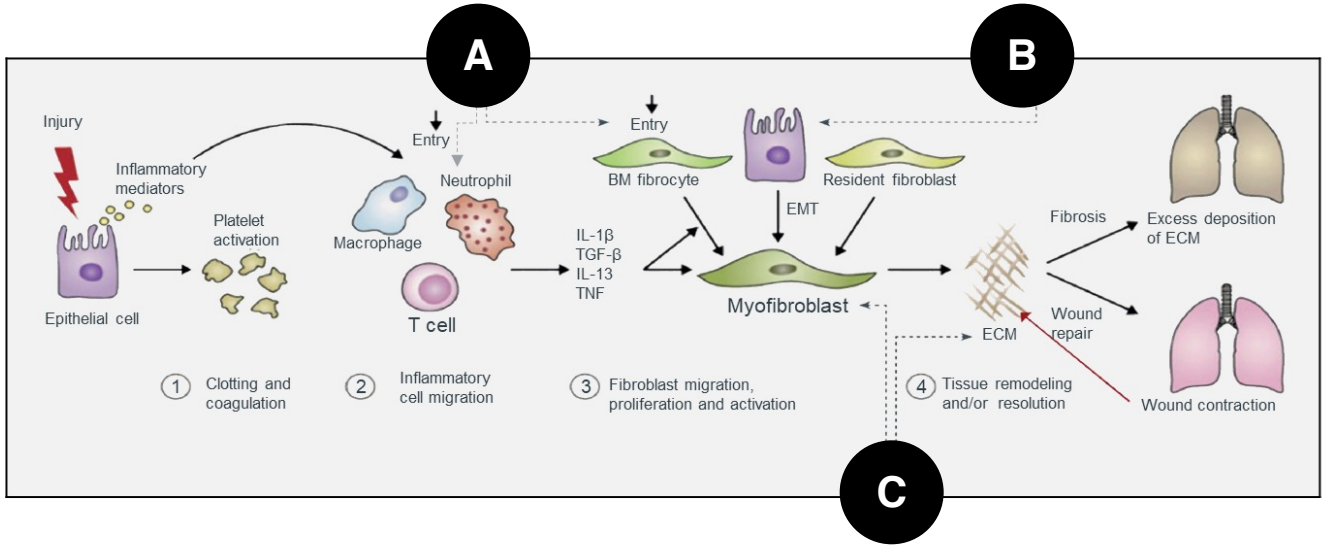
i-body® Fc fusion protein (~75kDa)



- AD-114 i-body® within **AD-214** is highly specific to the CXCR4 ligand binding pocket
- Selected for impact on anti-fibrotic signaling over other CXCR4 functions
- Dimer enhances avidity

- Combining the anti-CXCR4 i-body® and the Fc-domain of human IgG1 increases half life
- Effector functions removed to prevent cell killing
- This structure also improves manufacturability

In vitro and *ex vivo* studies support proposed multiple modes of action



A. Inhibiting inflammatory cell and fibrocyte recruitment into the damaged tissue

White cell migration studies

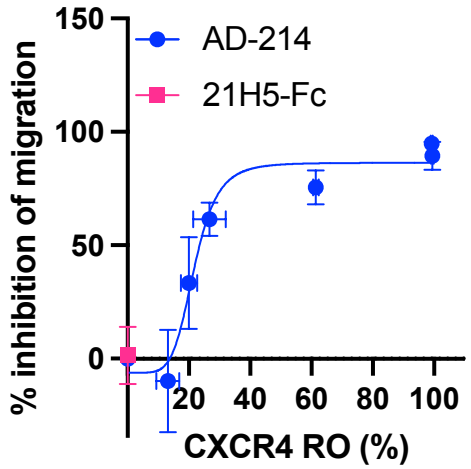
B. Inhibiting epithelial cell proliferation, secretion of pro-fibrotic factors and EMT

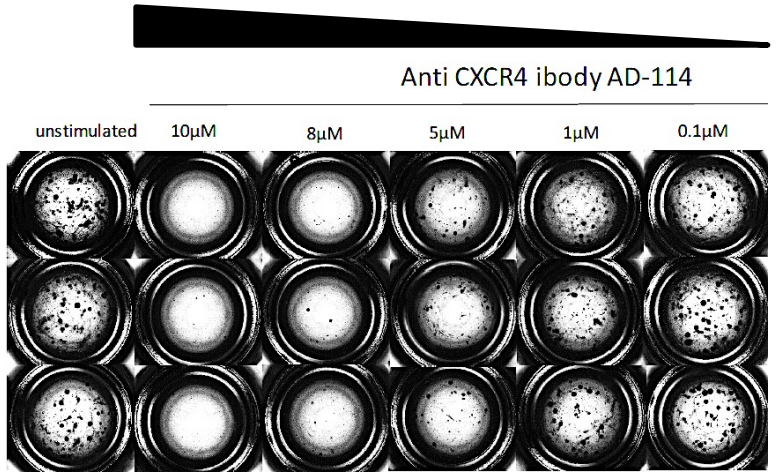
Airway basal cell proliferation

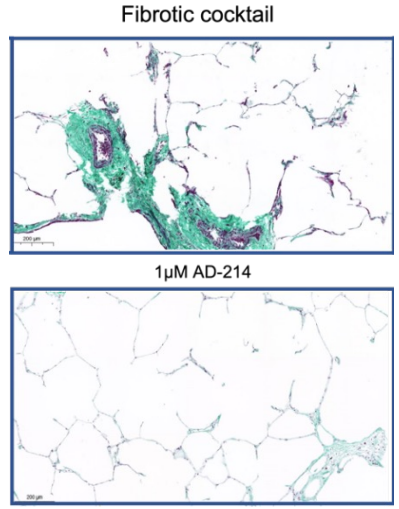
C. Inhibiting fibroblast migration, differentiation and ECM deposition during tissue remodelling

Precision cut lung slice collagen

EXAMPLES



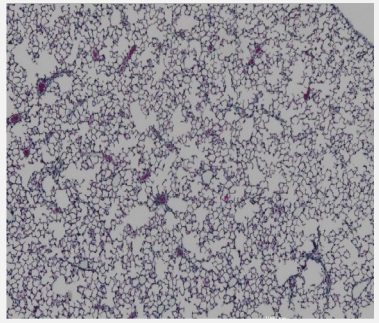




Schematic adapted from Wynn, 2011; AdAlta data

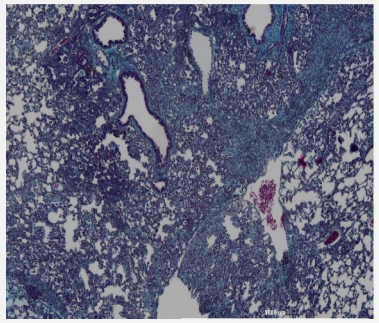
AD-214 efficacy validated in mouse model of IPF; suggestive of minimum effective dose

Normal mouse lung tissue



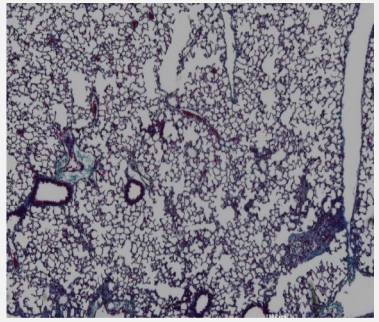
IPF mouse lung tissue

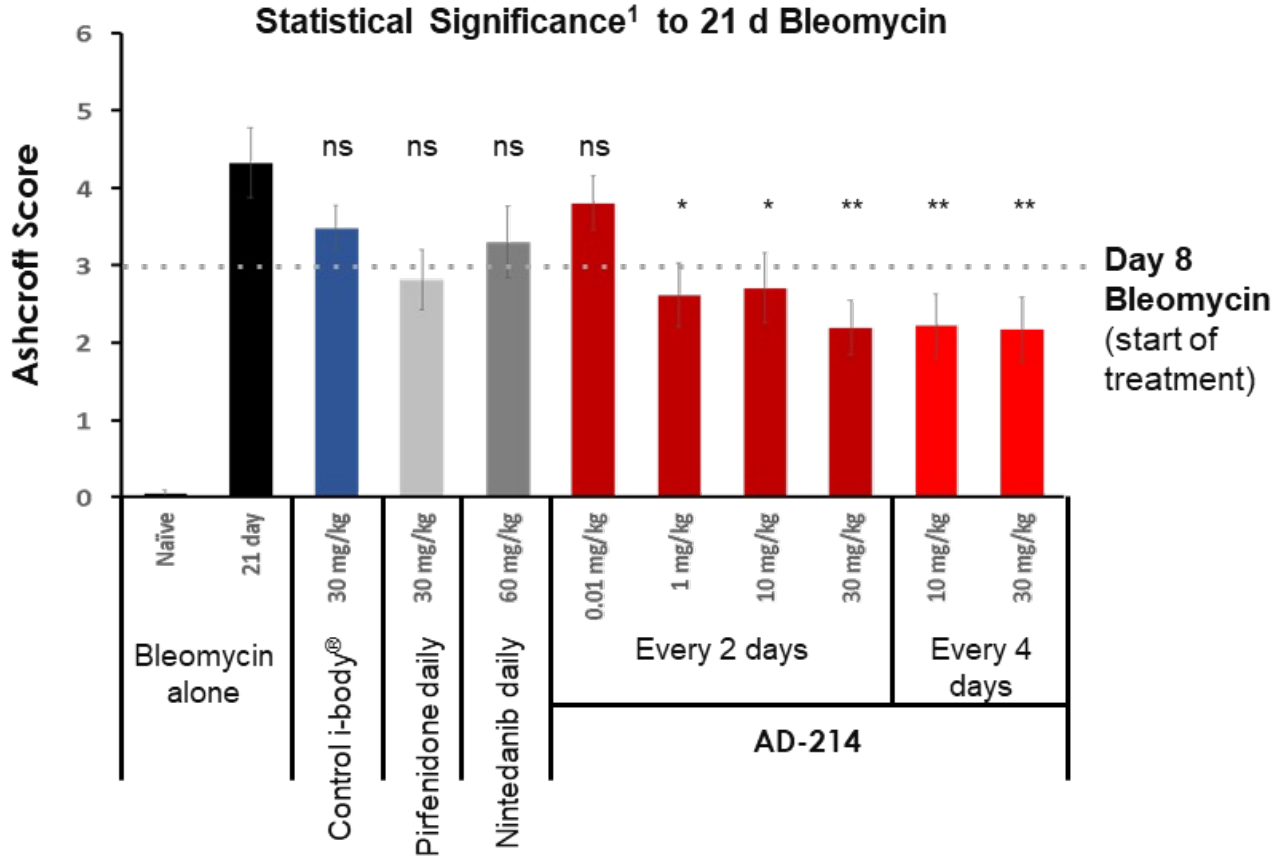
21 days after bleomycin



IPF mouse lung tissue + **AD-214**

21 days after bleomycin and **AD-214** at 10mg/kg every 4 days from day 8





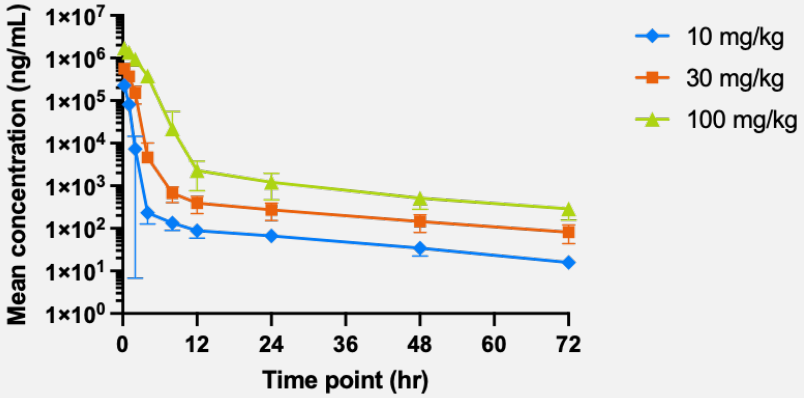
Results supportive of efficacy at human doses lower than 1 mg/kg if dosed sufficiently frequently

[1]Murigenics_20210208. (# Statistical significance assessed using ANOVA and post-hoc Dunnett's test; ns (not significant) = p >0.05, * = p<0.05, ** = p < 0.01 relative to 21-day bleomycin vehicle; negative control is an i-body® that does not bind specifically to CXCR4; error bars are standard error of the mean).

NHP toxicology studies support AD-214 CXCR4 engagement; Phase I dose selection

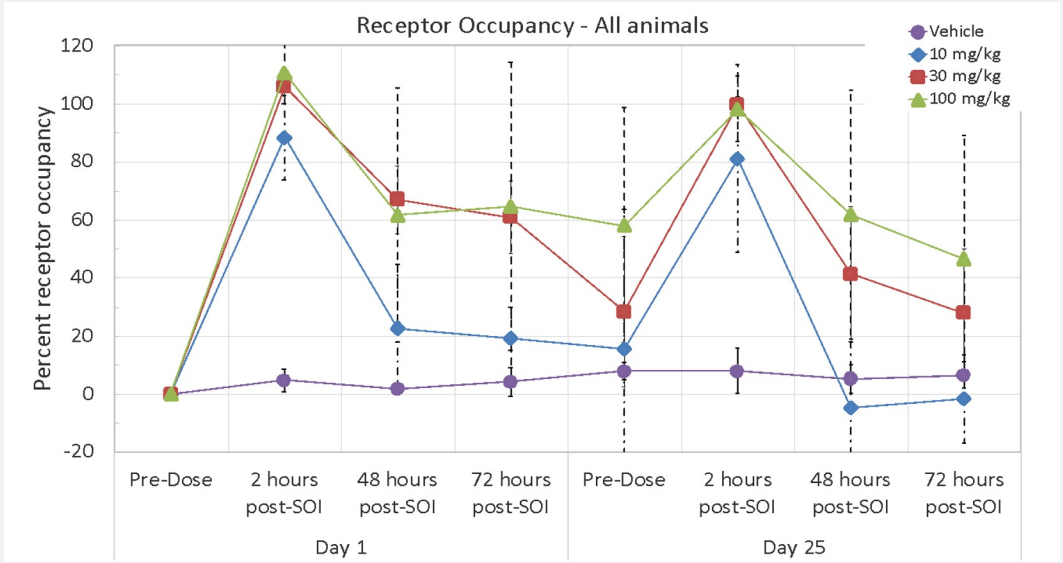
Pharmacokinetics

- Average elimination half-life 22-29 h
- AD-214 available for >3 days



Pharmacodynamics

- >60% occupancy of the CXCR4 receptor (RO) on T cells for 72 h at >30 mg/kg
- High receptor binding for >3 days



Supportive of human therapeutic dose window including 10 mg/kg intravenously, weekly or every second week

ITR Laboratories 20210201_AD-214 28-Day TK study ; mean +/- SD of male and female subjects

Intravenous AD-214 Phase I healthy volunteer study confirms robust safety profile[1]

AD-214 exposure (AUC), C_{max}, T_{max} increase in a dose proportional manner

Elimination half-life ($t_{1/2}$) 39 h at 20 mg/kg

✓ **AD-214** well tolerated in both single and multiple dose arms

- Phase I studied single doses to 20 mg/kg, multiple doses to 10 mg/kg (10 mg/kg extension completes Q1 2024)
- No dose limited adverse events
- No serious adverse events
- No concerning clinical lab results

✓ No immune response concerns observed

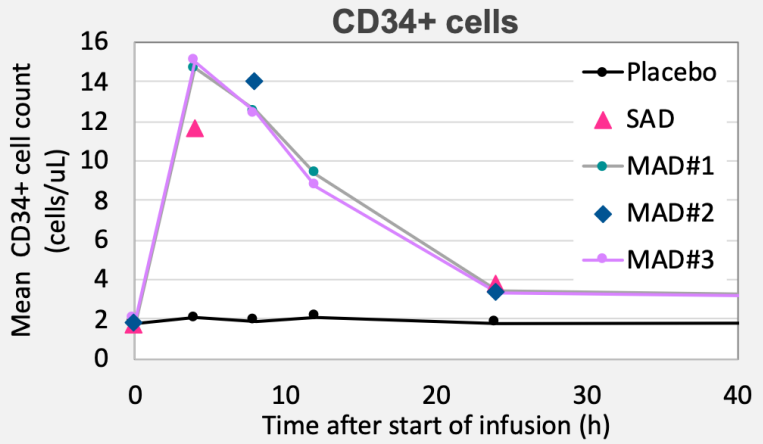
- No clinically significant, consistent cytokine release
- No clinical symptoms related to immune response observed
- Antidrug antibodies:
  - Detected in some healthy volunteers at 5 mg/kg AD-214.
  - Predominantly low titre, no evidence of tolerance or antibody induced drug clearance.
  - Interim results at 10 mg/kg consistent or better than these findings

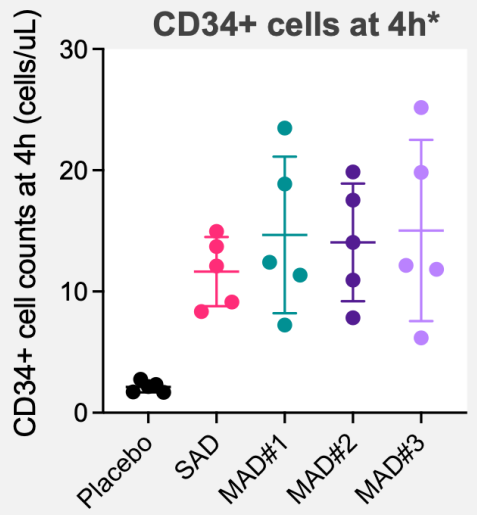
[1] Compiled from Tables and Listings of study NCT04415671 data collected and monitored by independent CRO [2]Data from 5mg/kg single and multiple dose cohorts

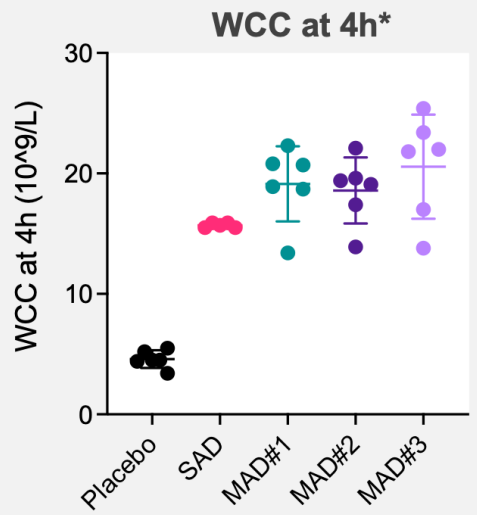
Transient increases in blood biomarkers demonstrate consistent engagement of the target receptor, CXCR4

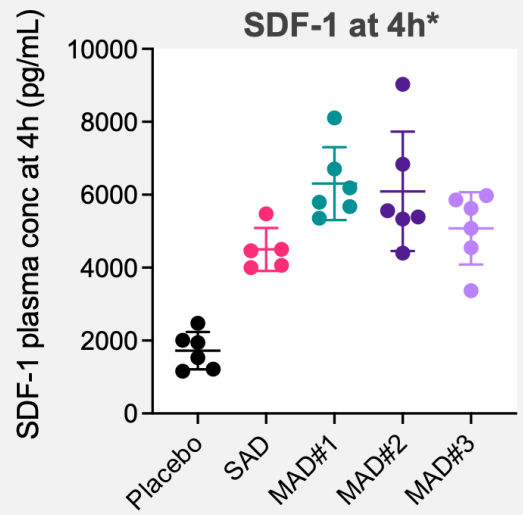
Biomarker data confirm single dose findings, consistent across multiple doses: no drug induced tolerance or accumulation

- White blood cell counts (WCC), haematopoietic stem cell (CD34+) counts and concentration of SDF-1 are biomarkers of CXCR4 engagement by AD-214
- Profile of biomarkers is consistent across multiple doses at 5 mg/kg*
- 100% T cell CXCR4 receptor occupancy achieved for at least 24h (data not shown, maximum duration analysis pending)









5 mg/kg data shown; 10 mg/kg interim data comparable

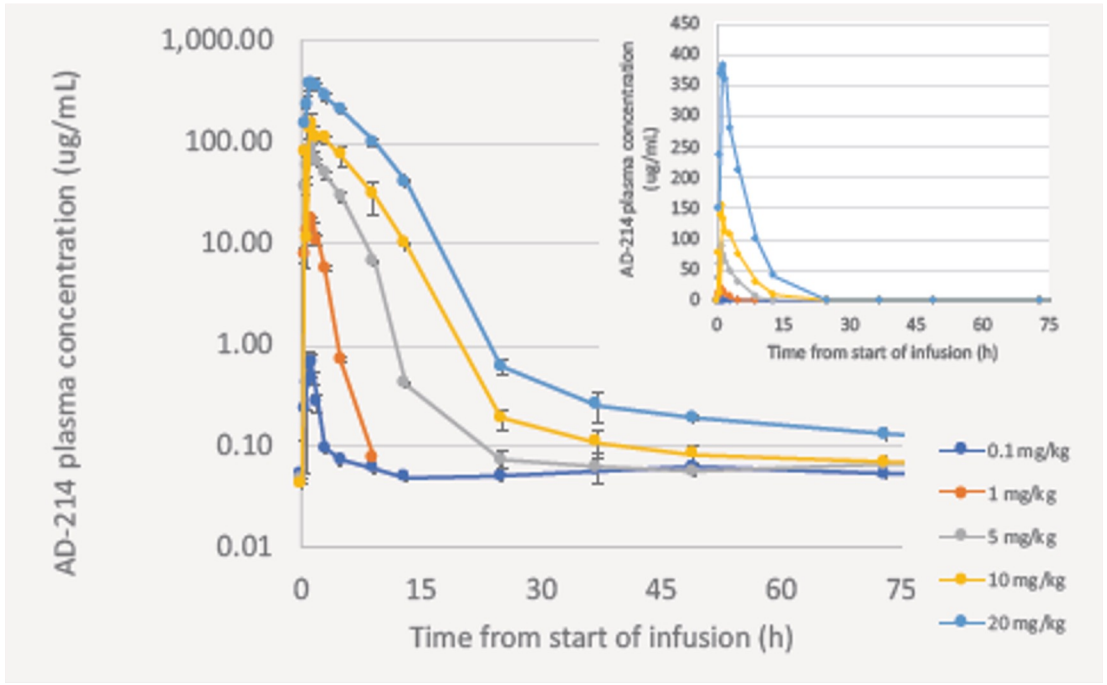
[1] Compiled from Tables and Listings of study NCT04415671 data collected and monitored by independent CRO [2]Data from 5mg/kg single and multiple dose cohorts

Phase 1 clinical study supports sustained AD-214 CXCR4 engagement

Understanding receptor occupancy is critical to inform dosing

- White blood cells naturally express CXCR4, providing accessible surrogate for AD-214 target engagement
- Sustained high levels of CXCR4 receptor occupancy (RO) by AD-214 on T cells observed even at very low circulating concentrations of AD-214: >60% RO at 21 days after 20 mg/kg infusion

If replicated on CXCR4 receptors cell involved in fibrosis (including immune cells), results support extended dosing intervals of ~2 weeks despite relatively rapid clearance from circulation



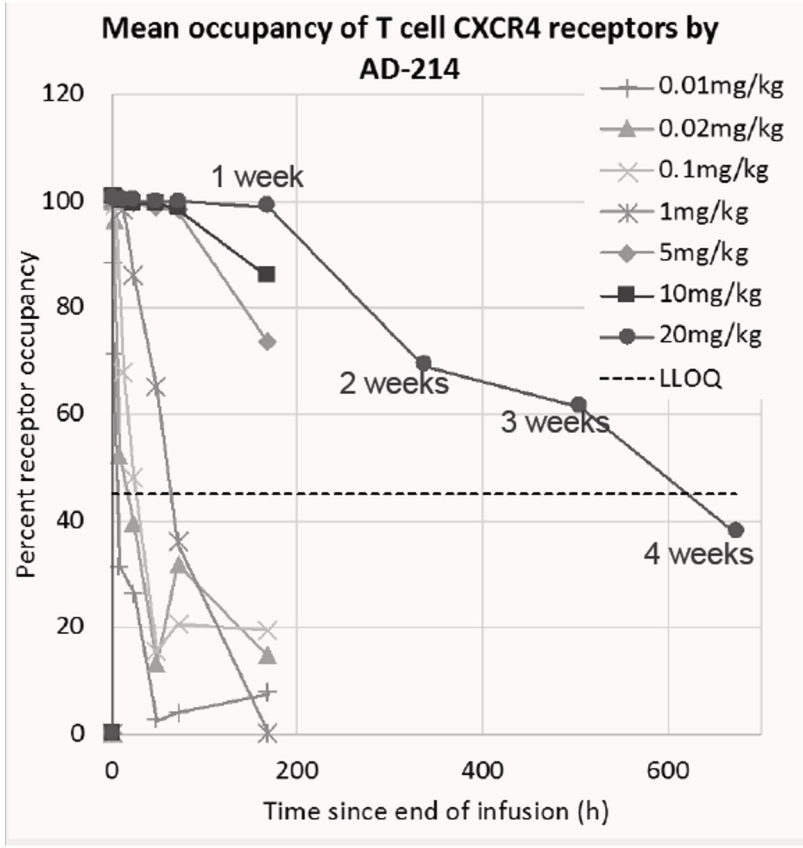
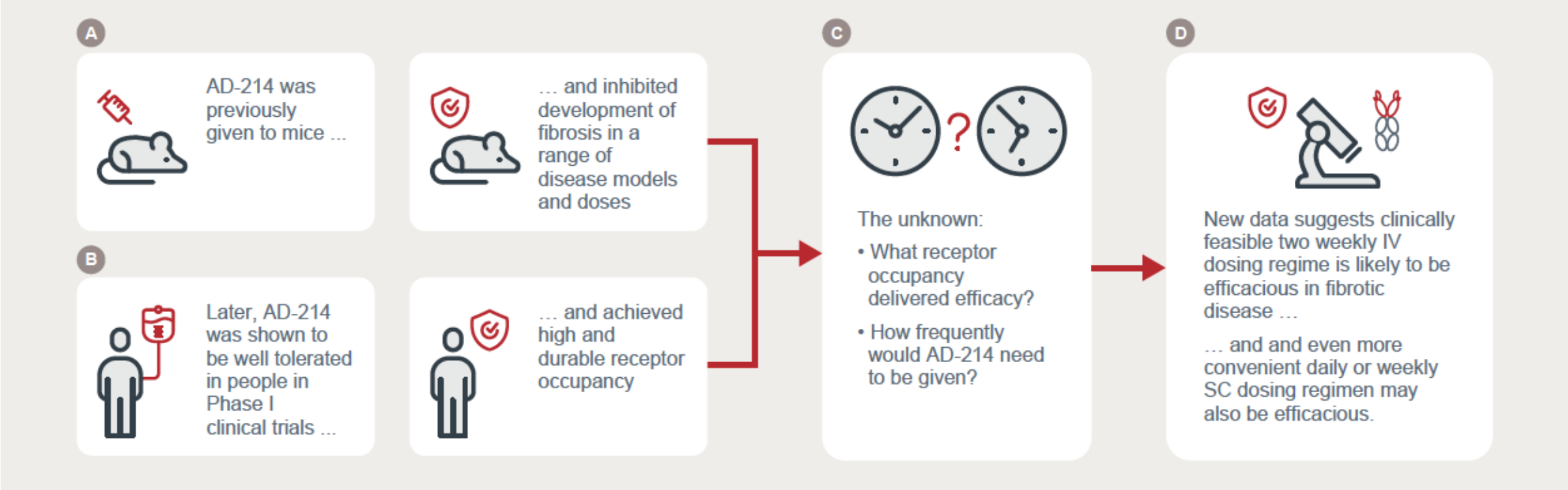


Figure created from data in Clinical Study Report: Protocol ID: ADA-AD-214-1A : Version 1 Dated 07 October 2022

Open question: what levels of receptor occupancy are needed for efficacy?



A. AD-214 has demonstrated efficacy in multiple animal models of fibrotic disease
B. In humans, AD-214 was able to maintain more than 60% receptor occupancy (blocking) for up to three weeks after IV infusion, depending on dose
C. Is this sufficient to achieve efficacy for target IV product profile (two weeks between doses)? Is a next generation SC product profile possible?
D. YES – new data shows that AD-214 does not require 100% receptor occupancy to meaningfully inhibit a model fibrotic process: efficacy of two weekly IV dosing regimens is plausible AND weekly or daily SC dosing regimens appear possible

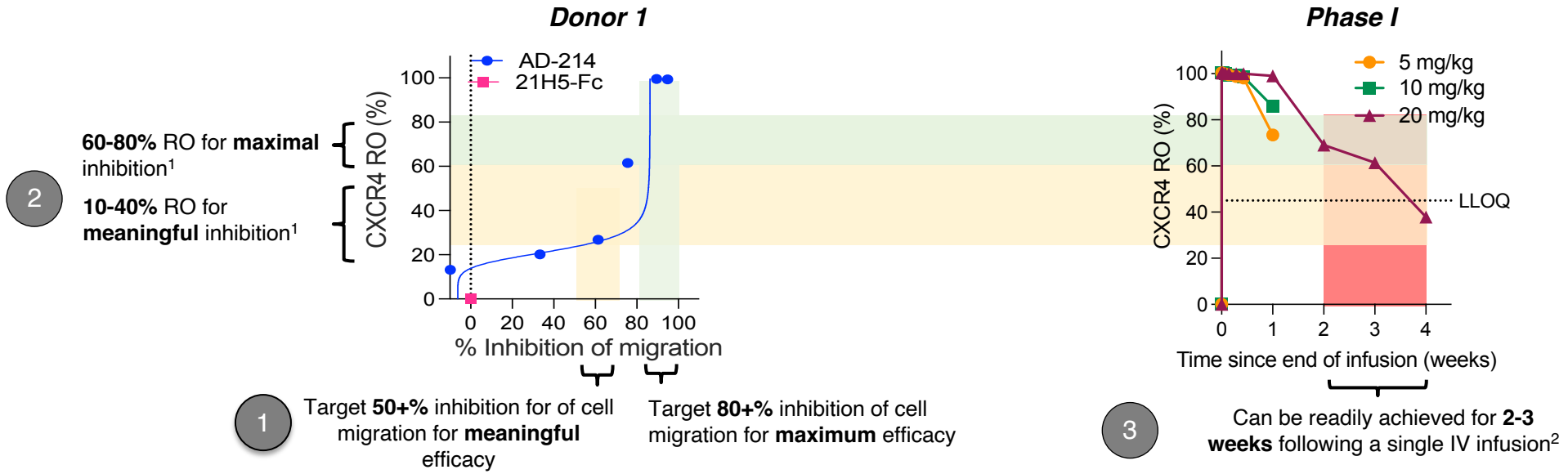
Source: ASX release 7 July 2023

Clinically viable, two weekly IV and weekly SC dosing regimens can maintain target receptor occupancy for efficacy

1. ***Ex vivo* cell migration is a model fibrotic process and inhibition of migration is a model of efficacy**
   - Maximum efficacy at >80% inhibition of migration (green). Meaningful efficacy at >50% inhibition (yellow)

2. **Less than full receptor occupancy (CXCR4 RO) is required for efficacy (meaningful inhibition of cell migration)**
   - 60-85% receptor occupancy is sufficient for maximum inhibition of cell migration
   - Meaningful inhibition at receptor occupancy as low as 10-40%

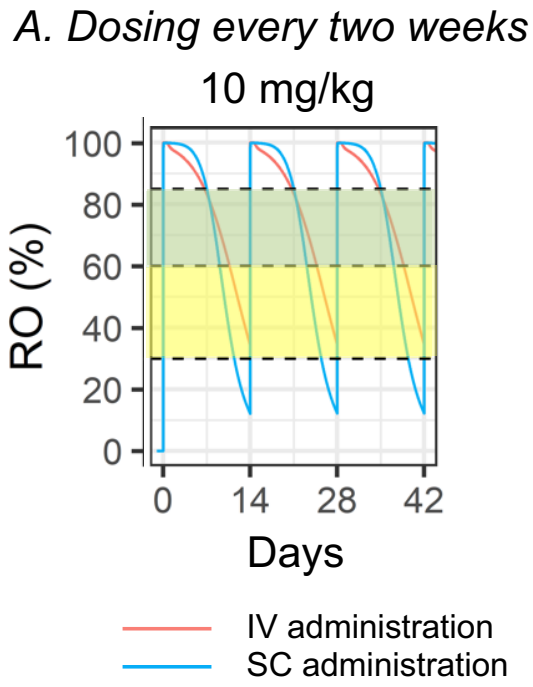
3. **Maintaining efficacious receptor occupancy levels is the objective of dose selection**
   - **Efficacious receptor occupancy can be maintained for at least two weeks after an IV infusion and one potentially week after SC injection in humans, a clinically viable dosing regimen[2]**

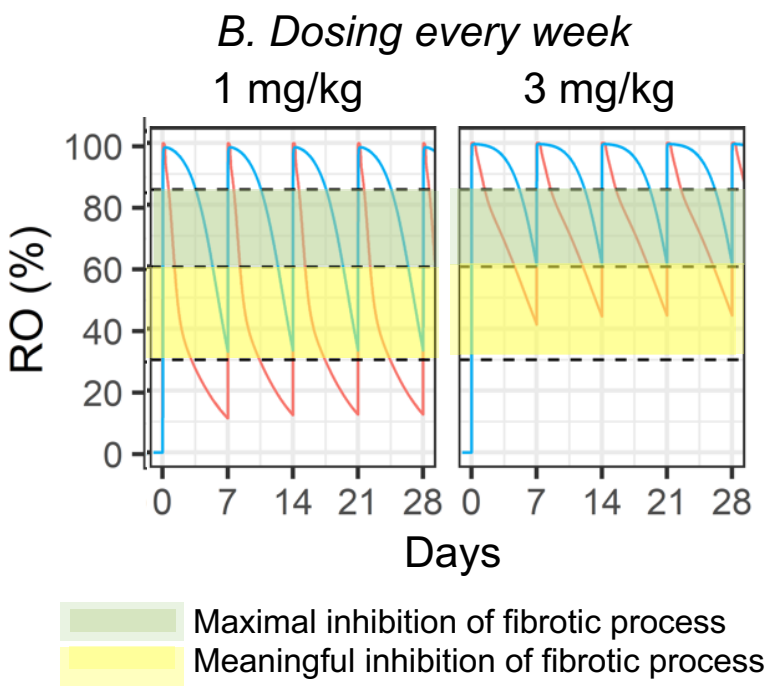


1. AdAlta studies correlated AD-214 concentration with level of CXCR4 receptor occupancy and level of inhibition of SDF-1a induced migration *ex vivo* on human T cells. Ranges are average of results from three healthy donors, only one donor shown
2. Clinical Study Report: Protocol ID: ADA-AD-214-1A : Version 1 Dated 07 October 2022

PK models suggest two weekly IV and potentially weekly SC dosing regimens achieve target receptor occupancy

Target IV dose for Phase II





Potential SC dose to introduce at Phase III or lifecycle management

Simulated CXCR4 receptor occupancy following IV (red) and SC (blue) administration of AD-214 doses.
Shading represents receptor occupancy (RO) required for maximal (green) and meaningful (yellow, more than 50%) inhibition of a model fibrotic process in ex vivo *experiments.*
Panel A: 10 mg/kg AD-214 administered every two weeks.
Panel B: 1 mg/kg (left) and 3 mg/kg (right) AD-214 administered every week.

AdAlta analysis based on PK/PD model developed by LYO-X

Phase I extension study validates model and safety of target Phase II dose

Receptor occupancy (RO) in line with model predictions for efficacy of 10 mg/kg infusion every two weeks

Predicted RO

- >80% at one week after infusion
- >60% at 10-11 days after infusion
- >30% at 14 days after infusion
- Consistent profile across multiple doses

Observed RO (mean)

- ✓ >90% at one week after infusion
- Not measured at 10-11 days after infusion
- ✓ >30% at 14 days after infusion
- ✓ Consistent profile across multiple doses

Tolerability: safety of target Phase II dose supported

5 mg/kg multiple (3) doses

- No dose limiting toxicity
- No serious adverse events (all AE's mild or moderate)
- Infusion related reactions in 3/8 participants; 2 dose interruptions
- Low level antidrug antibodies in 4/6 participants at 4 weeks; no impact on PK/PD
- Low level antidrug antibodies in 4/6 participants at 19 weeks

10 mg/kg multiple (3) doses

- ✓ No dose limiting toxicity
- ✓ No moderate adverse events (lower frequency mild AE's)
- ✓ Infusion related reactions in 1/8 participants; 0 dose interruptions
- ✓ Very low level antidrug antibodies in 2/6 participants; no impact on PK/PD
- PK/PD effect of antidrug antibodies at 16 weeks – TBD*

*Participants have received a 4th dose at 16 weeks (12 weeks after 3rd dose) to evaluate effect of immune response on pharmacokinetics (PK) and pharmacodynamics (PD) as measured by receptor occupancy (RO); results and full analysis Q1 2024

AD-214 is a first in class CXCR4 antagonist designed specifically for fibrotic disease, ready to move into Phase II

Product Profile: AD-214	
Disease Area	Fibrosis
Molecule class	Protein therapeutic (i-body®-Fc-fusion)
Mode of action	First-in-class CXCR4 antagonist
Indications	Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease (with kidney, eye and cancer indication extension potential)
Route of administration	Target: Intravenous (IV) Next generation: Subcutaneous (SC), inhaled
Clinical stage of development	Phase I complete; extension study under way Preparations for Phase II advancing
Regulatory	Orphan Drug Designation (US FDA) 10-12 years market exclusivity (US and EU)
IP	Composition of matter 2036 (granted) Method of treatment/dosing 2043 (pending)
Manufacturing	cGMP manufacturing at KBI Biopharmaceuticals, USA

Product development strategy

Target intravenous (IV) product profile

IV administration in clinic

Two weeks minimum between infusions: meets minimum product criteria for clinical adoption

Fastest, cheapest to clinical proof of concept

Progress to Phase II

Potential subcutaneous (SC) product profile

Patient self administration at home (like diabetes, arthritis)

Weekly or daily injections: maximum convenience, minimum costs

Enhanced market share, reduced COGS

Develop formulation, progress to Phase II

Choice of formulation to take through to Phase III

Based on relative success of each development

AdAlta

A modern targeting system for next generation drugs

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