28 April 2021

ASX Announcement

AD-214 RESULTS PRESENTED AT ILD DRUG DEVELOPMENT SUMMIT

MELBOURNE Australia, 28 April 2021: AdAlta Limited (ASX:1AD), the clinical stage biotechnology company developing novel therapeutic products from its i-body platform is pleased to announce that Chief Scientific Officer, Professor Mick Foley has been invited to present an update on the clinical development of lead product candidate, AD-214, at the Interstitial Lung Disease (ILD) Summit 2021 being held virtually from 27-29 April.

The ILD Summit 2021 showcases the latest scientific research that is innovating and upgrading ILD therapeutics at this trailblazing new meeting. The 1st Interstitial Lung Disease Drug Development Summit is a ground-breaking new conference dedicated to helping drive forward the development of effective therapies for chronic fibrosing ILDs and achieve success in anti-fibrotic drug development beyond Idiopathic Pulmonary Fibrosis (IPF).

Professor Foley's presentation will cover:

- The role of the CXCR4 receptor in fibrotic disease and the rationale targeting CXCR4 as a therapeutic option for IPF and other ILDs
- Non-clinical data showing CXCR4 expression in a range of cell-types known to contribute to IPF/ILD and comparing CXCR4 expression levels in healthy and diseased tissue, and
- Pre-clinical and initial clinical development of AdAlta's novel i-body enabled therapeutic, AD-214, which targets CXCR4, including anti-fibrotic efficacy and safety data from preclinical studies and safety and target engagement and occupancy in healthy volunteers from the Company's first in-human trial.

Professor Foley is joining a speaking panel of 20 industry and academic leaders. A copy of the presentation is attached.

Details of the session:

Session date / time:	Thursday, 29 April 2021 at 01:30am AEST (11:30am US EST)
Session title:	CXCR4/CXCL12: A Common Molecular Axis in Multiple Cell Types with Relevance in ILD

Authorised for lodgement by:

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April 2021

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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 is conducting Phase 1 clinical studies for its lead i-body candidate, AD-214. 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 discover i-bodies as diagnostic imaging agents against Granzyme B, a biomarker of response to immuno-oncology drugs.

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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AdAlta

next generation protein therapeutics

CXCR4/CXCL12: A common molecular axis in multiple cell types with relevance in ILD

ILD Drug Development Summit April 2021

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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.

CXCR4 plays a role in IPF

CXCR4 is a critical player in many **fibrotic indications** including:

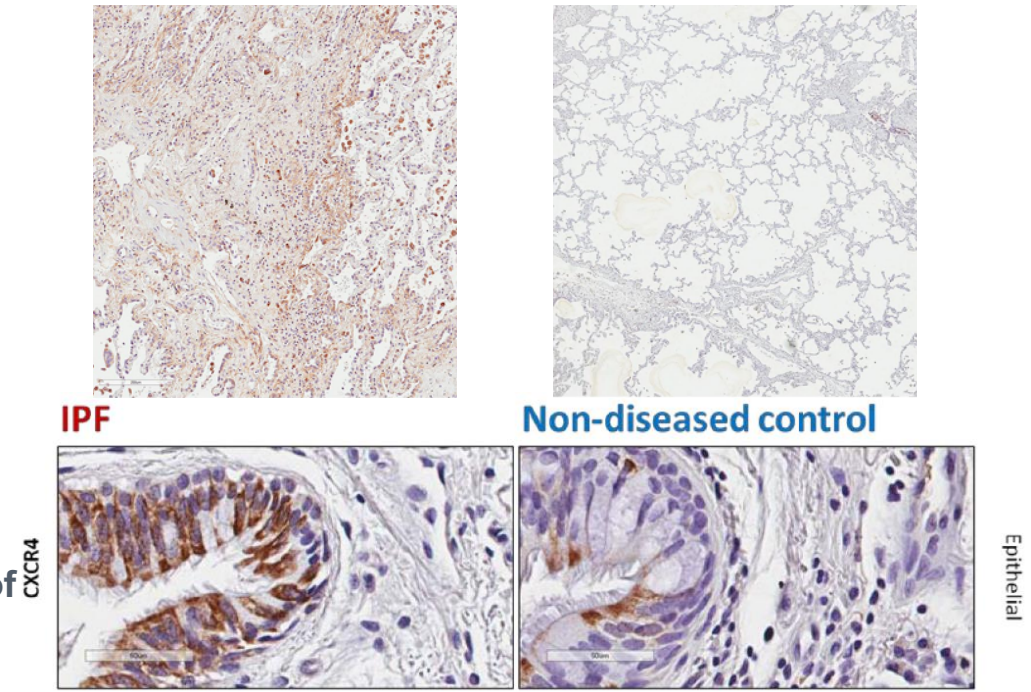
- Lung
- Kidney
- Heart
- Eye
- Skin

CXCR4 is also

- Important in **maintaining stem cells in bone marrow**
- Used by **HIV-1** as a co-receptor for viral entry into host cells
- Associated with more than **23 types of cancers**

CXCR4 is upregulated in IPF lung tissue

Very limited expression in normal or non-diseased tissues



Brown stain shows amount of CXCR4

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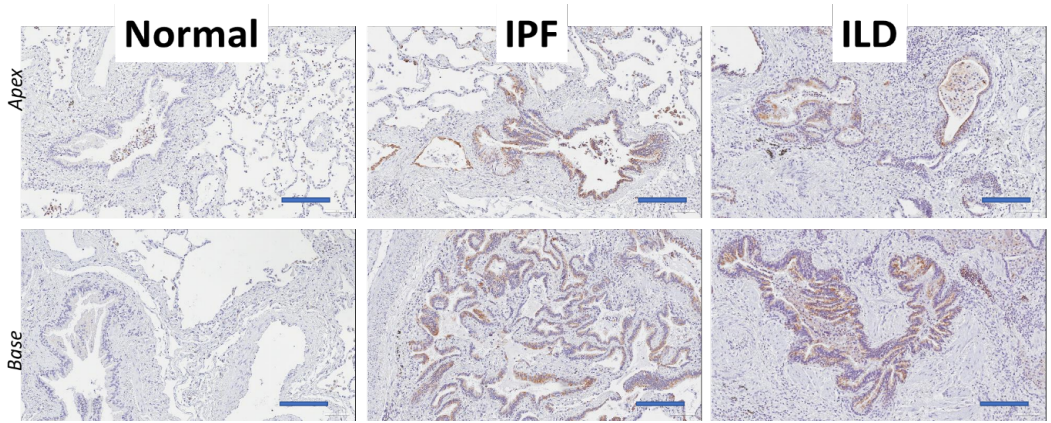
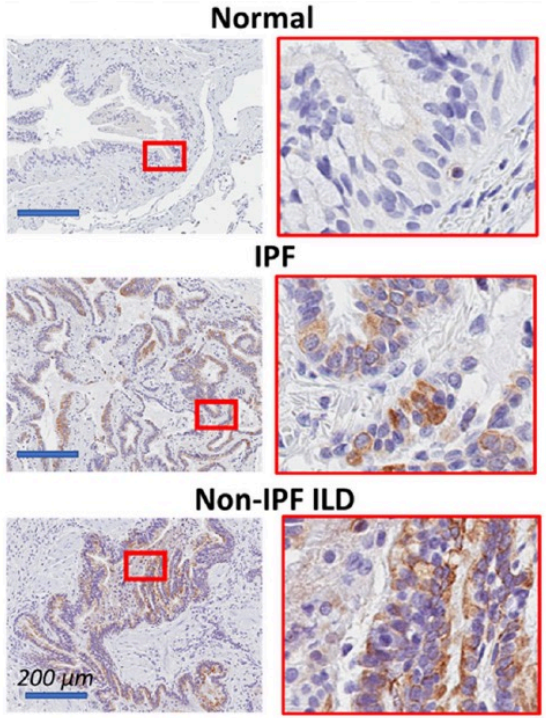
CXCR4 is expressed in both IPF and ILD patient lung tissue and in multiple cell types



- CXCR4 was abundantly expressed in **both IPF and ILF donors** compared with non-diseased controls
- CXCR4 is expressed on **circulating immune cells** and in patients with IPF and other fibrotic ILDs we have demonstrated that CXCR4 is significantly upregulated in the **fibrotic airway epithelial** and **fibrotic loci myeloid cells**



CXCR4 stained brown

Source: Jaffar et al, Respiratory Research (2020) 21: 221

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Why targeting CXCR4 could improve IPF/ILD outcomes

Observation

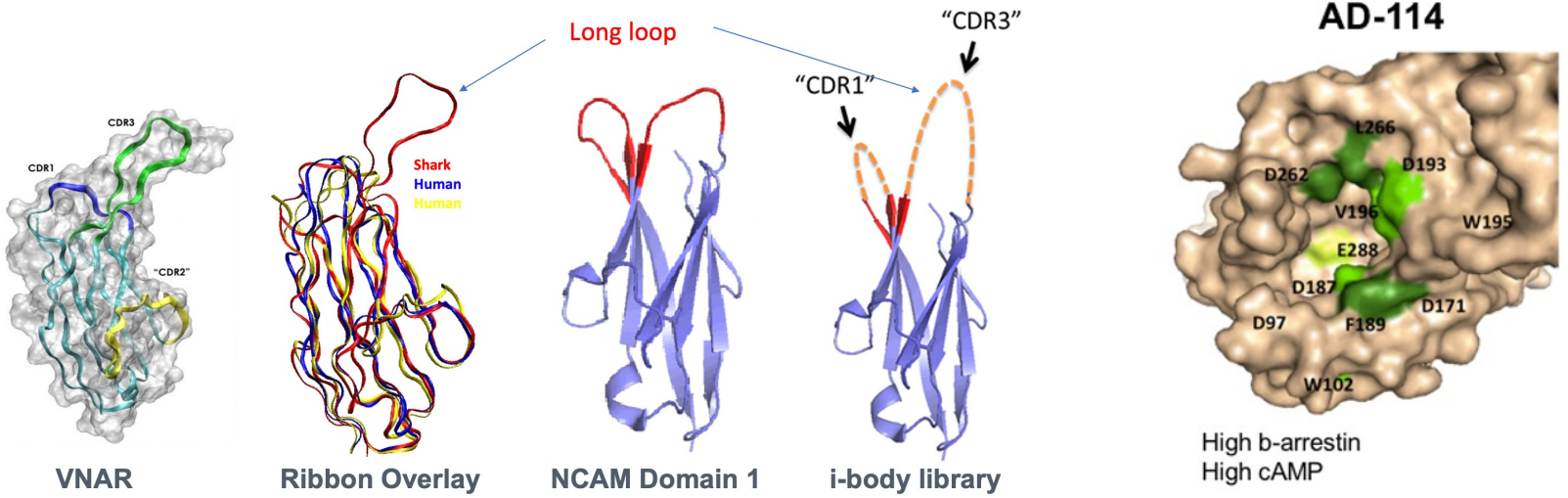
- CXCR4 is up-regulated in ILD patients as well as IPF patients
- CXCR4 is upregulated in epithelial and myeloid cells in fibrotic tissue
- CXCR4 also inhibits migration of fibroblasts and inflammatory cells such as macrophages in a disease specific way

Significance

- If AD-214 works in IPF it is more likely to work in ILD as well … and there are at least as many non-IPF ILD patients as IPF patients
- Epithelial cells involved in the fibrosis cascade: blocking CXCR4 could have a broader effect than simply shutting down collagen deposition
- Blocking CXCR4 may also have an immune modulation effect and inhibit immune/ inflammatory cell infiltration to the lungs

i-bodies: human single domains

- i-body inspired by the shark VNAR structure
- AD-114 is a CXCR4 binding i-body that binds in the ligand binding site and antagonizes the receptor



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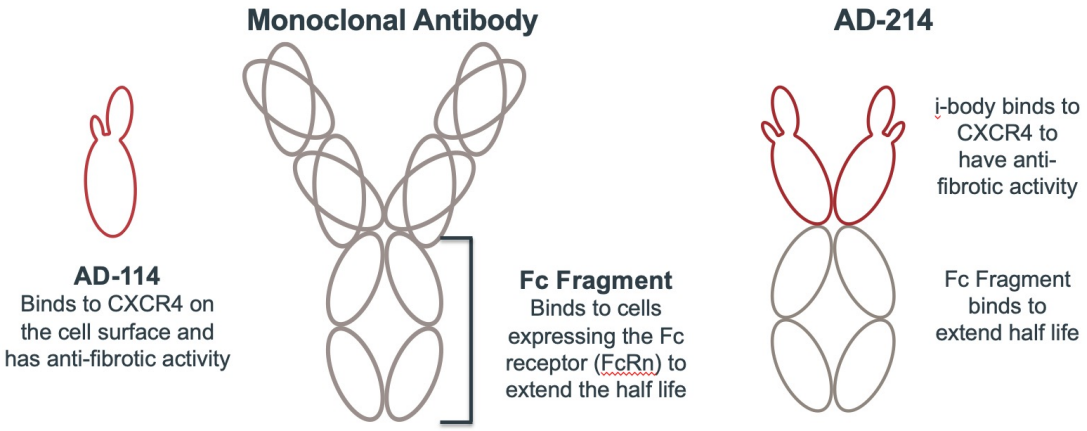
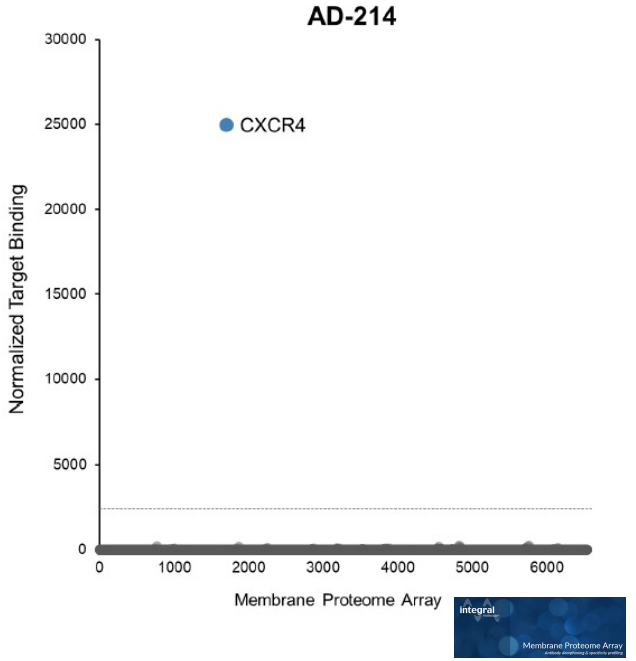
AD-214 retains specificity for CXCR4

- AD-214 consists of the CXCR4 binding i-body (AD-114) fused to human Fc
- AD-214 had no binding to proteins other than CXCR4

When combined, the i-body and Fc fragment create a superior drug, which will be better for patients and for potential commercial partners





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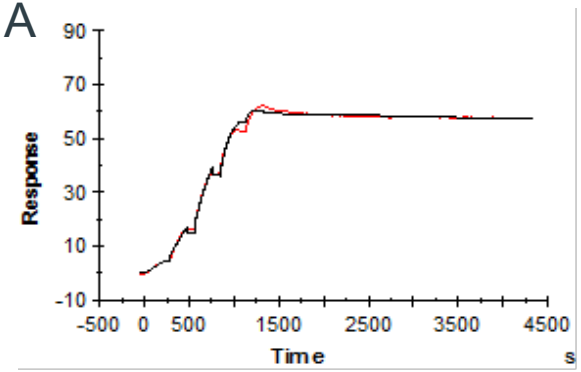
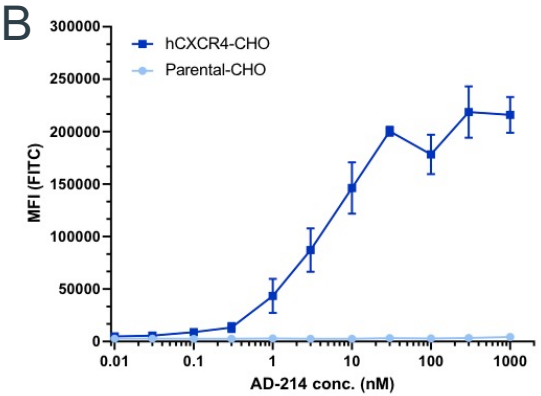
AD-214 binds with high affinity to CXCR4

- AD-214 binds to human CXCR4 lipoparticles with affinity of ~4pM (**A**)
- AD-214 binding to CXCR4 expressing CHO cells but not to parental cells (**B**)
- Flow cytometry shows that AD-214 can bind to CXCR4 expressed on human CD3^{+} T cells (**C**).

A



B



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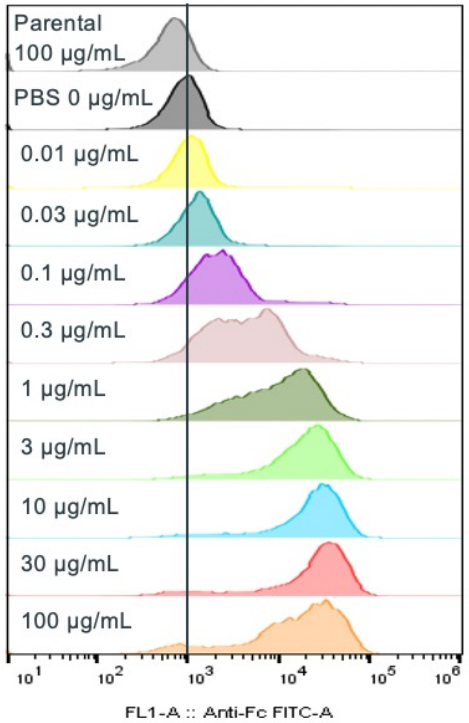

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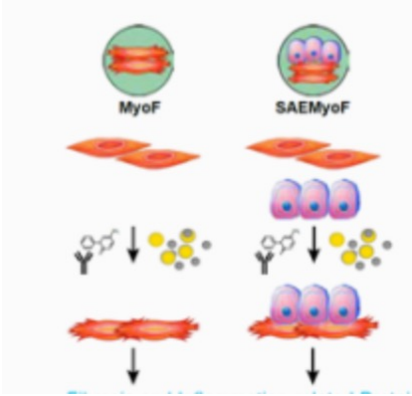
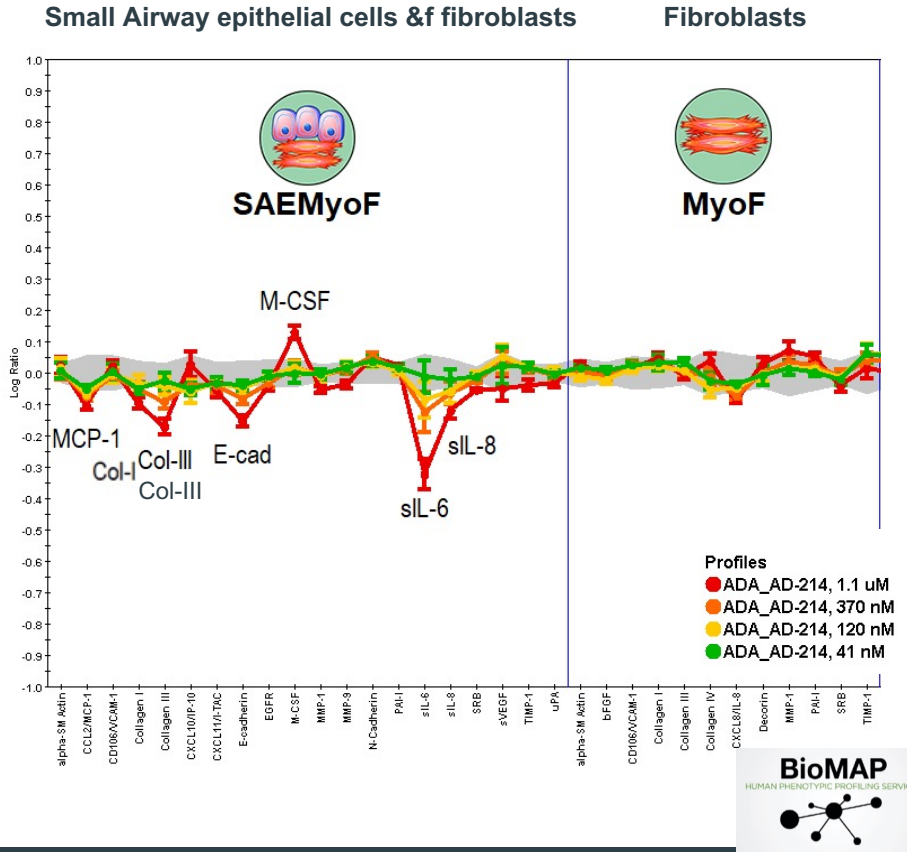
AD-214 Phenotypic profile lung fibrosis panel

SAEMyoF and MyoF consisting of a co-culture of lung fibroblasts and small airway epithelial cells.



Key activities of AD-214:

- AD-214 is not cytotoxic at the concentrations tested in this study.
- Fibrosis-related matrix activities: decreased Collagen I, Collagen III
- Inflammation-related activities: decreased MCP-1, sIL-8, sIL-6; increased M-CSF



BioMAP
HUMAN PHENOTYPIC PROFILING SERVICES

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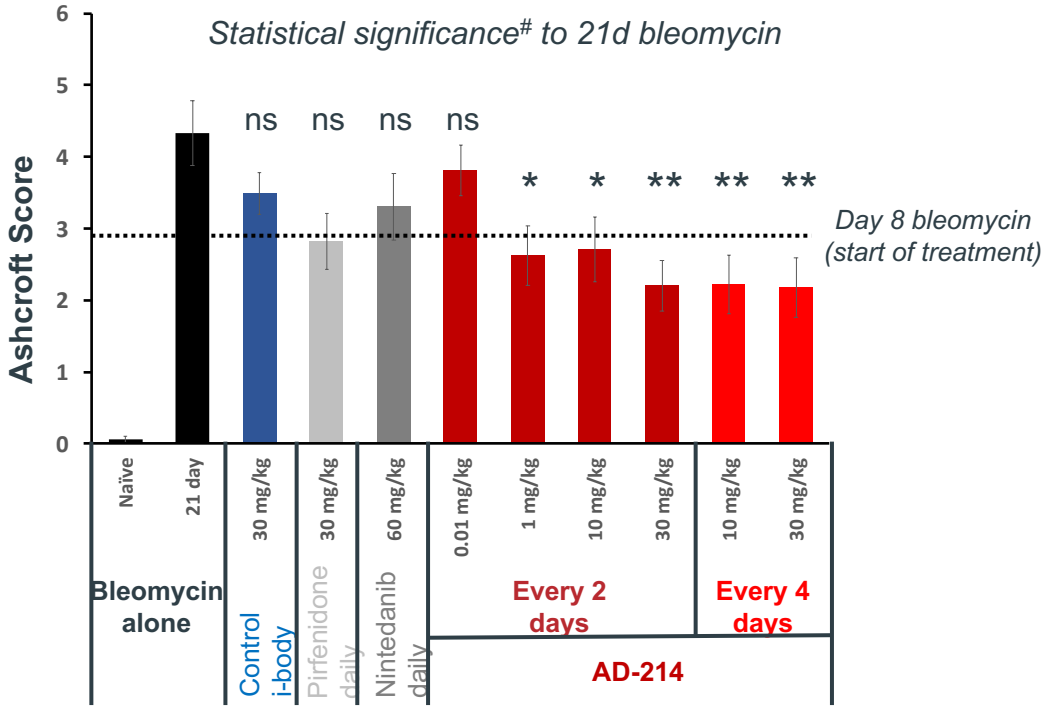
AD-214 attenuates fibrosis of the lung

- Bleomycin induced lung fibrosis
  - gold standard *in vivo* animal model of pulmonary fibrosis
- AD-214 significantly improved lung fibrosis pathology (Ashcroft score) when compared to the 21-day bleomycin vehicle-treated controls
  - 1, 10 and 30 mg/kg every second day
  - 10 and 30 mg/kg every fourth day

AD-214 efficacy demonstrated in gold standard IPF disease model

Supportive of potential human therapeutic window beginning as low as 1mg/kg



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

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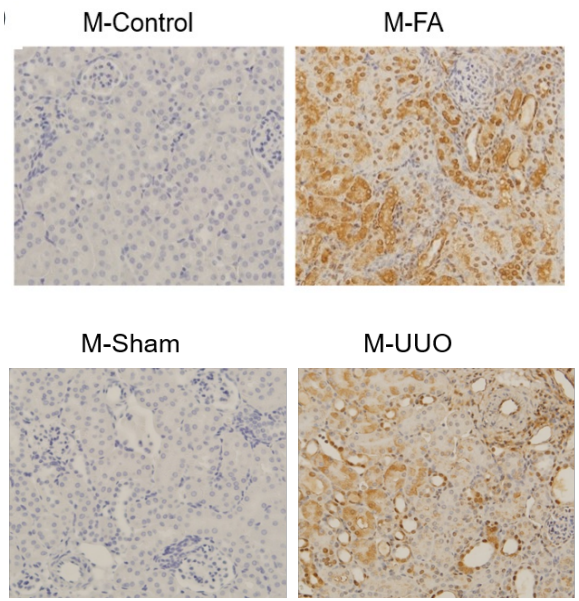
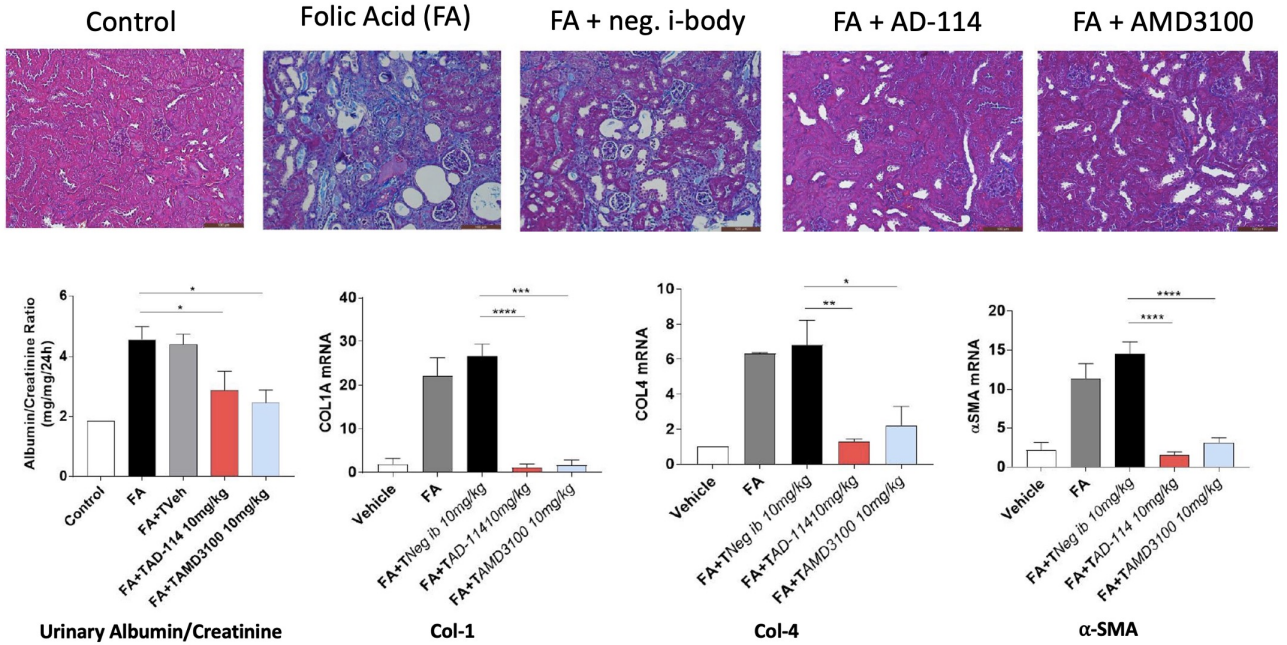
AD-114 is antifibrotic in a mouse model of kidney fibrosis

- CXCR4 is upregulated in several models of kidney fibrosis
- AD-114 protects from liver damage in therapeutic mode of Folic acid kidney injury





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NHP GLP toxicology: AD-214 well tolerated

3 non-human primate studies completed

Good Laboratory Practice (GLP) study to evaluate safety and toxicology

- 10mg/kg, 30mg/kg and 100mg/kg multiple doses over four weeks plus recovery (human equivalent dose 32mg/kg)
- AD-214 well tolerated with no deaths, no AD-214-related clinical signs, no changes in a panel of clinical observations
  - body weight
  - ophthalmoscopy
  - blood pressure
  - electrocardiography
  - respiratory function
  - neurological function
  - coagulation
  - urinalysis
  - organ weight
  - macroscopic and microscopic findings
- Minor, transient, completely reversible increase in total white cell and circulating CD34+ cells
- Small, transient, completely reversible decrease in serum total protein and albumin at highet dose only (100 mg/kg)

Tox study results were in line with expectations and in keeping with previous studies

No major organ toxicity has been observed on repeat dosing at high doses

No suggestion of off-target toxicities

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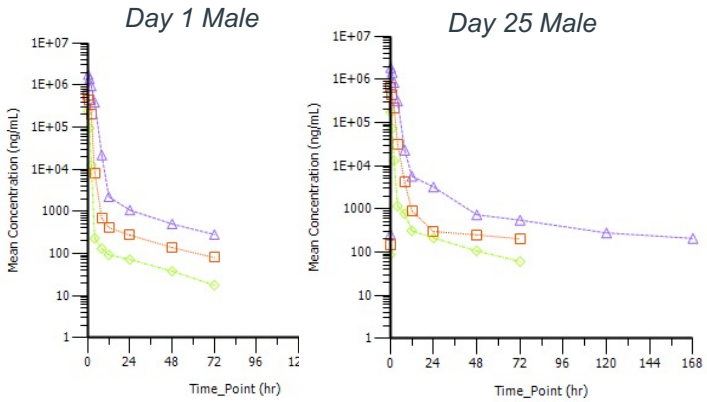
NHP PK and PD results

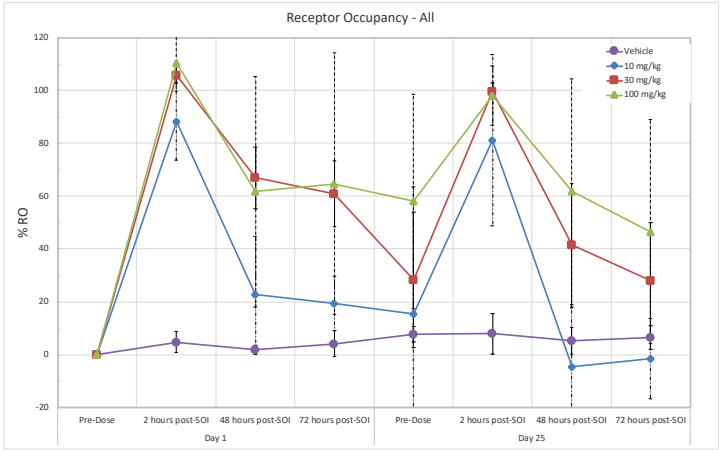
Pharmaco-kinetics

- Elimination half-life 22-29h



Pharmaco-dynamics

- >60% receptor occupancy* for 72h at >30mg/kg



Results supportive of therapeutic dose window ~10mg/kg IV, weekly or fortnightly

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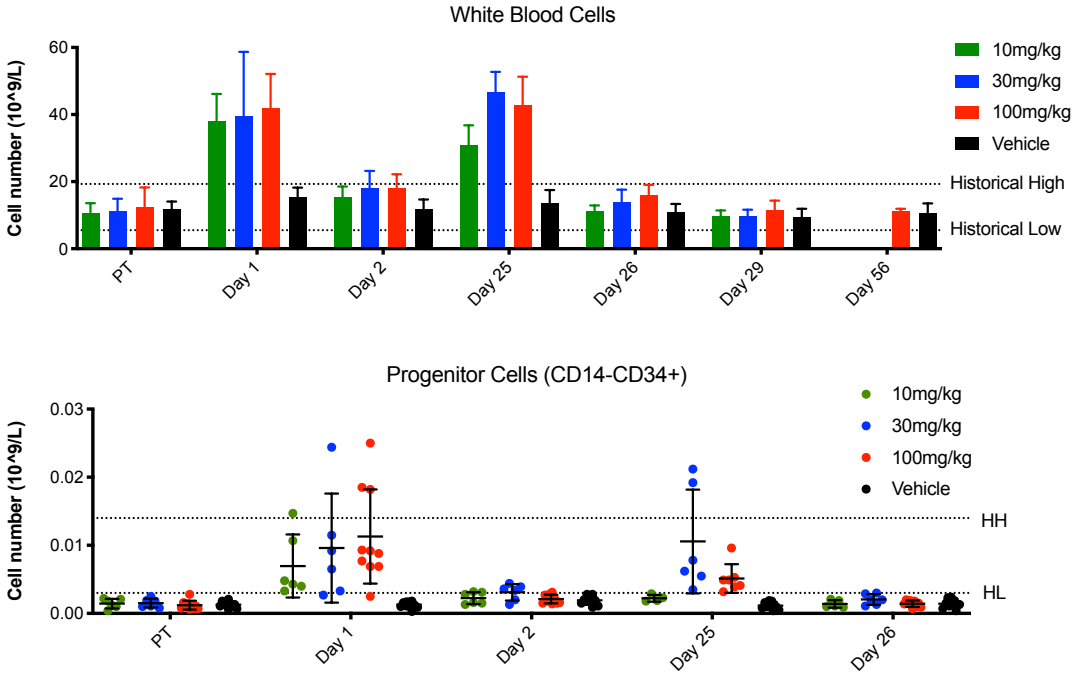
AD-214 4-week toxicology study: Hematology

- 10, 30, 100mg/kg AD-214 administered twice weekly for 4 weeks
- Transient increase in total WBCs 2 hours after administration
  - Back to baseline within 24 hours
- Similar transient increase in circulating haemopoietic progenitors
  - Back to baseline within 24 hours



Haematology and CD34+ cells monitored throughout the study

AD-214 Phase I program in healthy volunteers

Part A: HV SAD
Blinded/placebo controlled
0.01-20 mg/kg single dose
7 cohorts, 42 pts

Cohort	Participants (active:placebo)
0.01 mg/kg	2 (1:1)
0.02 mg/kg	2 (1:1)
0.10 mg/kg	8 (6:2)
1.0 mg/kg	7* (6:1)
5.0 mg/kg	7* (5:2)
10.0 mg/kg	8 (6:2)
20.0 mg/kg	8 (6:2)

Variable	Statistic	Pooled Placebo	Overall AD-214	Overall
	n	11	31	42
Age (years) at Screening	Mean	36.2	36.5	36.4
	SD	16.4	16.0	15.9
	Median	29.0	32.0	30.5
	Minimum	19	19	19
	Maximum	59	64	64
Sex n(%)	Female	7 (63.6%)	15 (48.4%)	22 (52.4%)
	Male	4 (36.4%)	16 (51.6%)	20 (47.6%)
Ethnicity n(%)	Asian	3 (27.3%)	7 (22.6%)	10 (23.8%)
	White	7 (63.6%)	23 (74.2%)	30 (71.4%)
	Other	1 (9.1%)	1 (3.2%)	2 (4.8%)

* Cohort unfilled due to recruitment issues

Single doses of AD-214 are well tolerated and achieve sustained, high receptor occupancy

AD-214 has an excellent safety profile

- No dose limiting toxicities or adverse events of clinical concern
- No concerning clinical laboratory results
- Consistent with Non-Human Primate (NHP) toxicology studies

AD-214 engages the CXCR4 receptor

- Clear markers of target (CXCR4) engagement observed

Receptor occupancy sustained at high levels for extended periods

- Supportive of longer dosing interval than projected from NHP if replicated in patients

Single dose of AD-214 is well tolerated

Adverse events (unblinded data)

- No dose limiting adverse events
- No serious adverse events
- No clinical laboratory adverse events
- Dose escalation steps completed without concern
- Adverse events were non-concerning
  - Predominantly mild
  - Three Grade 2 (moderate) adverse events

Immune response*

- No clinically significant cytokine release
- Isolated incidences of minor cytokine elevation
  - Transient and primarily low level elevation of IL-6 and IL-8 in some participants (including placebos)
- Antidrug antibodies: detected in 11 participants without any associated symptoms
  - Predominantly low titre
  - Characterisation pending

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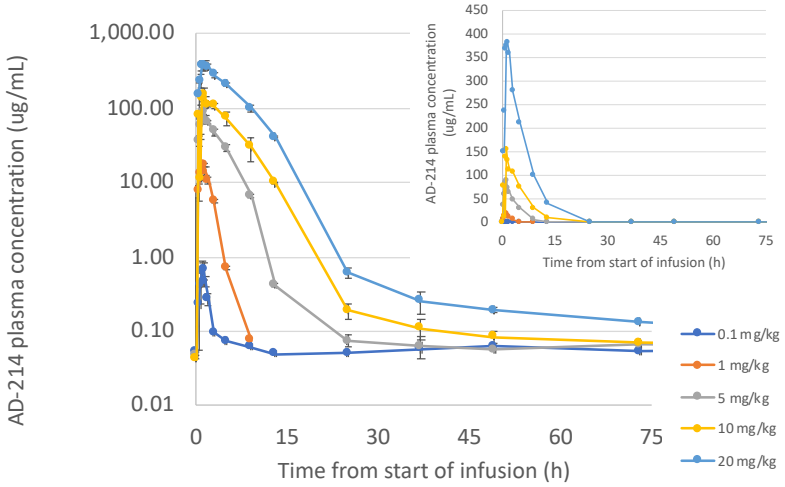
AD-214 pharmacokinetics increase proportionally with dose

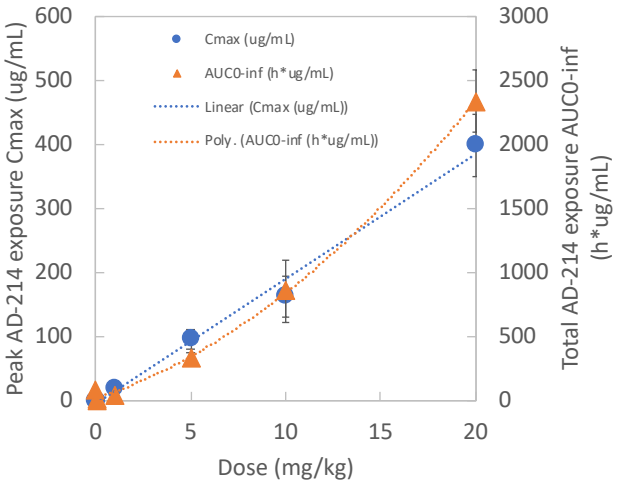
Observed

- Elimination half-life $t_{1/2}$ ~ 44±15 h
- Maximum & total exposure (C_{max} & $AUC_{0\text{-}inf}$) increase in ~ dose proportional manner

AD-214 plasma concentrations (log and linear scale)



Maximum and total plasma exposure



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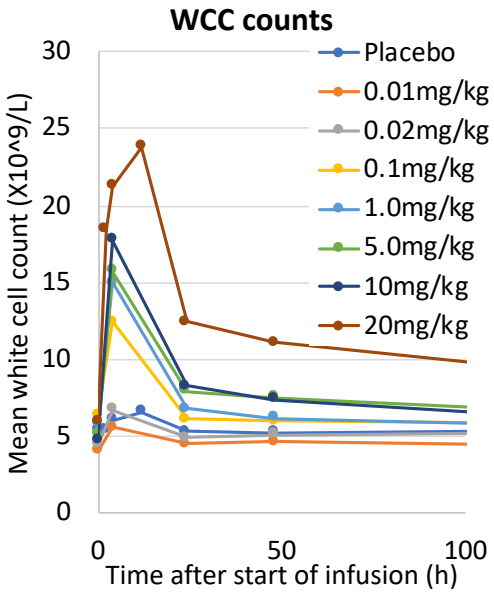
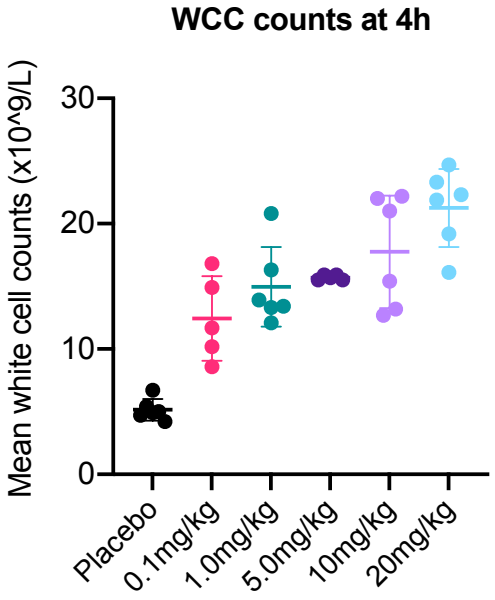
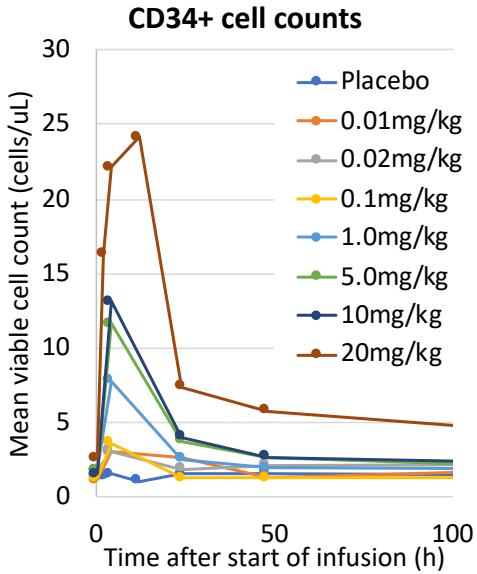
Transient white blood cell and blood stem cell increases indicate CXCR4 engagement

- Transient, dose dependent, increase in WCC and CD34+ counts at 4-12 hours consistent with CXCR4 blockade







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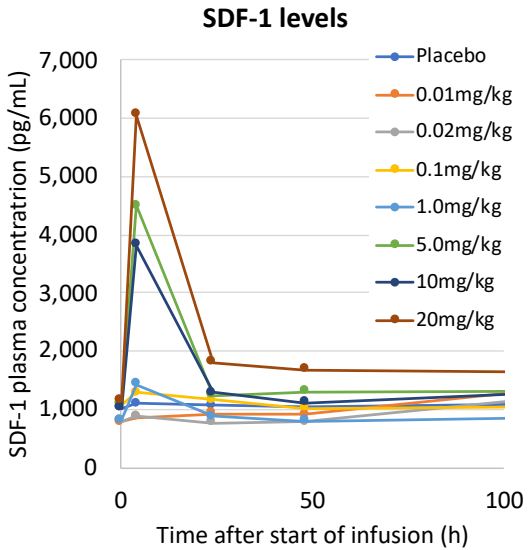
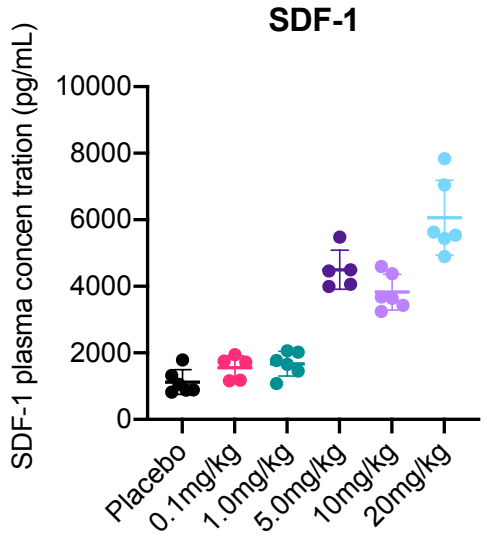
Transient increase in SDF-1 (natural ligand of CXCR4) suggests CXCR4 engagement

- Transient increases in SDF-1 levels at 4 hours in some participants, returning to baseline at 24h consistent with CXCR4 blockade
- Statistically significant increase at 20 mg/kg only





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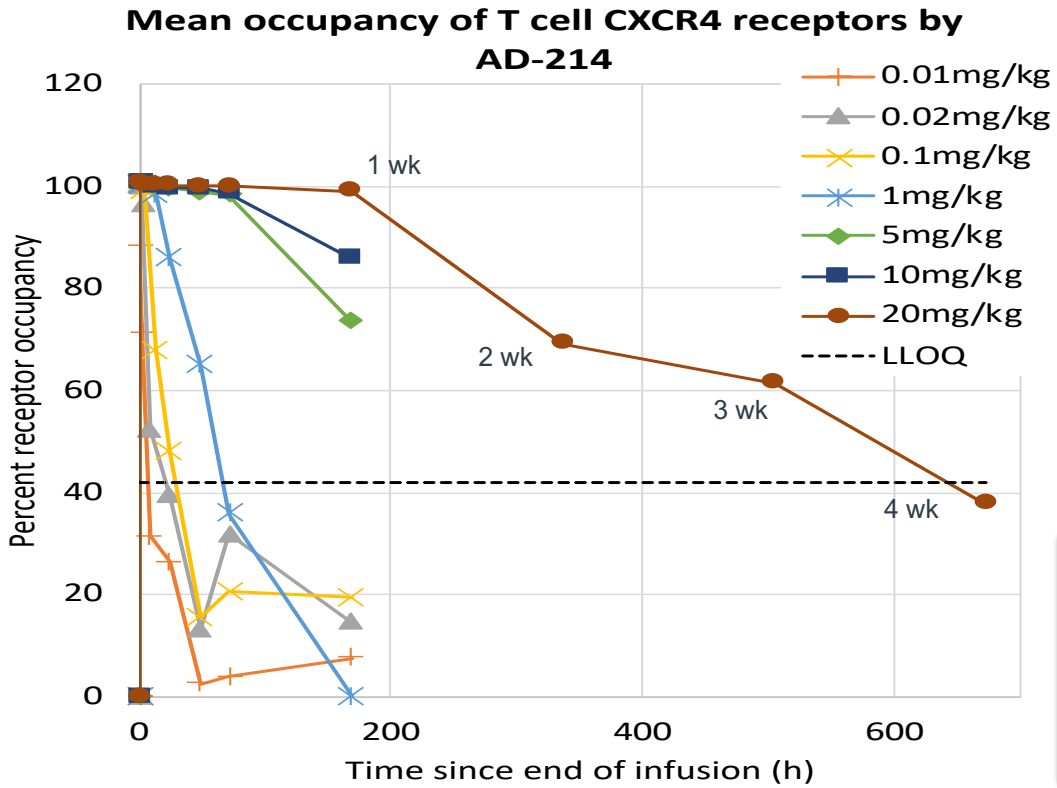
Sustained high levels of CXCR4 receptor occupancy* on T cells



- *CXCR4 is expressed on white blood cells in healthy individuals, providing an accessible proxy for AD-214 target engagement*

- Dose dependent level and duration of RO
- >70% CXCR4 RO at 7 days after 5-10 mg/kg infusion
- >60% CXCR4 RO at 21 days after 20 mg/kg infusion
- Duration of PD effect is considerably longer than PK profile

If replicated on CXCR4 receptors in tissues in IPF/ILD patients and other fibrotic patients, supports extended dosing intervals despite relatively rapid clearance from circulation

* Receptor occupancy was monitored for one week at all dose levels except 20 mg/kg (4 weeks)

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AD-214 Phase I program in healthy volunteers and patients

Phase 1 protocol in healthy volunteers

Complete

Part A: HV SAD
Blinded/placebo controlled
0.01-20 mg/kg single dose ✓
7 cohorts, 42 pts

Q2-Q4 2021

Part B: HV MAD*
Blinded/ Placebo controlled
3 doses, 5-15 mg/kg every 2 weeks
3 cohorts, 12 – 24 pts

- Dosing complete end 2021
- Supports Phase II/ FDA IND application in multiple indications

Phase 1b protocol in patients with IPF/ILD and other fibrotic diseases*

- AD-214 distribution and CXCR4 receptor occupancy in tissue in multiple disease states
- Safety in IPF/ILD in combination with SoC**

Commence Q3 2021

Arm 1: PET screening of fibrotic diseases
Open label with SoC**
~12 patients (~6 IPF/ILD) high CXCR4 disease

Arm 2: Multi-dose in IPF/ILD
Open label with SoC**
~6 patients, max 6 doses over 18 weeks +/- PET imaging

* First cohort has received second dose
** Standard of Care (includes pirfenidone, nintadanib or non-pharmacologic intervention)

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Implications for AD-214: a clinician's perspective

- **Un-met need in IPF/ILD** remains: need to progress new therapies
- Research at The Alfred suggests that **if targeting CXCR4 works in IPF it may also work in other ILD's**
- **AD-214 is well tolerated and ready to move forward** into multi-dose studies in healthy volunteers and patients
- The **data is supportive of extending dosing interval** to two weekly at least
- **AdAlta approach is methodical and appropriate**
  - **PET imaging strategy** is particularly important as an **innovative way to explore target engagement** in tissue early
- Key insights to come from multidose and early patient studies:
  - CXCR4 receptor engagement in tissue
  - Nature of the anti-drug antibodies that are expected with a biologic
  - Characterisation of biomarker responses: CD34+, white cells, SDF-1a

* Prof Glen Westall, leading Australian respiratory specialist and lung fibrosis expert at AdAlta Investor Briefing, March 2021