ARIA PHARMACEUTICALS

Ankylosing Spondylitis (AS)

August 2022

SOUND SCIENCE

ARIA IDENTIFIES THE THERAPEUTICS MOST LIKELY TO SUCCEED

Success Rates	Industry	ARIA PHARMACEUTICALS
in vivo	1-2%	**30%**[1]
Phase II	30%	**80%**[2]

Cumulative likelihood of success *in vivo* through Phase 2

50x Higher

1 – Significantly disease-modifying hits in preclinical animal models identified by Symphony; N=18 diseases, on average 10 molecules per disease
2 – Retrospective efficacy success rate of clinical trials of molecules identified by Symphony; N=18 diseases, 283 Ph2 CTs

ARIA'S STRATEGIC ADVANTAGE IN AS

MAXIMIZED LIKELIHOOD OF CLINICAL SAFETY – HUMAN SAFETY AT PHASE I

ESTABLISHED TOLERABILITY
LFA-1 inhibitors have safely completed Phase I

MAXIMIZED LIKELIHOOD OF CLINICAL EFFICACY – HUMAN EFFICACY AT PHASE II

HIGH CLINICAL PREDICTABILITY IN AS
Symphony predicted 96% of Phase III successes and 95% of Phase II successes in AS

ANKYLOSING SPONDYLITIS

MARKET

50 MILLION cases worldwide

CHRONIC, INFLAMMATORY RHEUMATIC DISEASE

SEVERE PAIN, STIFFNESS, AND FATIGUE – largely treated with rheumatoid arthritis medications

$4B

2024 Market ($/Year)[1]

SPEED AND SUCCESS

10 MOLECULES ADVANCED from hit prediction to *in vivo*

12 WEEKS from program start to *in vivo* results

LEAD MOLECULE TXR-1307 IN VIVO HIGHLIGHTS:

NOVEL MOA in AS

Significant **REDUCTION** in arthritis score
Significant **REDUCTION** in new bone growth

Significant **DECREASE** in AS score
Significant **IMPROVEMENT** in skin, ankle, and gut histology
Significant **DECREASE** in T1 MRI score

GOOD TOLERABILITY – clinically investigated mechanism

Source: (1) Pharmaceutical Intelligence Services, GlobalData LLC.

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HIGH UNMET MEDICAL NEED FOR AS

50 MILLION CASES WORLDWIDE

1.5 M US cases

2 OUT OF 3 adults living with AS are men

AFFLICTS PATIENTS BEFORE 30 80% of all patients

HETEROGENEOUS & COMPLEX DISEASE

PAIN AND INFLAMMATION mild to severe usually starting in the back

SIGNIFICANT SYMPTOMS pain, fatigue, gut inflammation, and spinal stiffness leading to hunched stature

SPINAL BONE FUSING occurs in 70% of AS patients

STANDARD OF CARE

NSAIDS – well tolerated, but not efficacious

TNFi – strong efficacy, but lack or loss of efficacy is common

SOCs DO NOT SLOW DISEASE PROGRESSION of spinal fusions, instead focusing on quality of life

INVESTIGATIONAL DRUGS

SELECTED AGENTS – RECENTLY COMPLETED OR IN ACTIVE AS CLINICAL TRIALS

Agent	Developer	Target(s)	Completed Phase	Primary Endpoint	Current Status	Response
Etanercept	Amgen	TNF-α & β	III	ASAS 20 Response	Approved	58% vs 23% (placebo)
Secukinumab	Novartis	IL-17A	III	ASAS 20 Response	Approved	MEASURE 1: 60.5% vs 36.8% (placebo)
Bimekizumab	UCB	IL-17A & F	III	ASAS 40 Response	III	BE MOBILE1: 47.7% vs 21.4% (placebo)
Filgotinib	Galapagos	JAK1	II	ASDAS change from baseline	II	TORTUGA: -1.5 vs -0.6 (placebo)
VAN-301	Valin Technologies	IL-17A	preclinical	Safety & Tolerability	I	N/A

NRS: spinal pain numerical rating scale
ASAS 20 & 40: Assessment in SpondyloArthritis International Society (Response Score) at 20 & 40 weeks

DISCOVERY PROCESS IDENTIFIES TXR-1307 IN 12 WEEKS

AI-Driven Discovery

Diverse Data, Methods:

- 25 data sources
- 65 methods
- 2M+ molecule chemistry library

50K Molecules

AI-Assisted Review

Novelty and Safety:

- Novel MOA
- Safety profile
- ADME properties

2K Molecules

Hit Diligence

PhD-led Deep Dive:

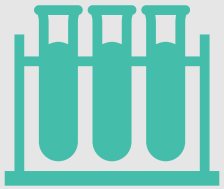
- MOA relevance
- MOA safety
- IP development path

70 Molecules

Preclinical

Optimal Disease Models:

- Test diverse MOAs
- CRO availability
- Rapid *in vivo* efficacy



10 Molecules

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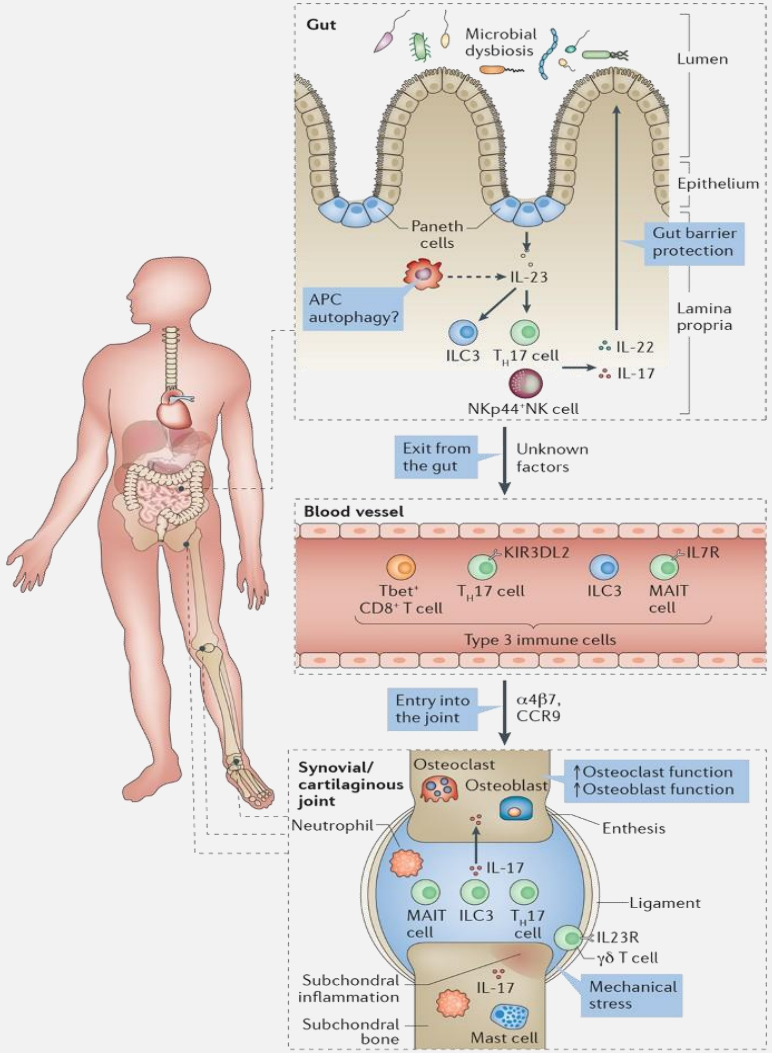
BIOLOGY OF AS

- Gut inflammation and type 3 immunity are implicated in AS pathology
- IL-17 and IL-23 act as major cytokines
- Type 3 immune, including IL17+ cells are enriched in the joints of AS patients, potentially indicating the innate immune system may be relevant
- IL-17 production is broadly upregulated in AS and may reflect a misregulation of IL-17-producing, type 3 immune cells
- Type 3 immune response is hypothesized to arise from the gut epithelium and traffic to synovial tissue



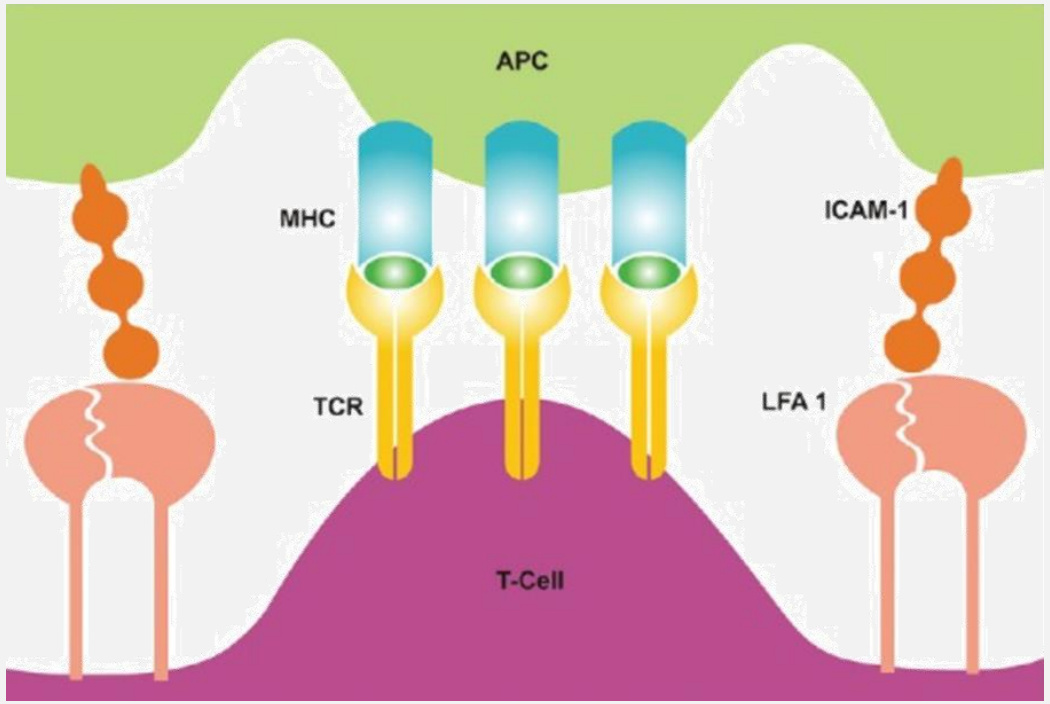
Ranganathan, *et al*., 2017. Nature Reviews Rheumatology

Ranganathan, *et al*., 2017. Nature Reviews Rheumatology
Zhu, et al; 2019. Bone Research

TXR-1307 IS AN LFA-1 ANTAGONIST

- Binds ITGB2 (LFA-1) to block interaction with ICAM-1
  - Prevents adhesion, activation, migration, and proliferation of lymphocytes to suppress inflammatory immune response amplification

- LFA-1
  - Regulates leukocyte trafficking, recruitment to sites of inflammation, and participation in phagocytosis
  - Influences T cell differentiation, including into Th1 & Th17 subsets and can promote Th1 cell differentiation and proinflammatory cytokine production[1]
  - Can illicit IFN-γ release by Innate T Lymphocytes[2]

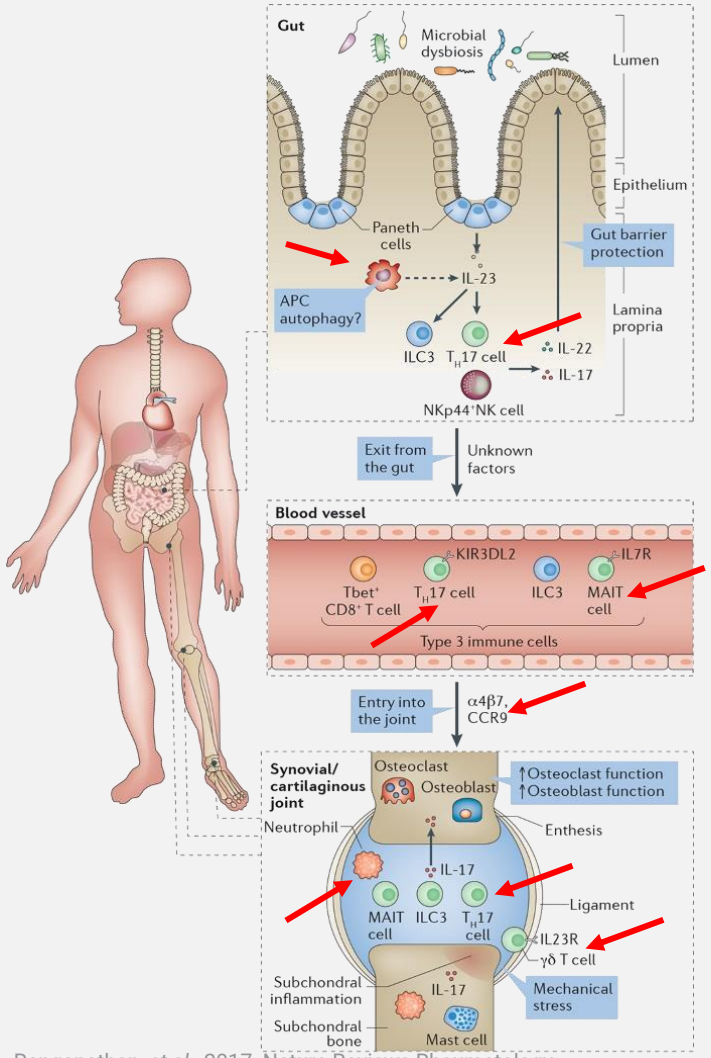


Abidi et al. 2016. *J Pharmacol Pharmacother.*7(4): 194–198.

1. Verma & Kelleher, 2017. J Immunol
2. Sharma *et al*.; 2018. J Immunol

LFA-1 ACTS ON AS AT MULTIPLE POINTS

- LFA-1 regulates type 3 immune cell activity including neutrophils[1], Th17 cells[2], and MAIT cells[3].
- In a mouse model of arthritis, antagonism of LFA-1 inhibits T cell proliferation, T cell adhesion to endothelial cells in joints, and proinflammatory Th1 cytokine production[4]
- LFA-1 co-stimulation with TCR regulates differentiation between αβ and γδ T cells[5] and can trigger apoptosis of peripheral γδ T cells[6]
- Acting through an α4β7 and CCR9 mechanism, LFA-1 plays a role in the migration of CD4+ T cells in the intestine[7]



Ranganathan, *et al*., 2017. Nature Reviews Rheumatology

1. Lefort & Ley, 2012. Front Immunol
2. Wang, *et al*.; 2007. Bioch & Biophy Res Com
3. Rouxel & Lehuen, 2018. Immunol & Cell Bio
4. Verma & Kelleher, 2017. J Immunol
5. Matsumoto, *et al*.; 1994. Eur J Immunol
6. Marski, *et al*., 2007. J Immunol

IN VIVO STUDY

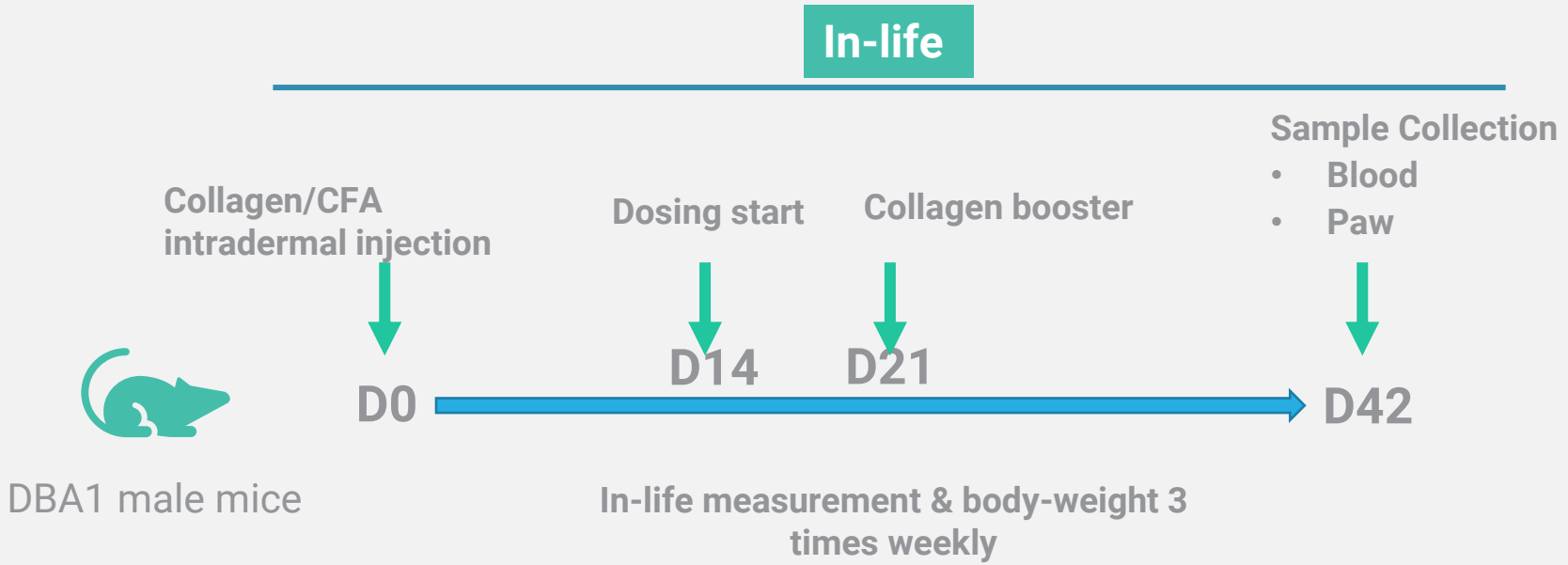
MOUSE COLLAGEN INDUCED ARTHRITIS MODEL

- Paw scores & hind paw measurement
- H&E staining
- Bone histology

REFERENCE THERAPY

- Dexamethasone & Cetuximab

INITIAL *IN VIVO* STUDY DESIGN



Efficacy Measures

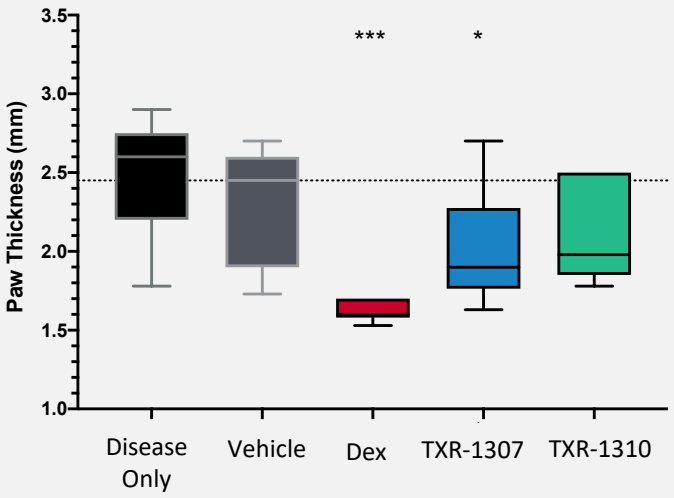
- Paw scores
- Hind paw measurement
- Bone histology

- Accessible POC model for initial drug candidate efficacy evaluation
- Test items dosed 1X daily from day 14 to 41
- Two candidates identified; TXR-1307 MOA selected for development, TXR-1310 MOA as backup

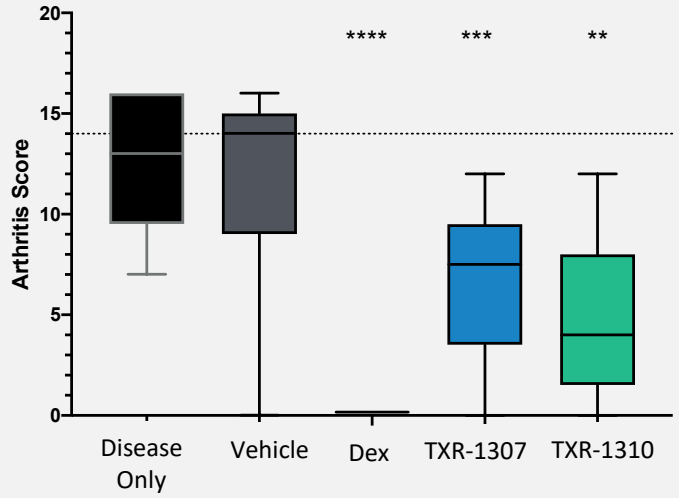
SCREENING IDENTIFIES TXR-1307, TXR-1310 TO ADVANCE

- TXR-1307 & TXR-1310 significantly reduce arthritis and new bone growth with a greatly improved toxicity profile to steroid-based standard of care treatments

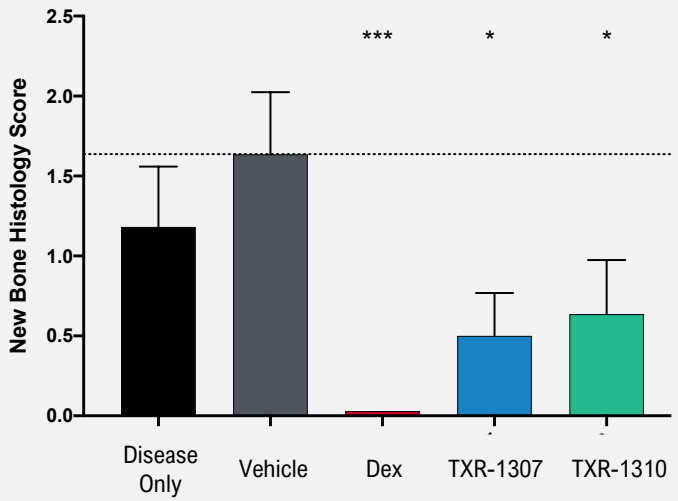
Paw Thickness Day 42



Arthritis Score Day 42



Histology New Bone



* p<0.05
** p<0.01
*** p<0.001
**** p<0.0001
N=10 per Group

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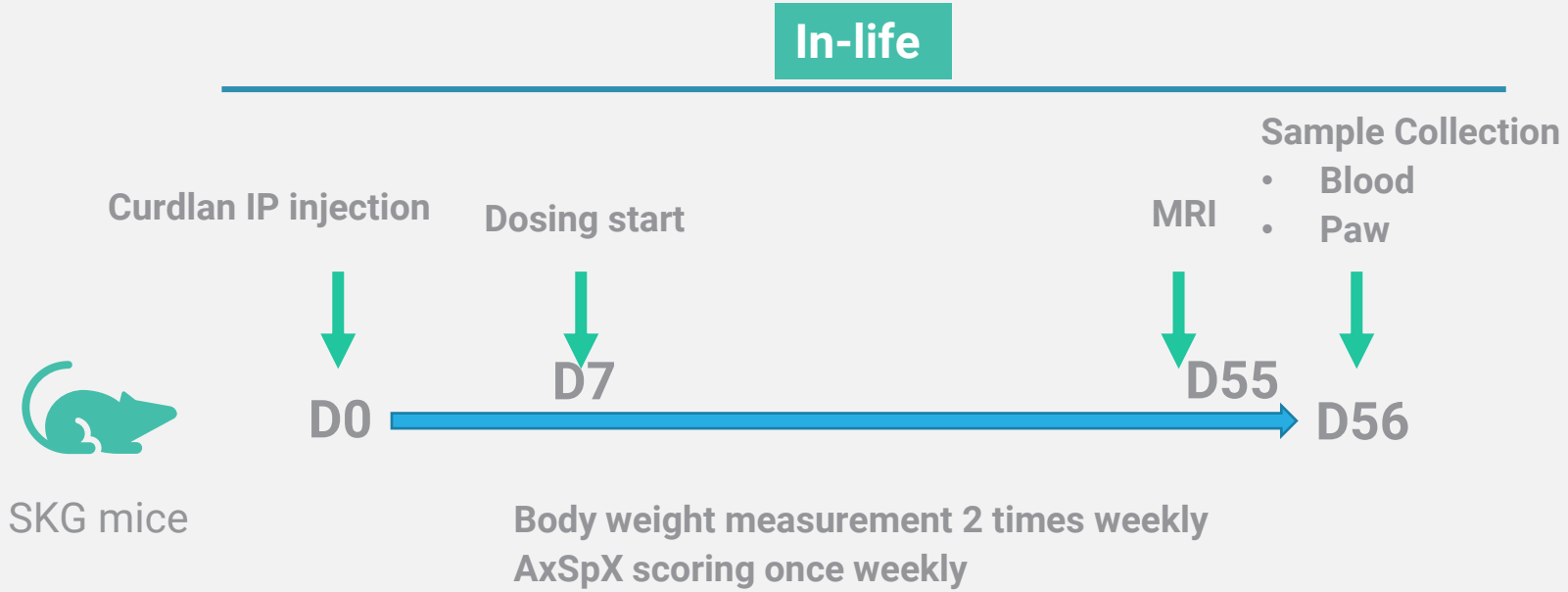
SECOND *IN VIVO* STUDY DESIGN

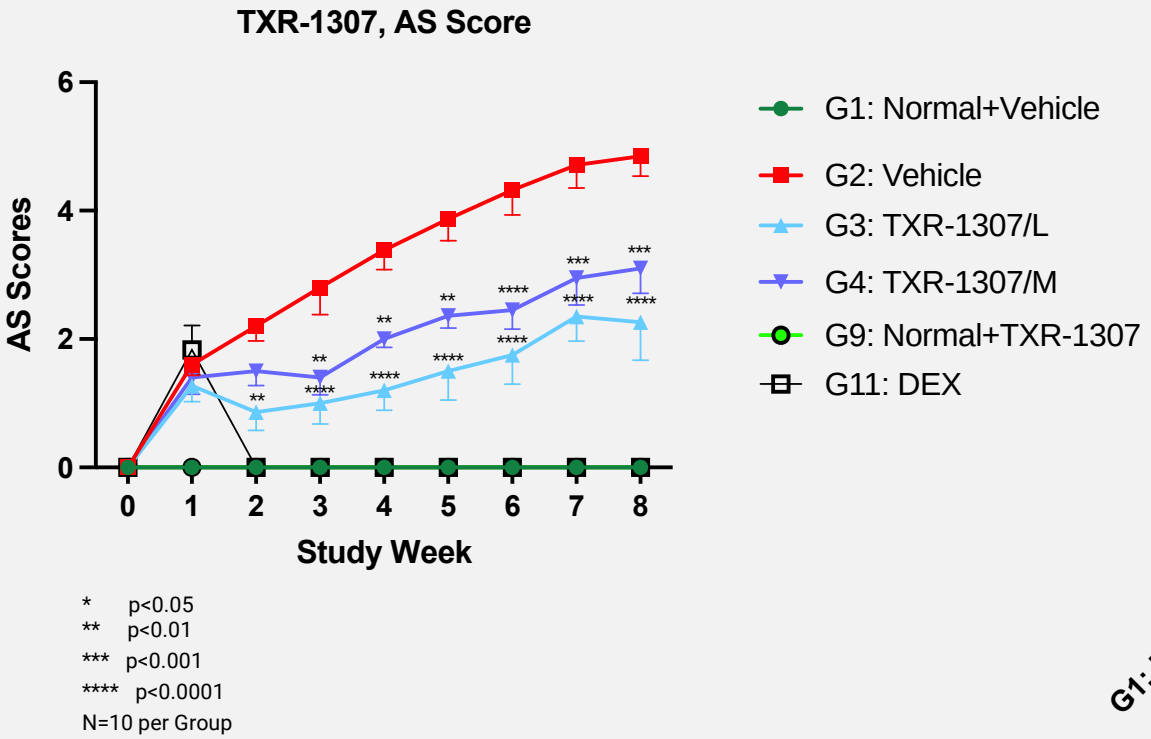


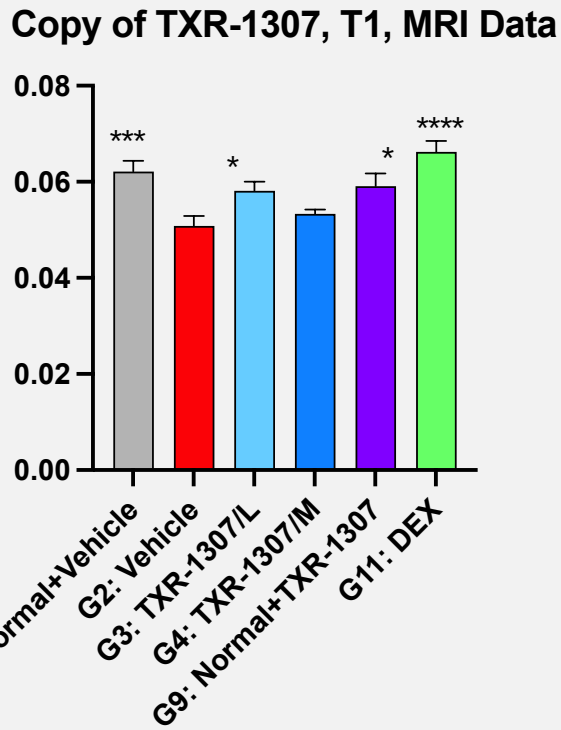
Efficacy Measures
- AxSpX in-life scoring
- Joint MRI scans
- Histology

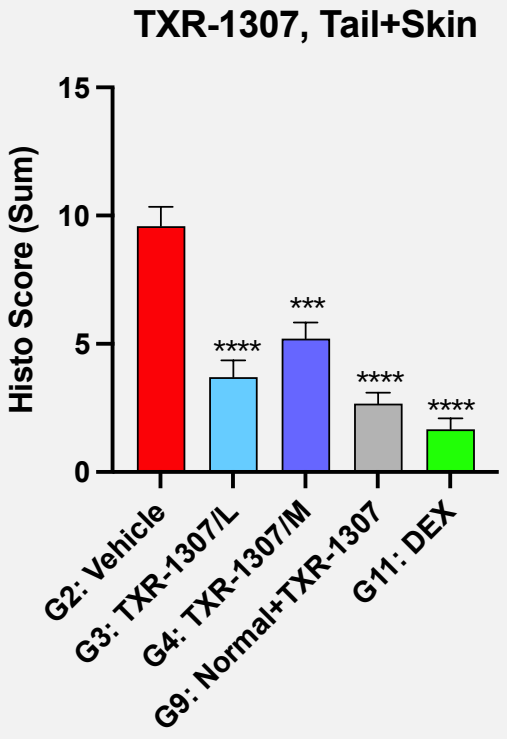
- β-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. Curdlan is fermented polysaccharides made from glucose
- Test items dosed 1X daily from day 7 to 55 (week 8)
- TXR-1307 MOA showed efficacy in AS mouse model & selected for development
- TXR-1310 MOA showed weaker efficacy signals

TXR-1307 SIGNIFICANTLY REDUCED AS DISEASE PHENOTYPES

- TXR-1307 significantly improved AS disease scoring, MRI measurements of joints, and histology from multiple tissues







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TXR-1307 ANKYLOSING SPONDYLITIS SCREENING SUMMARY

GOOD TOLERABILITY – excellent tolerability assessed by body weight

EFFICACY MEASURE, MRI ANALYSIS– significant decrease in T1 MRI score was also observed

EFFICACY MEASURE, ARTHRITIS SCORE – significantly decreased AS score

ARTHRITIS HISTOLOGY – significantly reduced histological scores of tails, skin, ankle, and guts

SUMMARY

- AS is a $4B/yr market with high unmet need for efficacious and tolerable treatments
  - Symptoms include pain, fatigue, and spinal fusion
  - NSAIDs used for symptom management – not disease modifying
  - Subsequent disease progression then treated by DMARDs such as TNF inhibitors
- TXR-1307 is an LFA-1 antagonist
  - LFA-1 influences T cell differentiation and migration as well as regulating type 3 immune cell activity – an important aspect of AS disease biology
  - Significant preclinical disease modification across multiple endpoints in 2 separate models
  - Additional pharmacology studies planned

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SoftBank Ventures ANDREESSEN HOROWITZ OS Fund Stanford StartX Med MIT STARTUP EXCHANGE