



Idiopathic Pulmonary Fibrosis (IPF)

May 2022



SOUND SCIENCE

ARIA IDENTIFIES THE THERAPEUTICS MOST LIKELY TO SUCCEED

Success Rates

Industry



in vivo

1-2%

30%¹

Phase II

30%

80%²

Cumulative likelihood of success *in vivo* through Phase 2

50x Higher

2

1 – Significantly disease-modifying hits in preclinical animal models identified by Symphony; N=18 diseases, on average 10 molecules per disease

Confidential

2 – Retrospective efficacy success rate of clinical trials of molecules identified by Symphony; N=18 diseases, 283 PIs/2018

ARIA'S STRATEGIC ADVANTAGE IN IPF

MAXIMIZED LIKELIHOOD OF CLINICAL SAFETY – HUMAN SAFETY AT PHASE I



ESTABLISHED TOLERABILITY

Dual AGTR1/EDNRA inhibitor has safely completed Phase I

MAXIMIZED LIKELIHOOD OF CLINICAL EFFICACY – HUMAN EFFICACY AT PHASE II



HIGH CLINICAL PREDICTABILITY IN IPF

Symphony predicted 100% of SOCs & Phase III successes and 50% of Phase II successes in IPF

IDIOPATHIC PULMONARY FIBROSIS (IPF)

MARKET



3 MILLION cases worldwide



3-5 YEARS - life expectancy after diagnosis



NINTEDANIB & PIRFENIDONE-
standard of care:
slow disease progression

\$3B

2024 Market
(\$/Year)¹

SPEED AND SUCCESS



10 OF 20 MOLECULES ADVANCED from hit prediction to *in vivo*



12 WEEKS from program start to *in vivo* results

LEAD MOLECULE TXR-1002 *IN VIVO* HIGHLIGHTS:



NOVEL MOA in IPF



Significant **REDUCTION** of collagen in lung tissue - comparable to nintedanib
LOWERS lung infiltration of neutrophils – lower than nintedanib
LOWERS lung infiltration of lymphocytes – comparable to nintedanib



GOOD TOLERABILITY – clinically investigated mechanism

HIGH UNMET MEDICAL NEED FOR IPF

3 MILLION CASES WORLDWIDE



**INCREASED INCIDENCE
WITH AGE** - 13 cases per 100k
age 50+



INCREASED PREVALENCE in
men compared to women
(0.0314% vs. 0.02745%)

3-5 YEARS LIFE EXPECTANCY



FIBROSIS & INFLAMMATION
caused by aberrantly activated
lung epithelium



**CHRONIC PROGRESSIVE
LUNG DISEASE** – progressive
lung scarring and interstitial
pneumonia



QUALITY OF LIFE – impaired
QOL, cough, shortness of
breath

2 APPROVED MEDICATIONS



STANDARD OF CARE is
nintedanib or pirfenidone



SLOWS disease progression, but
does not stop it; benefits
unknown at advance stages



TOLERABILITY – Limited use
(~30% patients do not tolerate
for >2 yrs) [†]

STANDARDS OF CARE

Pharmacologic Management of IPF

	Nintedanib	Pirfenidone
Mechanism of action	Tyrosine kinase inhibition (VEGFR, PDGFR, FGFR)	Inhibition of TGF-β production and downstream signaling, collagen synthesis and fibroblast proliferation (target unknown)
Enzyme metabolism	Ester cleavage (major), CYP3A4 (minor)	CYP1A2 (major), other CYP enzymes (minor)
Cautions	Risk of both bleeding and arterial thrombosis, risk of GI perforation (rare); anticoagulant and prothrombotic drugs should be avoided	CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) can raise pirfenidone levels; CYP1A2 inducers can lower pirfenidone levels (e.g. omeprazole, smoking)
Liver-function monitoring required	Yes	Yes
Common side effects	Diarrhea, GI distress	Anorexia nausea, photosensitivity
Clinical strategies to minimize side effects	Use of antidiarrheal agents, temporary dose reduction to 100 mg BID	Slow dose increase of 14-day period, medication taken with food, use of antacids, use of antiemetic agents, sun avoidance
Efficacy	Slows annual FVC decline by 50%	Slows annual FVC decline by 50%
FDA-approved dose	150 mg BID	801 mg TID

INVESTIGATIONAL DRUGS

SELECTED AGENTS - FAILED OR IN ACTIVE PHASE II/III IPF CLINICAL TRIALS

Agent	Developer	Target(s)	Completed Phase	Primary Endpoint	Current IPF Status	Response
PRM-151	Promedior/Roche	Macrophage polarization factor ¹	II	FVC rate of decline (52 wk)	Phase III	FVC stabilization
Pamrevlumab	Fibrogen	CCN2 (CTGF)	II	FVC rate of decline (52 wk)	Phase III	FVC stabilization
CC-90001	Celgene/BMS	JNK1	I	FVC rate of decline (52 wk)	Phase II	FVC stabilization
Nintedanib + Sildenafil	Boehringer Ingelheim	PDGFR, FGFR, VEGFR, PDE5	III	SGRQ, Dyspnea	Stopped	Not significant
Bosentan	Bayer	EDNRA, EDNRB	III	Time to worsening	Stopped	Not significant
Sildenafil	Pfizer	PDE5	III	6-Minute Walk Distance	Stopped	Not significant
Etanercept	Amgen	TNF-α	II	FVC rate of decline	Stopped	Not significant

1. Targets are not fully characterized. Drug acts as a macrophage polarization factor / regulates monocyte differentiation.

DISCOVERY PROCESS IDENTIFIES TXR-1002 IN 12 WEEKS

AI-Driven Discovery

Diverse Data, Methods:

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



50K Molecules

AI-Assisted Review

Novelty and Safety:

- Novel MOA
- Safety profile
- ADME properties

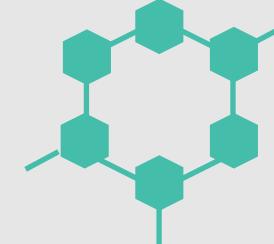


80 Molecules

Hit Diligence

PhD-led Deep Dive:

- MOA relevance
- MOA safety
- IP development path



20 Molecules

Preclinical

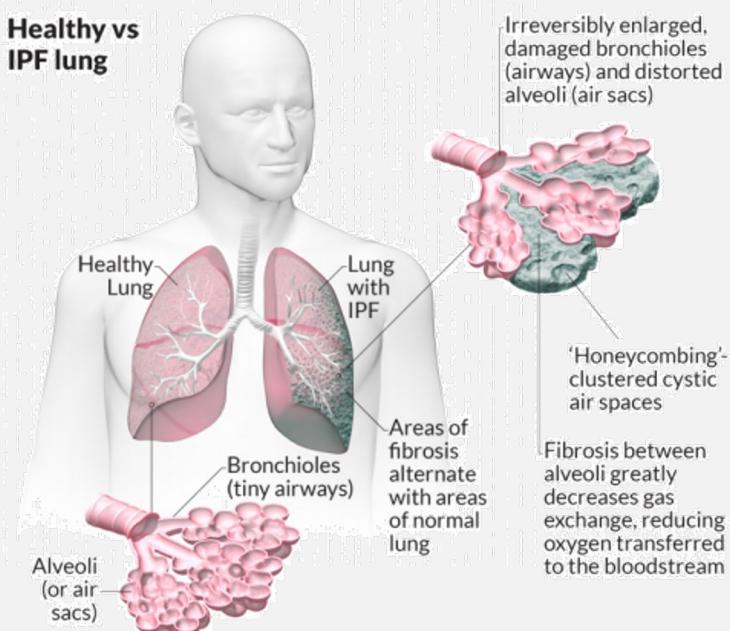
Optimal Disease Models:

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



10 Molecules

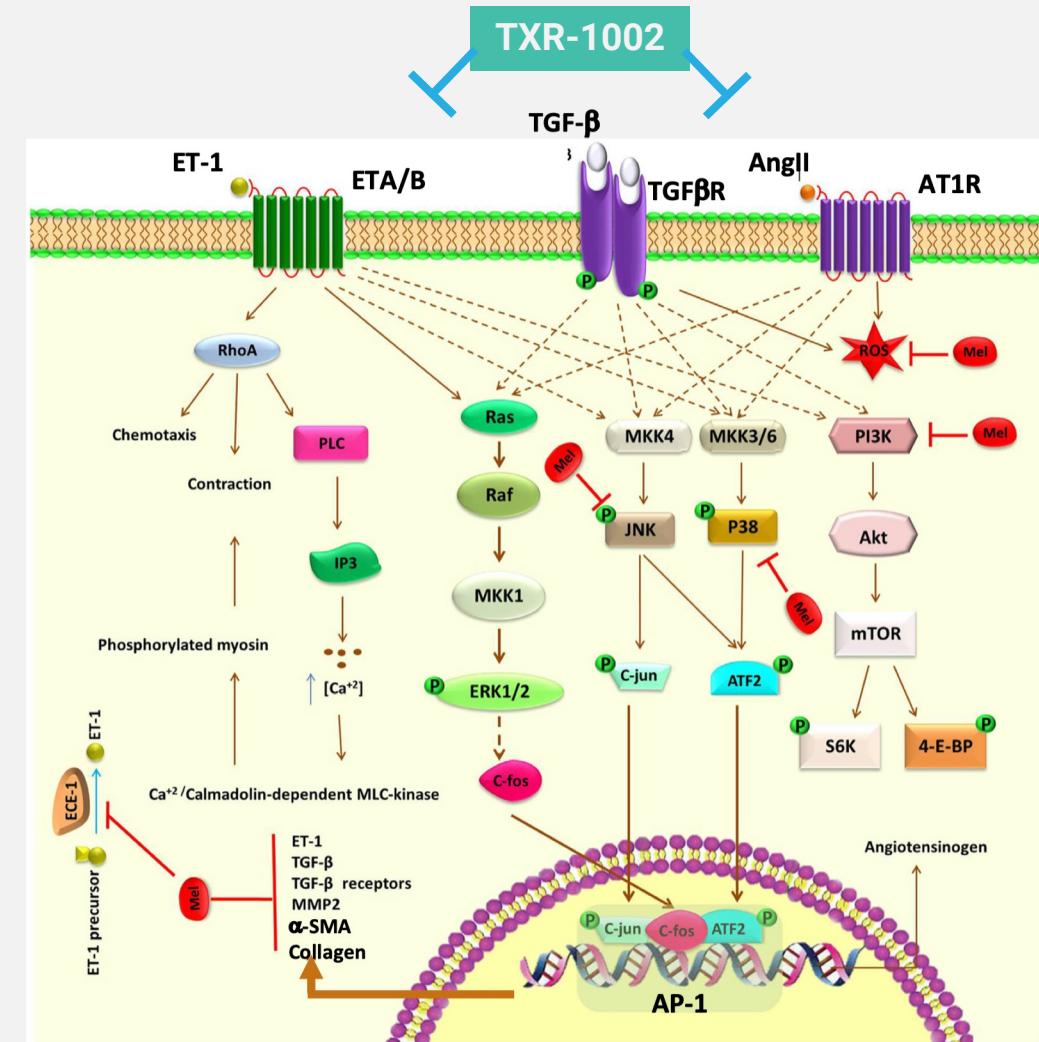
WHAT IS IPF: IDIOPATHIC PULMONARY FIBROSIS



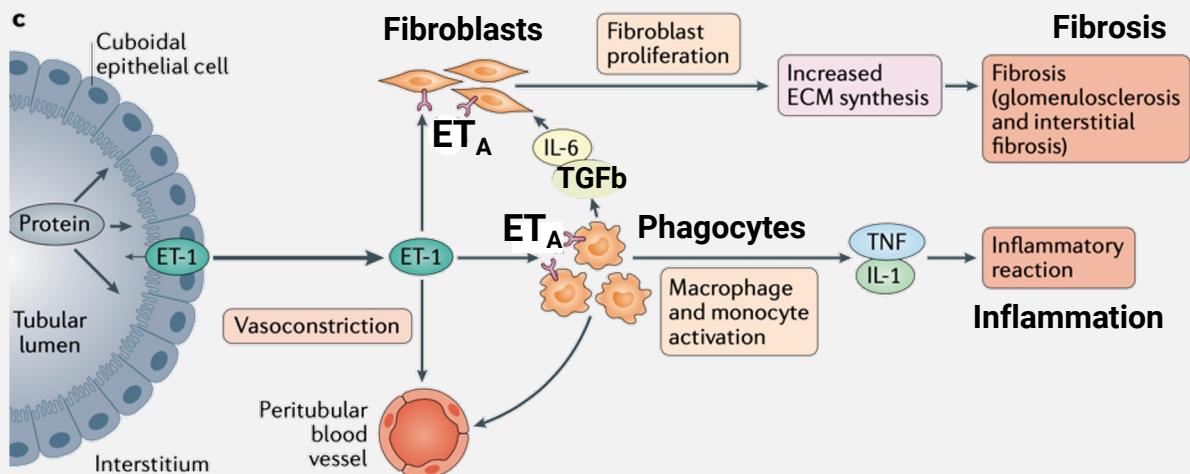
- IPF is progressive interstitial lung disease characterized by scarring of the lung tissue leading to respiratory failure and death with a median survival of 2- 3 years.
- The pathogenesis of IPF is not fully understood. However, it is currently thought that repeated lung injury or infection leads to aberrant wound healing process which causes massive extra cellular matrix deposition and scarring of the lung tissue that is characteristic of IPF.
- Nintedanib ameliorates IPF progression and symptoms by blocking the tyrosine kinases coupled to platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) receptors, and has been approved to treat IPF.
- The direct target(s) of Pirfenidone is unclear; however, it is known that downstream effects of target engagement include inhibition of TGF- β production, TGF- β receptor signaling and collagen synthesis
 - However, some patients do not respond well to these SOC drugs.

TXR-1002 IS A DUAL EDNRA, AGTR1 INHIBITOR

- Inhibition of Renin-Angiotensin System (RAS) activity via EDNRA and AGTR1
 - Inhibition of multiple signal transduction pathways
 - Inhibition of AP-1 transcription
 - Inhibition of myofibroblast proliferation
 - Inhibition of collagen, α -SMA, TGF- β , and MMP expression, ECM deposition, and fibrosis
- Inhibition of fibrosis and inflammation
- Potential treatment of pulmonary hypertension, a serious complication of IPF



EDNRA PROMOTES INFLAMMATION & PULMONARY PROCESSES



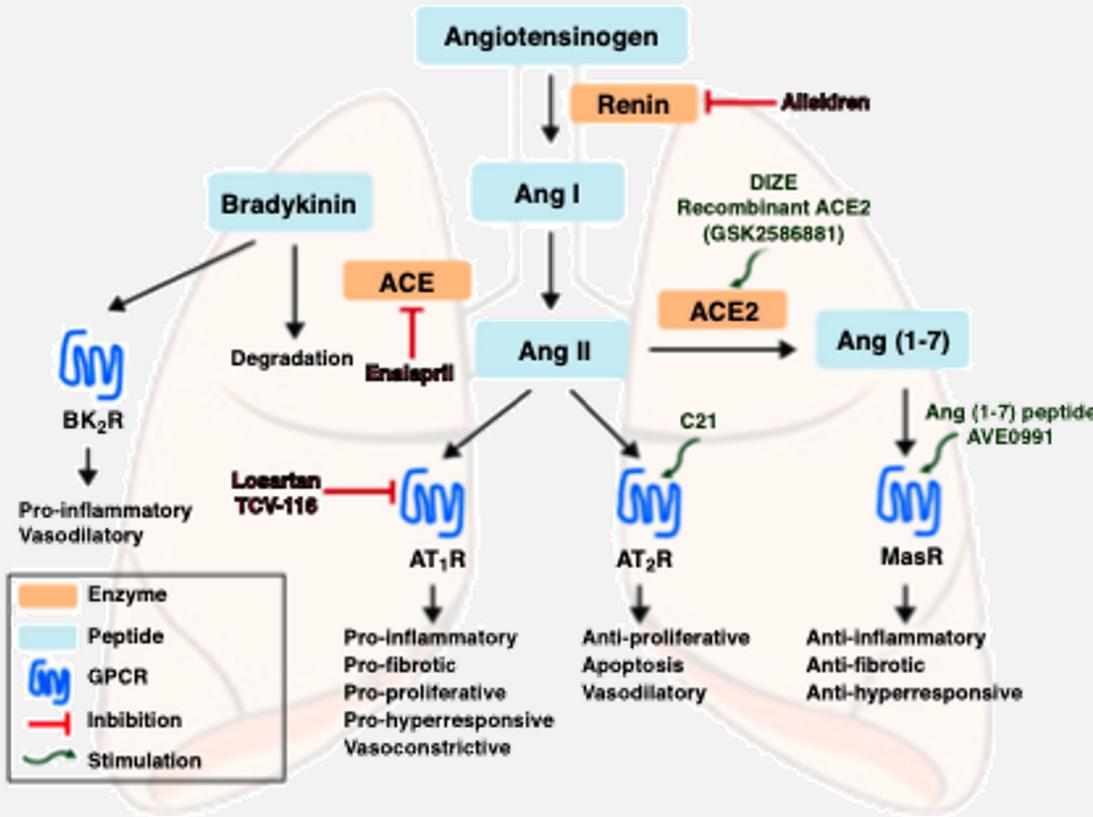
ET_A (EDNRA) – Fibroblasts, phagocytes (IPF relevance)

ET_B (EDNRB) – Endothelial cells (CV relevance)

- Endothelin system inhibition has established roles in lung biology¹
- EDNRA activates phagocytes to induce TNF and IL-1-mediated inflammation²
- ET1 (ligand for EDNRA) has established connections with lung fibrosis³
- EDNRA and EDNRA/B antagonism has mixed results in preclinical lung fibrosis models including several *in vivo* studies showing no effect^{4,5,6}
- EDNRA and EDNRA/B antagonists have failed clinically
- EDNRA and EDNRA/B inhibition is FDA-approved for pulmonary arterial hypertension (PAH)

1. Wong et. al., 2018. Current Opinion in Pharmacology
2. Dhaun and Webb 2019 *Nat Rev Cardio*
3. Zhu et. Al., 2017 *Frontiers in Pharmacology*
4. Mutsaers et al., 1998, *Pulm Pharmacol Ther*
5. Nuyen, et al., 2000, *Br J Pharmacol*
6. Park, et al., 1997, *Am J Respir Crit Care Med*

AGTR1 PROMOTES FIBROSIS AND INFLAMMATION PROCESSES



- Renin angiotensin system (RAS) inhibition has established roles in lung biology
- Chronic activation of RAS *in vivo* results in lung fibrosis leading to reduced pulmonary function¹
- AGTR1 (AT1R) inhibition improves the balance between profibrotic (TGF- β) and antifibrotic (PGE2) mediators²
- Inhibition of AGTR1 decreased lung fibrosis in several preclinical models including the mouse bleomycin IPF model^{1,2,3}
- 20-patient pilot clinical trial supports ATGR1 antagonism stabilizing IPF lung function with favorable tolerability⁴

Tan et al. 2018 *Curr Opin Pharm.* 40:9-17.

1. Wang, et al., 2015, *Sci Rep*

2. Molina-Molina, et al., 2006, *Thorax*

3. Otsuka et al., 2004, *Air Bio*

4. Couleuris, et al., 2012, *Lung*

REINFORCING ROLES SUGGEST POTENTIAL FOR SYNERGISTIC EFFICACY

- Individual mechanisms important, but no strong individual clinical effect
 - EDNRA inhibitor failed phase 3 study for IPF¹, but approved for PAH
 - AGTR1 inhibitor gave weak signal in underpowered pilot phase 2 study²
- Our hypothesis is the anti-fibrotic effects of AGTR1 inhibition along with the anti-inflammatory and anti-hypertensive effects of EDNRA inhibition will create a potent therapeutic effect
- This potential synergy demonstrated in FSGS, a disease with a similar fibrotic phenotype
 - In preclinical kidney fibrosis model, combination of EDNRA/B and AGTR1 antagonists outperform monotherapies³
 - Sparsentan, a well tolerated dual EDNRA, AGTR1 antagonist outperformed a solo AGTR1 antagonist in Phase 2 trial⁴. (Phase 3 ongoing)

1. Raghu et al, 2013, *Ann Intern Med*

2. Couluris, et al., 2012, *Lung*

3. Chang, et al., 2016, *Kidney Blood Press Res*

4. Trachtman et al., 2018, *J Am Soc Nephrol*

EDNRA, AGTR1 INHIBITION COUNTER IPF FIBROBLAST CHANGES

IPF-ASSOCIATED FIBROBLAST PHENOTYPIC CHANGES

- Myofibroblast differentiation
- Fibroblast proliferation, reduced apoptosis
- Matrix deposition
- Senescence-associated secretory phenotype
- Impaired autophagy
- Inflammation
- Increased ET-1 and EDNRA expression

ENDOTHELIN, ANGIOTENSIN RECEPTOR INHIBITION EFFECTS

- Suppress myofibroblast transition, differentiation
- Reduced fibroblast proliferation, increased apoptosis
- Suppress matrix deposition
- Suppressed secretory phenotype
- Induction of autophagy
- Suppress inflammation
- ET-1 or EDNRA expression a possible biomarker

- Combined, selective inhibition of EDNRA and AGTR1 can block or reverse phenotypic changes associated with IPF while maintaining an excellent tolerability profile
- Overcomes limitations associated with inhibition of only EDNRA/B or AGTR1

DISEASE & PRECLINICAL MODELS

- In IPF, aberrantly activated lung epithelium produces mediators of fibroblast migration, proliferation and differentiation into active myofibroblasts
 - These myofibroblasts secrete exaggerated amount of extracellular matrix (ECM) that subsequently remodel lung architecture
- Clinical manifestations are unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing that occurs without other symptoms. It is defined by the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP)
 - Hallmark features of UIP include epithelial cell hyperplasia, basement membrane denudation, alveolar consolidation and fibroblastic foci in a pattern that is spatially and temporally heterogeneous
- Understanding disease pathogenesis, identifying prognosticators, and novel therapeutics research rely on animal, largely murine models
 - Induced-Models: Bleomycin, Silica, Asbestosis, Fluorescent isothiocyanate (FITC)
 - Age-dependent Fibrosis
 - Cytokine overexpression models: TGF- β , IL-13, IL-1B, TNF- α
 - Familial models: Humanized (NOD/SCID mice)

HUMAN PATHOGENIC FEATURES/MECHANISMS IN PRECLINICAL MOUSE MODELS

Models	Pathological Features	Cell types Involved
Bleomycin	<ul style="list-style-type: none"> Direct cell injury via DNA damage Generation of free radicals, induction of oxidative stress Cell necrosis and/or apoptosis followed by inflammation and development of fibrosis Alveolar epithelial cells (AEC) hyperplasia in repetitive dosing model Resolution in single dose model 	Type I and II AECs Fibroblasts Myofibroblasts Macrophages Lymphocytes, neutrophils Endothelial cells, airway epithelial cells, and stem/progenitor cells
FITC	<ul style="list-style-type: none"> AEC and vascular permeability leads to lung fibrosis Ability to visualize injured areas of lung, fibrosis correlate closely with areas of FITC deposition Associated with acute lung injury, development of inflammation (including neutrophils) followed by development of fibrosis Durable fibrotic response lasting for months 	Dependent on Th2 cytokines (IL-13) and is regulated by chemokine motif ligand (CCL12)- mediated recruitment of fibrocytes in response to injury
Age-dependent Fibrosis	<ul style="list-style-type: none"> Epithelial stress in response to injury Fibroblasts poised to respond well to TGF-β signaling Fibroblasts from aged mice display decreases thymocyte differentiation antigen-1 (Thy-1), a hallmark of human myofibroblasts Natural infections with herpes virus cause fibrosis in aged but not young mice 	
TGF- β overexpression	<ul style="list-style-type: none"> AEC and airway epithelial cell injury Epithelial-mesenchymal transition Epithelial cell apoptosis and changes in soluble mediators that mimic human disease. Leads to persistent scarring, which may more closely mimic the fibrotic changes that occur in late IPF Fibrosis develops in absence of significant inflammation 	Models that rely on overexpression of TGF- β are relevant for dissecting downstream signaling pathways involved in multiple cell types.
Humanized NOD/SCID	<ul style="list-style-type: none"> IV instillation of human IPF fibroblasts into NOD/SCID/beige mice to study phenotype of human IPF <i>in vivo</i> Studies of how fibroblasts-autoimmune alterations affect other lung cell types are possible Currently does not allow studies of immune cell regulation of disease development Explore antifibrotic agents with human specificity 	Lungs of these mice show no evidence of fibrotic pathology before the instillation of IPF fibroblasts. The instillation of IPF fibroblasts results in focal fibrotic alveolar remodeling, cells activate murine epithelial cells. Pathological phenotype that is fibroblast-autonomous.

INITIAL IN VIVO STUDY DESIGN



BLEOMYCIN-INDUCED LUNG INJURY

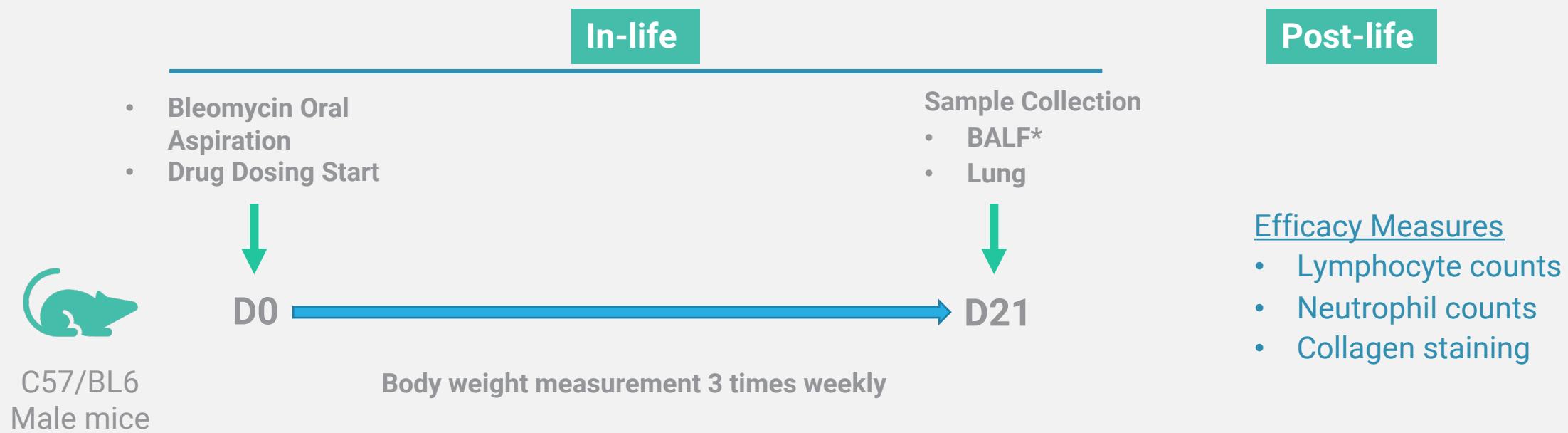
- Lymphocyte counts
- Neutrophil counts
- Collagen staining



REFERENCE THERAPY

- Nintedanib, PDGFR, FGFR, VEGFR inhibitor; SOC

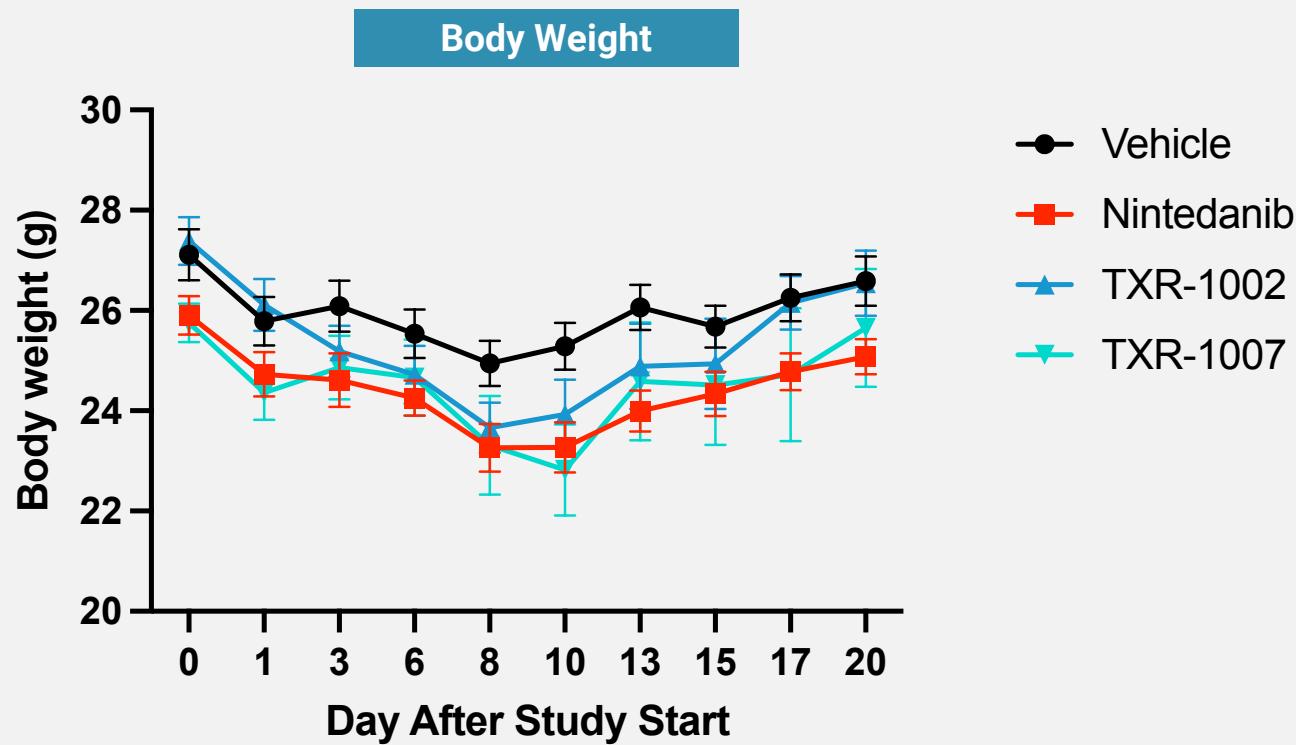
INITIAL IN VIVO STUDY DESIGN



- Bleomycin-induced lung injury in male mice
- Proof-of-concept model for initial drug candidate evaluation
- Two candidates identified; TXR-1002 MOA selected for development, TXR-1007 MOA as backup
- Additional lung fibrosis models available for further candidate investigation; e.g., TGF- β overexpression and/or a treatment paradigm instead of prophylaxis

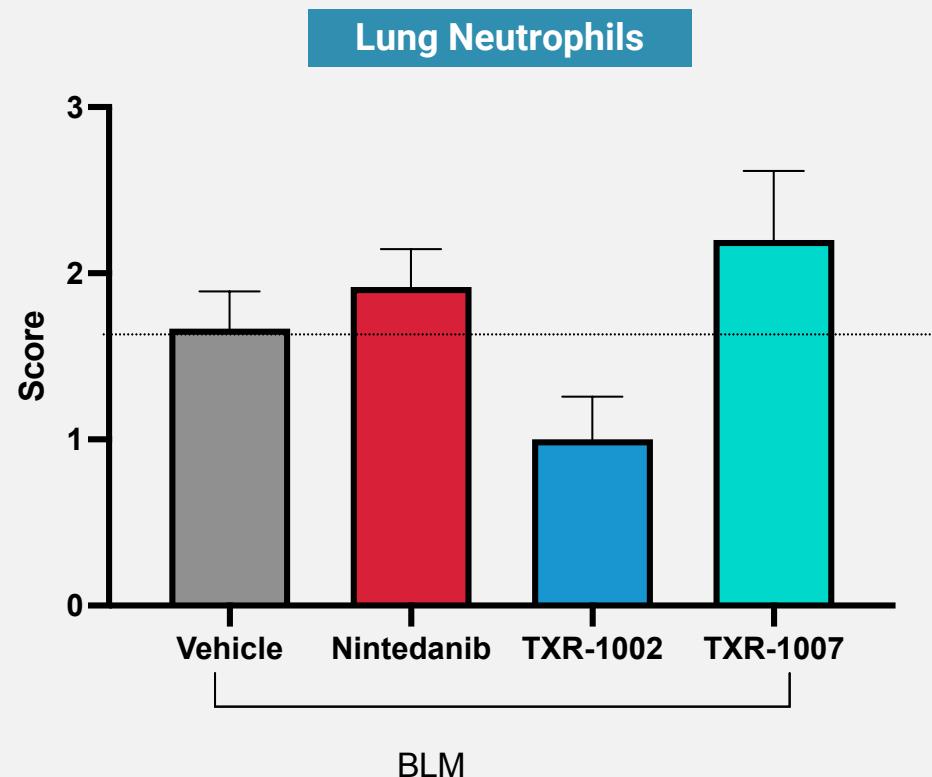
EXCELLENT TOLERABILITY FOR TXR-1002

- TXR-1002 and TXR-1007 did not exhibit significant body weight changes



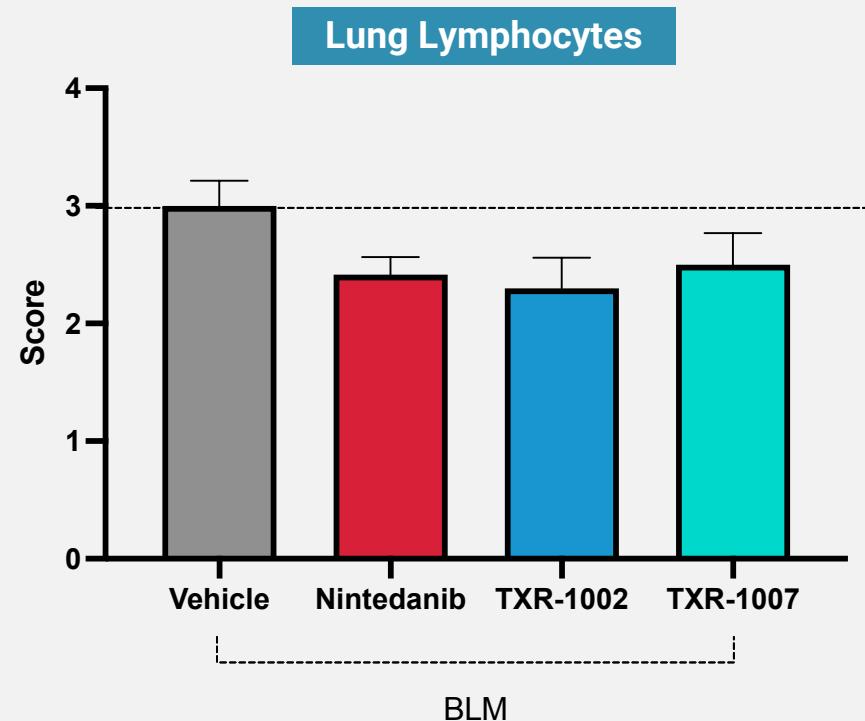
IN VIVO EFFICACY COMPARABLE TO STANDARD OF CARE

- TXR-1002 lowers lung infiltration of neutrophils (better than nintedanib)
- Directional – inflammation markers measured at day 21*



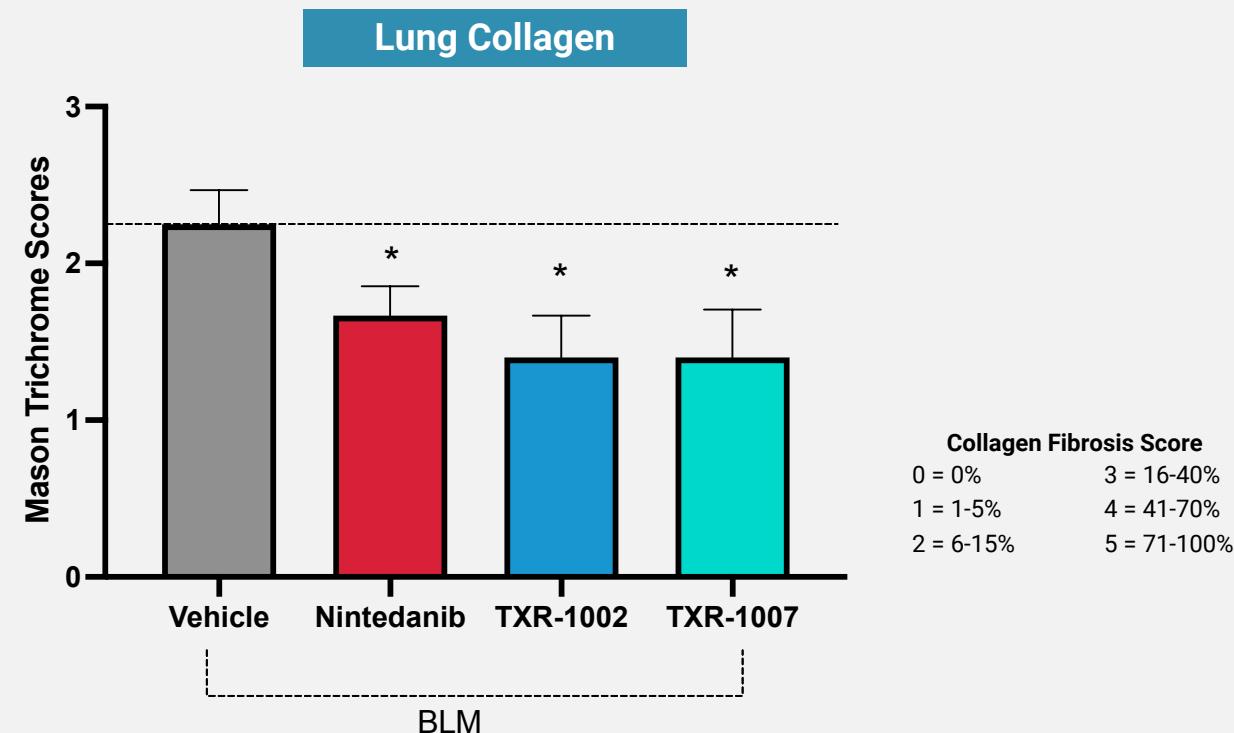
IN VIVO EFFICACY COMPARABLE TO STANDARD OF CARE

- TXR-1002 lowers lymphocytes (comparable to nintedanib)
- Directional – inflammation markers measured at day 21*



IN VIVO EFFICACY COMPARABLE TO STANDARD OF CARE

- TXR-1002 statistically significant reduction in collagen staining in lung tissue (comparable to nintedanib)



EFFICACY OF NINTEDANIB AND TXR-1002 IN BLEOMYCIN MODEL

EFFICACY MEASURE	NINTEDANIB	TXR-1002	COMMENTS
Lung Neutrophils	Decrease but not statistically significant vs. vehicle only	Decrease but not statistically significant vs. vehicle only	Higher decrease with TXR-1002 vs. nintedanib
Lung Lymphocyte	Decrease but not statistically significant vs. vehicle only	Decrease but not statistically significant vs. vehicle only	Decrease equivalent to nintedanib
Lung Collagen	Statistically significant decrease	Statistically significant decrease	Decrease equivalent to nintedanib

TXR-1002 INITIAL STUDY SUMMARY

TXR-1002 DEMONSTRATES POSITIVE INITIAL EFFICACY WITH A NEW MECHANISM



GOOD TOLERABILITY – clinically investigated mechanism



LUNG INFLAMMATION HISTOLOGY – decrease infiltrating neutrophils and lymphocytes



LUNG FIBROSIS HISTOLOGY – decreased fibrosis (key efficacy measure)

TXR-1002 SUPPORTED BY IPF KOL



Fernando Martinez
Weill Cornell Medicine

STRENGTHS

- “Encouraging, good data for TXR-1002 that is consistent”
- “Bleomycin model, although imperfect, is standardized and informative”

GUIDANCE

- “TXR-1002 worth pursuing in second bleomycin study* with PK and PD workup”
- “Models such as TGF- β 1 over-expression can be investigated in parallel with bleomycin”

SECOND IN VIVO STUDY DESIGN



BLEOMYCIN-INDUCED LUNG INJURY

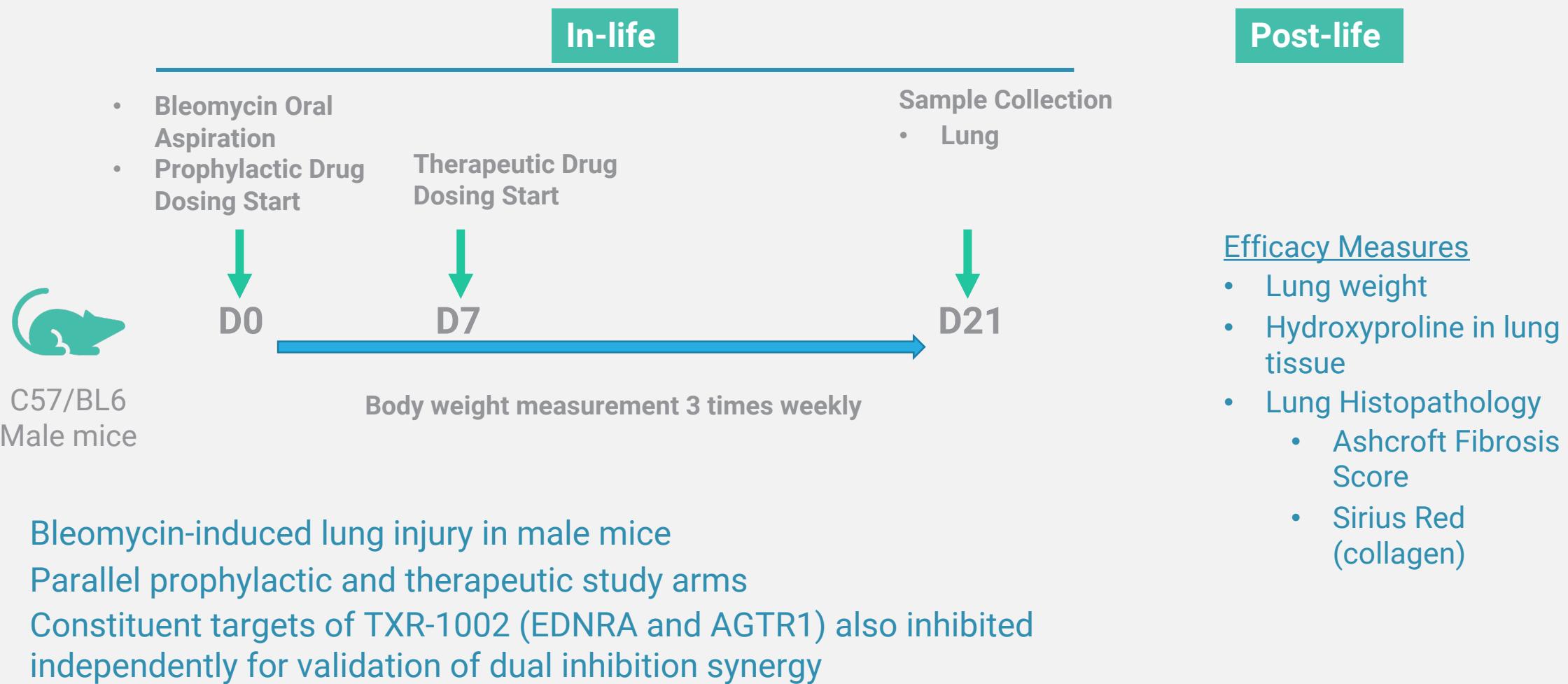
- Lung weight
- Collagen staining
- Lung Histopathology



REFERENCE THERAPIES

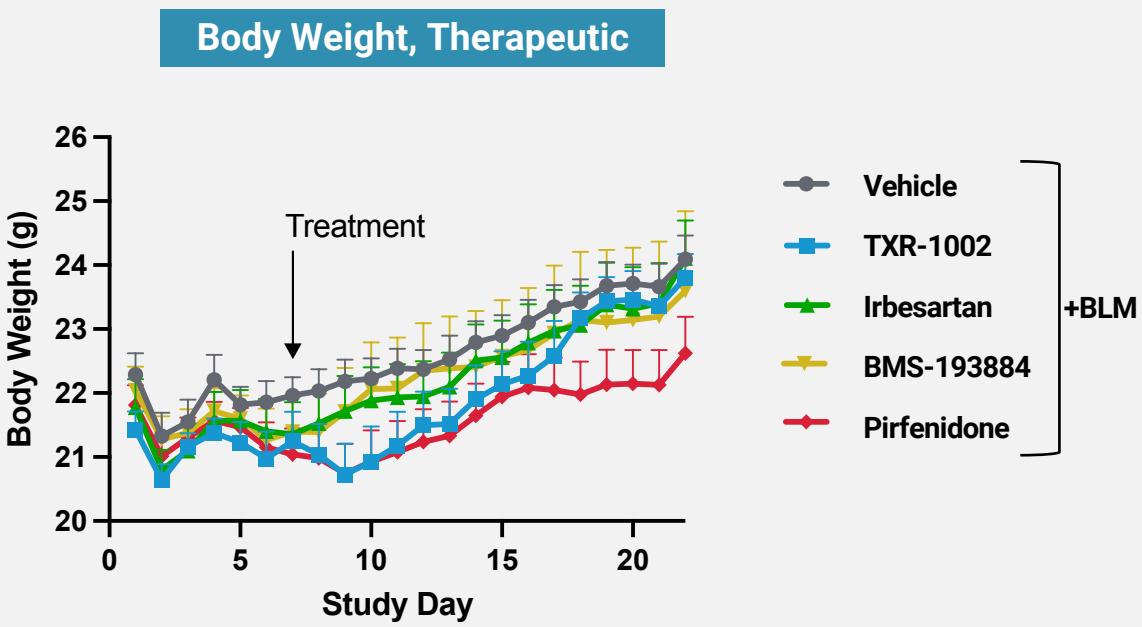
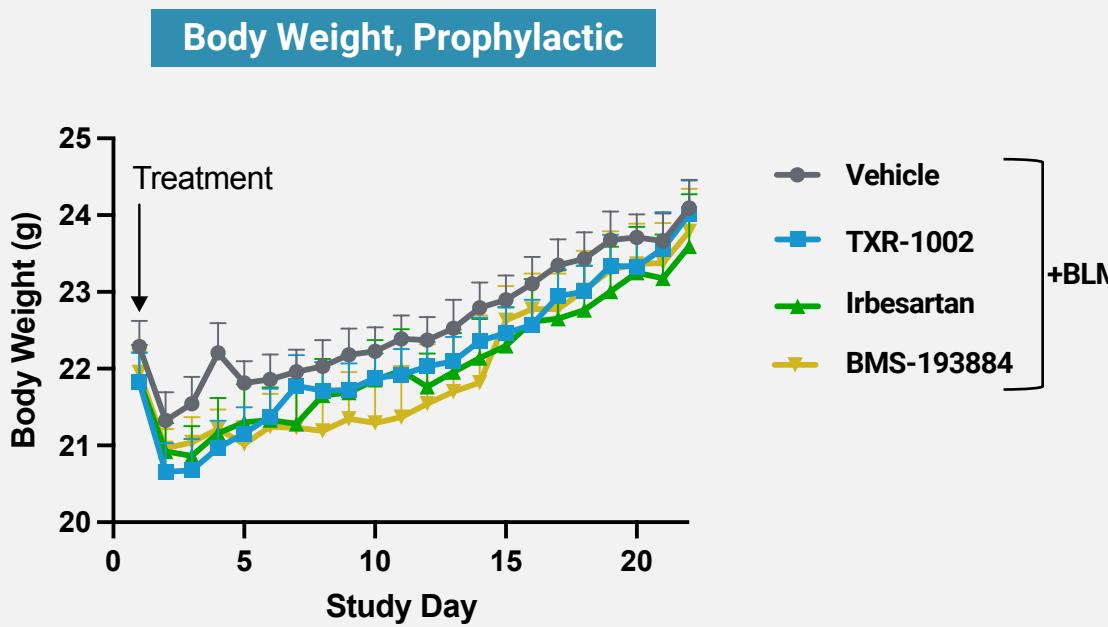
- Pirfenidone – target unknown; SOC
- Irbesartan – AGTR1 inhibitor
- BMS-193884 – EDNRA inhibitor

SECOND IN VIVO STUDY DESIGN



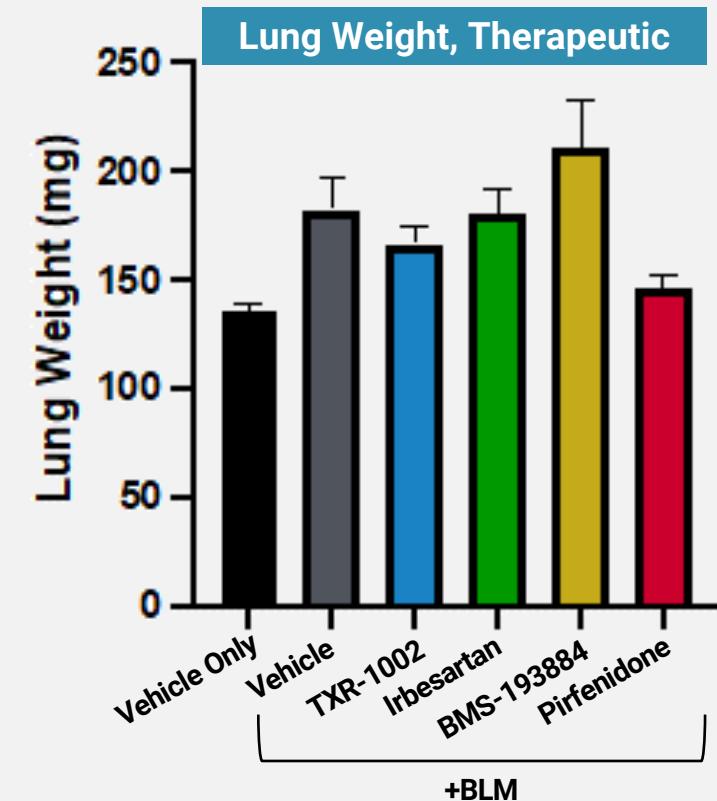
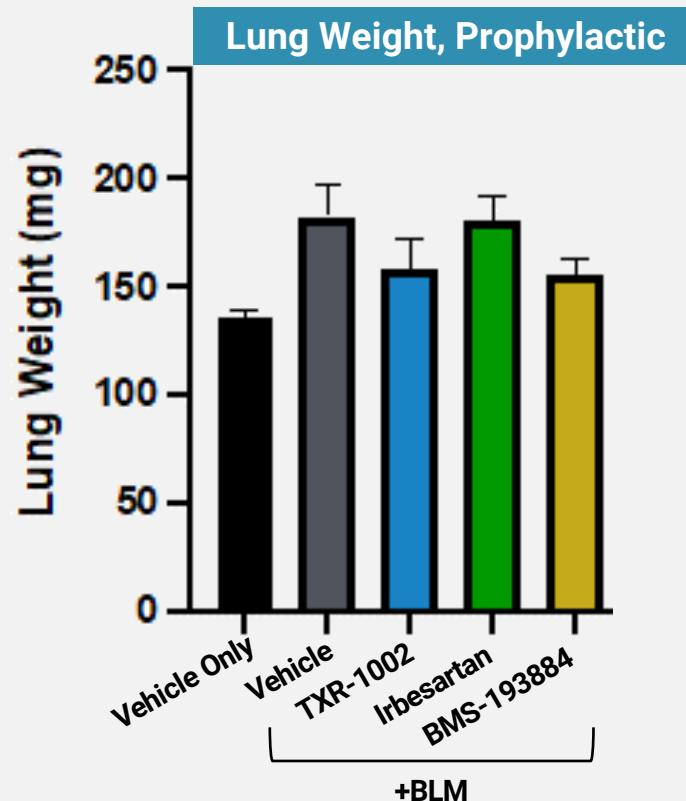
EFFECT ON BODY WEIGHT: MEASURE OF TOLERABILITY

- TXR-1002 did not exhibit significant body weight changes



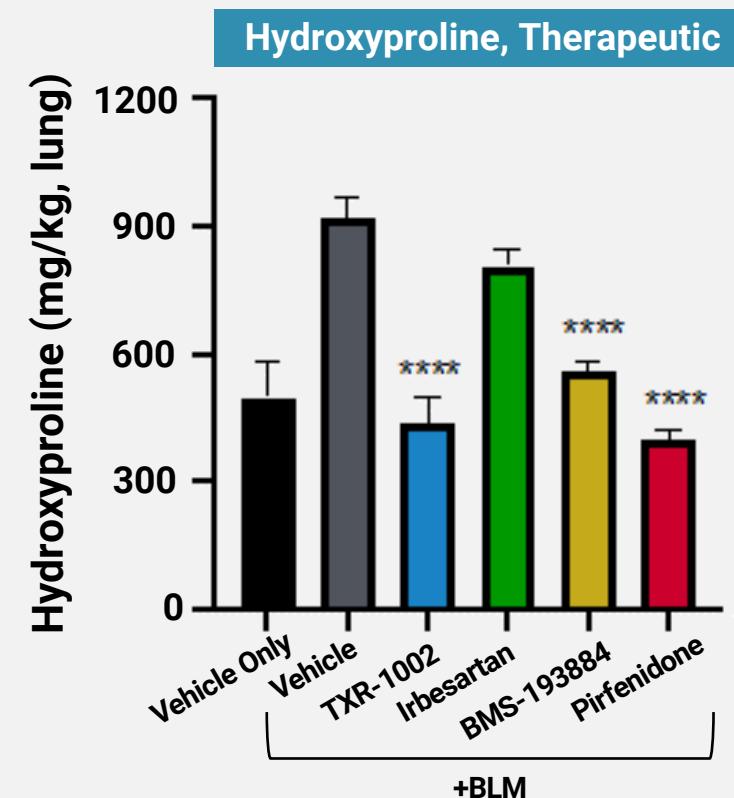
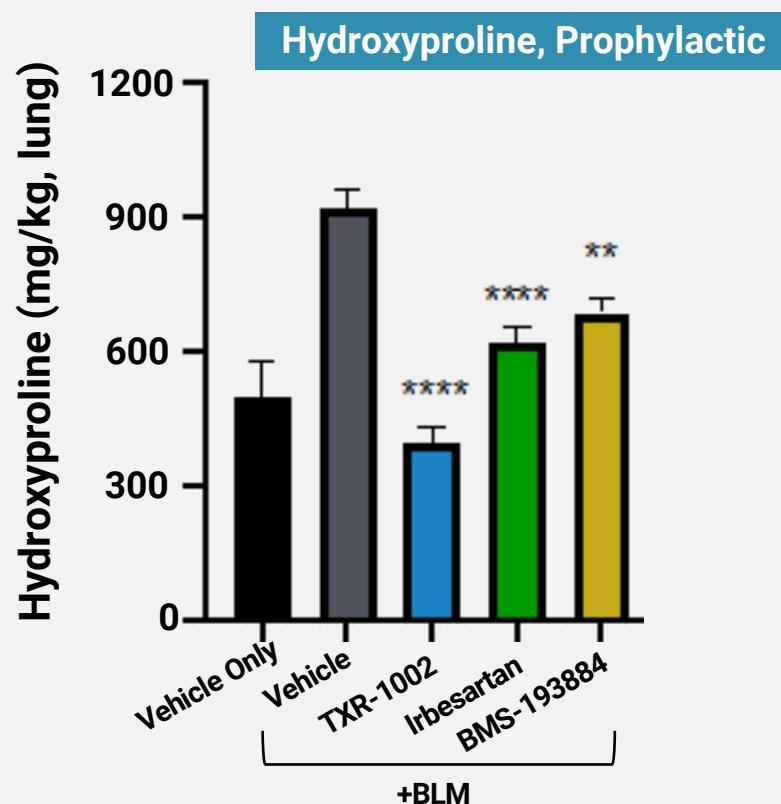
EFFECT ON ABSOLUTE LUNG WEIGHT: MEASURE OF TOLERABILITY

- TXR-1002 showed no change in lung weight comparable to vehicle control & positive control



EFFECT ON LUNG FIBROSIS (HYDROXYPROLINE)

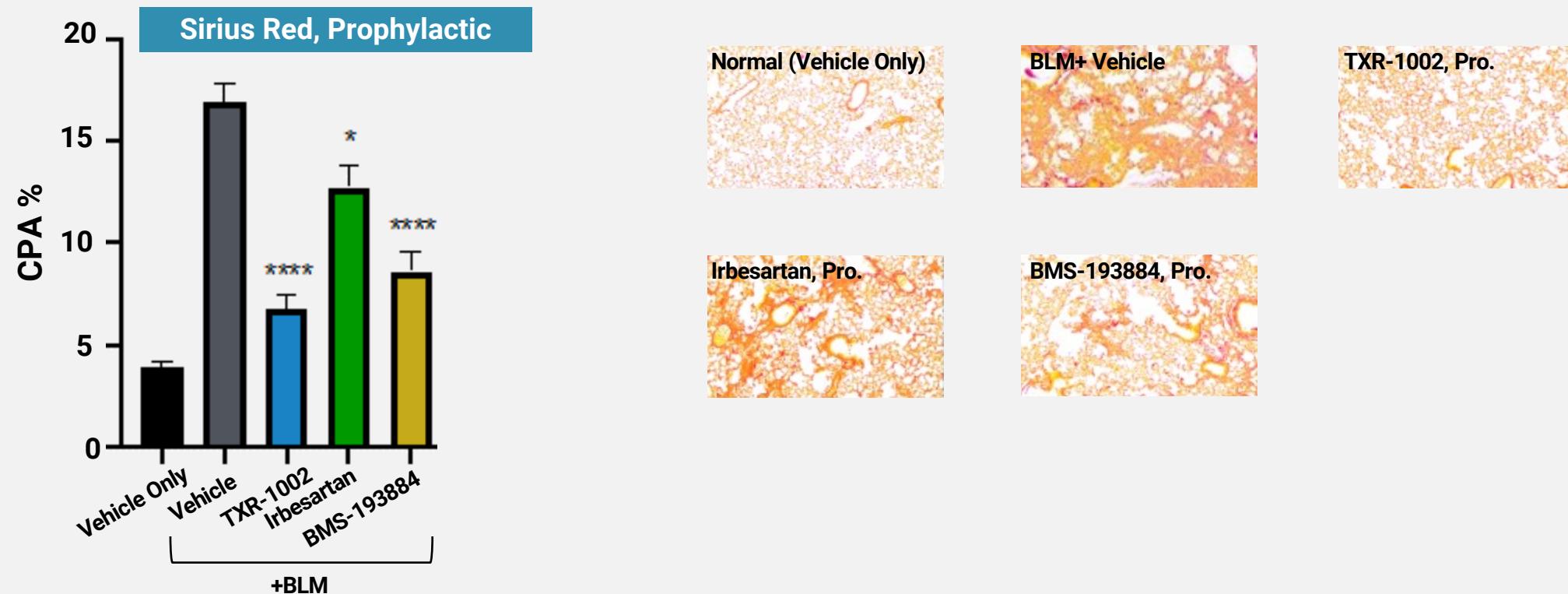
- TXR-1002 significantly reduces hydroxyproline in lung tissue (comparable to pirfenidone)
- TXR-1002 reduces hydroxyproline more than Irbesartan or BMS-193884



Data indicates Mean \pm SEM. *p<0.05, ***p<0.001 vs BLM+vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-14.

EFFECT ON LUNG FIBROSIS - PROPHYLACTIC

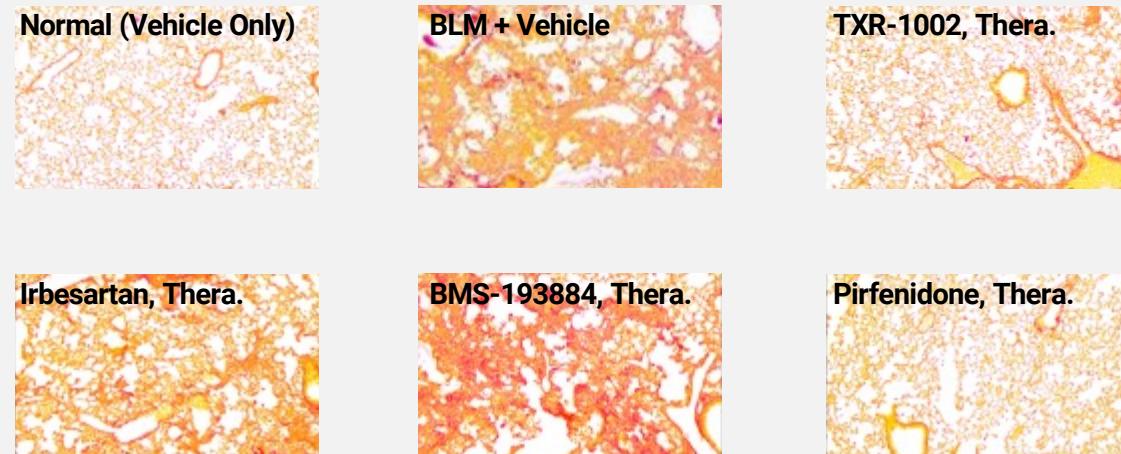
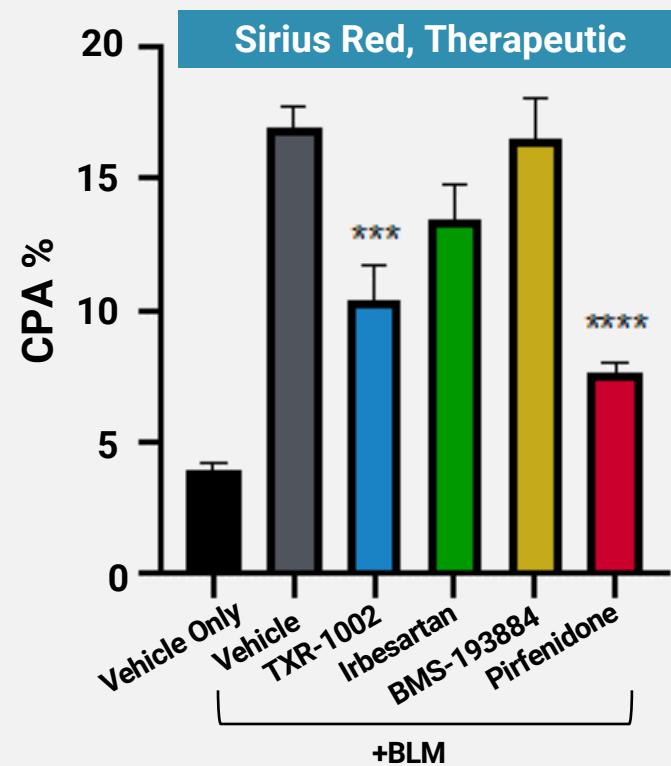
- TXR-1002 significantly reduces Sirius Red (Collagen) staining in lung tissue
- TXR-1002 reduces Sirius Red (Collagen) staining more than Irbesartan and comparable to BMS-193884



Data indicates Mean±SEM. *p<0.05, ***p<0.001 vs BLM+vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-14.

EFFECT ON LUNG FIBROSIS - THERAPEUTIC

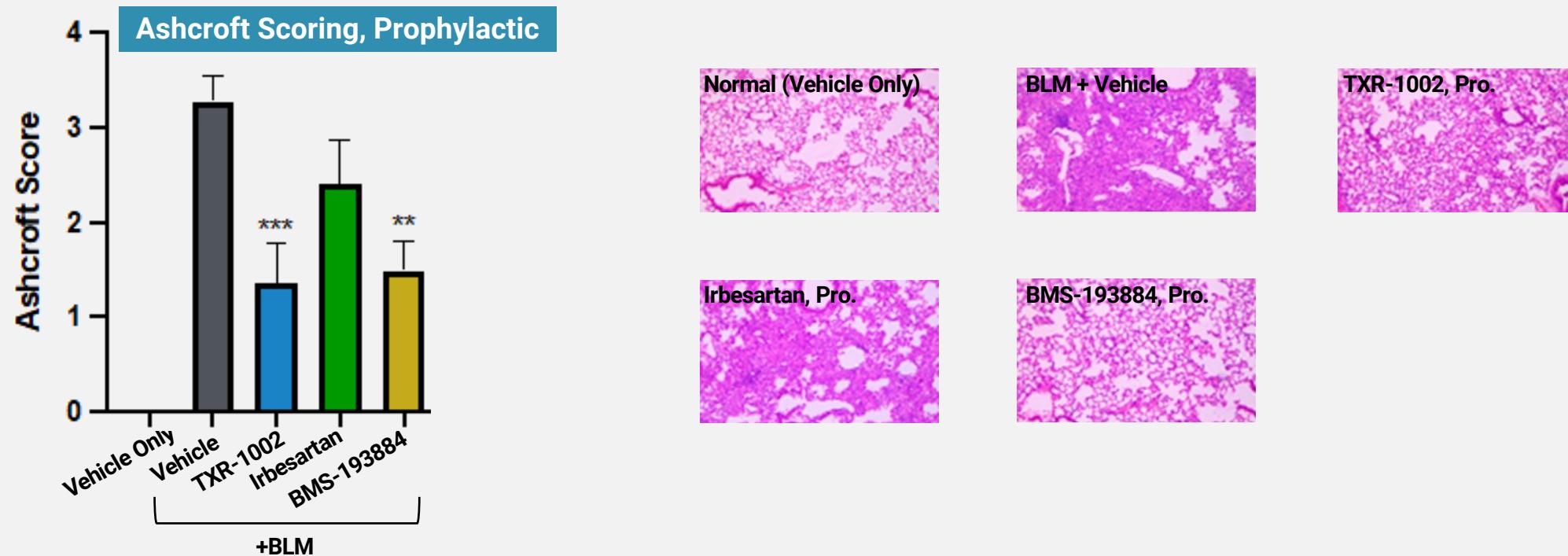
- TXR-1002 significantly reduces Sirius Red (Collagen) staining in lung tissue
- TXR-1002 reduces Sirius Red (Collagen) staining more than Irbesartan or BMS-193884



Data indicates Mean \pm SEM. *p<0.05, ***p<0.001 vs BLM+vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-14.

EFFECT ON LUNG FIBROSIS - PROPHYLACTIC

- TXR-1002 statistically significant reduction in Ashcroft scoring in lung histopathology
- TXR-1002 reduces Ashcroft scoring more than Irbesartan and comparable to BMS-193884



Data indicates Mean±SEM. *p<0.05, ***p<0.001 vs BLM+vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-14.

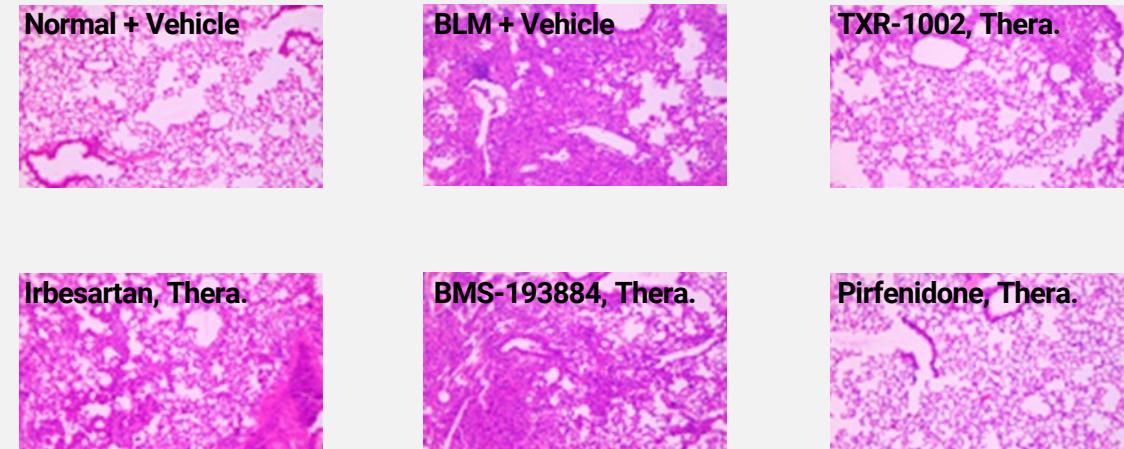
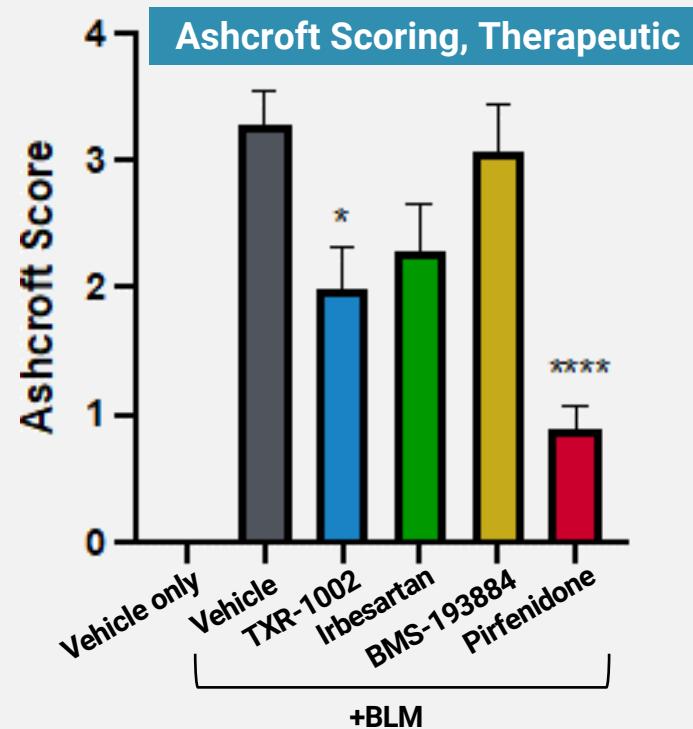
33

Bleomycin = BLM

Confidential

EFFECT ON LUNG FIBROSIS - THERAPEUTIC

- TXR-1002 significantly reduces Ashcroft scoring in lung histopathology
- TXR-1002 reduces Ashcroft scoring more than Irbesartan or BMS-193884



Data indicates Mean±SEM. *p<0.05, ***p<0.001 vs BLM+vehicle one-way ANOVA followed by Dunnett's multiple comparisons test, n = 8-14.

EFFICACY & COMPARISON OF PIRFENIDONE AND TXR-1002 IN THERAPEUTIC BLEOMYCIN MODEL

EFFICACY MEASURE	Pirfenidone	TXR-1002	COMMENTS
Lung Hydroxyproline	Statistically significant decrease vs. BLM+Vehicle	Statistically significant decrease vs. BLM+Vehicle	Equivalent to Pirfenidone
Lung Histopathology Fibrosis: % Collagen Proportionate Area	Statistically significant decrease vs. BLM+ Vehicle	Statistically significant decrease vs. BLM+Vehicle	Equivalent to Pirfenidone
Lung Histopathology Fibrosis: Ashcroft Score	Statistically significant decrease vs. BLM+Vehicle	Statistically significant decrease vs. BLM+Vehicle	Similar to Pirfenidone

COMPARISON OF TXR-1002 TO INDIVIDUAL INHIBITORS IN THERAPEUTIC BLEOMYCIN MODEL

EFFICACY MEASURE	TXR-1002 (AGTR1i/ETAi)	Irbesartan (AGTR1i)	BMS-193884 (ETAi)	COMMENTS
Lung Hydroxyproline	Statistically significant decrease	Not much decrease	Statistically significant decrease	TXR-1002 (dual inhibitor) reduces more than AGTR1i or ETAi
Lung Histopathology Fibrosis: % Collagen Proportionate Area	Statistically significant decrease	Not much decrease	Not much decrease	TXR-1002 statistically better than individual inhibition of AGTR1i or ETAi
Lung Histopathology Fibrosis: Ashcroft Score	Statistically significant decrease	Not much decrease	Not much decrease	TXR-1002 superior to AGTR1i and ETAi

TXR-1002 SECOND STUDY SUMMARY: THERAPEUTIC/TREATMENT DOSING

TXR-1002 DEMONSTRATES POSITIVE EFFICACY WITH THERAPEUTIC DOSING



GOOD TOLERABILITY – clinically investigated mechanism



LUNG FIBROSIS – significant decreased fibrosis, equivalent to Pirfenidone



LUNG FIBROSIS HISTOLOGY – significant decreased fibrosis, superior to AGTR1 or ETA inhibitors individually

FURTHER EFFICACY MEASURES TO BE TESTED

TXR-1002	FURTHER EFFICACY MEASURE
To be tested in a repeat therapeutic bleomycin model	<ul style="list-style-type: none">• Dose response curve• PK/PD correlation & downstream biomarkers (a-SMA, TGF-β, cytokines, etc.)• Measurement of mRNA for gene expression in lung tissue
TGF- β 1 over-expression model	<ul style="list-style-type: none">• Leads to persistent scarring, which may more closely mimic the fibrotic changes that occur in late IPF• Epithelial cell apoptosis• Changes in the soluble mediators

LEAD IDENTIFICATION REVEALS AGTXR-258 & AGTXR-300 FOR OPTIMIZATION

- AGTXR-258, AGTXR-300 & AGTXR-513 with double digit nanomolar potency similar range as reference
- Patentable new chemical entity, provisional application filed

Screening Parameters		Criteria	Sparsentan	AGTXR-258	AGTXR-300	AGTXR-513
Patentability		Secured IP space	Hit (Tool)	promising	promising	promising
In-vitro biology	AGTR1_IC ₅₀ μM	≤ 0.100(0.3) μM	0.022	0.030	0.118	0.037
	EDNRA_IC ₅₀ μM	≤ 0.100 (0.3) μM	0.028	0.060	0.190	0.090
In-vitro ADME	Aq. Solubility (PBS, pH 7.4) μM	>50 μM	96	96.5	110	
	Caco2_A-B (x10 ⁻⁶ cm/s), ER	A-B_P _{app} > 5, ER < 2	10, 1.85	4.4/4.5	2.5/10	7.4/4
	Hepatocyte Stability, %QH (m/r/h)	< 60%	87/30/40	95/55/60	88/22/26	94/51/38
	Plasma and blood stability	> 70% remaining at 2 h	TBD	TBD	TBD	TBD
	CYP inhibition_3A4, 2D6, 2C9, 2C19	< 50% inh @10 μM	TBD	TBD	TBD	TBD
	%PPB (h,r,m)	< 99% bound	TBD	98.95, 99.5, 99.04	98.8, 99.15, 99.51	ongoing
In vivo PK	Mouse_IV (1 mpk)	t _{1/2} (h), AUC _{0-t} (ng·h/mL)	t _{1/2} > 4 h	3.06, 683	10.53, 190	6.81, 1820
		CL (mL/min/kg), V _d (L/kg)	Cl-< 20% of HBF	27, 5.10	0.78	9.19, 5.44
	Mouse_PO (5 mpk)	C _{max} (ng/mL), AUC _{0-t} (ng·h/mL)	good exposure	(10mpk) 2877, 5019	135, 180	159, 2458
		%F	> 20	61.3	20.65	27
	Rat_IV (1 mpk)	C0 (ng/mL), t _{1/2} (h), AUC _{0-t} (ng·h/mL)	T _{1/2} > 4h	4.1, 12000,	1205, 2.13, 496	2.14, 555
		CL (mL/min/kg), V _d (L/kg)	Cl-< 20% of HBF	1.9, 0.5	33.3, 6	28.86, 5.27
	Rat_PO (10 mpk)	C _{max} (ng/mL), AUC _{0-t} (ng·h/mL)	Good exposure	1854, 25245	ND	55.49, 336
		%F	> 40	40	ND	11.99
						35.3

AGTXR-258 & AGTXR-300 LEAD IDENTIFICATION SUMMARY



IN VITRO BIOLOGY – Identified series with double digit nM potency & selectivity against AGTXR2



IN VITRO ADME – Moderate permeability & low efflux. Stable & low predicted clearance in liver microsomes. No CYPs liability. High clearance in mouse hepatocytes; low to moderate in rat & human



IN VIVO PK – Novel compounds with good oral bioavailability, moderate half-life in mouse & rat PK



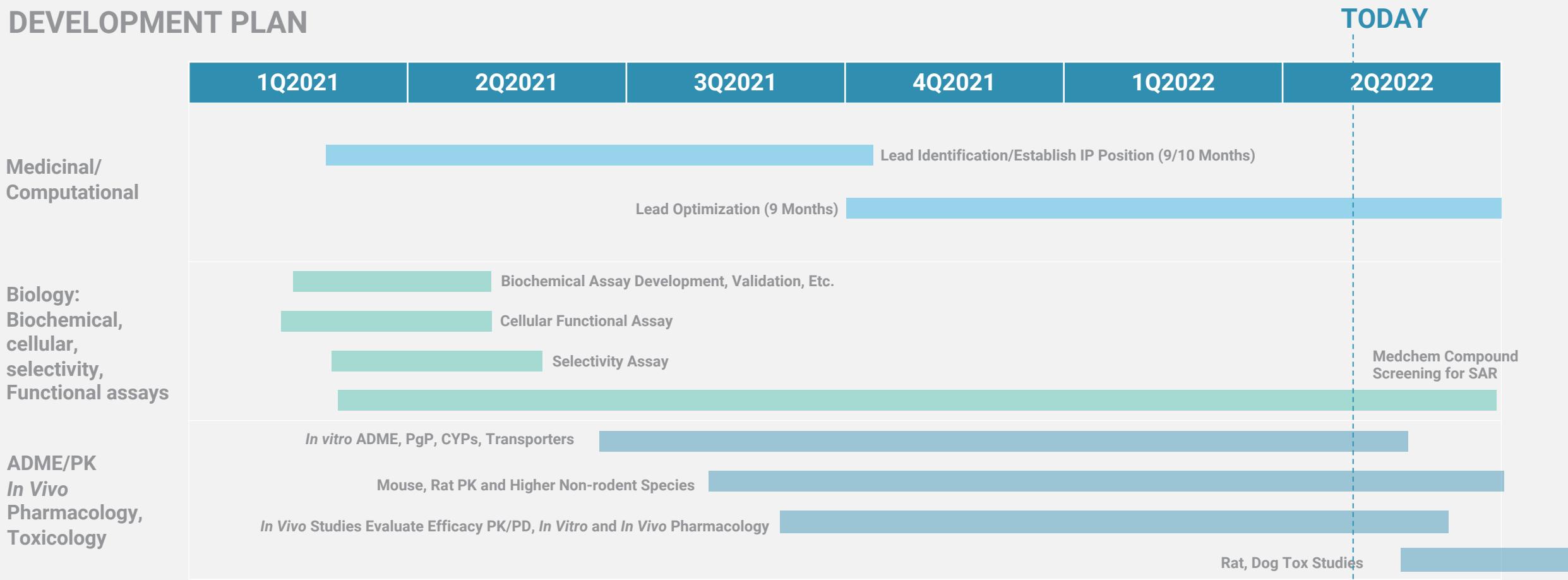
IN VIVO EFFICACY – Rat Bleomycin IPF model validation with nintedanib: lung histology ongoing. Dose-dependent activity demonstrated with Sparsentan & AGTXR-258 in acute target engagement model. AGTXR-300 significantly reduced lung fibrosis in mouse bleomycin-induced model



IP – Two provisional patent applications filed – May 2022

LEAD DISCOVERY THROUGH IND CANDIDATE

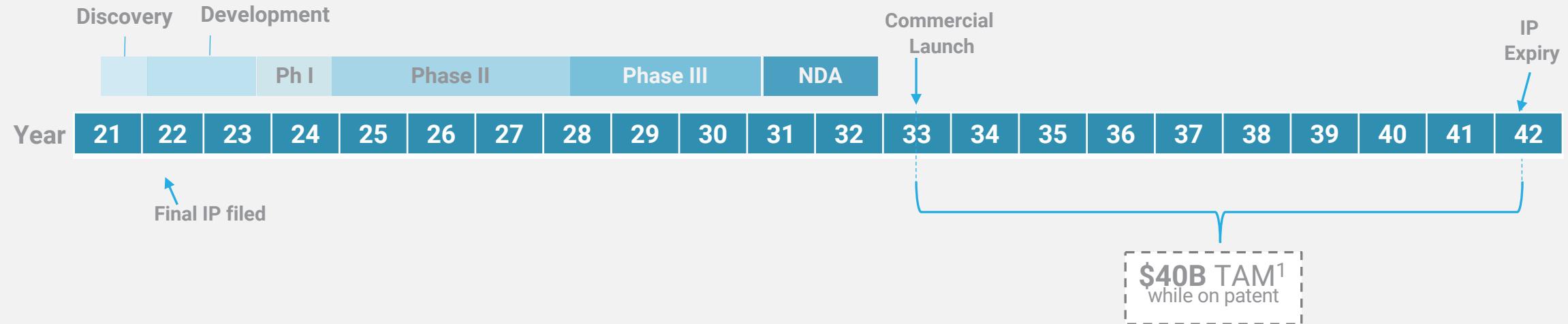
DEVELOPMENT PLAN



UPCOMING DEVELOPMENT PLANS

- Name development candidate upon close of financing, expected Q4-2022
 - In meantime will continue to optimize as we await resources
- Post close of financing, Kick off IND-enabling activities
 - Initiate CMC scale up, etc., within 1 quarter
 - Initiate toxicology studies within 2-3 quarters
 - Initiate regulatory activity within 2-3 quarters
- IND filing expected roughly EOY 2023 to beginning of 2024
- Initiation of Phase I one quarter after IND filing

DEVELOPMENT COSTS AND MARKET OPPORTUNITY



	Discovery	Development	Phase I	Phase II	Phase III	NDA
Approx. Cost (\$60M total)	(~\$100K) ²	(~\$6M) ³	(~\$6M) ⁴	(~\$15M) ^{4,5}	(~\$30M) ⁴	(~\$2M) ⁴
Exemplar Deals	N/A ⁷	AstraZeneca – Redx (2020) Single asset: • \$17M upfront • \$360M milestones • single-digit royalties	Galapagos – OncoArendi (2020) Single asset: • \$30M upfront • \$400M milestones • double-digit royalties	Roche – Promedior (2020) Company acquisition ⁶ : • \$390M upfront • \$1,000M milestones	N/A ⁸	Roche – InterMune (2014) Company acquisition ⁶ : • \$8,300M

1. Source: Global data 7 major markets

2. Incurred cost

3. Contracted costs

4. Estimated costs

5. Benchmarked to Nintedanib trials

6. Lead program for acquisition was IPF asset

7. This program is in development

8. No relevant exemplar deals

SUMMARY

- IPF is a \$3B/yr market with 2 approved drugs
 - Nintedanib and Pirfenidone are current standards of care with limited efficacy & tolerability
- TXR-1002 is a dual inhibitor
 - Reinforcing roles suggest potential for synergistic efficacy, which has been clinically supported in FSGS, a disease with a similar fibrotic phenotype
 - Significant results in prophylactic bleomycin-induced IPF mouse model, subsequently validated
 - Significant results in therapeutic bleomycin-induced IPF mouse model demonstrates dual-target synergy versus individual inhibitors
- Novel chemical series identified demonstrating potency and selectivity
 - Two provisional patent applications filed in May 2022



www.ariapharmaceuticals.com

SoftBank
Ventures

ANDREESSEN
HOROWITZ

OS Fund

Stanford
StartX Med

MIT
STARTUP
EXCHANGE