Theravance Biopharma®

Medicines That Make a Difference®

Appendix

August 3, 2021

Investment highlights

Theravance Biopharma®
Medicines That Make a Difference®

Innovative, commercial-stage biopharma with strong development track record

Decades-long track record of driving innovative products to market for diseases of high unmet need

Wholly-owned and partnered pipeline of differentiated assets

Diversified pipeline of organ-selective medicines for rare disease, respiratory, GI and ocular indications

Organ-selective approach serves as an engine for new opportunities

Three major clinical readouts expected by early-2022

Multiple near-term catalysts provide opportunity for value

Applying organ-selective expertise to biologically compelling pathways aiming to better serve patients

Strong base of cash flow, anchored by Yupelri and our economic interest in TRELEGY

Underlying stream of derisked, long-tailed cash flow

Topline growth poised for potential acceleration

Multiple commercial and near-commercial products create growing revenue profile

Key programs for large patient populations supported by proven development and commercial expertise

	Program	Indication	US Patients[1]	Research	Phase 1	Phase 2	Phase 3	Filed	Marketed	Collaborator
	Ampreloxetine (TD-9855) NRI	Symptomatic nOH	~350k				Phase 3			Wholly-owned
Organ-Selective	**Izencitinib (TD-1473)** GI JAKi	UC	~900k				Phase 2b/3			Janssen Biotech, Inc.
		CD	~800k			Phase 2				
	TD-5202 Irreversible JAK3i	Celiac Disease UC CD	~5mm		Phase 1					
	YUPELRI® (revefenacin) LAMA	COPD	>8mm						Marketed	VIATRIS
	Nezulcitinib (TD-0903) Inhaled JAKi	Acute and chronic lung inflammation	>32mm			Phase 2				Wholly-owned
	TD-8236 Inhaled JAKi	Asthma	~25mm			Phase 2				
	Inhaled ALK5i	Idiopathic pulmonary fibrosis	~140k		Phase 1					

	Program	Indication		Research	Phase 1	Phase 2	Phase 3	Filed	Marketed	Rights
Economic Interests	**TRELEGY[2]** FF/UMEC/VI	COPD	>8mm						Marketed	GSK & Innoviva, Inc.
		Asthma	~25mm						Marketed	
	Skin-selective JAKi	Dermatological diseases	>8mm	Research						Pfizer

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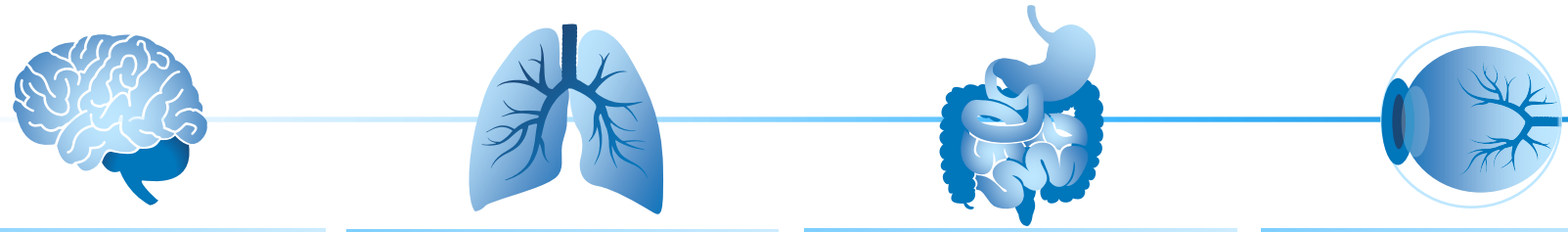
1. TBPH estimate derived from integrating multiple data sources 2. TBPH holds 85% economic interest in upward-tiering royalty stream of 6.5% – 10% payable by GSK (net of TRC expenses paid and the amount of cash, if any, expected to be used by TRC pursuant to the TRC Agreement over the next four fiscal quarters). 75% of TRC income received is pledged to service outstanding notes, 25% of royalties received retained by TBPH. All statements concerning TRELEGY ELLIPTA based on publicly available information. ALK5i, transforming growth factor β receptor I kinase inhibitor; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; FF/UMEC/VI, fluticasone furoate/umeclidinium/ vilanterol; JAKi, Janus kinase inhibitor; LAMA, long-acting muscarinic receptor antagonist; nOH, neurogenic orthostatic hypotension; NRI, norepinephrine reuptake inhibitor; UC, ulcerative colitis.

Research and development portfolio of designed molecules: brain, lung, GI and eye



Symptomatic nOH
(Neurogenic orthostatic hypotension)

COPD
(chronic obstructive pulmonary disorder) — APPROVED

Asthma

COVID-19

Lung Transplant Rejection

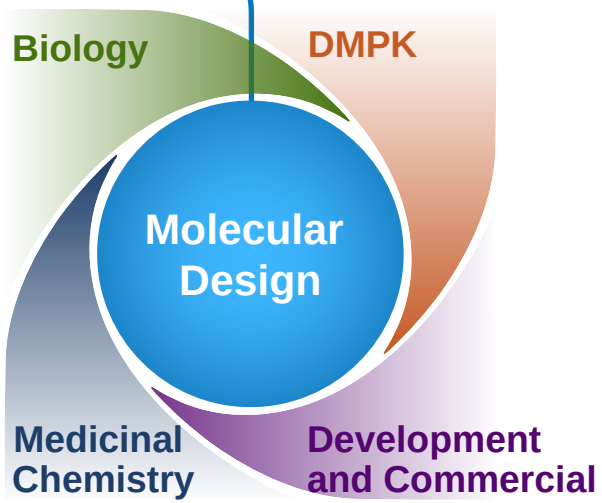
IPF (idiopathic pulmonary fibrosis)

CD
(Crohn's disease)

UC
(ulcerative colitis)

Celiac Disease

DME
(diabetic macular edema)



DMPK, drug metabolism and pharmacokinetics; GI, gastrointestinal.

Early stage pipeline, value creation opportunities

Program	Indication	Patient Population	Status
TD-8236	Uncontrolled Asthma	~25mm *Moderate and Severe* US Asthmatics*[1]	Phase 2; evaluating back-up compounds
TD-5202	Celiac Disease Ulcerative Colitis Crohn's Disease	~5mm *US Patients*[2,3]	Phase 1 Complete
Inhaled ALK5i	IPF	~140k *US Prevalence; currently orphan disease*[4,5]	Phase 1
Ocular JAKi	Diabetic Macular Edema	~2.7mm *US Prevalence*[6]	Preclinical

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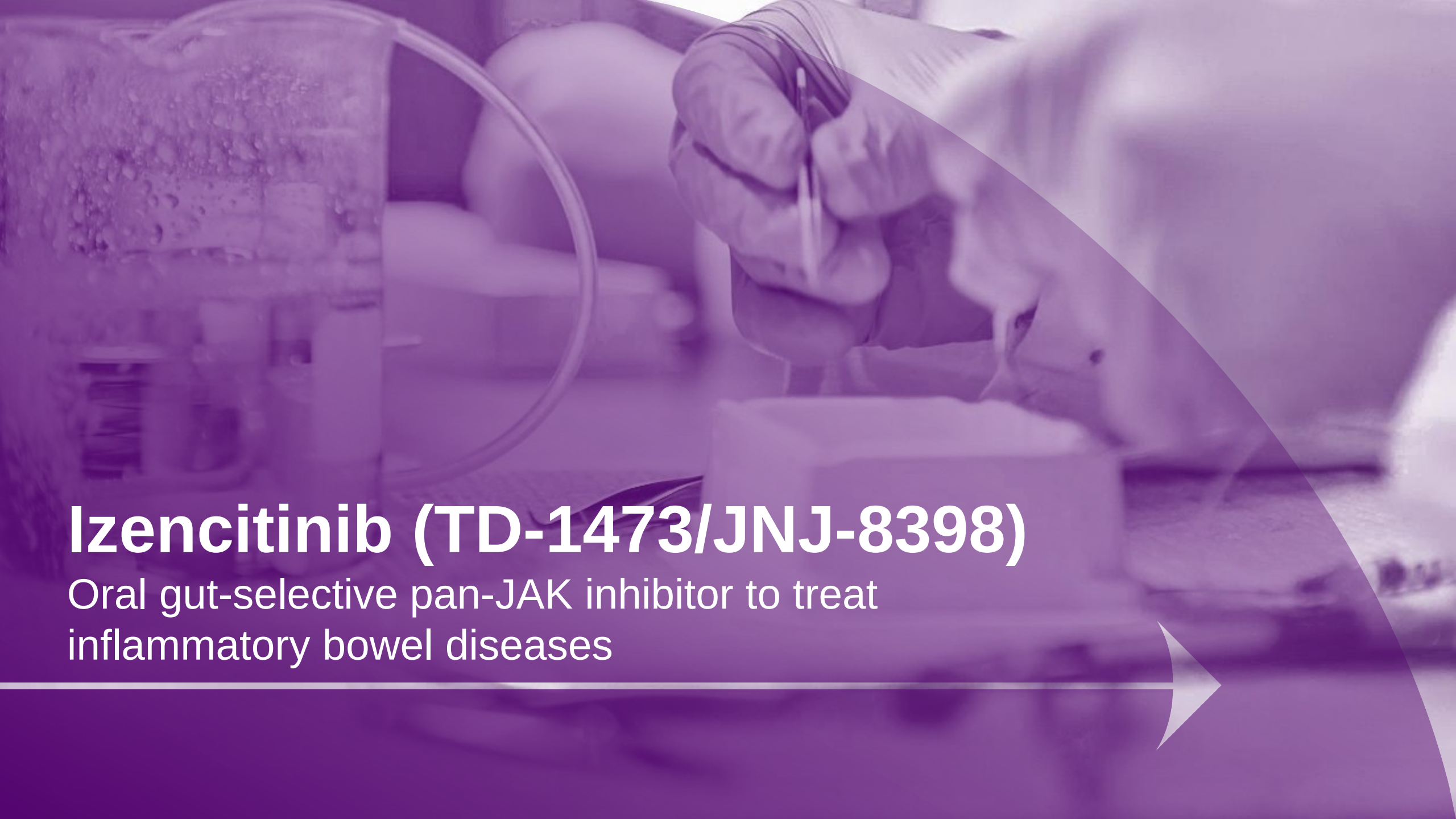
*Asthma that requires high-dosage ICS + LABAs to prevent the disease from being uncontrolled, or asthma that remains uncontrolled despite treatment.
1. https://www.aafa.org/asthma-facts/. 2. 1% prevalence in US, BeyondCeliac.org. 3. 2018 US population 327M Census.gov. 4. Raghu G, et al. Lancet Resp. 2014: 2(7):566-572; 5. Raghu G, et al. Eur Respir J. 2016: 48(1):179-186. 6. © 2016 DR/Decision Resources, LLC.
ALK5i, transforming growth factor β receptor I kinase inhibitor; IPF, idiopathic pulmonary fibrosis; JAKi, Janus kinase inhibitor..



Izencitinib (TD-1473/JNJ-8398)

Oral gut-selective pan-JAK inhibitor to treat inflammatory bowel diseases

Izencitinib: a novel approach to JAK inhibition for IBD

IBD MARKET DYNAMICS

- 6.8mm global cases in 2017[1]
- 1.6mm current US patients[2]
- ~900k US Ulcerative Colitis patients[3]
  ~800k current US Crohn's patients[4]
- $16bn global IBD treatment market in 2018[5]
- $31bn US disease burden[2]
- Biologics have become mainstay of treatment in moderate-to-severe patients

Favorable Phase 1b data led to late-stage IBD studies

Phase 1b data[6]

- Demonstrated gut selectivity
  - High colonic concentration with low systemic drug exposures, consistent with pre-clinical data
  - For the goal of maximized therapeutic index
- Demonstrated numerically higher rates of clinical outcomes with reductions in biomarkers after only 4 weeks of treatment
  - Numerical improvements in rectal bleeding and mucosal healing

IBD represents an area of high unmet need

Izencitinib

Preclinical and clinical data package represents a potential breakthrough approach for the treatment of IBD

- Oral, gut-selective agent
- Potent inhibition of Tyk2
- Anti-inflammatory activity in disease model
- Low systemic exposure with high colonic concentrations
- Favorable Phase 1b data

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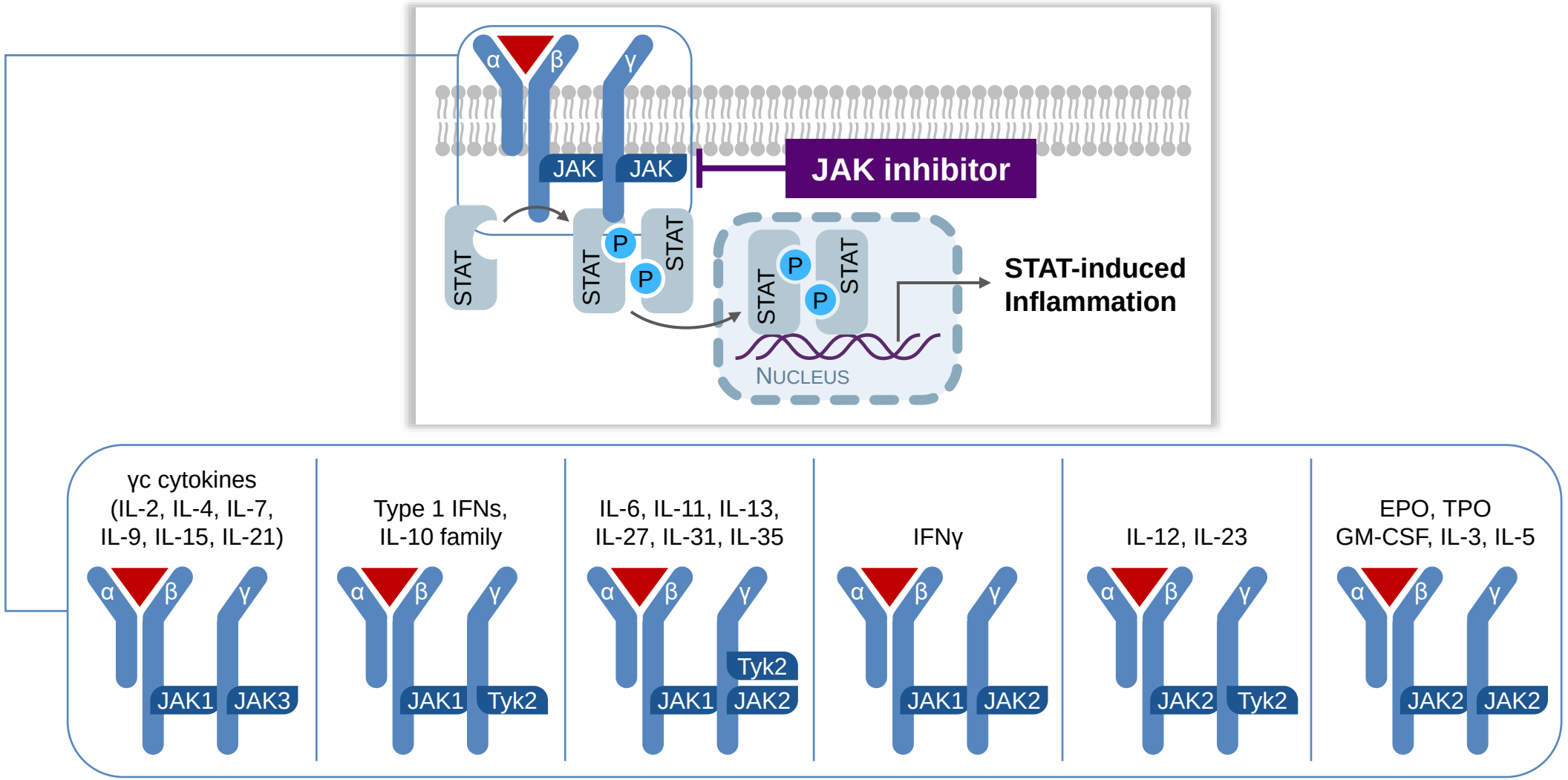
1. GBD 2017 Inflammatory Bowel Disease Collaborators. Lancet 2020;5:17-30. 2. https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated%20IBD%20Factbook.pdf.
3. https://med.stanford.edu/news/all-news/2020/02/stanford-scientists-link-ulcerative-colitis-to-missing-gut-micro.html 4. https://www.healthline.com/health/crohns-disease/facts-statistics-infographic
5. https://www.transparencymarketresearch.com/inflammatory-bowel-disease.html 6. Sandborn et al. J Crohns Colitis;2020:14:1202-13.
IBD, inflammatory bowel disease; JAK, Janus kinase; Tyk, tyrosine kinase.

JAK-STAT pathway: orchestrating signaling of multiple pro-inflammatory cytokines

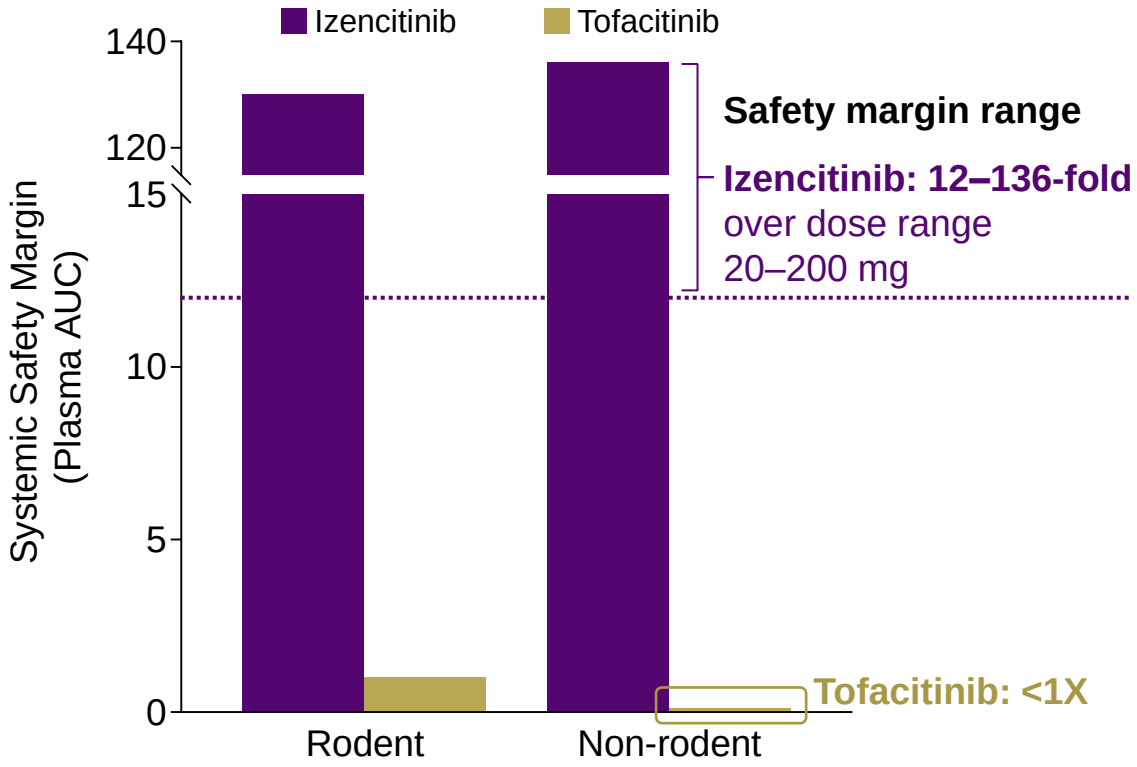


Clark JD, et al. J Med Chem 2014; 57:5023-5038.

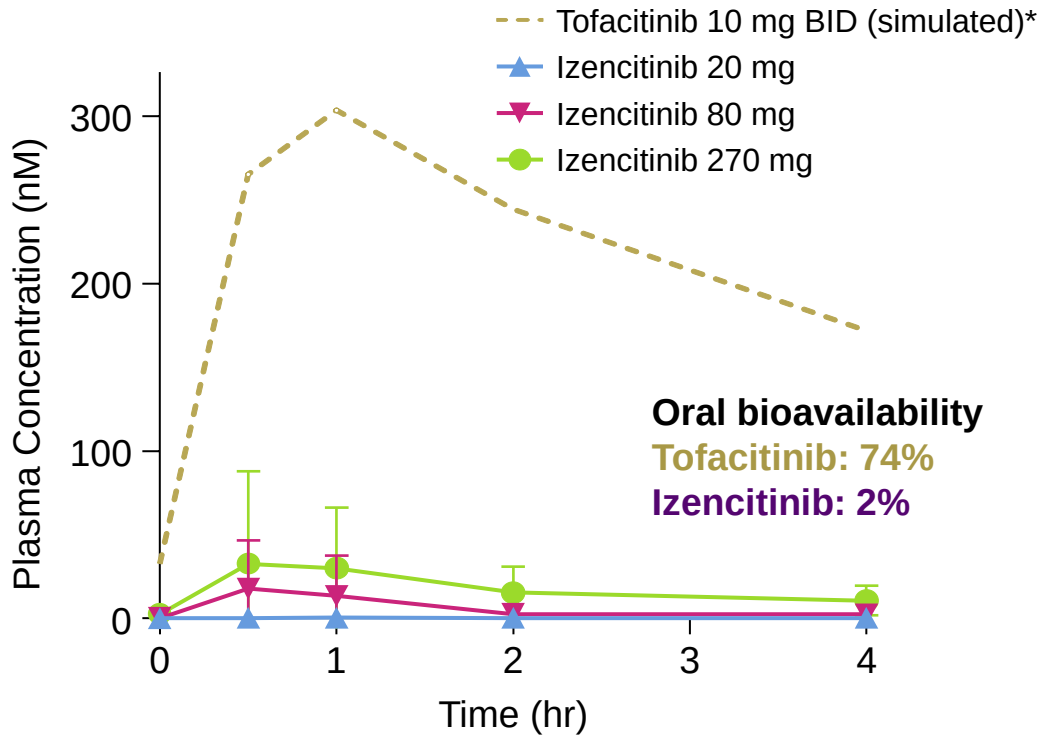
EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; Tyk, tyrosine kinase.

Izencitinib's oral, gut-selective, pan-JAK approach is designed to reduce systemic side effects

High margins of systemic safety in nonclinical studies



Low systemic plasma concentrations in UC patients



Gut selectivity confers low systemic exposure and offers the potential for reduced adverse effects

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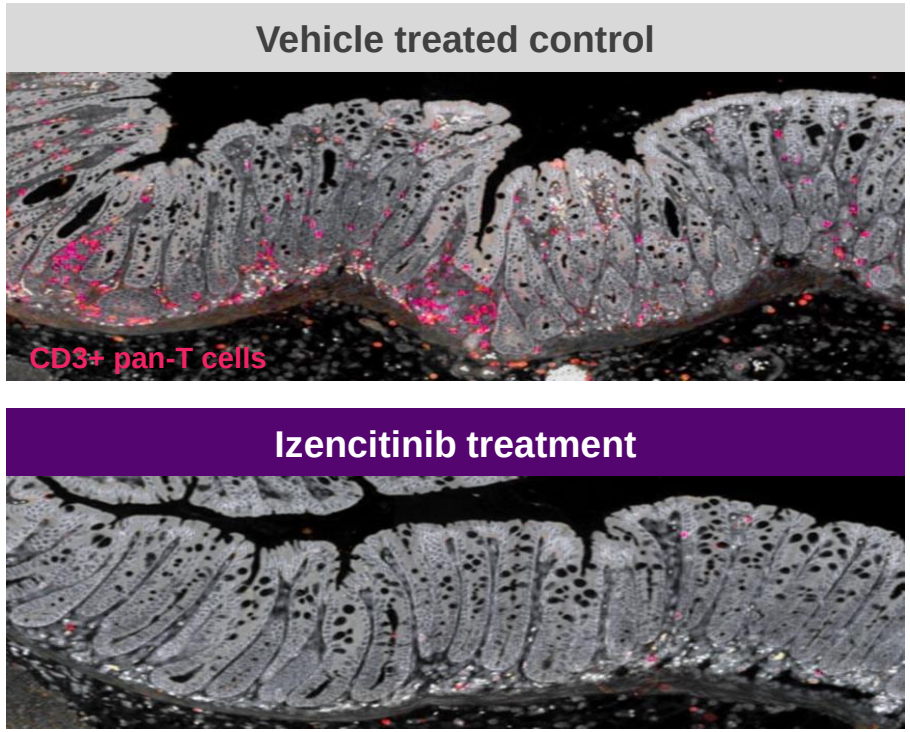
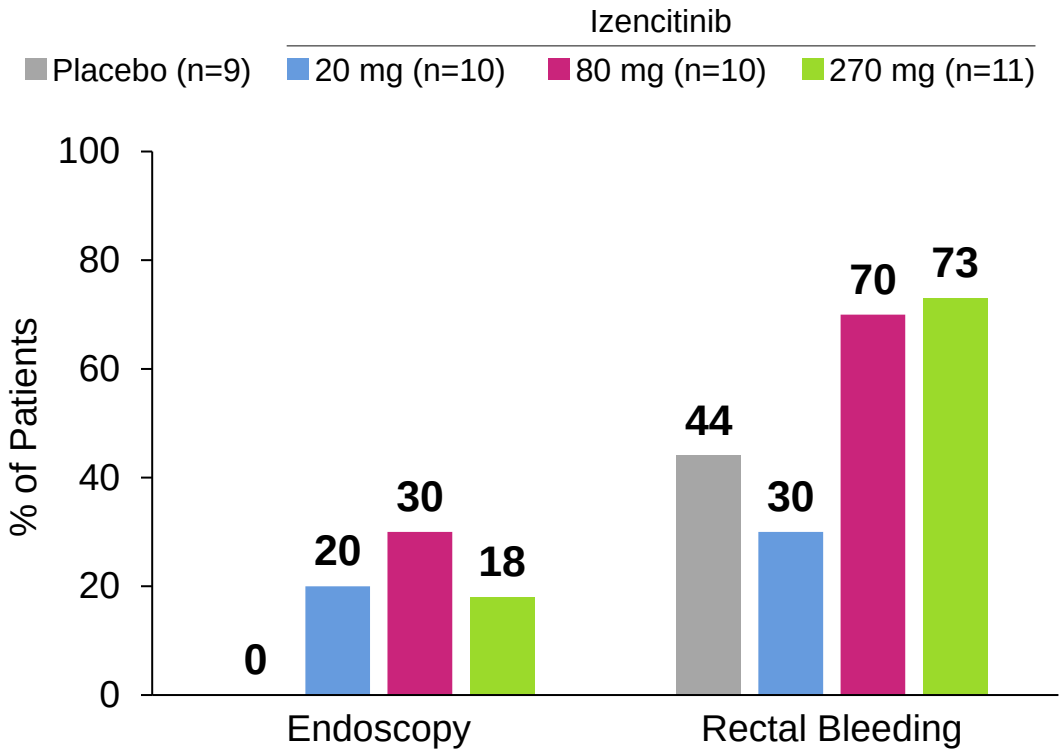
*Simulated tofacitinib concentrations extracted from Dowty ME, et al. J Pharmacol Exp Ther 2014;348:165-73.
Margins of safety reflect the ratio of nonclinical to clinical plasma exposures at the highest studied clinical dose (izencitinib) or approved dose (tofacitinib).
Rodent species was rat for izencitinib and tofacitinib; non-rodent species was dog for izencitinib and monkey for tofacitinib.
AUC, area under curve; BID, twice daily; hr, hour; JAK, Janus kinase; UC, ulcerative colitis.

Izencitinib's oral, gut-selective, pan-JAK approach is designed to maximize efficacy in IBD

Blocks inflammation and penetrates deep within mouse colon



Demonstrates improvement in UC patients in Phase 1b



The gut-selective approach is intended to maximize concentration where it matters, at the site of action in the GI tract

GI, gastrointestinal; IBD, inflammatory bowel disease; JAK, Janus kinase; UC, ulcerative colitis.

Pre-clinical and Phase 1b results led to late stage IBD studies with izencitinib

Favorable data from this innovative exploratory Phase 1b study[1]

- Confirmed gut selectivity
  - High colonic concentration with low systemic drug exposures, consistent with pre-clinical data
  - For the goal of maximized therapeutic index
- Demonstrated numerically higher rates of clinical outcomes with reductions in biomarkers after only 4 weeks of treatment
  - Numerical improvements in rectal bleeding and mucosal healing
- Led to decision to proceed with development of izencitinib

Global collaboration with **Janssen Biotech, Inc.** leverages joint development expertise with the potential for up to a total of $1B in milestone payments to **TBPH** plus profit-share in US (33% TBPH, 67% Janssen) and double-digit royalties to TBPH ex-US[2]

Ulcerative colitis (0157)

RHEA PROGRAM

Phase 2b/3: 8 weeks (N=240)
Dose-finding induction

Phase 3: 8 weeks (N=640)
Dose-confirming induction

Responders → **Maintenance phase[3]: 44 weeks**

Long-Term Safety Study[4]: 3 years (0164)

Ongoing; Phase 2b data expected Q3 2021

Crohn's disease (0173)

DIONE STUDY

Phase 2: 12 weeks (N=160)
Dose-finding induction

Active treatment extension: 48 weeks

Ongoing; data expected late Q4 2021 / early Q1 2022

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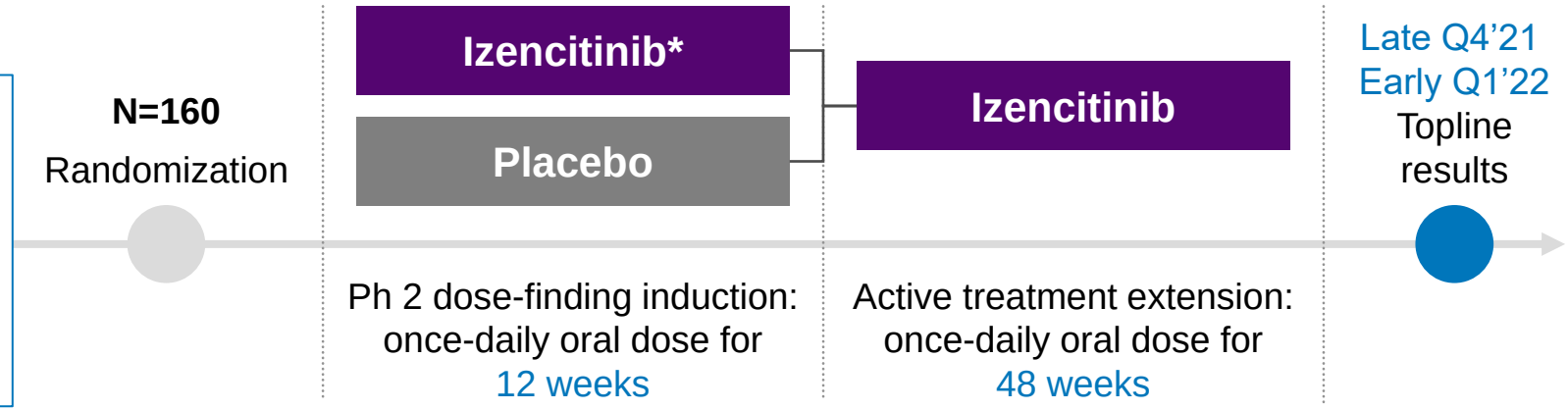
1. Sandborn et al. J Crohns Colitis;2020:14:1202-13.
2. Deal value up to $1B in payments to TBPH, including $100M upfront previously received; subject to Janssen opt-in.
3. Maintenance study will have induction responder patients re-randomized to active doses compared to placebo at 44 weeks.
4. Patients may enter the Long-Term safety study by completing or terminating Maintenance study due to loss of response.

Izencitinib: Phase 2 study in Crohn's disease

DIONE STUDY Study 0173

Key inclusion criteria: Age ≥18 y with moderately-to-severely active CD (CDAI 220–450) with corticosteroid dependence or failure of conventional or biologic therapy

Geographies: South Africa, Asia, Australia, Europe, Middle East, New Zealand, UK, USA



Endpoints

- **Primary:** Improvement in CDAI score at week 12 in patients with moderately to severely active CD
- **Exploratory:**
  - Clinical response measured by CDAI at 12 weeks
  - CDAI clinical remission at 12 weeks
  - SES-CD change from baseline to Week 12
  - Endoscopic response [Time Frame: 12 weeks]
  - SFAP clinical remission [Time Frame: 12 weeks]

Program Status

- Ongoing

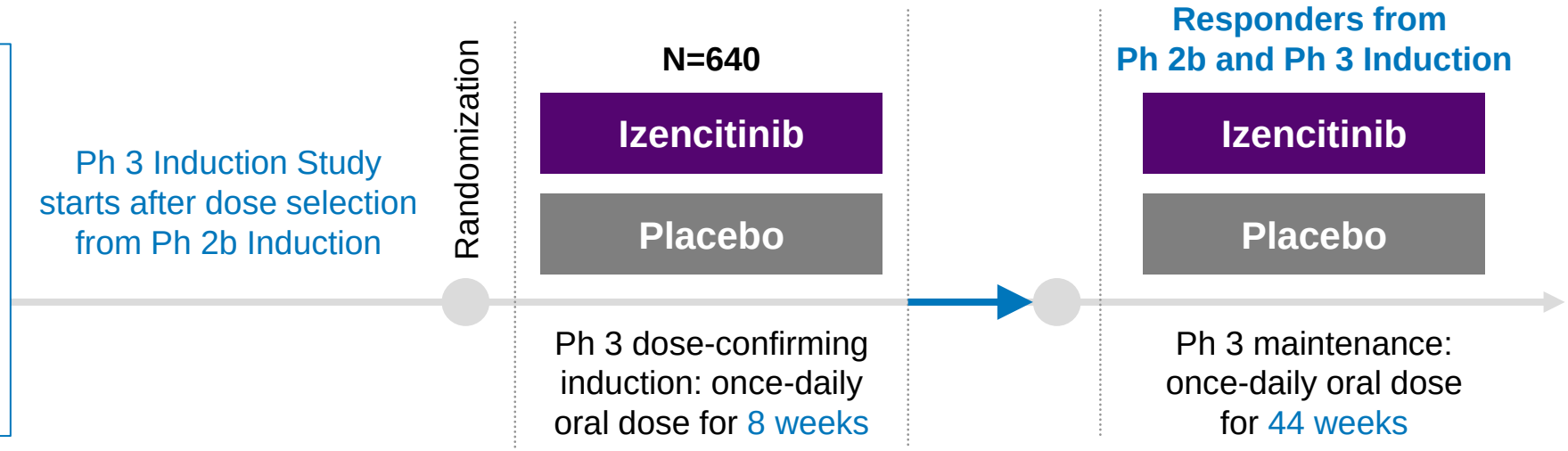
*2 izencitinib doses.
NCT03635112
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; SFAP, Stool Frequency and Abdominal Pain.

Izencitinib: Phase 3 studies in ulcerative colitis

RHEA PROGRAM Study 0157

Key inclusion criteria: Age ≥18 y with moderately-to-severely active UC with corticosteroid dependence or failure of conventional or biologic therapy

Geographies: South Africa, Asia, Australia, Europe, Middle East, North America, Japan



Endpoints

- **Primary:**
  - Induction & Maintenance: clinical remission by aMS components at Week 8 and Week 44
- **Secondary:**
  - Induction & Maintenance: endoscopic healing, symptomatic remission, clinical response by aMS, mucosal healing, maintenance of clinical response, corticosteroid-free remission, maintenance of clinical remission

Program Status

- Phase 3 Induction study to begin post Phase 2b completion
- Phase 3 Maintenance study ongoing

NCT03758443

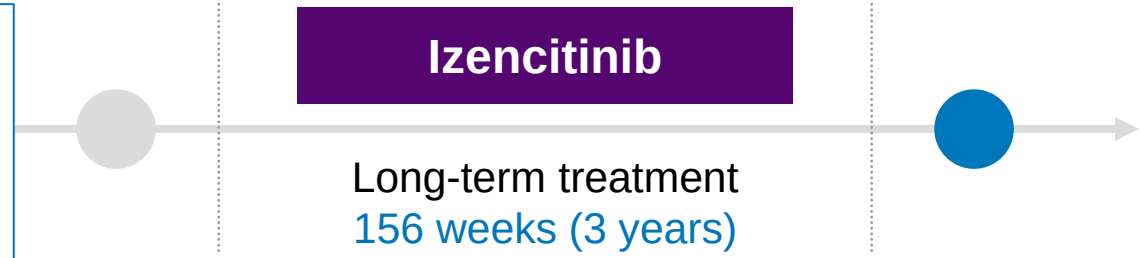
aMS, adapted Mayo Score; UC, ulcerative colitis.

Izencitinib: Phase 3 study in ulcerative colitis

RHEA PROGRAM Study 0164

Key inclusion criteria: Eligible patients from Ph 3 Maintenance Study of Protocol 0157

Geographies: South Africa, Asia, Australia, Europe, Middle East, North America, Japan



Assessments

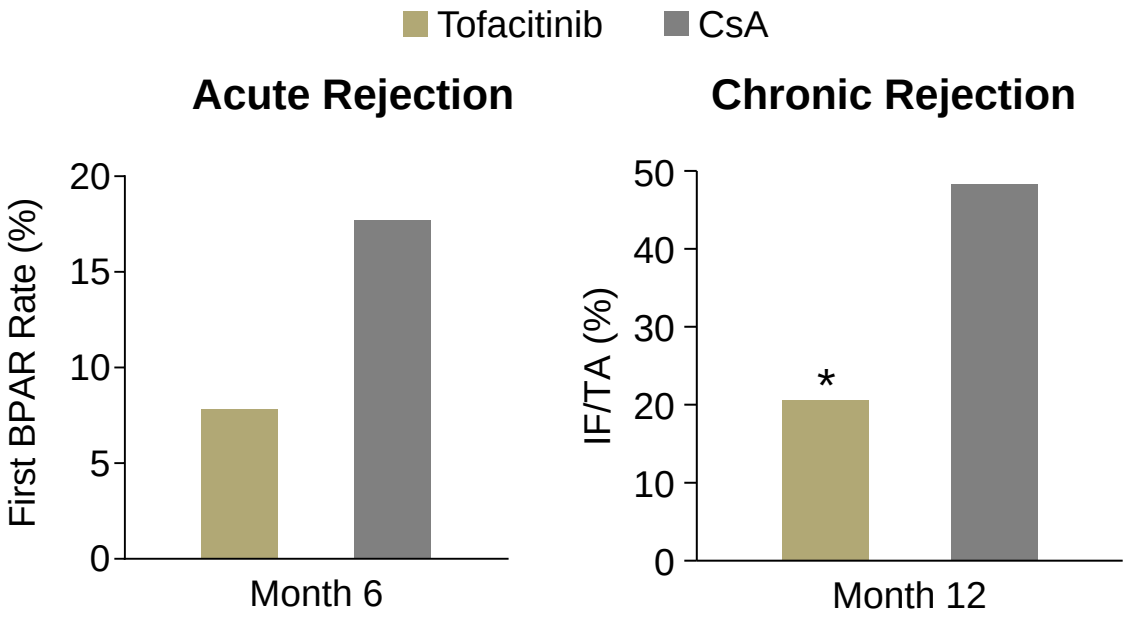
- Safety and tolerability of izencitinib administered for up to 3 years in patients with moderate-to-severe UC after participation in the Protocol 0157 Maintenance Study

NCT03758443
UC, ulcerative colitis.

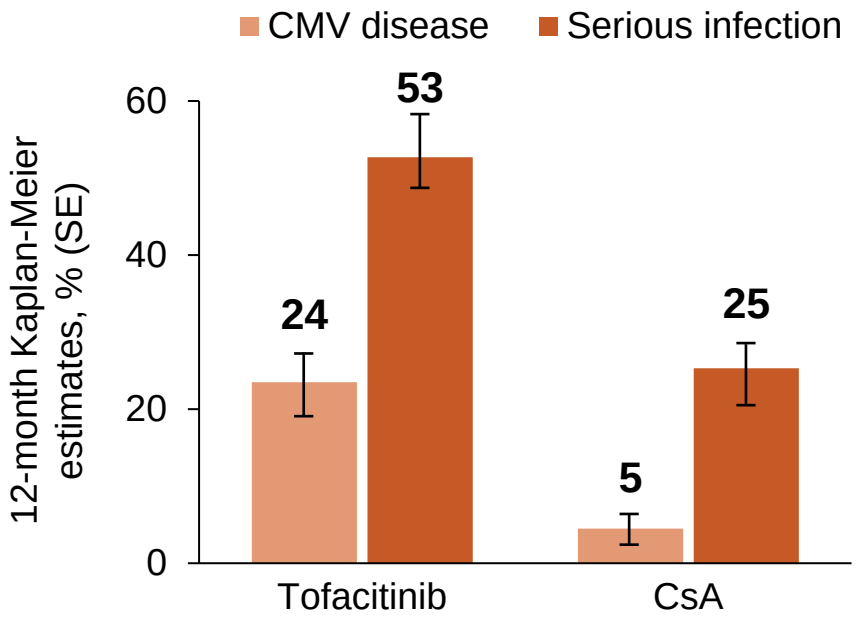
Pan-JAK inhibitors can prevent transplant rejections

Noninferiority trial of tofacitinib vs cyclosporine (CsA) in kidney transplant recipients[1]

Tofacitinib is superior to CsA in efficacy measures



Increased infection risk with tofacitinib over CsA



- JAK inhibition was superior to cyclosporine in prevention of acute and chronic rejections
- Serious infections increased with systemic JAK inhibitors including CMV

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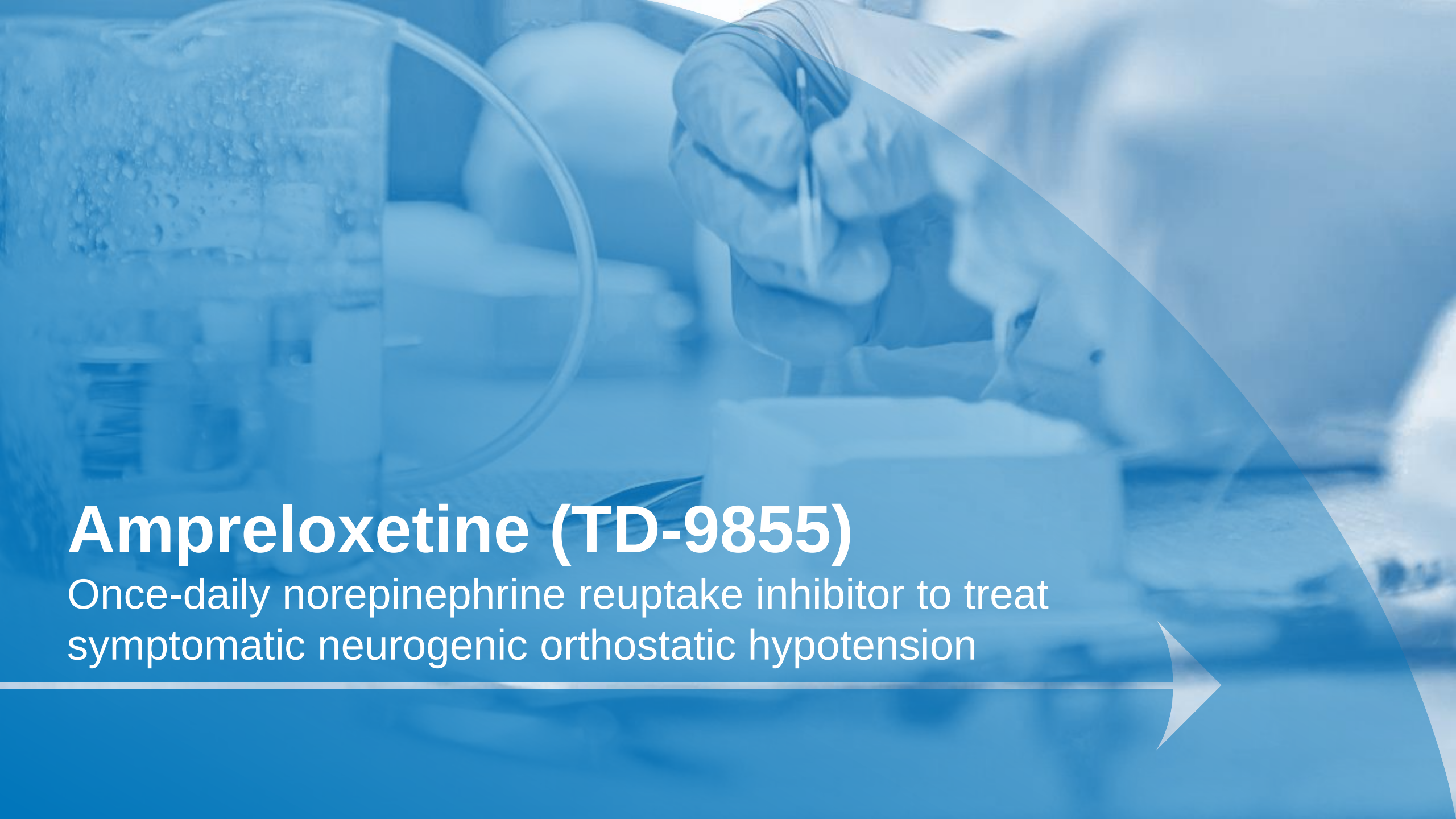
1. Vincenti F, et al. Am J Transplant 2015;15:1644-53.
*p<0.001 vs CsA.
BPAR, biopsy-proven acute rejection; CMV, cytomegalovirus; IF/TA, interstitial fibrosis/tabular atrophy; JAK, Janus kinase; SE, standard error.



Ampreloxetine (TD-9855)

Once-daily norepinephrine reuptake inhibitor to treat symptomatic neurogenic orthostatic hypotension

Ampreloxetine: new approach in nOH

MARKET DYNAMICS

~350K US patients[1]:
70–80% of MSA patients[2]
30–50% of PD patients[3] have nOH[4]

Specialist network in place: concentrated group of neurologists/ cardiologists treat patients; 'at risk' patients already identified and managed by specialty institutions

Physicians report **urgency to treat** due to high impact on patients' QoL, high risk of injury from falls and caregiver burden

Established nOH Tx paradigm: nOH included in medical treatment guidelines for PD/MSA patients; once diagnosed with nOH, patients prescribed drug

nOH profoundly impacts QoL

Study 0169 primary endpoint:
Change from baseline in OHSA Question 1

OHSA measures core nOH symptom:
Dizziness / lightheadedness due to brain hypoperfusion

Clinically significant endpoint: 1-point OHSA improvement

SYMPTOMS

- Dizziness or lightheadedness
- Fatigue
- Difficulty walking
- Weakness
- Impaired cognition
- Pain (back of head/neck/shoulders)
- Blurred vision
- Tremulousness
- Vertigo

IMPACT

Depression
Social isolation
Poor QoL
Falls (fractures/head trauma)
Morbidity

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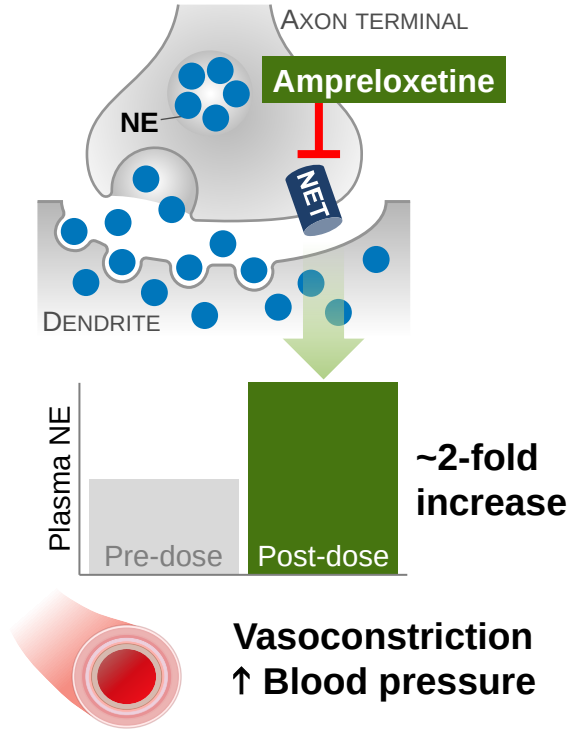
1. https://www.parkinson.org/Understanding-Parkinsons/Statistics; https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Multiple-System-Atrophy.
2. Claassen DO, et al. BMC Neurol 2018;18:125 https://doi.org/10.1186/s12883-018-1129-x. 3. Low PA. AMJC 2015;21:13,October 30 https://www.ajmc.com/view/ace0034_oct15_noh_low. 4. Not all patients are treated with prescription medication.
MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; OHSA, orthostatic hypotension symptom assessment; PD, Parkinson's disease; QoL, quality of Life; Tx, treatment.

Ampreloxetine: a once-daily, potent and selective norepinephrine reuptake inhibitor with a differentiated MOA for treating nOH

Ampreloxetine is designed to target and correct the norepinephrine imbalance…

NE Release at Neurovascular Junction



~2-fold increase

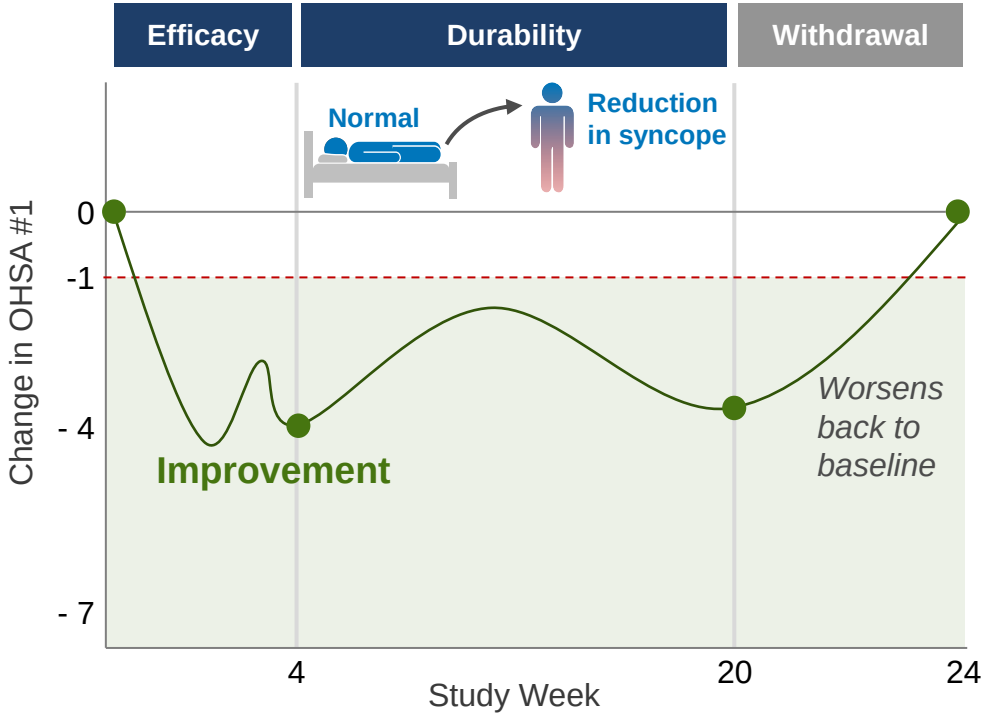
Vasoconstriction
↑ Blood pressure

…with potential for market differentiation…

Current nOH treatment options:

- No durable effect
- Multiple daily dosing
- Black box warning for SH

…and demonstrated a clinically meaningful and durable impact[1]



Our goal: ampreloxetine to be the first treatment to demonstrate a sustained impact for patients managing the chronic and debilitating symptoms of nOH

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1. Kaufmann H, et al. Mov Disord. 2019;34(suppl 2). Poster presented at the 2019 International Congress of Parkinson's and Movement Disorder Society.
Note: a 1-point change in the OHSA#1 score is considered clinically meaningful.
MOA, mechanism of action; NE, norepinephrine; NET, norepinephrine transporters; nOH neurogenic orthostatic hypotension; OHSA #1, orthostatic hypotension symptom assessment question #1; SH, supine hypertension.

Ampreloxetine: potential to provide meaningful and durable symptom improvement to underserved patients

Phase 3 Registrational Program

Study 169: 4 weeks (N=188)
Randomized, double-blind, placebo-controlled, parallel group

SEQUOIA
An ampreloxetine study for nOH

Study 170: 22 weeks (N=254)
Randomized 6-week withdrawal phase

Completers → **Extension study: 3 years**

REDWOOD
An ampreloxetine study for nOH

- Phase 3 registrational program ongoing; 4-week efficacy data expected Q3 2021

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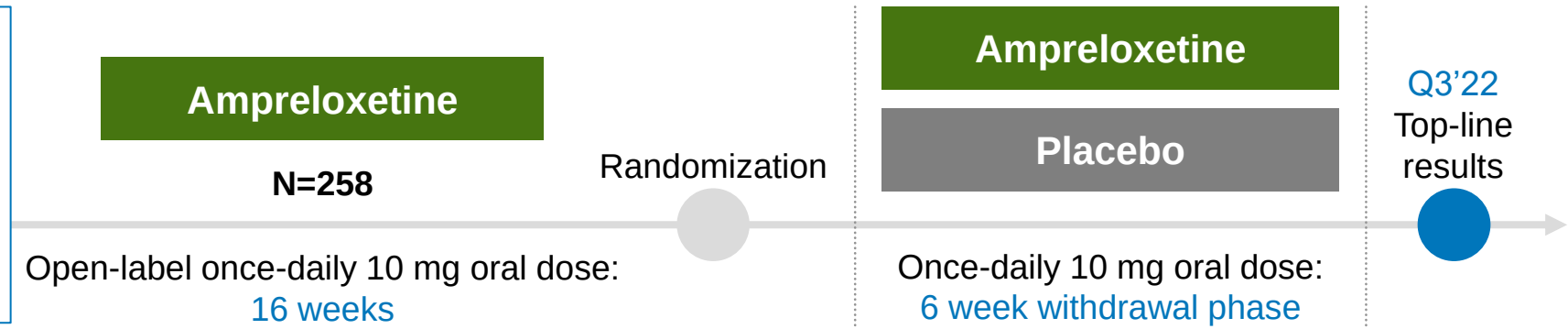
All subjects who complete Study 169 may enroll into 170; all subjects who complete 170 may enroll into extension study/171.
Baseline OHSA #1 (Orthostatic Hypotension Symptom Assessment Question 1) >4 points. Negative change indicates improvement in symptoms; improvement of 1 point is defined as the MCID (minimal clinically important difference).
Discontinuation rates for the Phase 3 trials as of Jan. 2020: 0169 – 5.3 percent; 0170 – 33.3 percent

Ampreloxetine: Phase 3 registrational program
Placebo-controlled, randomized withdrawal study

REDWOOD Study 0170
An ampreloxetine study for snOH

Key inclusion criteria: Age >30 y with symptomatic nOH with OHSA #1 score ≥4

Geographies: Argentina, Australia, Canada, Europe, New Zealand, Russia, UK, US



Objectives

- **Primary:** 1-pt worsening from baseline in both OHSA #1 score* and PGI-S during withdrawal phase
- **Secondary:** Changes from baseline at Week 6 post-randomization
  - OHSA #1
  - OHSA composite score
  - OHDAS composite score
  - PGI-S
  - % Time spent standing
  - Average no. of steps taken

Program Status

- Phase 3 registrational program ongoing
- All participants who complete Study 0170 are eligible for Extension Study 0171

*Negative change indicates improvement in symptoms; improvement of 1 point is defined as the MCID (minimal clinically important difference).
Discontinuation rates for the Phase 3 trials as of Jan. 2020: 0170 – 33.3%.
NCT03829657
nOH, neurogenic orthostatic hypotension; OHDAS, orthostatic hypotension daily activities scale; OHSA, orthostatic hypotension symptom assessment; PGI-S, patient global impression of disease severity.

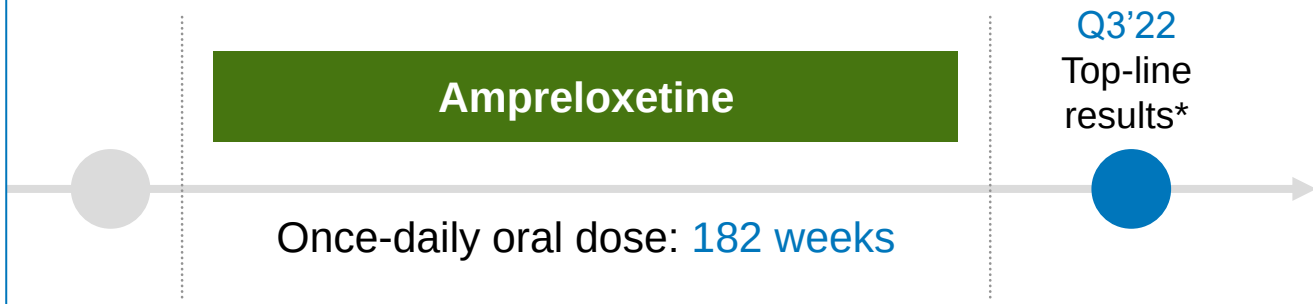
Ampreloxetine: Phase 3 program
6-month safety study + 3-year optional extension

OAK
An ampreloxetine study for snOH

Study 0171

Key inclusion criteria: patients who completed Study 0170 and, in investigator's opinion, would benefit from long-term treatment with ampreloxetine

Geographies: Argentina, Australia, Canada, Europe, New Zealand, Russia, UK, US



Assessments

- Through Week 26:
  - Physical and neurological exams
  - Vital signs
  - ECGs
  - Clinical laboratory tests
  - Concomitant medications
  - AEs
  - Treatment compliance
  - Incidence of falls
  - Changes from baseline in C-SSRS

Program Status

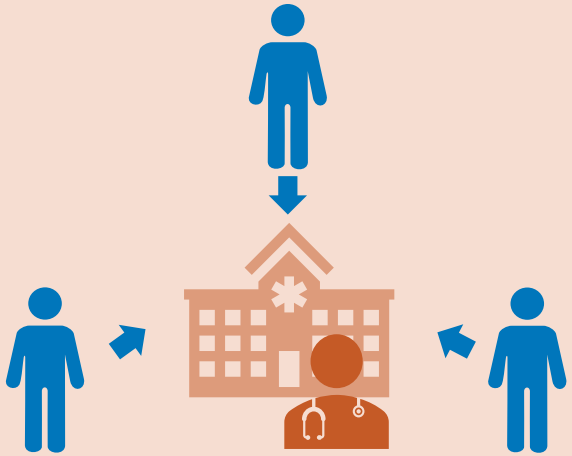
- Includes patients who completed Study 0170

*Through week 26; for FDA filing
NCT04095793
AE, adverse event; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram.

Decentralized trials move activities from the clinic to home

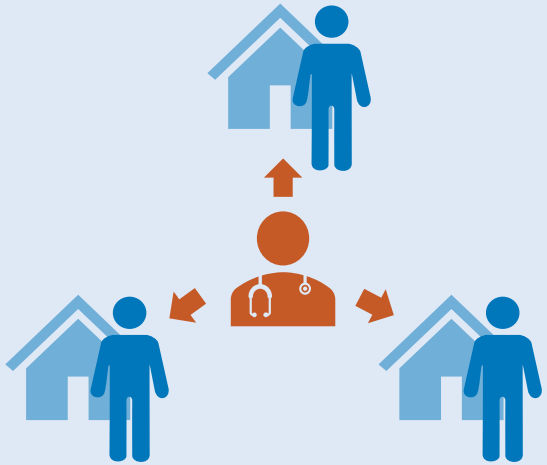
Global clinical trials are being decentralized along a continuum

Traditional Trial Operations



- Site-centric operating model
- Burden on site resources
- Patient burden

Decentralized Trial



- Patient-centric model
- Leverage technology for remote visits, monitoring and data collection
- Established home health and distribution channels

Source: Theravance Biopharma Clinical Operations.

Ampreloxetine: has the potential to transform Theravance Biopharma into an independent commercial biopharma

Established disease, targeted market

Established nOH treatment paradigm

nOH is included in medical treatment guidelines for PD and MSA patients; once diagnosed, patients get on drug treatment quickly

Specialist networks in place

A concentrated group of neurologists and cardiologists treat patients with nOH; ‘at risk’ patients already identified and managed by specialty institutions

An urgency to treat

Physicians report high urgency to treat snOH due to the high impact on patients’ QoL, high risk of injury from falls and caregiver burden

A strong value proposition

Manageable opportunity

TBPH’s infrastructure capable of commercializing ampreloxetine in the US with limited and targeted additions to current resources

Understanding of current access barriers

Meaningful value proposition will drive patient access; Ampreloxetine has the potential to improve the durability of treatment effect and thereby reduce costly events associated with nOH

Established patient advocacy

Strong message from PD and MSA advocacy groups that patients need new therapies to better manage nOH

MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; PD, Parkinson’s disease; QoL, quality of life; snOH, symptomatic neurogenic orthostatic hypotension.

Nezulcitinib (TD-0903) Program

Nebulized lung-selective pan-JAK inhibitor to treat:

- Acute hyperinflammation of the lung in COVID-19
- Chronic inflammation for the treatment and prevention of lung transplant rejection

Nezulcitinib (TD-0903): breaking new ground with inhaled JAKi

Focused execution in acute lung injury (ALI) driven by patient need

COVID-19 MARKET DYNAMICS

- >149M COVID-19 patients globally[1]; >32M patients in US[2]
- 56% of US population ≥1 vaccine dose; 40% fully vaccinated[3]
- Virus still surging in communities / parts of the world[1]
- 5 variants of concern in US[4]
- Declining but substantial proportion of population refusing vaccination[5]
- Disproportionate burden on people of color[6]

Treatments needed for hospitalized COVID-19 patients with acute lung injury

TD-0903 Dose finding placebo controlled data[7]

- Generally well-tolerated
- Low systemic exposure
- Positive trend in clinical status, reduced hospital stay
- No deaths in 3, 10 mg cohorts
- Improved oxygenation from baseline to Day 7
- Improved inflammatory biomarkers

Only therapeutic in development with nebulized lung-targeted approach

BUILDING A PIPELINE IN A PRODUCT

Potential areas for exploration:

- ALI in COVID-19 in hospitalized patients
- Preventing progression of lung hyperinflammation that leads to hospitalization
- Accelerated recovery of long-haul COVID-19 patients
- Future applications for coronavirus and influenza inflammation
- Prevention of lung transplant rejection

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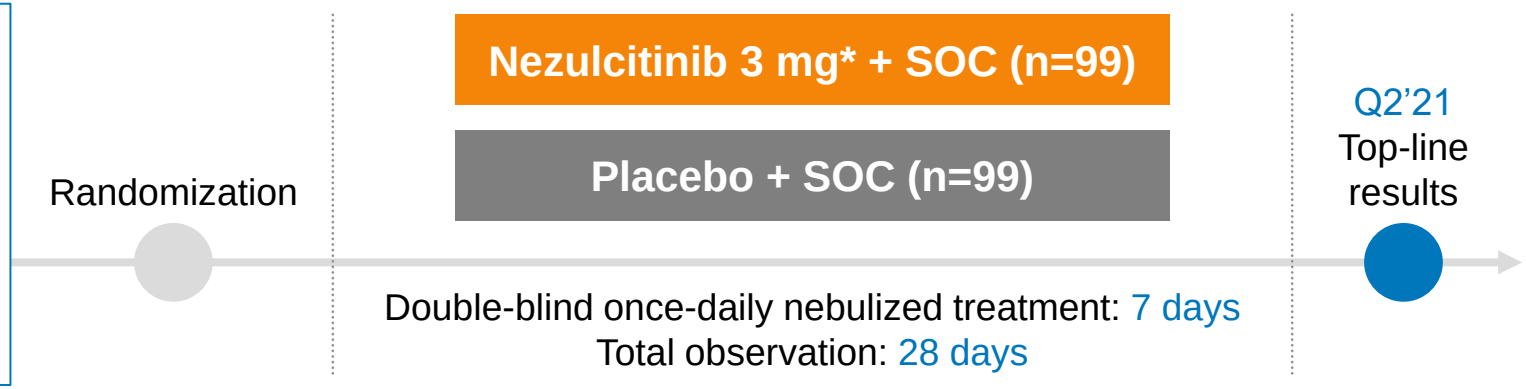
1. https://www.kff.org/coronavirus-covid-19/fact-sheet/coronavirus-tracker/ as of 4.29.21
2. https://coronavirus.jhu.edu/map.html as of 4.25.21
3. https://covid.cdc.gov/covid-data-tracker/#vaccinations as of 5.3.21
4. https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html as of 4.2.21
5. https://www.aamc.org/news-insights/herd-immunity-closer-we-think as of 4.25.21
6. https://www.kff.org/coronavirus-covid-19/issue-brief/latest-data-on-covid-19-vaccinations-race-ethnicity/ as of 4.25.21
7. https://www.medrxiv.org/content/10.1101/2021.03.09.21252944v1, n=25

Nezulcitinib: Randomized, double-blind, placebo-controlled Ph 2 study in hospitalized patients with COVID-19 requiring oxygen support

Part 2 Study 0188

Key inclusion criteria: Hospitalized patients aged 18–80 y requiring supplemental oxygen to maintain >90% saturation (not requiring IMV) with positive SARS-CoV-2 test <72 h prior to randomization and symptom onset >2–10 d prior to hospitalization

Geographies: South Africa, Europe, UK, USA



Objectives

- **Primary:** Number of respiratory-free days from randomization through Day 28
- **Secondary:** Tolerability, PK
- **Exploratory**: Clinical status, duration of hospitalization, repeat-dose safety

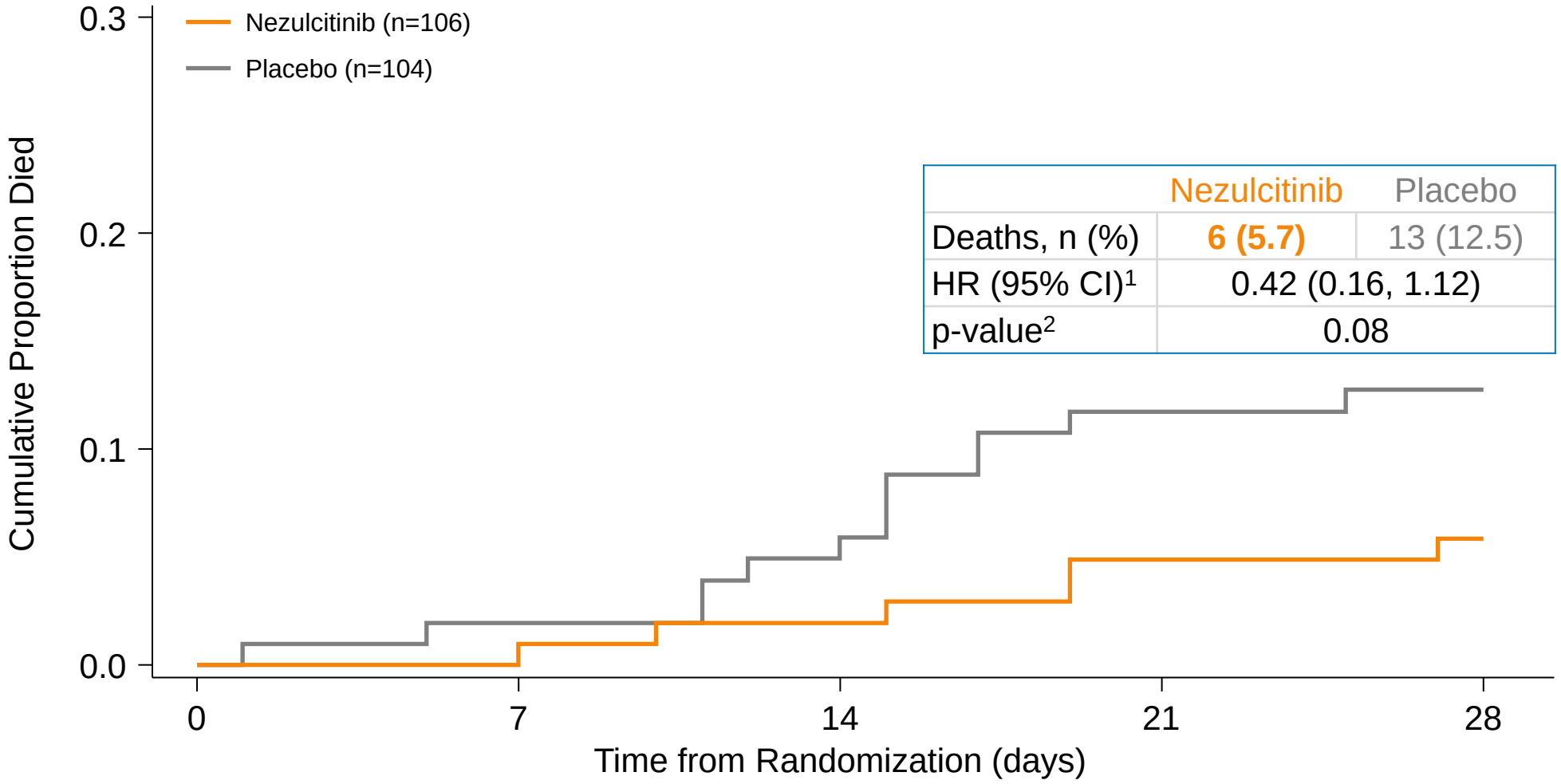
*Loading dose (double the standard dose) administered on Day 1.
NCT04402866
IMV, invasive mechanical ventilation; PK, pharmacokinetics; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOC, standard of care, includes remdesivir, dexamethasone, anticoagulation.

Potential for nezulcitinib to improve lung immune system balance across disease progression

	Asymptomatic or pre-symptomatic	Mild illness	Moderate illness	Severe illness	Critical illness	COVID recovery
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of LRT disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure	
Testing	Screening test; if patient has known exposure, diagnostic test	Diagnostic test	Diagnostic test	Diagnostic test	Diagnostic test	
Isolation	Yes	Yes	Yes	Yes	Yes	
Proposed disease pathogenesis			Viral replication			
				Inflammation		
Potential treatment		Antiviral therapy				
		Antibody therapy		Systemic anti-inflammatory		
		Prevent progression	Nezulcitinib ongoing program		Aid lung recovery	

LRT, lower respiratory tract; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

Nezulcitinib showed a trend of improvement in 28-day all-cause mortality rate and time to mortality (ITT)



	Nezulcitinib	Placebo
Deaths, n (%)	**6 (5.7)**	13 (12.5)
HR (95% CI)[1]	0.42 (0.16, 1.12)	
p-value[2]	0.08	

1. Hazard ratio (nezulcitinib vs placebo) and 95% CI calculated from Cox proportional hazards model adjusting for baseline age strata (≤60 vs >60 years).
2. Unstratified log-rank p-value comparing distribution of nezulcitinib vs placebo.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat.

Executive summary of safety results

	Nezulcitinib n=103	Placebo n=102
Adverse events	34.0%	41.2%
Serious adverse events	9.7%	15.7%
Liver abnormalities or disease	9.7%	7.8%
Serious infections	1.0%	2.0%
Venous thromboembolism	0	4.9%

- Nezulcitinib was well tolerated when administered once-daily for up to seven days

Safety data based on 205 treated patients.

Nezulcitinib Phase 2 COVID-19 trial summary

- **Efficacy outcomes, n=210 (ITT)**
  - **Primary:** No statistically significant difference between nezulcitinib and placebo for RFDs from randomization through Day 28
  - **Secondary:** No difference in change from baseline at Day 7 in SaO_2/FiO_2 ratio, proportion of patients in each category of the 8-point Clinical Status scale, and proportion of patients alive and respiratory failure-free at Day 28
  - A favorable trend in improvement for nezulcitinib when compared to placebo for 28-day all-cause mortality and time to recovery
- **Post-hoc analyses for baseline CRP, n=201**
  - CRP <150 mg/L (n=171): Nezulcitinib showed improvement in time to recovery and 28-day all-cause mortality
  - CRP ≥150 mg/L (n=30): No differences between groups
- Nezulcitinib was well-tolerated when administered once-daily for up to seven days
- Plasma exposure was low, consistent with expectations for a lung-selective medicine

CRP, C-Reactive protein; ITT, intent-to-treat; RFDs, Respiratory Failure-Free Days; SaO_2/FiO_2, percent oxygen saturation in arterial blood/fractional percentage of inspired oxygen.

TD-8236

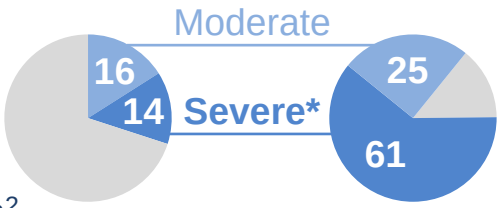
Potential first inhaled JAKi for asthma

High medical and economic burden in uncontrolled asthma

PATIENT POPULATION

339M
cases worldwide[1]

25M
US cases
8% of adults
8% of children[2]



Healthcare utilization[3]

~$58B US medical costs[4]

~$15B US asthma market (October 2020)[5]

CURRENT TREATMENT LANDSCAPE

ICS + LABA (often fail to control disease)
Approved biologics (affect subsets of patients)

- XOLAIR (omalizumab)
- NUCALA (mepolizumab)
- CINQAIR (reslizumab)
- FASENRA (benralizumab)
- DUPIXENT (dupilumab)

Step-up for severe asthma: LTRAs, tiotropium, OCS, biologics

JAK/STAT cytokines implicated in moderate-to-severe asthma

T2-high	T2-low
IL-4	**IL-23**/IL-12
IL-13	**IL-6**
IL-5	IL-27
TSLP	IFN-γ

Bold: biologics in development or approved.

STRATEGIC OPPORTUNITY

TD-8236

Potential to transform the treatment of respiratory inflammation by treating moderate-to-severe asthma regardless of T2 phenotype, including patients who remain symptomatic despite compliance on high-dose ICS

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*Asthma that requires high-dosage ICS + LABAs to prevent the disease from being uncontrolled) or asthma that remains uncontrolled despite treatment.
1. World Health Organization; 2. https://www.aafa.org/asthma-facts/; 3. Sadatsafavi, M., et al. Can Respir J 2010;17:74-80. 4. Nurmagambetov T, et al. Ann Am Thorac Soc 2018;15:348-56; 5. TBPH estimate based on multiple data sources. ICS, inhaled corticosteroids; IFN, interferon; IL, interleukin; JAK, Janus kinase; LABA, long-acting β2 agonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; STAT, signal transducer and activator of transcription; T2, type 2; TSLP, thymic stromal lymphopoietin.

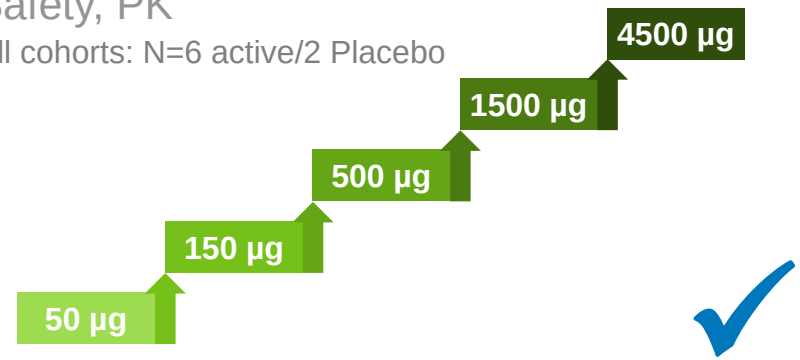
TD-8236: Phase 1 clinical trial design

Parts A & B completed September 2019; Part C enrollment completed — data reported in Q4 2020

Part A: SAD (Healthy volunteers)

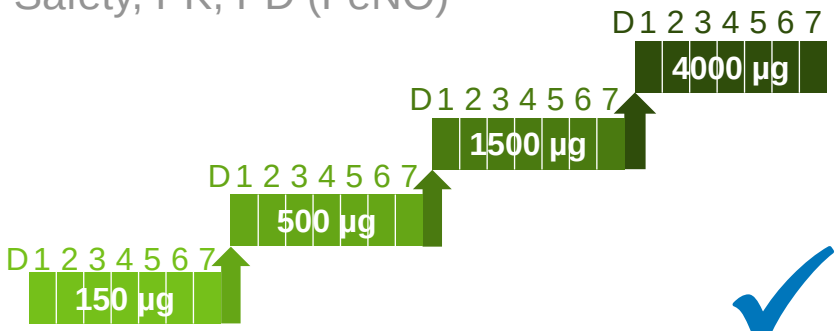
Safety, PK

All cohorts: N=6 active/2 Placebo



Part B: MAD (Mild asthmatics)

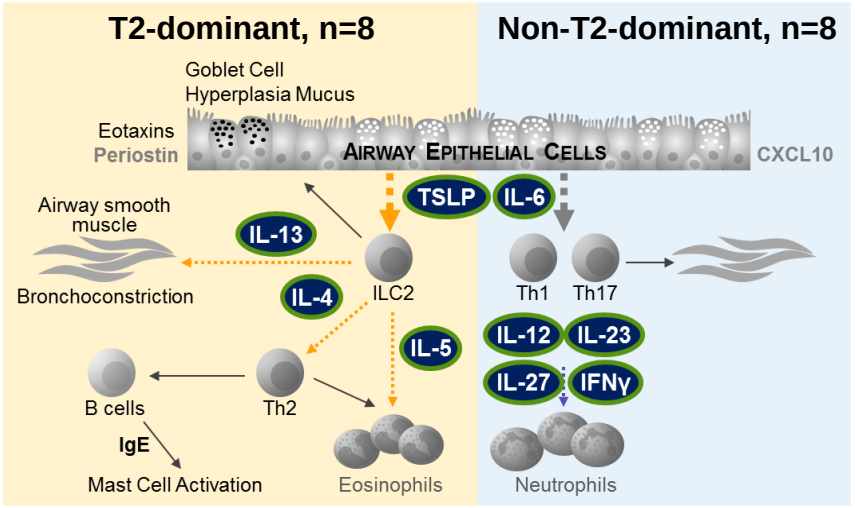
Safety, PK, PD (FeNO)



Part C: MoA Biomarkers

(Moderate-to-severe asthmatics + ICS)

N=16 active/8 placebo



- Goal: build confidence in compound, MoA and dose in early-development
- **Endpoints: FeNO; pSTAT1 and pSTAT6 in bronchoalveolar lavage fluid; cytokines; epithelial gene expression**

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CXCL, chemokine (C-X-C motif) ligand; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cells; MAD, multiple-ascending dose; MoA, Mechanism of Action; PK, pharmacokinetic; PD, pharmacodynamic; pSTAT, phosphorylated signal transducer and activator of transcription; SAD, single-ascending dose; T2, type 2; Th2, T helper type 2; TSLP, thymic stromal lymphopoietin.

TD-8236: Positive Phase 1 trial in healthy subjects and patients with mild and moderate-to-severe asthma

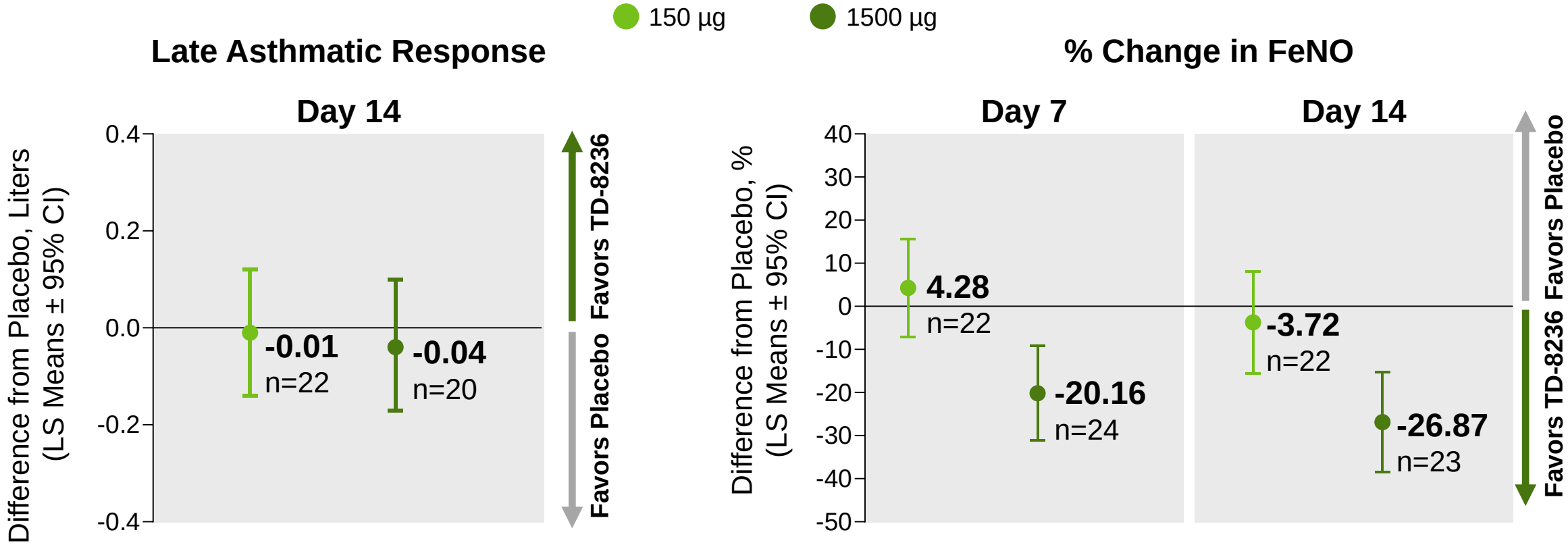
Phase 1 Profile	Healthy Volunteer Single Dose (Part A)	Mild Asthma Multiple Dose (Part B)	Moderate-to-Severe Asthma [+ ICS] Multiple Dose (Part C)
Generally well tolerated	✓	✓	✓
Minimal systemic exposure	✓	✓	✓
PK and PD profile consistent with once-daily dosing	✓	✓	✓
Biologic activity in lungs of patients with asthma		✓ ↓ FeNO	✓ ↓ FeNO, pSTAT1, pSTAT6

- Biomarkers of JAK target engagement (pSTAT1 and pSTAT6) significantly reduced in lungs of T2 high and T2 low moderate/severe asthmatics on top of ICS
- Ongoing analysis of effect of TD-8236 on additional biomarkers including cytokines and gene expression

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; JAK, Janus kinase; PD, pharmacodynamic; PK, pharmacokinetic; pSTAT, phosphorylated signal transducer and activator of transcription; T2, type 2.

No impact of TD-8236 on the Late Asthmatic Response (LAR)

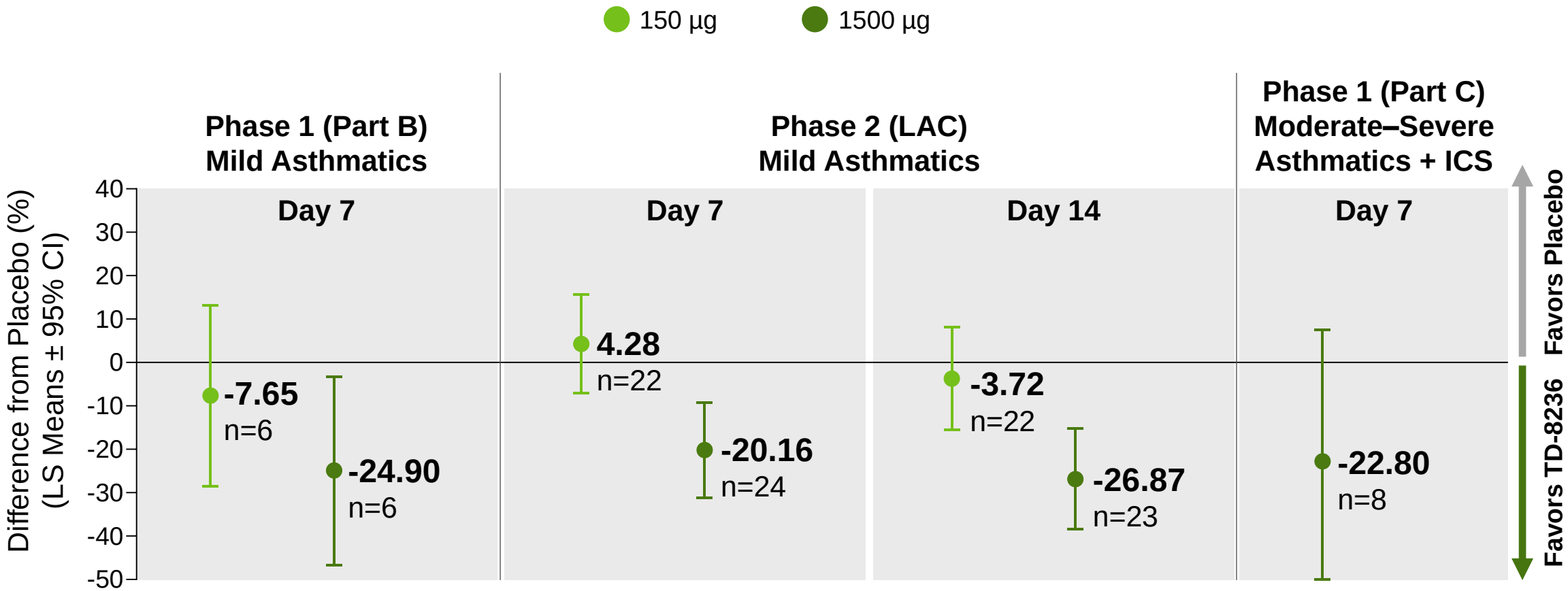
Significant reductions in inflammation marker (FeNO) and favorable safety and tolerability



- TD-8236 was generally well tolerated as a single-daily dose administered for 14 consecutive days

Primary Endpoint: Weighted Mean Area Under the Curve, 3–8 h.
CI, confidence interval; FeNO, fractional exhaled nitric oxide; LS, least-squares.

TD-8236 FeNO reductions consistent across Phase 1 and 2



- FeNO reductions observed in moderate-to-severe asthmatics taking inhaled corticosteroids

CI, confidence interval; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; LAC, lung allergen challenge; LS, least-squares.

TD-5202

Organ-gut selective irreversible JAK3 inhibitor
to treat inflammatory intestinal diseases

Celiac disease has no current treatments and serious health consequences

PATIENT POPULATION

1%
Global prevalence[1]

3.3M
US patients[2,3]

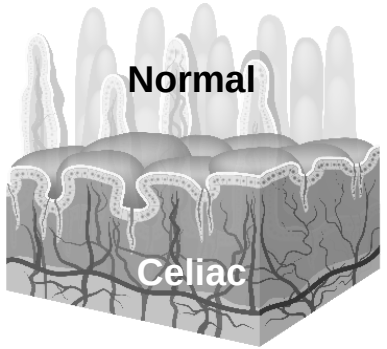
4–4.5x
increase in US over past 50 y[4]

>2x
higher healthcare costs than controls[5]

CURRENT TREATMENT LANDSCAPE

No approved treatment
Only available intervention is strict life-long gluten-free diet

30% of diagnosed patients are poorly controlled despite best dietary efforts[6]



STRATEGIC OPPORTUNITY

TD-5202

Organ-gut selective irreversible JAK3 inhibitor:
potential to deliver significant value for both patients and payers

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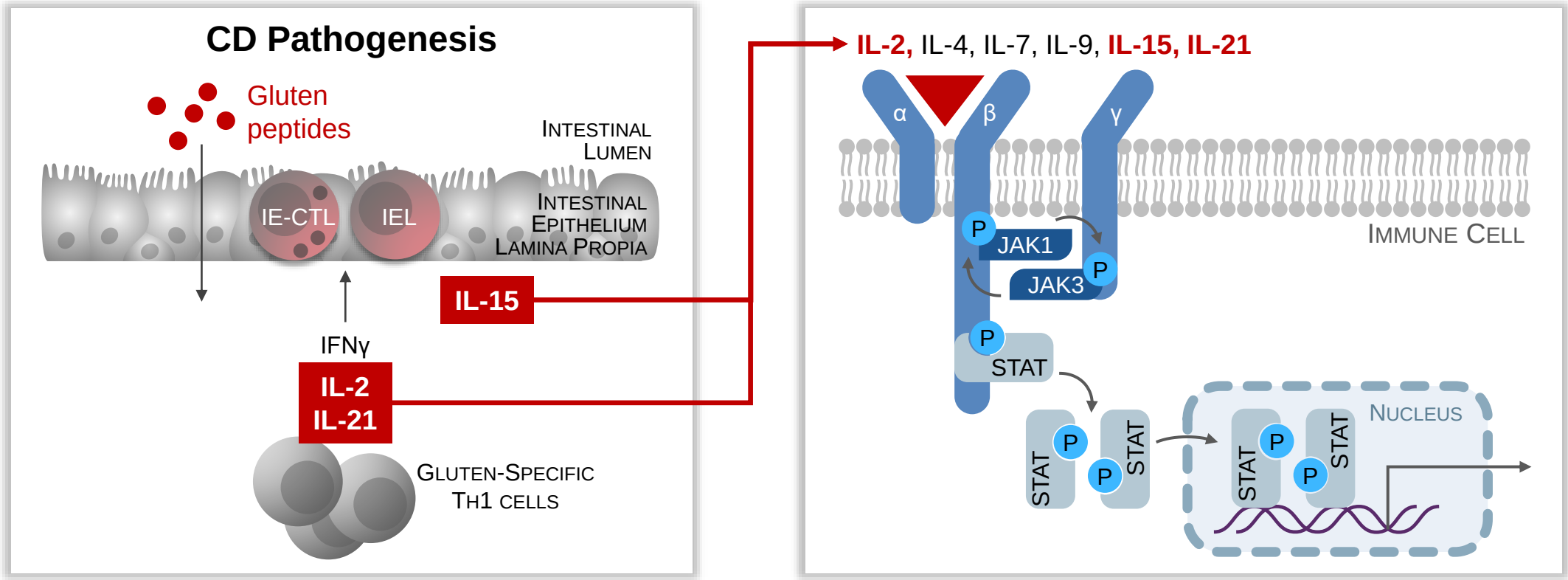
1. http://www.drschaer-institute.com/us/celiac-disease/epidemiology-1033.html; 2. 1% prevalence in US, BeyondCeliac.org; 3. 2018 US population 327M Census.gov.
4. Reunala T, et al. Nutrients 2018;10;pii: E602; 5. Guandalini et al. Digestive Diseases Sciences 2016;61:2823-30; 6. Theravance Market Research.
JAK, Janus kinase.

JAK3-dependent cytokines play central role in pathogenesis of celiac disease



- Proof-of-relevance from recent positive Phase 2 data with systemic JAK3 inhibitor in alopecia areata, another T-cell mediated disease
- Localized JAK3 inhibition has the potential to avoid systemic immunosuppression (genetic JAK3 deficiency leads to severe immunodeficiency)

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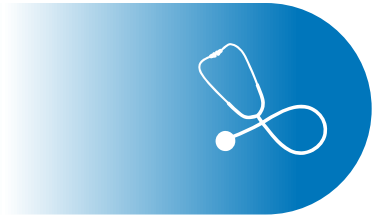
Figure adapted from Jabri B and Sollid L. J Immunol 2017;198:3005-14.
CD, Crohn's disease; IE-CTL, intraepithelial cytotoxic lymphocyte; IEL, intraepithelial lymphocyte; IFN, interferon; IL, interleukin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; Th1, T helper 1 cells.

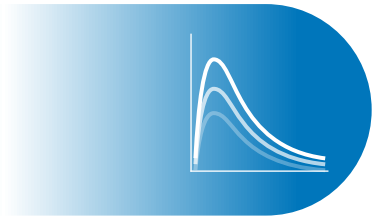
TD-5202 First-in-human overall results summary

TD-5202: generally well-tolerated (single dose ≤2000 mg, multiple doses ≤1000 mg BID) for 10 consecutive days in healthy subjects



- No serious or severe AEs were reported
- All treatment-emergent AEs in TD-5202-treated subjects were mild in severity

- No clinically significant changes from baseline in vital signs and ECG assessments
- No clinically significant changes in chemistry or hematology parameters
  - No changes in NK cell count



- Systemic exposures were dose proportional from 100 to 1000 mg BID
- Low steady-state systemic exposures: mean $C_{max,ss}$ ~11-fold below the protein-adjusted JAK IC_{50} at the highest tested dose (1000 mg BID), consistent with a gut-selective approach

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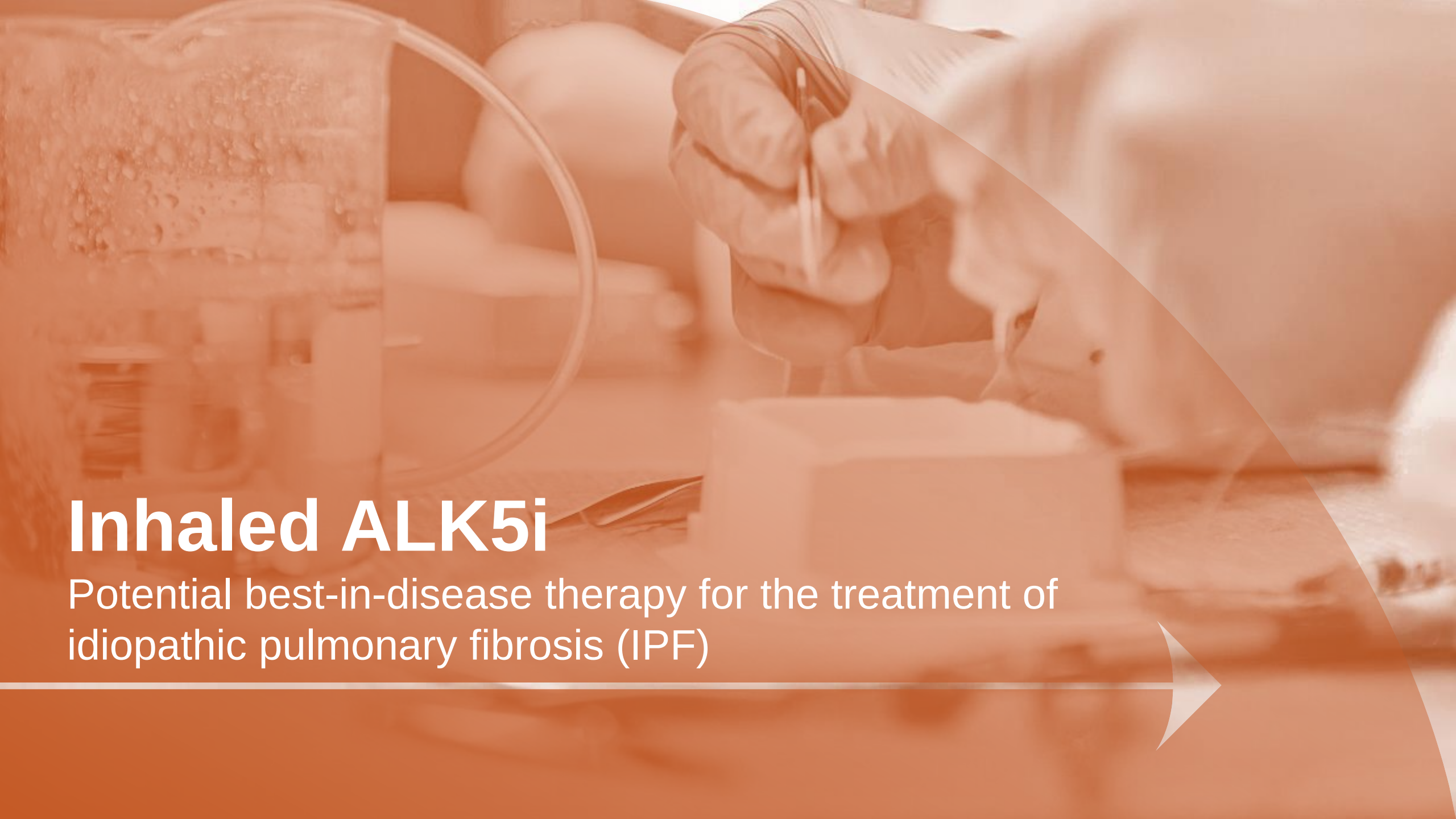
AE, adverse event; BID, twice daily; $C_{max,ss}$, maximal steady-state concentration; ECG, electrocardiogram; IC_{50}, inhibitory concentration at which 50% of JAK signaling is blocked; JAK, Janus kinase; IC_{50}, NK, natural killer.



Inhaled ALK5i

Potential best-in-disease therapy for the treatment of idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) remains a fatal chronic lung disease with limited treatment options

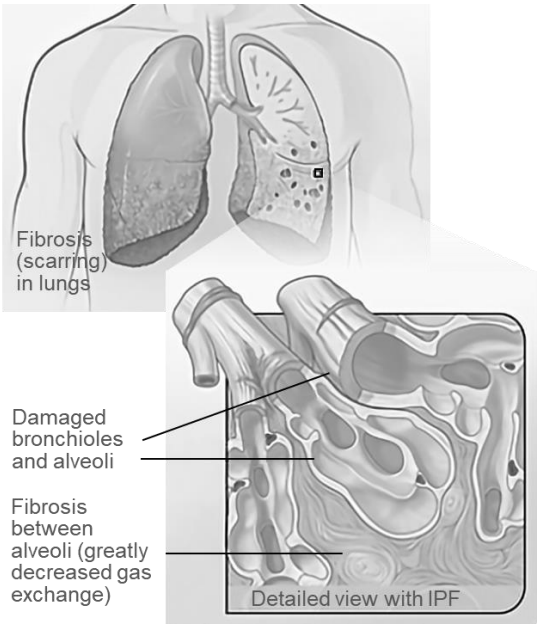
PATIENT POPULATION

140,000
US prevalence;
currently orphan disease[1,2]

Profound dyspnea, unrelenting cough, impairment of activities of daily living

Mortality with IPF remains high

Lungs with IPF[3]



CURRENT TREATMENT LANDSCAPE

Limited treatment options

2 currently approved therapies, with modest efficacy and poor tolerability

STRATEGIC OPPORTUNITY

Inhaled ALK5i

Potential first-in-class inhaled ALK5 inhibitor anti-fibrotic agent for IPF
Despite treatment with the current SoC, IPF patients continue to experience disease progression and exacerbation

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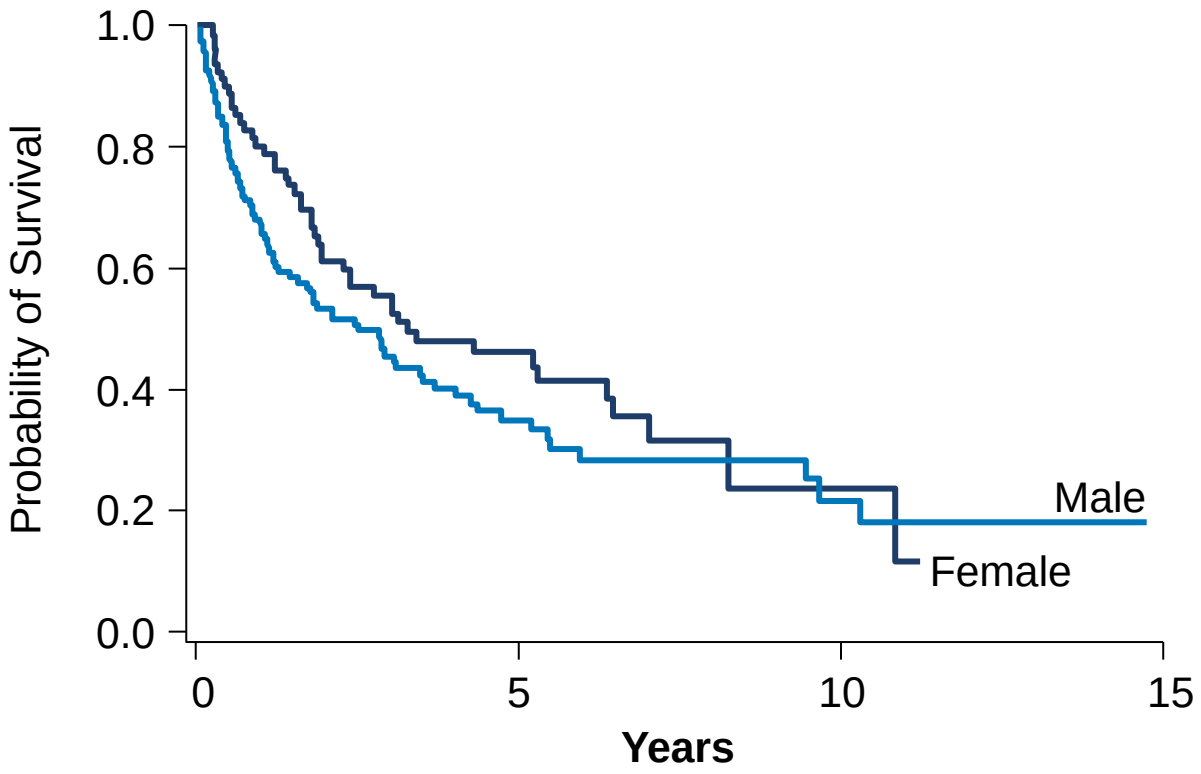
1. Raghu G, et al. Lancet Resp. 2014: 2(7):566-572; 2. Raghu G, et al. Eur Respir J. 2016: 48(1):179-186; 3. National Heart Lung and Blood Institute (NIH), Public Domain, https://commons.wikimedia.org/w/index.php?curid=29590103.
ALK5i, transforming growth factor β receptor I kinase inhibitor; Soc, Standard of Care.

Significant opportunity remains for effective IPF treatments



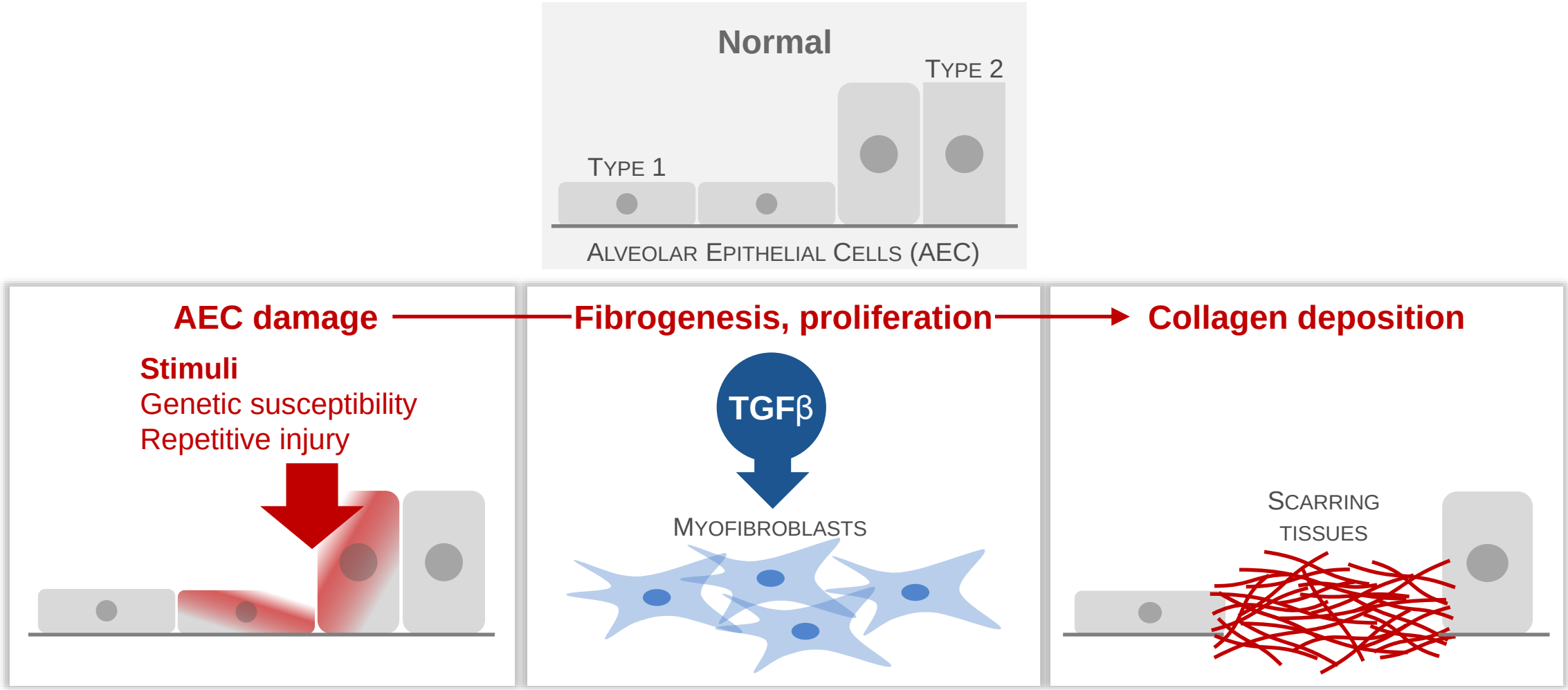
- Mortality with IPF remains high
  - <50% alive 3 years after diagnosis[1]

Goal **To arrest disease progression with improved tolerability**

1. King TE, et al. Am J Respir Crit Care Med 2001;164:1171-81.
IPF, idiopathic pulmonary fibrosis.

Targeting the TGFβ pathway

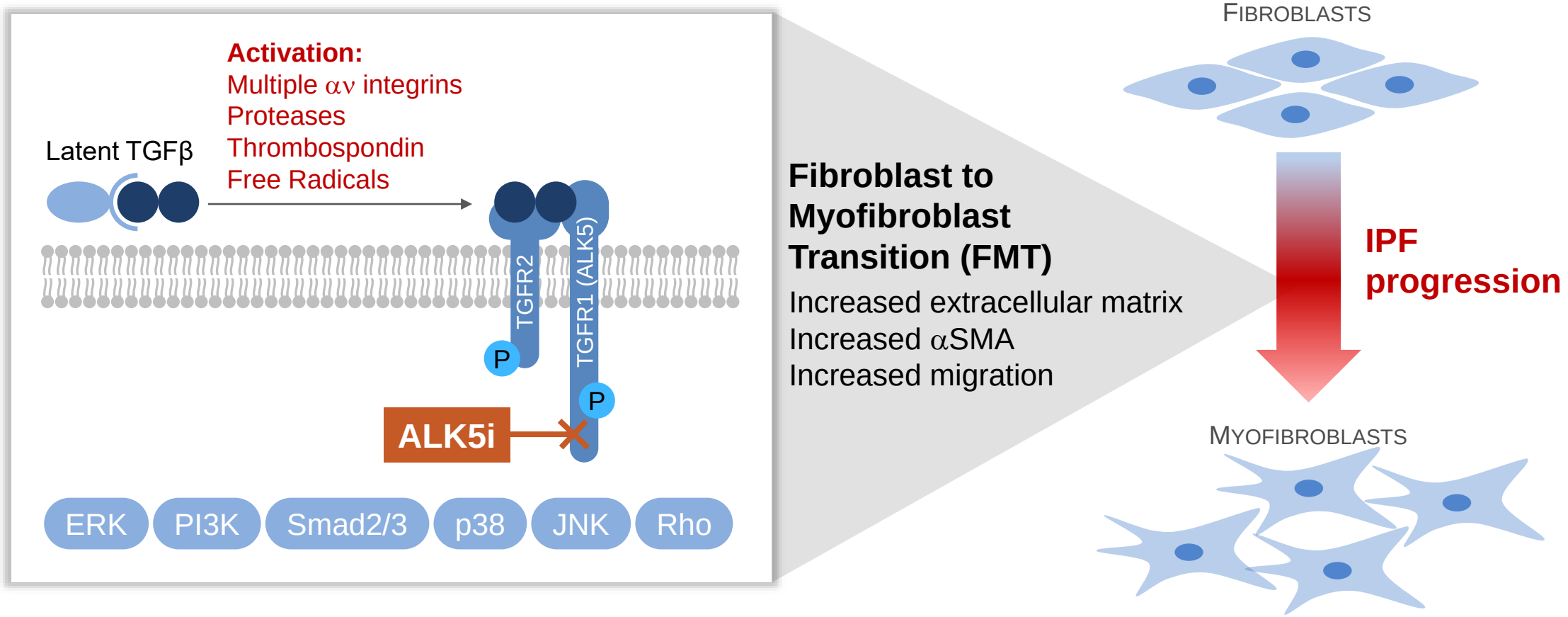
A core signaling pathway that drives fibrosis



TGFβ, transforming growth factor β.

Selectively targeting the TGFβ pathway through ALK5 inhibition

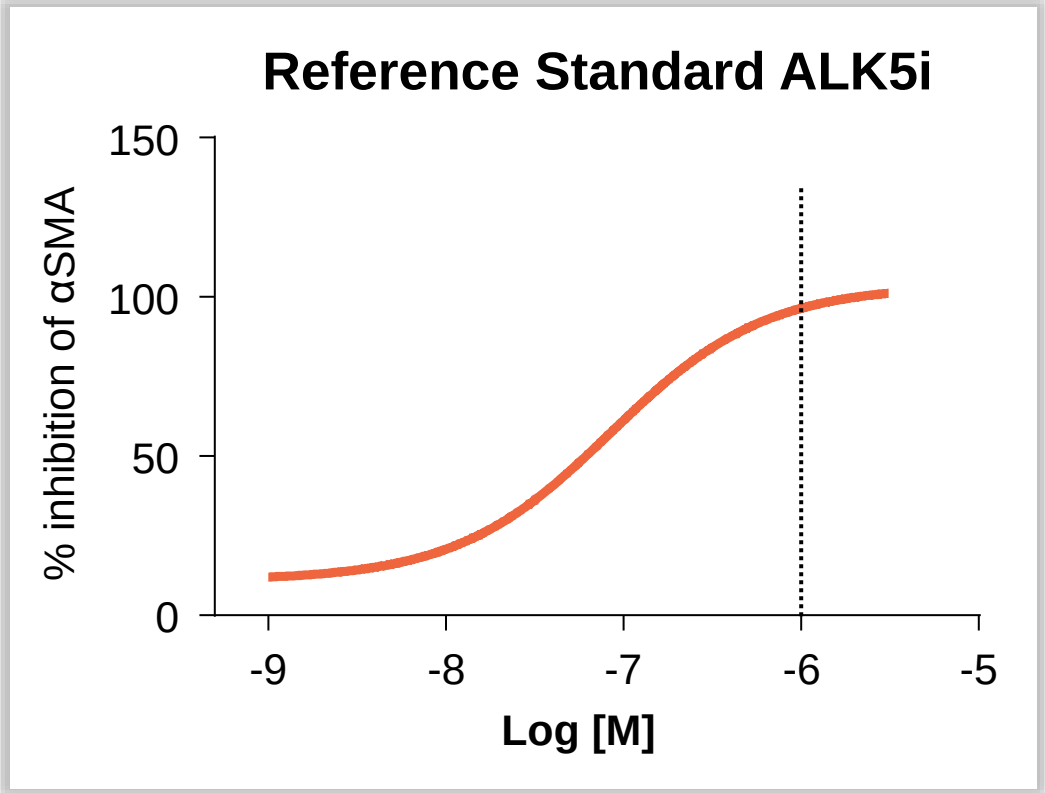
Inhibiting a core signaling pathway that drives fibrosis regardless of activation mechanism

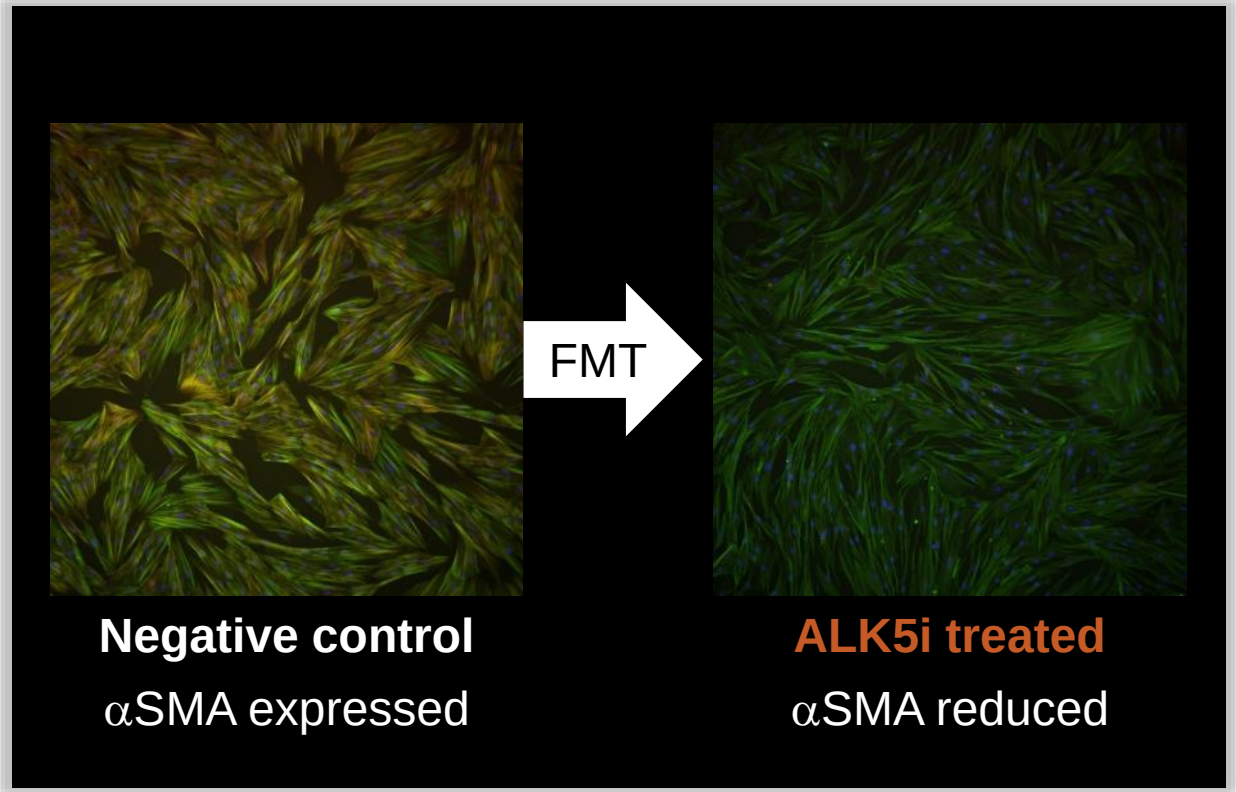


Adapted from: Neuzillet C, et al. Oncotarget 2013;5:78–94.

αSMA, α-smooth muscle actin; ERK, extracellular signal-regulated kinase; IPF, idiopathic pulmonary fibrosis; JNK, c-Jun N-terminal kinase; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; Smad2/3, mothers against decapentaplegic homolog 2/3; TGFR (ALK5), transforming growth factor receptor.

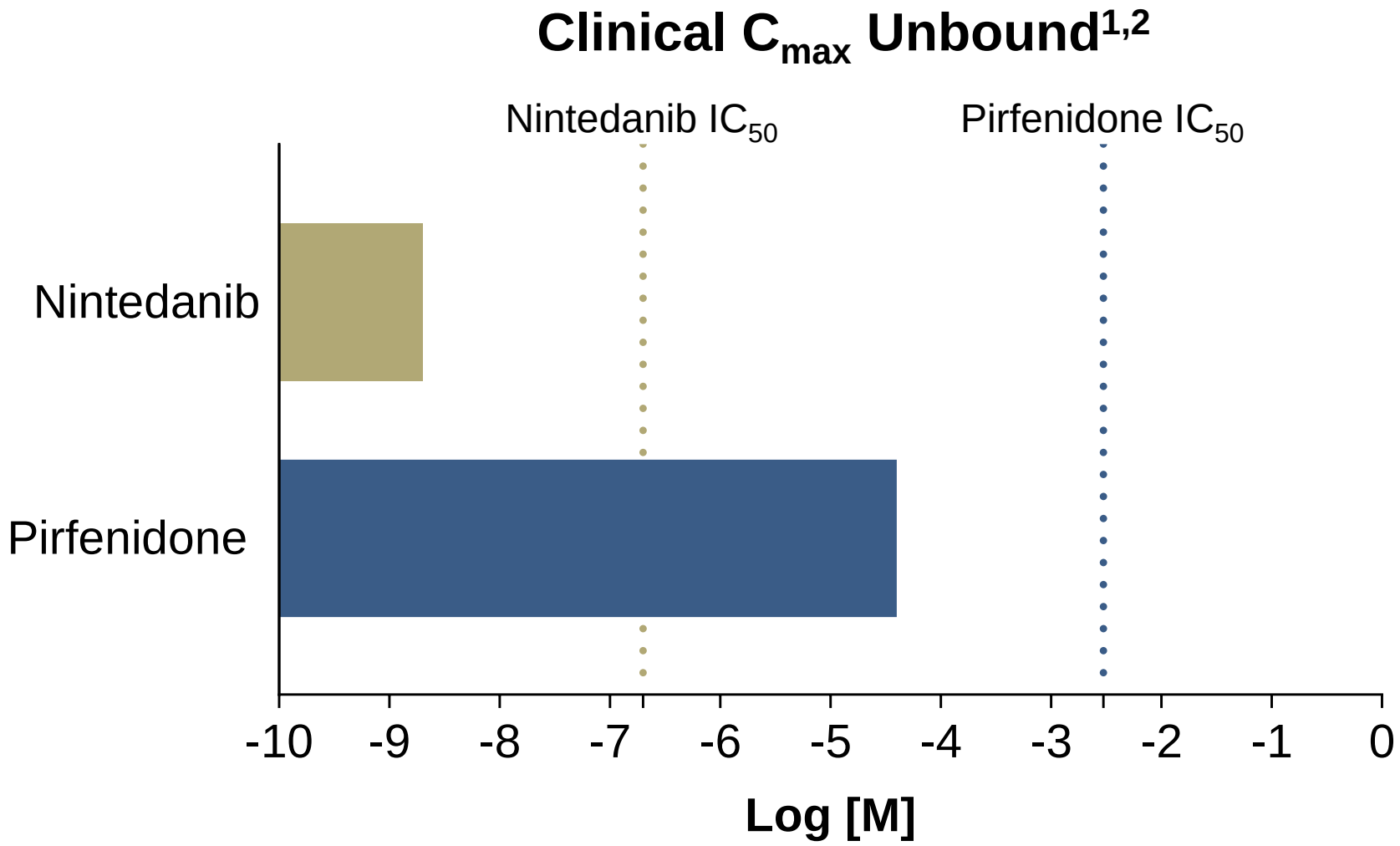
ALK5 inhibition directly interrupts FMT in IPF





ALK5i, transforming growth factor β receptor I kinase inhibitor; αSMA, α-smooth muscle actin; FMT, fibroblast to myofibroblast transition.

Current treatment options have no effect on FMT at clinically relevant concentrations

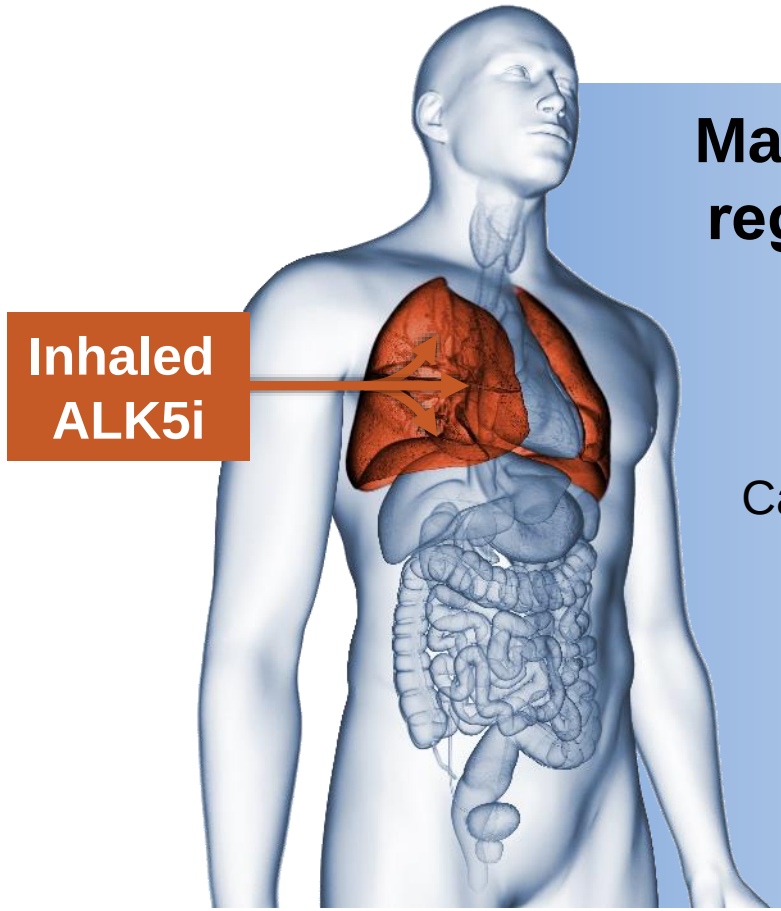


1. https://www.tga.gov.au/sites/default/files/auspar-nintedanib-esilate-160208.pdf.
2. Ogura T, et al. Eur Respir J. 2015;45:1382-92.

C_{max}, maximal concentration; FMT, fibroblast to myofibroblast transition; IC_{50}, half maximal inhibitory concentration.

Lung selectivity avoids unwanted systemic side effects

Minimizing systemic inhibition of a cytokine essential for homeostasis



Maintaining key systemic regulatory roles of TGFβ

Wound repair
Bone healing
Cardiovascular homeostasis
Tumor suppression
Endocrine function

Modified from: Akhurst RJ, Hata A. Nat Rev Drug Discov 2012;11:790-811.
ALK5i, TGFβ receptor I kinase inhibitor; TGFβ, transforming growth factor β.

Ocular JAKi

Potential best-in-disease, pan-JAK inhibitor with long-acting ocular anti-inflammatory activity

Diabetic macular edema causes blindness in diabetics

PATIENT POPULATION

2.7 million
US prevalence[1]

#1 cause of blindness in diabetes[2]

140% higher direct and indirect healthcare costs in patients with DME vs diabetics without ocular disease[3]

CURRENT TREATMENT LANDSCAPE

1st **Anti-VEGF treatments** Most patients have suboptimal response

2nd **Intraocular steroids** Side effects limit utility

Nonpharmacological treatments (e.g. laser coagulation) limited efficacy and significant adverse events

STRATEGIC OPPORTUNITY

Ocular JAKi

Potential to offer an alternative treatment for DME patients who are not optimally responding to treatment with VEGFi

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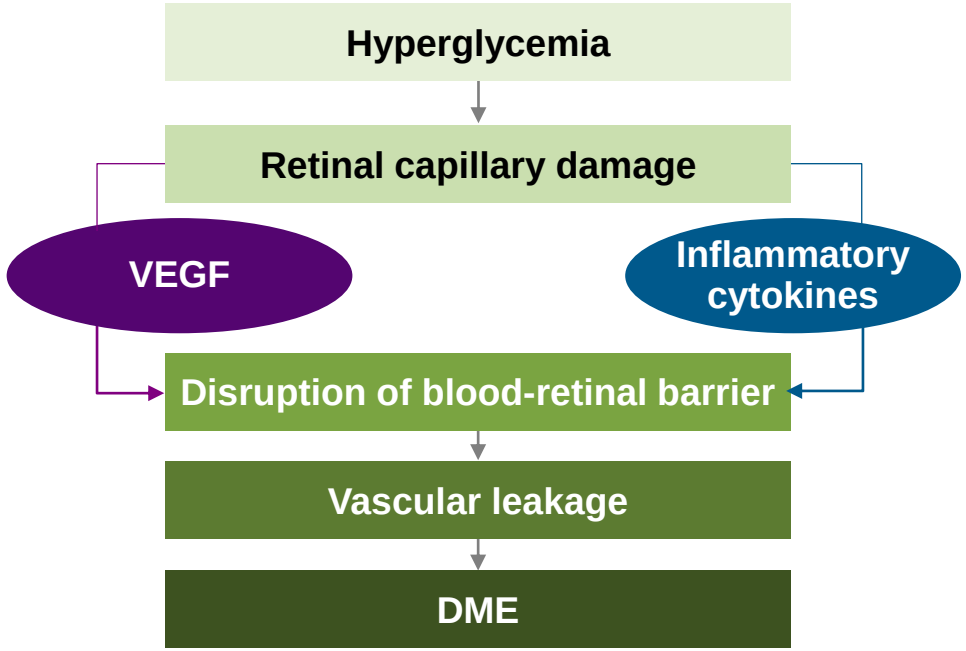
2. Romero-Aroca, World J Diabetes 2011;2(6): 98-104. 3. Lee et al Curr Med Res Opin 2008;24:1549-59.
Images from Angiogenesis Foundation, www.scienceofdme.org.
DME, Diabetic macular edema; JAKi, Janus kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Inflammation, not just VEGF, is a key driver of DME



Current Pharmacological Treatments

Intraocular anti-VEGF agents

- One third do not respond to anti-VEGF while another third have a suboptimal response[1]
- Require frequent intravitreal injections

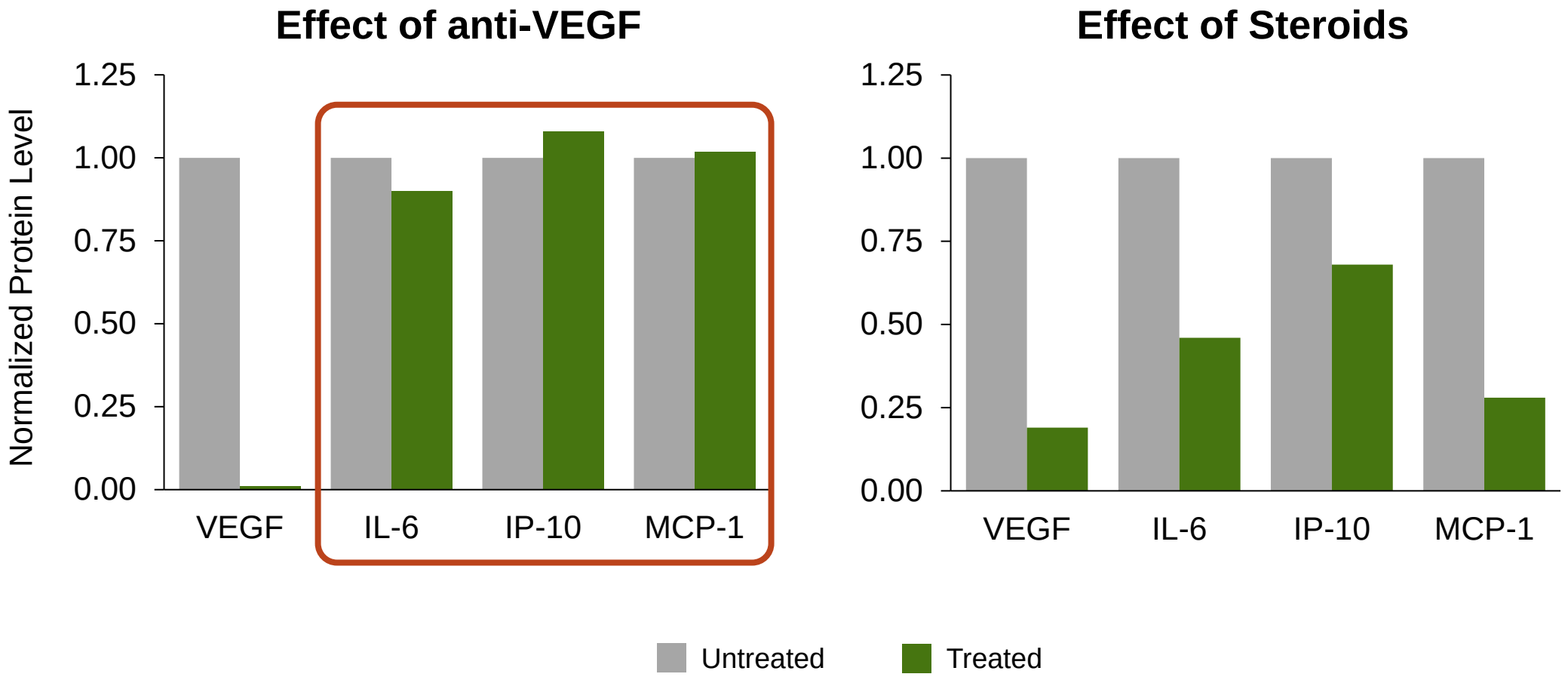
Intraocular steroids

- High frequency of formation of cataracts and glaucoma

Need for broad, sustained release, anti-inflammatory with a safer side-effect profile

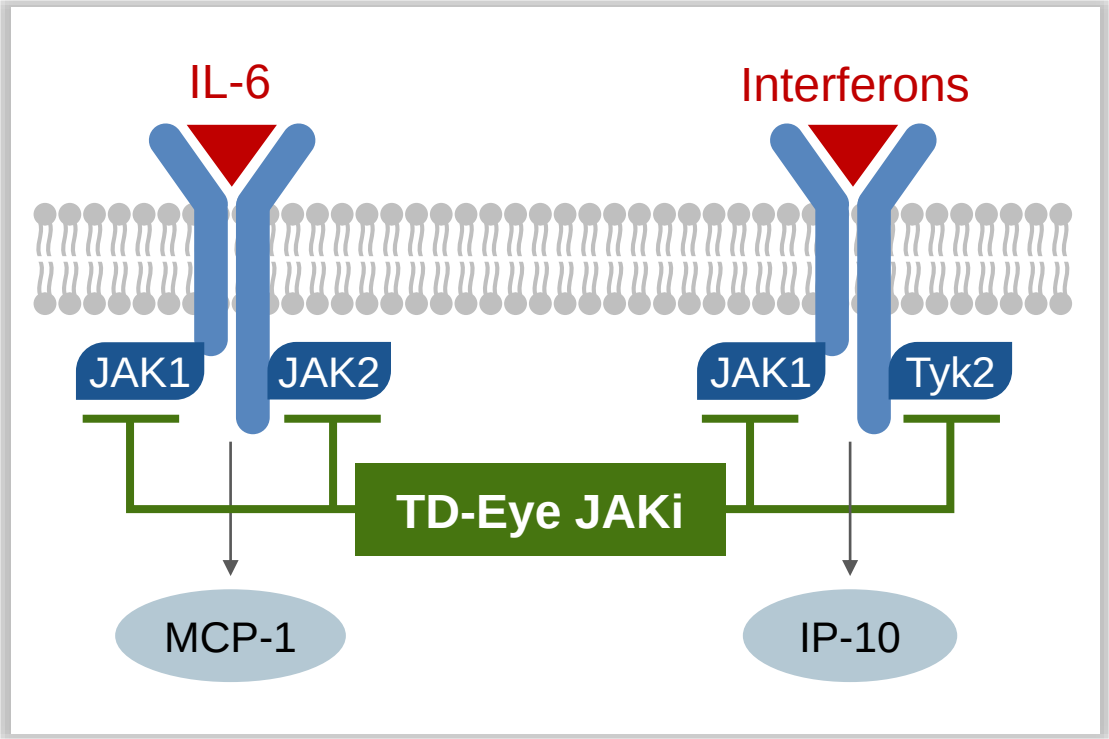
1. Gonzalez VH, et al. Am J Ophthalmol 2016;172:72-79.
DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

Unmet need for an anti-inflammatory drug: opportunity for eye-selective JAK inhibition



Adapted from Sohn HJ, et. al. Am J Ophthalmol 2011; 152:686-694.
IL-6, interleukin-6; IP-10, interferon γ-induced protein 10; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor.

Ocular pan-JAK inhibition has the potential to address key disease pathways in DME

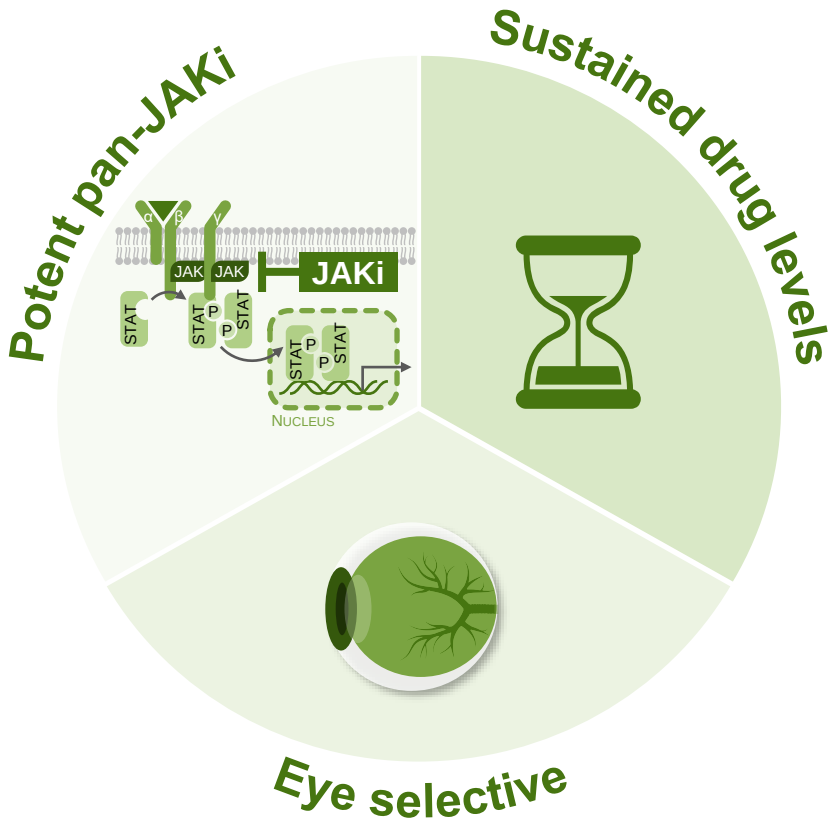


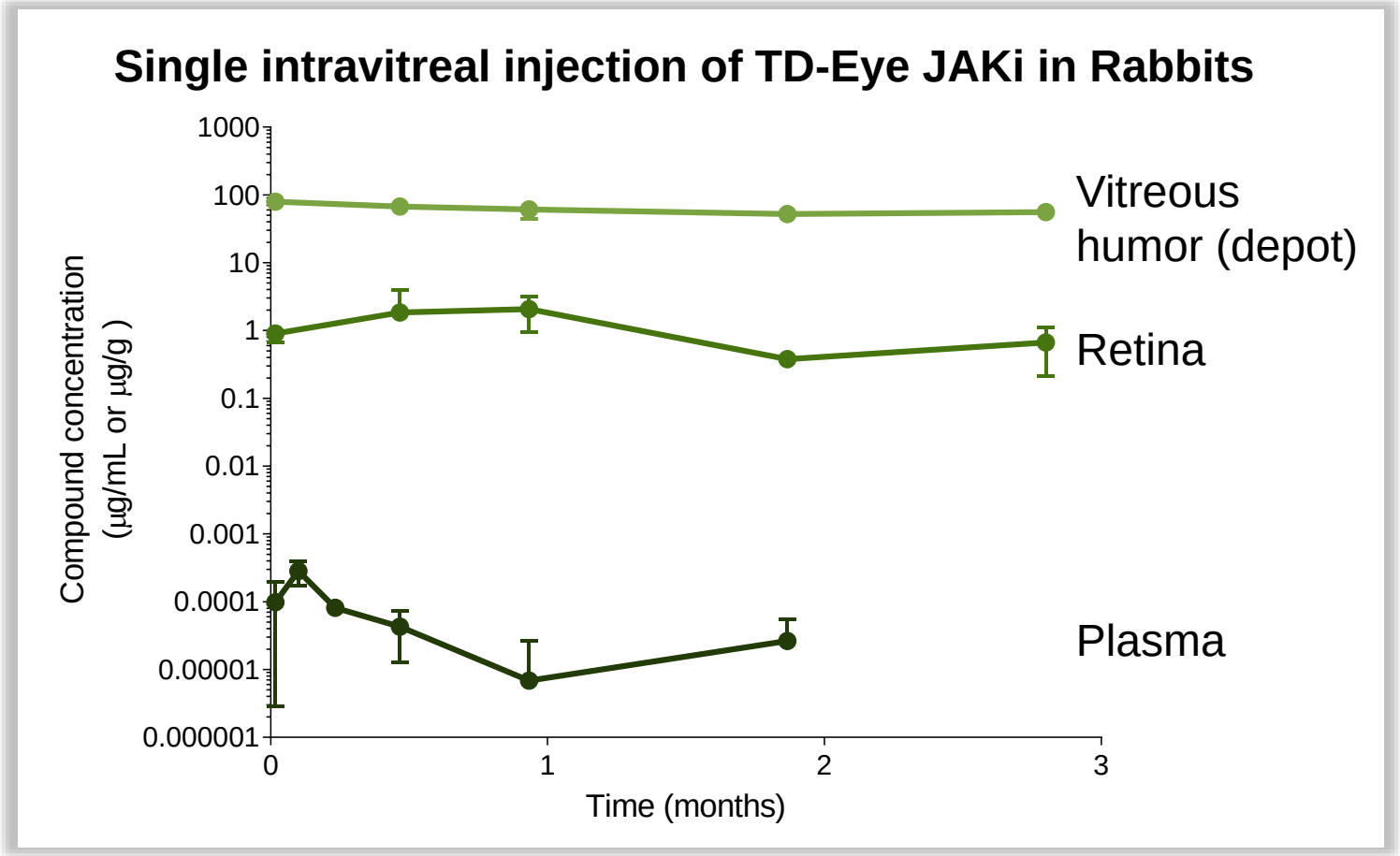
TD-EyeJAKi inhibits key DME inflammatory pathways:

- IL-6 and interferon signaling pathways in human primary cells
- IL-6 induced pSTAT3 and interferon-induced IP-10 in the back of the eye *in vivo*

DME, diabetic macular edema; IL-6, interleukin-6; IP-10, interferon γ-induced protein 10; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; pSTAT, phosphorylated signal transducer and activator of transcription; Tyk, tyrosine kinase; VEGF, vascular endothelial growth factor.

A pan-JAK inhibitor designed for eye selectivity with projected dosing interval of at least three months





JAK, Janus kinase.