

TD-0903: Nebulized pan-JAKi for Acute Lung Injury Associated with COVID-19

April 9, 2020



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Forward looking statements

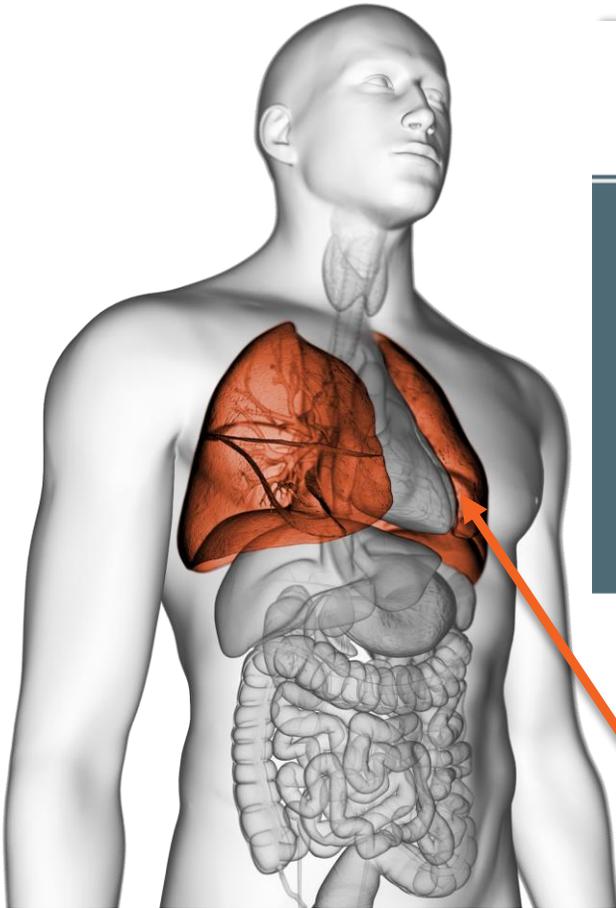
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Examples of forward-looking statements in this presentation may include the Company's strategies, plans and objectives, the Company's regulatory strategies and timing of clinical studies (including the data therefrom), the potential characteristics, benefits and mechanisms of action of the Company's product and product candidates, the potential that the Company's research programs will progress product candidates into the clinic, the Company's expectations for product candidates through development and potential regulatory approval and commercialization (including their differentiation from other products or potential products), the Company's expectations regarding its allocation of resources, product sales or profit share revenue, the repayment of its notes, expected future commercial performance of Trelegy Ellipta and the Company's expectations for its 2020 operating loss, excluding share-based compensation and other financial results.

The company's forward-looking statements are based on the estimates and assumptions of management as of the date of this presentation and are subject to risks and uncertainties that may cause the actual results to be materially different than those projected, such as risks related to impacts of the COVID-19 global pandemic on our business, delays or difficulties in commencing, enrolling or completing clinical studies, the potential that results from clinical or non-clinical studies indicate the Company's compounds or product candidates are unsafe or ineffective, risks that product candidates do not obtain approval from regulatory authorities, the feasibility of undertaking future clinical trials for our product candidates based on policies and feedback from regulatory authorities, dependence on third parties to conduct clinical studies, delays or failure to achieve and maintain regulatory approvals for product candidates, risks of collaborating with or relying on third parties to discover, develop, manufacture and commercialize products, risks associated with establishing and maintaining sales, marketing and distribution capabilities with appropriate technical expertise and supporting infrastructure, potential future disagreements with Innoviva, Inc. and TRC LLC, the uncertainty of arbitration and litigation and the possibility that an arbitration award or litigation result could be adverse to the Company.

Other risks affecting the company are described under the heading "Risk Factors" and elsewhere in the Company's Form 10-K filed with the SEC on February 27, 2020, and other periodic reports filed with the SEC.

Lung selective JAK inhibitor targeted at cytokine storm



THE LANCET

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COVID-19: consider cytokine storm syndromes and immunosuppression

[Puja Mehta](#) • [Daniel F McAuley](#) • [Michael Brown](#) • [Emilie Sanchez](#) • [Rachel S Tattersall](#) • [Jessica J Manson](#)  • et al.

[Show all authors](#) Published: March 16, 2020 • DOI: [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)



As of March 12, 2020, coronavirus disease 2019 (COVID-19) has been confirmed in 125 048 people worldwide, carrying a mortality of approximately 3·7%,¹ compared with a mortality rate of less than 1% from influenza.

There is an urgent need for effective treatment. Current focus has been on the development of novel therapeutics, including antivirals and vaccines. Accumulating evidence suggests that a subgroup of patients

TD-0903

Pan-JAK Inhibitor Designed Specifically for Lung Diseases

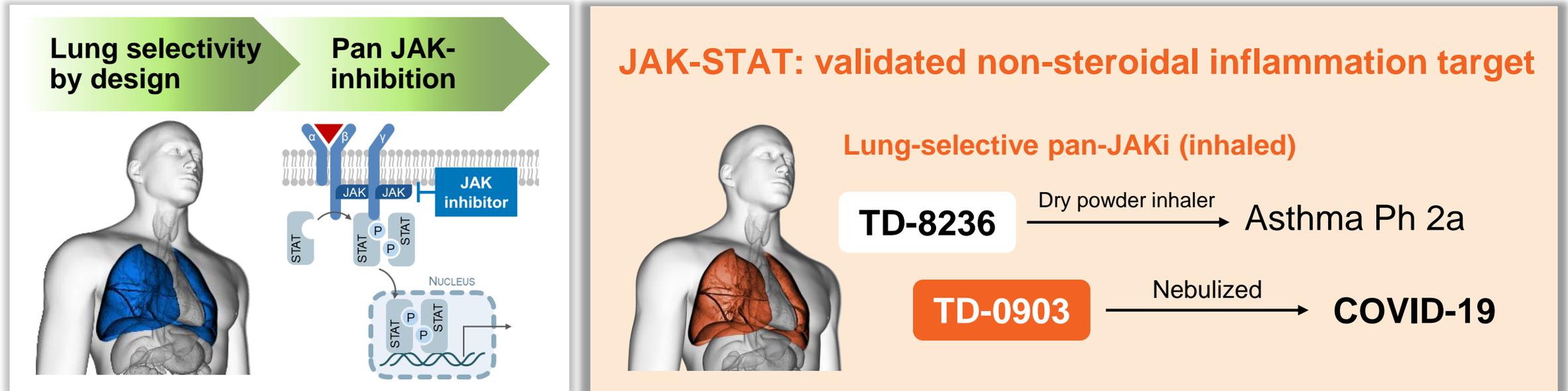
Leveraging >20 years of experience in design of novel respiratory drugs

Respiratory experience

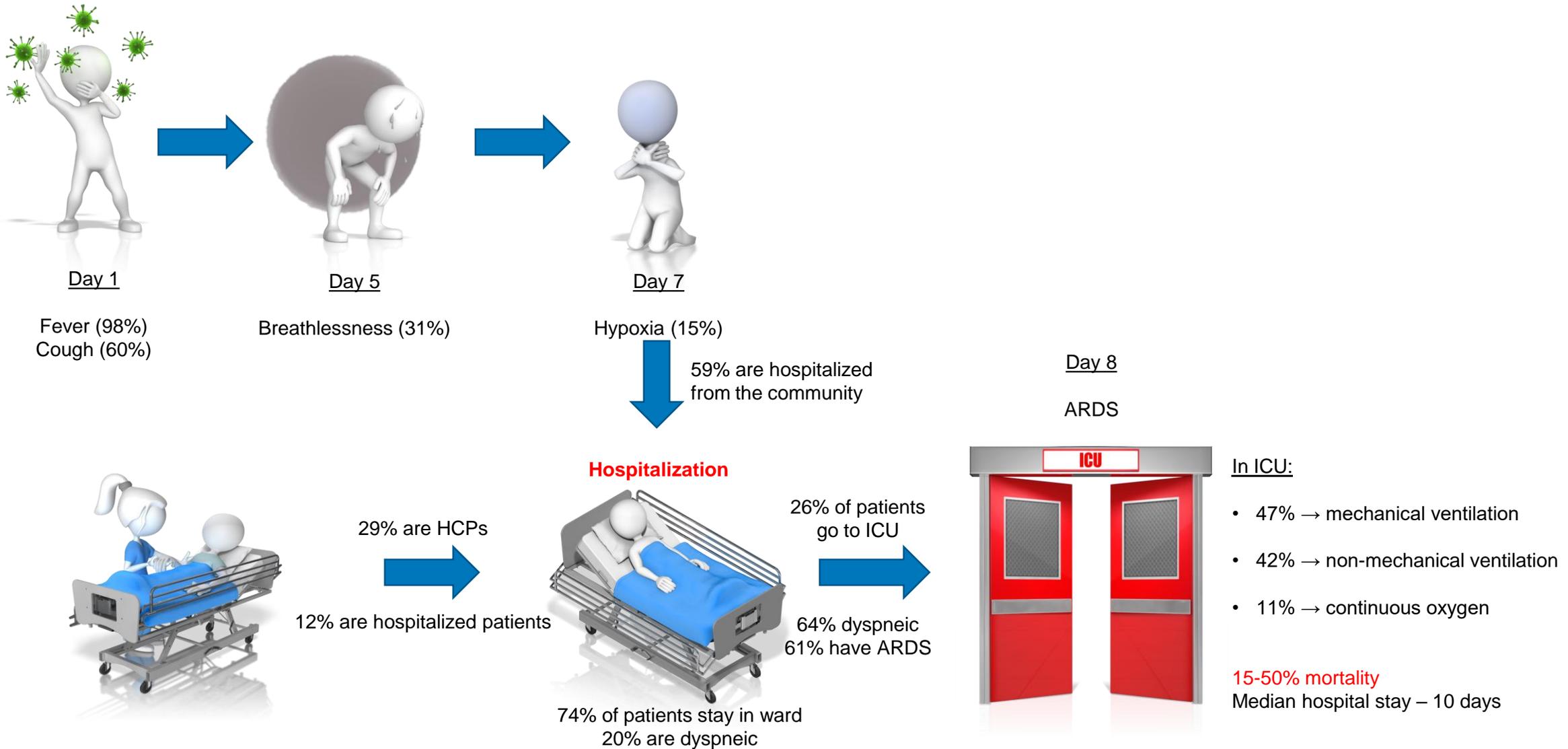
- ▶ Three commercial programs with GSK collaboration* (ANORO ELLIPTA, BREQ ELLIPTA, TRELEGY ELLIPTA)
- ▶ Discovered and developed YUPELRI® (revefenacin) inhalation solution, the first and only once-daily, nebulized bronchodilator approved for maintenance treatment for COPD

Organ-selective therapeutic targets

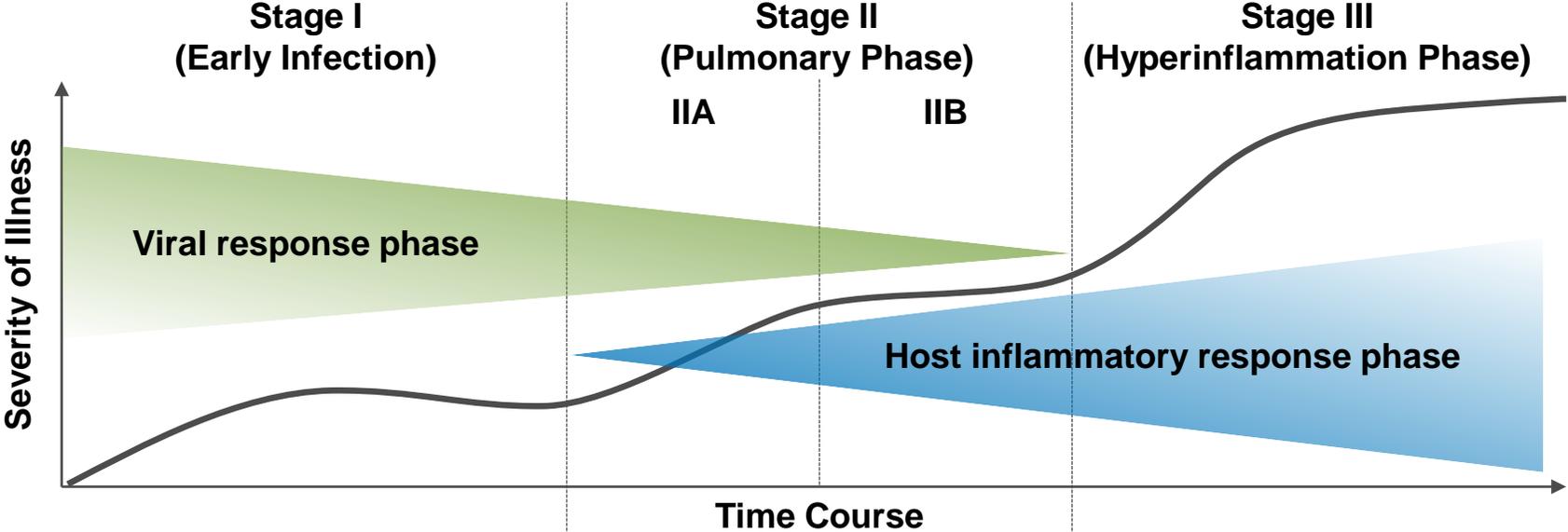
- ▶ Driving discovery, development and commercialization of organ-selective small-molecule medicines



Clinical course for patients who develop ALI and ARDS



Host Inflammatory Response to COVID-19 Drives ALI and ARDS



Clinical symptoms	Mild constitutional symptoms Fever >99.6°F Dry cough, diarrhea, headache	Shortness of breath Hypoxia (PaO ₂ /FiO ₂ ≤300 mmHg)	ARDS SIRS/shock Cardiac failure
Clinical signs	Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)	Abnormal chest imaging Transaminitis Low normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation
Potential therapies	Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions		
	Reduce immunosuppression	Corticosteroids, human immunoglobulin, IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors	

Adapted from Siddiqi HK, et al. J Heart Lung Transplant 2020 Mar 20.

Inhaled pan-JAK inhibitor could suppress dysregulated immune response (“cytokine storm”) in the lung

Inflammatory Response to Pathogenic hCoV Infections

Protective/regulated inflammation

CAUSES

- Non-robust virus replication
- Early IFN response
- ↑↑ Inflammatory monocyte-macrophage & neutrophil infiltration
- ↑↑ Proinflammatory cytokines and chemokines

CONSEQUENCES

- Minimal epithelial & endothelial cell apoptosis
- Reduced vascular leakage
- Optimal T cell and antibody responses
- Effective virus clearance

OUTCOMES

Protective immunity

Host survival

Pathogenic/dysregulated inflammation

- Robust virus replication
- Delayed IFN response
- ↑↑↑↑ Inflammatory monocyte-macrophage & neutrophil infiltration
- ↑↑↑↑ Proinflammatory cytokines and chemokines

- Enhanced epithelial & endothelial cell apoptosis
- Increased vascular leakage
- Suboptimal T cell and antibody responses
- Impaired virus clearance



Key targets for blockade by a lung-selective nebulized pan-JAK inhibitor

ALI

ARDS

Death

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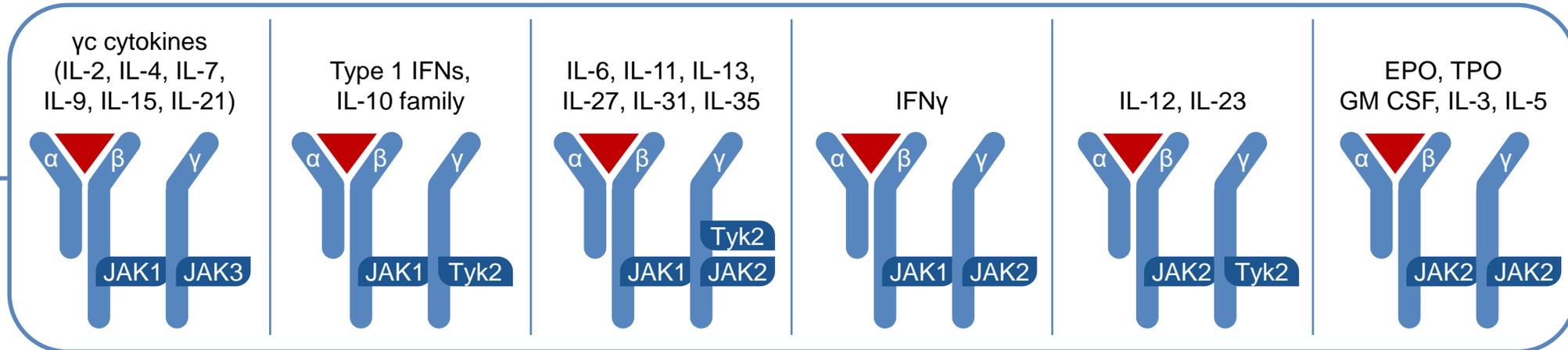
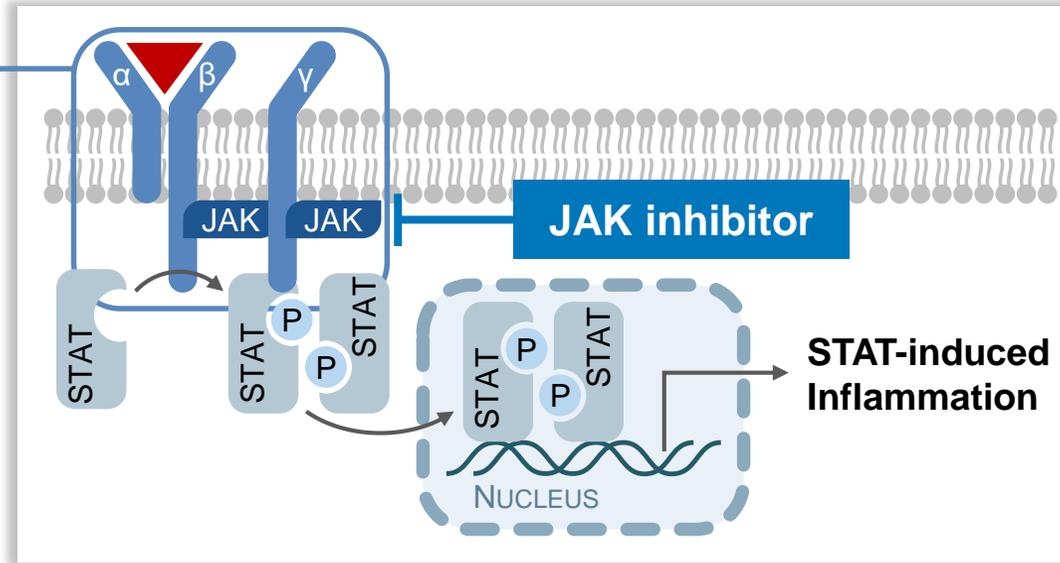
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COVID-19: consider cytokine storm syndromes and immunosuppression

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- A cytokine profile resembling sHLH is associated with COVID-19 disease severity, characterized by increased IL-2, IL-7, GCSF, IP-10, MCP-1, MIP1- α and TNF- α
- A multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765)

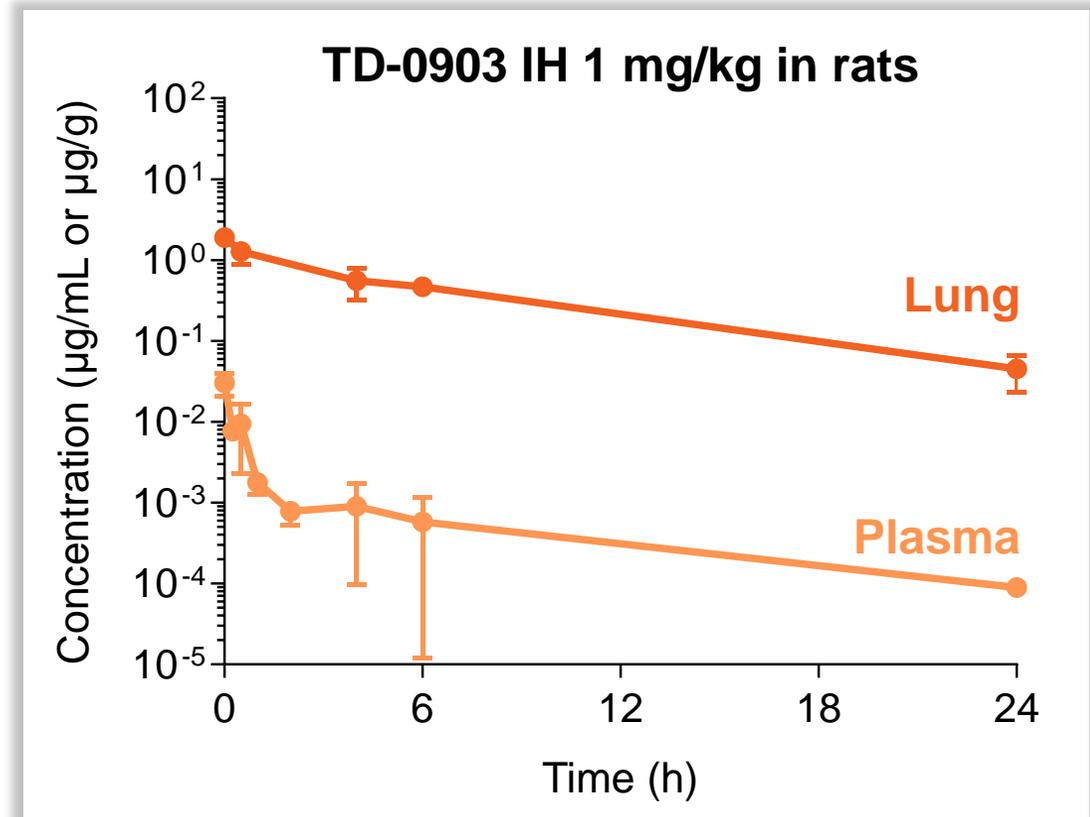
Pan-JAK inhibition: decrease signaling of multiple pro-inflammatory cytokines associated with COVID-19



TD-0903: Potent, lung-selective inhaled pan-JAKi

DESIGN: MAXIMAL ANTI-INFLAMMATORY ACTIVITY IN PULMONARY TISSUE WHILE MINIMIZING SYSTEMIC EXPOSURE

- ▶ High affinity for JAK1, JAK2, JAK3, and Tyk2 kinase domains
- ▶ High potency for inhibition of cytokine-induced activation of JAK-STAT signaling pathways
 - In vitro: human epithelial and immune cells
 - In vivo: murine inhalation cytokine-challenge models
- ▶ Lung-selective design
 - High lung to plasma ratios (rat ~170, dog ~850)
 - Rapid systemic clearance with no evidence of systemic immunosuppression
 - PK/PD modeling supports extended duration of action
- ▶ Well tolerated in 28-day rat and dog GLP studies
- ▶ Phase 1 FIH Study - Ethics Committee submission approved
- ▶ CTA enabling package submitted and under review with MHRA



Hospitalized COVID-19 patients with ALI have varying levels of ventilatory support

**Mechanical
Ventilation**



**High-Flow
Nasal Cannulation**



**Non-Invasive
Ventilation**



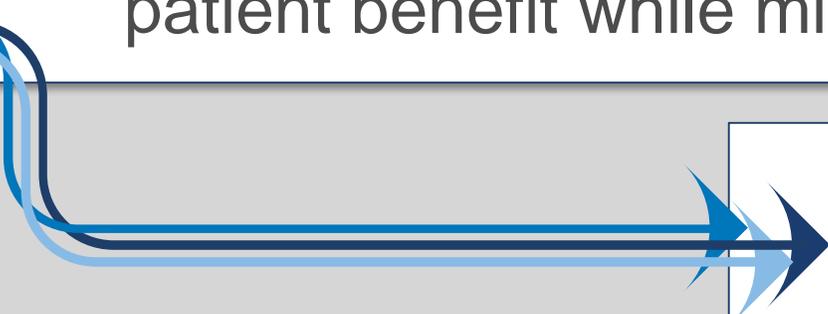
**Mask
Oxygen**



Nebulized delivery of an inhaled JAKi is optimal for hospital use

Our Mission

Transform the treatment of serious diseases through the discovery, development, and commercialization of **organ-selective medicines** designed to maximize patient benefit while minimizing patient risk



Apply lung selective JAK inhibition to fight cytokine storm in COVID-19