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

April 9, 2020
Forward looking statements

Under the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995, the company cautions investors that any forward-looking statements or projections made by the company are subject to risks and uncertainties that may cause actual results to differ materially from the forward-looking statements or projections.

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

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%, 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, including COVID-19...
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, BREO 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

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**Lung selectivity by design**

**Pan JAK-inhibition**

**JAK-STAT: validated non-steroidal inflammation target**

Lung-selective pan-JAKi (inhaled)

**TD-8236**
Dry powder inhaler
Asthma Ph 2a

**TD-0903**
Nebulized
COVID-19

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* Prior to Theravance Biopharma’s spin-off from Innoviva, Inc. in June 2014.

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DPI, dry powder inhaler; GSK, GlaxoSmithKline PLC; JAK, Janus kinase inhibitor; LTx, lung transplant; STAT, signal transducer and activator of transcription.
Clinical course for patients who develop ALI and ARDS


Day 1
Fever (98%) Cough (60%)

Day 5
Breathlessness (31%)

Day 7
Hypoxia (15%)
59% are hospitalized from the community

Day 8
ARDS

In ICU:
- 47% → mechanical ventilation
- 42% → non-mechanical ventilation
- 11% → continuous oxygen

15-50% mortality
Median hospital stay – 10 days

Hospitalization
26% of patients go to ICU
64% dyspneic
61% have ARDS

74% of patients stay in ward
20% are dyspneic

29% are HCPs
12% are hospitalized patients

Day 8
59% are hospitalized from the community

58% of patients stay in ward
20% are dyspneic

29% are HCPs
12% are hospitalized patients

In ICU:
- 47% → mechanical ventilation
- 42% → non-mechanical ventilation
- 11% → continuous oxygen

15-50% mortality
Median hospital stay – 10 days
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)
- 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

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

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

- **OUTCOMES**
  - ALI
  - ARDS
  - Death

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

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
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