PRM-151 IN
IDIOPATHIC PULMONARY FIBROSIS
AND
MYELOFIBROSIS

Beth Trehu, MD, FACP; Promedior
Bernt van den Blink, MD, PhD; Erasmus Medical Center
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Preclinical Collaborators
Jeremy Duffield, U Washington
David Brenner, UCSD
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Cory Hogoaboam, Cedars-Sinai
Erica Herzog, Yale U.
Darrell Pilling, Rice U.
Richard Gomer, Texas A&M
Mark Lupher

Quantitative Imaging Consultants
Brian Bartholmai, MD, Mayo Rochester
Ryan Chamberlain, PhD, Imbio

MF Investigators and Staff
Srdan Verstovsek, MD Anderson
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Most importantly, THANK YOU, to all the patients with IPF and MF who made these clinical trials possible.
PRM-151 IS RECOMBINANT HUMAN PENTRAXIN-2

Pentraxin-2 (PTX-2)
- 125 kD homopentameric plasma protein
- Regulator of innate immunity and fibrosis
- Produced and cleared by the liver
- Plasma levels 30-50 µg/mL
- Plasma levels lower in fibrotic diseases

PRM-151
- Recombinant human PTX-2
- Manufactured in CHO cells
- In clinical development for fibrotic diseases
PTX-2 binds to damaged tissue and regulates macrophages to drive resolution of fibrosis.

**Proinflammatory macrophages**
- MIP1α, IL-1β
- IP10, NOS2

**Profibrotic macrophages**
- M2 Mφ, CCL17, IL-13Rα2, MARCO, FIZZ1, CCL2, OSM, ST2

**Restorative macrophages**
- IL-10, MMPs
- TIMPs

**Fibrocyte**
- Collagen

Ca²⁺-dependent DAMP binding sites
Mono/Mφ FcγR binding sites

PTX-2/PRM-151 PREVENTS FIBROSIS IN 20 PRECLINICAL MODELS

- Ocular Fibrotic Disease Models; Rabbit, Mouse
  - Bleomycin; Rat, Mouse
  - TGF-β; Mouse
- Chronic Asthma; Mouse
- Acute Asthma; Mouse
- Ischemia/Reperfusion; Mouse
- Alport’s; Mouse
- Hypertrophic Scar; Pig, Mouse, Rat
- Carbon Tetrachloride; Mouse
- Bile duct ligation; Mouse
- Lung
- Liver
- Kidney
- Sk
- Bone marrow
- In injury-associated system
PTX-2 PREVENTS FIBROSIS IN LUNG, KIDNEY & LIVER

• Lung Fibrosis (TGFβ model)
  • Human PTX-2 20mg/kg IP q2d, d0-28

• Kidney Fibrosis (UUO model)
  • Human PTX-2, 20mg/kg IP q2d, d0-14

• Liver Fibrosis (Bile Duct Ligation)
  • Human PTX-2 10mg/kg IP q2d, d1-13
  • Courtesy of D. Brenner and T. Kisseleva, UCSD
PTX-2/PRM-151 REVERSES EXISTING FIBROSIS AND IMPROVES ORGAN FUNCTION IN LUNG AND KIDNEY

Bleomycin-induced lung fibrosis in mice and rats

Human PTX-2: 5mg/kg IP q2d, d11-19
Murray et al. 2010 PLoS One. 5:e9683

Rat PTX-2 1.6mg/kg IP q2d, d7-21

Kidney Fibrosis in Alport Syndrome (coll4a3/-) Mice

PRM-151 10 mg/kg IP, d29-31 then q 2 weeks | Nakagawa et al. American Soc Nephrology Annual Meeting 2013
CLINICAL DEVELOPMENT OF PRM-151 FOCUSED ON TWO ORPHAN INDICATIONS TO MEET OBJECTIVES

- Strong Preclinical and Phase 1 Foundation
  - Preclinical data: long-lasting effect after short term dosing
  - Phase 1a Healthy Volunteers: No dose limiting toxicity

- Indications: Myelofibrosis and Idiopathic Pulmonary Fibrosis

- Phase 2 Objectives
  - Demonstrate improvement in organ function
    - Objective, measurable endpoints
    - Correlation with survival
  - Demonstrate decrease in fibrosis
    - Tissue biopsies
    - New imaging techniques
  - Optimize Dose and Schedule
MYELOFIBROSIS (MF): MONOCYTIC BONE MARROW MALIGNANCY WITH ACCESSIBLE TISSUE AND OBJECTIVE OUTCOME MEASURES

- Bone marrow fibrosis
- Anemia, abnormal White Blood Cell and Platelet counts
- Splenomegaly, Hepatomegaly due to Extramedullary Hematopoiesis
- Symptoms Linked to Splenomegaly and Elevated Cytokines: IL-6, TNF-α, CRP
- 2-5 year median survival

Thiele Haematologica 2005; 90: 1128-1132
PRM-151 MAY ADDRESS MF UNMET NEED FOR THERAPY THAT IMPROVES ENDPOINTS CORRELATED WITH SURVIVAL

- MF Efficacy assessed by IWG-MRT Response Criteria
- Response requires confirmation at 12 weeks
- PRM-151 has potential to
  - Reverse fibrosis
  - Restore normal hematopoiesis
  - Induce differentiation of malignant monocytic clone

<table>
<thead>
<tr>
<th>Elements of IWG-MRT Response Criteria</th>
<th>Correlates with Survival</th>
<th>Improved by ruxolitinib (approved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>✓</td>
<td>□</td>
</tr>
<tr>
<td>Platelets</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>White Blood Cells</td>
<td>✓</td>
<td>□</td>
</tr>
<tr>
<td>Blasts</td>
<td>✓</td>
<td>□</td>
</tr>
<tr>
<td>BM Fibrosis</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Symptoms</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>□</td>
<td>✓</td>
</tr>
</tbody>
</table>
ADAPTIVE STUDY DESIGN PERMITS RAPID PROOF OF CONCEPT AND OPTIMIZATION OF DOSE AND SCHEDULE

Stage 1: 24 Patients

- Weekly PRM-151 + ruxolitinib
- Monthly PRM-151 + ruxolitinib
- Weekly PRM-151
- Monthly PRM-151

Criteria for Moving to Stage 2

- ≥ 1 response

Stage 2: 80 Patients

- Expansion of Stage 1 OR Additional Dose/Regimens

- 20 Patients

- 20 Patients

- 20 Patients

• 24 week treatment period
• Clinical and Laboratory Response Assessments every 4 weeks
• Bone Marrow biopsy every 12 weeks
• Patients with clinical benefit can continue beyond 24 weeks
IDIOPATHIC PULMONARY FIBROSIS (IPF)

- Characterized by excessive fibroblast proliferation /differentiation and ECM deposition

- Leading to progressive lung dysfunction
  - Reduced lung volume (decline in FVC)
  - Impaired gas exchange (decline in O2% sat)
  - Increased stiffness of the lungs
  - Shortness of breath, cough, reduced exercise capacity and eventually death

- Survival worse than most cancers
RATIONALE FOR PRM-151 IN IDIOPATHIC PULMONARY FIBROSIS (IPF)

- Immense unmet medical need
- Therapeutically dosed PRM-151 attenuated fibrosis and improved oxygenation in animal model of pulmonary fibrosis
- PTX-2 levels are reduced in patients with IPF
  - Lower levels correlate with lower FVC % predicted
- PRM-151 was safe in Phase 1a Healthy Volunteers study
- Prevention and/or reversal of fibrosis by PRM-151 could halt progression and potentially improve lung function
**PRM-151 IPF STUDY DESIGN**

<table>
<thead>
<tr>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>W1</th>
<th>W2</th>
<th>W3</th>
<th>W4</th>
<th>W5</th>
<th>W6</th>
<th>W7</th>
<th>W8</th>
<th>W9</th>
</tr>
</thead>
</table>

**PRM-151 @ 1 mg/kg, 5 mg/kg, or 10 mg/kg or Placebo**

IV days 1, 3, 5, 8 and 15

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**Screening**

-4 -3 -2 -1

**Observation**

W1 W2 W3 W4 W5 W6 W7 W8 W9

S S S S S S S S S S S

PFTs

6 min walk

SGRQ

CT

---

Clinicaltrials.gov: Identifier NCT01254409

*S* = Safety
## TREATMENT EMERGENT ADVERSE EVENTS:
### NO SERIOUS ADVERSE EVENTS

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<thead>
<tr>
<th>TEAE</th>
<th># Placebo (N=6)</th>
<th></th>
<th># PRM-151 (N=15)</th>
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<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
<td>Moderate</td>
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<tr>
<td>Cough</td>
<td>2</td>
<td></td>
<td>6</td>
<td>1</td>
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<tr>
<td>Productive Cough</td>
<td></td>
<td>2</td>
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<tr>
<td>Fatigue</td>
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<tr>
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<td></td>
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<td>2</td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Dyspnea, Exertional</td>
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<tr>
<td>Back Pain</td>
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<tr>
<td>Pruritus</td>
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</tr>
<tr>
<td>Dizziness</td>
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<tr>
<td>Nasopharyngitis</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Non-cardiac chest pain</td>
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<tr>
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<tr>
<td>Lymphadenopathy</td>
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Mean FVC % predicted *increased* by 2.4% in all PRM-151 treated subjects
Mean FVC % predicted *decreased* by 1.5% in placebo subjects

6/14 PRM-151 treated patients show 5-10% relative Change from Baseline at 8 weeks
EXPLORATORY ANALYSIS OF IMAGING BIOMarkers

- HRCT is a prognostic biomarker in IPF
  - Findings correlate with disease severity:
    - PFT/survival
- HRCT may identify subtle changes not reflected in FVC, yielding valuable additional data
- Great tool for assessing response?

- However: poor inter- and intra observer agreement
- Opportunity for automated quantitative imaging
AUTOMATED QUANTITATIVE IMAGING

- Analysis and quantification of parenchymal lung abnormalities

- Individual voxels are classified and colour-coded into classes of abnormalities (normal/ground glass/reticulation etc)

- Volume and percentage of Interstitial abnormalities predictive of survival *

- Explore (retrospective analysis) the use of imaging biomarkers as outcome measure

*F. Maldonado et al ERJ Express. Published on April 5, 2013
**AUTOMATED QUANTITATIVE IMAGING: EXAMPLE OF WORSENING**

**Subject Treatment Change from Screening to Day 57**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Treatment</th>
<th>Change from Screening to Day 57</th>
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<tbody>
<tr>
<td></td>
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<td>FVC%</td>
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<tr>
<td>202</td>
<td>Placebo</td>
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**Legend:**
- Normal
- Ground Glass
- Reticular
- Honeycomb
- Normal /LAA
AUTOMATED QUANTITATIVE IMAGING: EXAMPLE OF STABLE DISEASE

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<tr>
<td></td>
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<td>FVC%</td>
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<td></td>
</tr>
<tr>
<td>210</td>
<td>1 mg/kg</td>
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### AUTOMATED QUANTITATIVE IMAGING: EXAMPLE OF IMPROVEMENT

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<tr>
<td></td>
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<td>FVC%</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>206</td>
<td>5 mg/kg</td>
<td>8</td>
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#### Notes:
- **FVC%**: Forced Vital Capacity%
- **DLCO**: Diffusing Capacity of the Lung for Carbon Monoxide
- **6MWT**: 6-Minute Walk Test
- **SGRQ**: St. George’s Respiratory Questionnaire
- **IMBIO Quantitative Imaging**
  - **ILD**: Interstitial Lung Disease
  - **Non ILD**: Non-Interstitial Lung Disease
  - **Interpretation**: Improved

#### Diagram Notes:
- **Normal**
- **Ground Glass**
- **Reticular**
- **Honeycomb**
- **Normal /LAA**
CONCLUSIONS

- PTX-2/PRM-151 shows broad preclinical efficacy in numerous fibrotic disease models
- PRM-151 Safety Profile in humans remains excellent
- Encouraging efficacy signals in IPF patients support Phase 2 planning
- First Stage of Phase 2 MF trial fully enrolled
  - Final data available later this year
  - Bone marrow biopsies provide opportunity for direct demonstration of anti-fibrotic activity
- Planning for Stage 2