Forward-Looking Statements

This presentation and the oral commentary contain “forward-looking” statements that involve substantial risks and uncertainties. All statements other than statements of historical facts, including statements regarding our future financial condition, timing for and outcomes of clinical results, business strategy and plans and objectives for future operations, are forward looking statements. These forward-looking statements include terminology such as “believe,” “will,” “may,” “estimate,” “continue,” “anticipate,” “contemplate,” “intend,” “target,” “project,” “should,” “plan,” “expect,” “predict,” “could,” “potentially” or the negative of these terms Forward looking statements are our current statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned clinical development, the timing of and our ability to initiate or enroll clinical trials, and our ability to make regulatory filings and obtain and maintain regulatory approvals for lonafarnib, ubenimex, PEG IFN Lambda, exendin 9-39 and our other product candidates, our intellectual property position, the potential safety, efficacy, reimbursement, convenience clinical and pharmaco-economic benefits of our product candidates, commercial opportunities, including potential market sizes and segments, our ability to commercialize, expectations regarding clinical trial data and FDA outcomes, our results of operations, cash needs, spending of the proceeds from this offering, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

Forward-looking statements involve known and unknown risks, uncertainties, assumptions and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements represent our beliefs and assumptions only as of the date of this presentation. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

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Agenda

12:00 PM  Welcome  
- Company and Pipeline Overview  
- HDV Program Update / Next Steps  
  David Cory  
  Eiger

12:15 PM  Autoimmunity and Inflammation in PAH  
  Mark Nicolls, MD  
  Stanford

12:40 PM  Clinical Stage Therapies in PAH  
  Roham Zamanian, MD  
  Stanford

1:00 PM  Phase 2 LIBERTY Study Update  
  Joanne Quan, MD  
  Eiger

1:15 PM  Panel Discussion and Q&A  
  All
Mission

Eiger is a clinical-stage biopharmaceutical company committed to develop and commercialize novel products for the treatment of Orphan diseases.

Eiger has built a diverse, late-stage portfolio of well-characterized product candidates with the potential to address diseases for which the unmet medical need is high, a novel biology for treatment has been identified, and for which an effective therapy is urgently needed.

The Eiger management team has extensive experience in the clinical development and commercialization of a broad range of therapeutics, including Orphan Designation drugs.
Orphan Disease Focus

- 5 - Phase 2 programs in the clinic
- 4 - Well characterized compounds
- 4 - Therapeutically diverse orphan diseases
- Phase 2 POC data generated in lead programs
- Phase 2 data from all programs planned in 12-18 months
- Multiple shots on goal for clinical & regulatory success
## Development Pipeline

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lonafarnib</td>
<td>Hepatitis Delta</td>
<td></td>
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<tr>
<td>PEG IFN Lambda</td>
<td>Hepatitis Delta</td>
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<td>Exendin 9-39</td>
<td>Post-Bariatric Hypoglycemia</td>
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<td>Ubenimex</td>
<td>Pulmonary Arterial Hypertension</td>
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<td>Ubenimex</td>
<td>Lymphedema</td>
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Increase in HDV Testing in the U.S.
Poster Presentation at Digestive Disease Week 2017

Increasing % of Chronic HBV Patients Tested for HDV

Poster, DDW 2017, “Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review”
*Koh, C. et al, AASLD 2014, “Prenylation inhibition with lonafarnib decreases hepatitis D levels in humans”
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*Koh, C. et al, AASLD 2014, “Prenylation inhibition with lonafarnib decreases hepatitis D levels in humans”
Increased HDV Patient Diagnosis
Poster Presentation at Digestive Disease Week 2017

Estimated ~ 110,000 Individuals Co-infected with HBV/HDV in the U.S.

Poster, DDW 2017, Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10 Review
Phase 2: LOWR HDV Program
Key Findings from EASL 2017*

- All-oral LNF 25 or 50 mg BID + RTV suppresses HDV-RNA < LOQ
  - 5 of 14 (36%) patients < LOQ at Week 24
    - 1 patient PCR-negative at Week 24

- Addition of PEG to LNF 25 mg BID + RTV results in highest response rates
  - 4 of 5 (80%) patients < LOQ at Week 24
  - 3 of 5 (60%) patients PCR-negative at Week 24
    - 2 patients PCR-negative at 24 weeks post-treatment **

- 60-78% of patients normalized ALT at Week 24

- AEs predominantly mild / moderate for LNF 25 / 50 mg regimens

* QD dosing (LOWR HDV 3) and BID dose escalation (LOWR HDV 4) also presented at EASL 2017
** Low level viremia off-therapy
Potential Approaches for Development*
Goal: Provide Physicians & Patients Multiple Options to Treat HDV

- **Lonafarnib + Ritonavir**
  - All-Oral TRx

- **PEG IFN Lambda**
  - Monotherapy Sub Q TRx

- **Lonafarnib + Ritonavir + Lambda**
  - Combination TRx

* Investigational treatments to be discussed with regulatory agencies
PAH Product Timeline of Approvals
PAH Product Timeline of Approvals

Flolan® (epoprostenol)

1990 1995

GlaxoWellcome
PAH Product Timeline of Approvals

Flolan®
(epoprostenol)
1995

GlaxoWellcome
PAH Product Timeline of Approvals

Flolan® (epoprostenol)

1995

1990

2020

GlaxoWellcome
PAH Product Timeline of Approvals

- Flolan® (epoprostenol): 1995
- Tracleer® (bosentan): 2001

GlaxoWellcome

ACTELION
PAH Product Timeline of Approvals

- Flolan® (epoprostenol) 1995
- Tracleer® (bosentan) 2001
- Remodulin® (treprostinil) 2002
PAH Product Timeline of Approvals

- **Flolan®** (epoprostenol), 1995
- **Tracleer®** (bosentan), 2001
- **Remodulin®** (treprostinil), 2002
- **Ventavis®** (iloprost), 2004
PAH Product Timeline of Approvals

- Flolan® (epoprostenol) - 1995
- Tracleer® (bosentan) - 2001
- Remodulin® (treprostinil) - 2002
- Ventavis® (iloprost) - 2004
- Revatio® (sildenafil) - 2005
PAH Product Timeline of Approvals

- **Flolan® (epoprostenol)**: 1995
- **Tracleer® (bosentan)**: 2001
- **Remodulin® (treprostinil)**: 2002
- **Ventavis® (iloprost)**: 2004
- **Revatio® (sildenafil)**: 2005

The timeline shows the development and approval of various PAH (Pulmonary Arterial Hypertension) treatments from 1995 to 2005, highlighting key products and their respective companies.
PAH Product Timeline of Approvals

- **1995**
  - Flolan® (epoprostrenol)

- **2001**
  - Tracleer® (bosentan)

- **2002**
  - Remodulin® (treprostinil)

- **2004**
  - Ventavis® (iloprost)

- **2005**
  - Revatio® (sildenafil)

- **2007**
  - Letairis® (ambrisentan)
PAH Product Timeline of Approvals

- **Flolan®** (epoprostenol) 1995
- **Tracleer®** (bosentan) 2001
- **Remodulin®** (treprostinil) 2002
- **Ventavis®** (iloprost) 2004
- **Revatio®** (sildenafil) 2005
- **Letairis®** (ambrisentan) 2007
- **Adcirca®** (tadalafil) 2009
PAH Product Timeline of Approvals

- **Flolan® (epoprostenol)**: 1995
- **Tracleer® (bosentan)**: 2001
- **Remodulin® (treprostinil)**: 2002
- **Ventavis® (iloprost)**: 2004
- **Letairis® (ambrisentan)**: 2007
- **Revatio® (sildenafil)**: 2005
- **Orenitram® (treprostinil)**: 2013
- **Adcirca® (tadalafil)**: 2009
- **Adempas® (riociguat)**: 2015
- **Opsumit® (macitentan)**: 2016
- **Opsumit® (macitentan)**: 2016
PAH Product Timeline of Approvals

1995
- Flolan® (epoprostenol)

2001
- Tracleer® (bosentan)

2002
- Remodulin® (treprostinil)

2004
- Ventavis® (iloprost)

2005
- Revatio® (sildenafil)

2007
- Letairis® (ambrisentan)

2009
- Adcirca® (tadalafil)

2013
- Orenitram® (treprostinil)

2015
- Uptravi® (selexipag)

2020
- Adempas® (riociguat)
- Opsumit® (macitentan)
- Opsumit® (treprostinil)
Pulmonary Arterial Hypertension

- PAH is a $4 Billion+ worldwide Orphan Disease market*
- 12+ approved agents for PAH are vasoactive
- Combinations have had a dramatic impact on PAH
- Vasodilators fail to reverse vascular remodeling
- Long term survival remains poor
- Novel targets needed
- Disease-modifying agents desired

Targeting Leukotriene B\textsubscript{4} in PAH

Mark Nicolls, MD

Professor of Medicine
Chief, Division of Pulmonary & Critical Care Medicine,
Stanford University School of Medicine / VA Palo Alto
Disclosures

• Cofounder, Eiccose LLC (programs now in Eiger BioPharmaceuticals, company currently investigating the role of LTB$_4$ modulation in clinical PAH: LIBERTY Study)

• Clinical Consultant for Eiger BioPharmaceuticals
Outline

• Animal Model – How we came to be interested in inflammation.
• The role of regulatory T cells (Tregs)
• History of leukotrienes in PH
• LTB₄ biology in experimental PH
• Intervention in animal models
• Human analysis
• Role of BMPRII
PAH is an inflammatory disease
Autoimmunity in Pulmonary Hypertension

- Association of autoimmune disorders and pulmonary hypertension recognized over 50 years ago

- Idiopathic PH also has evidence of immune dysregulation:
  - ANA+ (30-40%)
  - anti-Ku Ab+ (23%)
  - antiphospholipid Ab+ (10-15%)
  - unique anti-endothelial cell anti-fibroblast antibodies
Abnormal Treg activity favors PAH

Abnormal Tregs in Systemic Sclerosis

• Reduced Treg subsets in SSc patients.

• Activated and resting regulatory T cell exhaustion in SSc
  • Mathian et al, *Ann Rheum Dis* 2012; 71:1227-34

• ↓ frequency & functional defect of peripheral Treg cells SSc patients reversed by HSCT
  • Baraut et al, *Bone Marrow Transplantation* 2014; 49, 349–354
Model

- Athymic inbred nude rats
- VEGF receptor-2 antagonist
  - SU5416
  - 20 mg sc x 1 (d0) or
  - DMSO (vehicle control)
Leukotrienes

Amy Tian, PhD

Leukotrienes involve the metabolism of arachidonic acid (AA) through the action of lipoxigenases (5-LO and p5-LO) to produce various leukotrienes, including LTA₄, LTA₄H, LTB₄, LTC₄, and LTC₄S. These compounds can act as leukocyte attractants and smooth muscle vasoconstrictors.

- **Leukocyte attractant**: LTA₄, LTA₄H, LTB₄
- **Smooth muscle vasoconstrictor**: LTC₄, LTC₄S
LEUKOTRIENE C₄ AND D₄ IN NEONATES WITH HYPOXEMIA AND PULMONARY HYPERTENSION

Kurt R. Stenmark, M.D., Simon L. James, F.R.A.C.P., Norbert F. Voelkel, M.D., Warren H. Toews, M.D., John T. Reeves, M.D., and Robert C. Murphy, Ph.D.

Abstract Persistent pulmonary hypertension of the newborn is a syndrome consisting of severe hypoxemia and pulmonary hypertension that appears within hours of birth. Since certain leukotrienes (C₄, D₄, and E₄) are known to produce some of the features of persistent pulmonary hypertension of the newborn, including pulmonary vasoconstriction, bronchoconstriction, decreased lung compliance, and pulmonary edema, we studied five newborns with the syndrome to determine whether these leukotrienes were present in their airways. We found leukotriene C₄ and leukotriene D₄ in the lung lavage fluids of all five newborns who had the clinical diagnosis of persistent pulmonary hypertension and who required ventilatory assistance. In contrast, leukotrienes were not demonstrated in a control group of 14 infants requiring ventilatory assistance who did not have the clinical diagnosis of persistent pulmonary hypertension.

We conclude that leukotrienes may have a role in persistent pulmonary hypertension of the newborn. (N Engl J Med 1983; 309:77-80.)
Why did Kurt Stenmark and Bob Murphy care about leukotrienes in PH in 1983?

- “Certain leukotrienes (C₄, D₄, E₄) – can cause pulmonary vasoconstriction….”

- “We wondered whether leukotrienes might be present in persistent PH of newborn”
5-Lipoxygenase (5-LO) and PH: 1990s

Inhibition of 5-Lipoxygenase-activating Protein (FLAP) Reduces Pulmonary Vascular Reactivity and Pulmonary Hypertension in Hypoxic Rats

Norbert F. Voelkel, Rubin M. Tudor, Kelly Wade, Marius Höper, Robert A. Lepley, Jennifer L. Goulet, Beverly H. Koller, and Frank Fitzpatrick

Pulmonary Hypertension Center, Departments of Pathology and Pharmacology, University of Colorado Health Sciences Center, Denver, Colorado 80262; and Department of Medicine, University of North Carolina, Chapel Hill, North Carolina 27599

J. Clinical Invest 1996; 97:2491-2498

5-Lipoxygenase and 5-Lipoxygenase Activating Protein (FLAP) Immunoreactivity in Lungs from Patients with Primary Pulmonary Hypertension

Laurel Wright, Rubin M. Tudor, Jun Wang, Carlyne D. Cool, Robert A. Lepley, and Norbert F. Voelkel

Division of Pulmonary Sciences and Critical Care Medicine, Departments of Medicine, Pathology, Pediatric Oncology, and Pharmacology, University of Colorado Health Sciences Center, Denver, Colorado

Why did Norbert Voelkel and Rubin Tuder care about 5-LO in PH in the 90s?

- Blocking leukotrienes (indomethacin, diethylcarbamazine) inhibited hypoxia- and monocrotaline-induced PH.

- **Hypothesis:** “inflammation is an important aspect in the pathogenesis of PPH and, specifically that key inflammatory enzymes participating in leukotriene synthesis are more abundantly present in pulmonary vessels an alveolar macrophages of PPH patients.”
5-Lipoxygenase (5-LO) and PH: 2000s

\[
\text{AA} \xrightarrow{p5-LO} \text{LTA}_4 \xrightarrow{5-LO} \text{LTA}_4 \xrightarrow{\text{LTA}_4} \text{LTC}_4 \xrightarrow{\text{LTC}_4} \text{LTB}_4 \]

- Leukocyte attractant
- Smooth muscle vasoconstrictor

Effect of 5-lipoxygenase on the development of pulmonary hypertension in rats

Inflammation, endothelial injury, and persistent pulmonary hypertension in heterozygous BMPR2-mutant mice

Joseph Loscalzo
Why did Ying-Yi Zhang and Joe Loscalzo care about leukotrienes in PH in 2000s?

• Building on prior work in field
• Interested in three questions:
  – Does ↑ 5-LO cause PH? (NO)
  – Does ↑ 5-LO facilitate PH caused by other factors? (YES)
  – Does ↑ 5-LO + BMPR2 haploinsufficiency = PH (YES)
Leukotrienes

Amy Tian, PhD

AA \xrightarrow{5-LO} LTA_4 \xrightarrow{LTA_4H} LTB_4 \quad \text{Leukocyte attractant}

AA \xrightarrow{p5-LO} LTA_4 \xrightarrow{LTC_4S} LTC_4 \quad \text{Smooth muscle vasoconstrictor}
Invasion of Activated Macrophages in PH

Activated macrophages near diseased arterioles secrete LTB$_4$: high in BAL and blood

Rising LTB$_4$-secreting macrophages in PH lungs

Increased LTB$_4$ in BAL of PH

Increased LTB$_4$ in serum of PH
Macrophages from PH lungs kill pulmonary artery endothelial cells

**Annexin V**

**PI**

**Cleaved Caspase-3**

**DAPI**

Normal Lung

PH Lung

Endothelial cells after 24 h culture
Macrophage-derived LTB₄ Sufficient to Kill PAECs

PAECs cultured with normal macrophages transfected with S271E 5-LO

Increased LTB₄ in BAL of PH

PAECs cultured with 200 nM LTB₄
Mechanism of LTB$_4$-mediated PAEC Apoptosis

LTB$_4$ $ightarrow$ BLT1

↓Sphk1 $\rightarrow$ ↓S1P $\rightarrow$ ↓eNOS $\rightarrow$ ↓NO
LTB₄ Induces Pulmonary Artery Smooth Muscle Cell Growth

Fold Change of Proliferation

Fold Change of Protein/DNA Ratio

LTB4+U75302

0 nM 200 nM 400 nM 200 nM

* NS *
LTB₄ Induces Pulmonary Arteriolar Fibroblast Proliferation


Jin Qian, MD PhD

Amy Tian, PhD
LTB₄ Induces Pulmonary Arteriolar Fibroblast Migration

LTB₄ induces Pulmonary Arteriolar Fibroblast Differentiation into Myofibroblasts

Interrogating the Leukotrienes in PH: Blocking LTB₄ Reverses Advanced Disease

![Diagram showing the relationship between LTB₄ and various compounds including Bestatin, JNJ, Montelukast, and LY293111.](image)

Bar graph showing the effect of different compounds on RVSP (mmHg) and survival (%).
Initiating LTB₄-directed Therapies in Advanced Disease Opens Closed Vessels
Selective LTB₄ Antagonism is More Effective than Blocking Eicosanoids
Our studies show that the biosynthetic machinery is highly active in the epicenter of pulmonary hypertension: the plexiform lesion.
Elevated LTB₄ Levels in PH Patients

New R01 with clinical study to correlate serum LTB₄ levels with clinical disease activity in PAH

- Roham Zamanian (Medical Director of Stanford PH Program)
- 294 patients evaluated
- 50-60 with SSc-PAH

Elevated \( \text{LTB}_4 \) Levels in Systemic Sclerosis PAH

Creating BMPR2\(^{+/-}\) Transgenic Rat

- BMPR2 mutations strongly associated with fPAH
- Zinc finger nuclease technology
- 527 base pair frameshift mutation
  - exon 5 (kinase domain), 50% human mutations
- Rats did not spontaneously develop PH
- No pronounced differences with SU5416 / MCT
- 3 years!!
BMPR2 Mutation Synergizes with LTB₄ to Cause PH
LTB₄ Mediates PAECs Transformation in a BMPR2-Dependent Fashion
1. Blocking LTB₄ decreases macrophage recruitment and related inflammation
   (Multiple studies dating back to 1980s)
   - THEN NEW DISCOVERIES 2013-2015-

2. Blocking LTB₄ limits:
   • Apoptosis of *normal* endothelial cells
   • Abnormal growth of *normal* pulmonary smooth muscle cells
   • Activation, proliferation and migration of adventitial fibroblasts
     (Science Translational Medicine 2013, Hypertension 2015)
     - AND NOW, ADDING TO THESE EFFECTS -

3. Blocking LTB₄ removes growth factor for *abnormal* transformed cells
   (Manuscript to be submitted Summer 2017)
Ubenimex _kills_ diseased PAH lung cells

1 week after therapy started: vessels open _as abnormal cells die_

pulmonary endothelial cells

pulmonary smooth muscle cells
Summary

apoptosis-resistant intimal cells

- LTB4 as growth factor for transformed endothelium
Acknowledgements

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Amy Tian
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**Stanford**
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**NHLBI Stanford Proteomics Center**
Marlene Rabinovitch
Garry Nolan

**Michigan**
Marc Peters-Golden

**VCU**
Norbert Voelkel

**Funding**
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NIH Trial (ASC01)
NHLBI R56HL082662
NHLBI R01 HL125739
P01HL014985
Therapies in Development for Treatment of Pulmonary Arterial Hypertension

Roham T. Zamanian, MD, FCCP

Associate Professor of Medicine
Director, Adult Pulmonary Hypertension Clinical Service
Division of Pulmonary & Critical Care Medicine
Stanford University School of Medicine
Disclosures

Personal financial relationships with commercial interests relevant to medicine, within the past 3 years:

**Consultant:** United Therapeutics, Bayer, Actelion, Selten, Vivus, Gilead

**Industry-Sponsor Research:** United Therapeutics, Actelion, Eiger, REATA

**Stock-options & Shares:** Genentech (spouse); Selten (self)

**Patents:** FK506 for treatment of PAH

Personal financial relationships with non-commercial interests relevant to medicine, within the past 3 years:

**Research Grants:**
- Vera Moulton Wall Center for Pulmonary Vascular Disease
- NIH/NHLBI
PAH: A Hemodynamic Disease

Normal Heart

PAH

Constriction of pulmonary arterioles

PVR = pulmonary vascular resistance; PAOP = pulmonary artery occlusion pressure

Enlarged right ventricle
Current Therapeutic Options for PAH

**Traditional Therapies**
- Supplemental O₂
- Diuretics
- Oral vasodilators
  - CCB
- Anticoagulants
  - Warfarin
- Inotropic agents
  - Digitalis

**FDA Approved Therapies for PAH**
- Prostanoids / IP
  - Epoprostenol (IV)
  - Treprostinil*
  - (IV / SQ / Oral / Inhaled)
  - Inhaled Iloprost
  - Selexipeg (oral)
- Endothelin Receptor Antagonists (ERA)
  - Bosentan*
  - Ambrisentan
  - Macitentan
- Phosphodiesterase-5 (PDE-5) Inhibitors
  - Sildenafil*
  - Tadalafil
- Guanylate Cyclase Stimulator (GCS)
  - Riociguat

* Patent Expired / Expiring
# Investigational Agents for PAH

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Delivery</th>
<th>MOA</th>
<th>Clinical Status By Stage</th>
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<tbody>
<tr>
<td>bardoxolone methyl</td>
<td>Oral</td>
<td>antioxidant inflammation modulator</td>
<td>Phase 3</td>
</tr>
<tr>
<td>ralinepag</td>
<td>Oral</td>
<td>prostacyclin receptor agonist</td>
<td>Phase 2</td>
</tr>
<tr>
<td>ubenimex</td>
<td>Oral</td>
<td>LTA₄ hydrolase inhibitor aminopeptidase inhibitor</td>
<td>Phase 2</td>
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<tr>
<td>rituximab</td>
<td>IV</td>
<td>anti-CD20</td>
<td>Phase 2</td>
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<tr>
<td>tacrolimus</td>
<td>Oral</td>
<td>BMPR2 activator</td>
<td>Planned</td>
</tr>
<tr>
<td>KAR5585</td>
<td>Oral</td>
<td>tryptophan hydrolase inhibitor</td>
<td>Planned</td>
</tr>
<tr>
<td>acebilustat</td>
<td>Oral</td>
<td>LTA₄ hydrolase inhibitor</td>
<td>Planned</td>
</tr>
</tbody>
</table>
Bardoxolone Methyl
Nrf2 Activator / NF-kB suppressor

• Oral, Nrf2 activator and NF-κB suppressor
  - Previously called antioxidant inflammation modulator (AIM)
  - Previously studied in renal cancer, chronic kidney disease (CKD)

• CKD in Type 2 Diabetes
  - Phase 2 successful (Abbott partnership)
  - Phase 3 halted due to SAEs and mortality in bardoxolone arm

• Phase 2 in PAH (LARIAT study):
  - double-blind, randomized, PBO-controlled
  - dose ranging study with 2.5, 5, 10, 20 mg QD (N=24)
  - WHO Group 1 patients on 1-2 background therapies
  - Primary Objectives
    ▪ change in 6MWD from baseline to 16 weeks
    ▪ safety and tolerability through 16 weeks
    ▪ determine recommended dose range for further study
Bardoxolone Methyl  
Phase 2 LARIAT Study – Results

- Increased 6MWD on background PAH therapies vs PBO
- 6MWD increases seen at lowest dose; no dose-response
- No hemodynamic measurements
- AE profile manageable

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Absolute Δ6MWD(^a) (95% Confidence Interval)</th>
<th>Placebo-corrected treatment effect (95% Confidence Interval)</th>
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</thead>
<tbody>
<tr>
<td>Bardoxolone Methyl 2.5 mg</td>
<td>6</td>
<td>30.3 (13.5, 47.0)</td>
<td>30.0 (6.0, 53.9)</td>
</tr>
<tr>
<td>Bardoxolone Methyl 5 mg</td>
<td>6</td>
<td>14.0 (-2.8, 30.9)</td>
<td>13.7 (-10.5, 37.9)</td>
</tr>
<tr>
<td>Bardoxolone Methyl 10 mg</td>
<td>4</td>
<td>19.7 (-0.8, 40.2)</td>
<td>19.4 (-7.2, 46.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td>0.2 (-16.8 – 17.1)</td>
<td>-</td>
</tr>
</tbody>
</table>
Bardoxolone Methyl
Phase 3 CATALYST Study in CTD-APAH Patients

- CTD-APAH on \( \leq 2 \) background Rx, 1:1 bardoxolone methyl or PBO
- Estimated enrollment 130-200 patients, international sites
- QD dosing for 24 wks; start at 5 mg and dose-escalate to 10 mg at Wk 4
- Primary endpoint: change from baseline in 6MWD versus PBO at Wk 24
- Secondary endpoint
  - Time to first clinical improvement as measured by improvement in WHO FC
  - Increase from baseline in 6MWD by at least 10%
  - Decrease from baseline in creatine kinase
    - surrogate biomarker for muscle injury and inflammation by 10%
- No hemodynamic measurements
- CATALYST data expected during the first half of 2018
Ralinepag
Prostacyclin (IP) Receptor Agonist

- Oral, selective prostacyclin receptor agonist
- Phase 2, randomized, double-blind, PBO controlled
- Primary endpoints: improvement in PVR and 6MWD
- Dose-titration to a maximum tolerated dose, 22-week dosing
- 60 patients, international sites
- Data expected 3Q 2017
Ubenimex
Inhibits LTB₄ Production

- Oral, small molecule, LTA₄H inhibitor
- Immune modulator, anti-proliferative
- Well-characterized, safe and well tolerated
- Marketed in Japan by Nippon Kayaku
- Approved as adjuvant to chemotherapy for NLL*
- Never introduced in the US or EU
- Phase 2 LIBERTY study in PAH ongoing

*Non-Lymphocytic Leukemia
Clinicaltrials.gov NCT02736149
Rituximab in SSc-PAH
Monoclonal Antibody to CD20

• Marketed for NHL, CLL, RA, GPA*

• Phase 2, randomized, double-blind, PBO controlled study

• 48 week study, 2 IV infusions, 1000 mg, every 2 weeks

• 60 patients, US sites, NIH Sponsorship

• Objective: Evaluate effect of rituximab on disease progression in SSc-PAH patients receiving stable-dose of prostacyclin, ERA and/or PDE-5

• Primary Endpoint: Change in PVR baseline to 24 weeks

• Secondary Endpoints: 6MWD, time to clinical worsening, QoL, digital ulcers, Raynaud phenomenon, DLCO and O₂ saturation

* Non-Hodgkins Lymphoma, Chronic Lymphocytic Leukemia, Rheumatoid Arthritis, Granulomatosis Polyangitis

Clinicaltrials.gov NCT01086540
FK506 (tacrolimus*)
Activator of BMP Signaling

• Compassionate Use (n=3, 1 year)
  - Low-dose FK506 stabilized clinical course and RV function in 3 end-stage PAH patients

• Phase 2a TrANsFoRM PAH study (n=40, 16 weeks)
  - Evaluate safety, tolerability and efficacy of FK506
  - Identify potential responders to therapy to guide “patient enrichment strategies” for a Phase 2b/3 efficacy study
  - Study completed

• Next Steps:
  - Validate biomarker approach
  - Inform Phase 2b/3 study for patient enrichment

*calcineurin-inhibitor immunosuppressant indicated for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants
Clinicaltrials.gov NCT01647945
KAR5585
Tryptophan Hydrolase Inhibitor

- Designed to reduce peripheral serotonin (5HT)
  - Goal: Reduce 5HT-associated vascular remodeling and fibrosis

- Preclinical data in PAH animal models
  - Reduced vascular remodeling and occlusions

- Phase 1 SAD and MAD clinical studies completed

- Plans to initiate a double-blind, randomized Phase 2 trial
Acebilustat
LTA$_4$ Hydrolase Inhibitor

- Oral, small molecule, LTA$_4$H inhibitor
- Phase 2 study in Cystic Fibrosis ongoing
- Activity in bleomycin-induced PAH mouse model
  - Reduction in fibrotic tissue volume
  - Reduction in systolic pulmonary artery pressure
- Company announced plans to file PAH IND in Q3 2017
  - Plans to initiate Phase 2 in PAH in Q4 2017
Increasing 6MWD Improves Mortality
Approved Therapies Have Improved 6MWD

Number at Risk

Time from Enrollment (Months)

| 6MWD <165 m | 204 | 183 | 165 | 146 | 138 |
| 6MWD 165-440 m | 1,556 | 1,528 | 1,482 | 1,431 | 1,390 |
| 6MWD >440 m | 610 | 607 | 602 | 598 | 587 |

Patients with Baseline 6MWD

- 6MWD <165 m (n=204)
- 6MWD 165-440 m (n=1,556)
- 6MWD >440 m (n=610)

1-year survival estimate ± SE

- 68.4%±3.3%
- 90.4%±0.7%
- 96.9%±0.7%


Note: One-year survival estimates are shown for patients with a baseline 6MWD <165 m (blue), 165-440 m (green), and >440 m (orange). Stars mark the 1-year survival estimates for patients with a 6MWD of >440-m threshold (white star) and patients with a 6MWD of ≤165-m threshold (black star). 6MWD=6-minute walking distance; m=meter; SE = standard error.
Registration End Points in PAH Clinical Trials

Hemodynamics (PVR) Measurements Important

- Six Minute Walk Distance (6MWD)
- Pulmonary Vascular Resistance (PVR)

Outcomes Trials Differentiate Follow On Compounds

- Time to First Morbidity or Mortality Event
  - selexipag (2\textsuperscript{nd} oral prostacyclin)

- Time to First Event: Death, Morbidity, Clinical Worsening
  - macitentan (3\textsuperscript{rd} endothelin antagonist)
Registration End Points in PAH Clinical Trials

6MWD Remains Approvable Primary Endpoint for Registration

- Six Minute Walk Distance (6MWD)
- Pulmonary Vascular Resistance (PVR)

Outcomes Trials Differentiate Follow On Compounds

- Time to First Morbidity or Mortality Event
  - selexipag (2nd oral prostacyclin)

- Time to First Event: Death, Morbidity, Clinical Worsening
  - macitentan (3rd endothelin antagonist)
Carl Hicks, former Executive VP of Pulmonary Hypertension Association, with daughter, Meaghan
Meaghan at Stanford Hospital in 2007
LIBERTY:
Phase 2 Study Update

Joanne Quan, MD
Chief Medical Officer
Eiger BioPharmaceuticals
Ubenimex
Marketed in Japan Since 1987

- Oral, small molecule, LTA₄H inhibitor
- Blocks production of LTB₄
- Approved adjuvant to chemotherapy for non-lymphocytic leukemia in JP
- Approved dose: 30 mg daily
  - Within first 5 years of approval > 45,000 patients treated
  - Well-characterized, safe and well-tolerated
- Daily doses up 900 mg / day documented
- Never introduced in the US or EU; NCE Status
- Orphan Designation in PAH in US / EU Granted
- US Patent Allowance for Claims in PAH Granted
LIBERTY: Study Design

• Proof of concept study for LTB₄ inhibition in PAH

• Randomized, double-blind, placebo-controlled, parallel-group study

• 45 sites in North America (US, Canada)

• Enrollment target: 45 – 60 patients
  – 2:1 active:placebo

• Study drug dose = Ubenimex 150 mg TID
  – Goal: dose sufficient to maximize clinical signal
  – Dose ranging, if needed, to be explored in Phase 3
LIBERTY: Patient Population

- WHO Group 1: iPAH, APAH, including CTD-PAH
- WHO/NYHA Functional Class II or III
- Required to be on stable dose of $\geq 1$ PAH-specific drug
- All approved PAH-specific therapies allowed
- 6 Minute Walk Distance (6MWD) $\geq 150$ m and $\leq 550$ m
- Right-Heart Catheterization (RHC) demonstrating:
  - $mPAP \geq 25$ mmHg
  - $PCWP \leq 15$ mmHg
  - $PVR \geq 300$ dyn-sec/cm$^5$
- No significant obstructive or restrictive lung disease

$mPA = \text{pulmonary arterial pressure},\ PCW = \text{pulmonary capillary wedge, PVR = pulmonary vascular resistance}$
• Primary Efficacy Endpoint
  – Δ in Pulmonary Vascular Resistance (PVR)

• Secondary EfficacyEndpoints
  – Δ in 6MWD
  – Δ in WHO/NYHA Functional Class
  – Time to clinical worsening
  – Quality of Life
  – Δ in disease markers (BNP/NT-pro BNP)

• Pharmacokinetic

• Safety
A Randomized, Double-Blind, Placebo-Controlled Study of Ubenimex in Patients with Pulmonary Arterial Hypertension

Months 1-6

N≈40

Standard of Care¹
+ Ubenimex 150 mg TID

N≈20

Standard of Care¹
+ PBO

Primary Endpoint:
Pulmonary Vascular Resistance

Secondary Endpoint:
Six Minute Walk Distance (6MWD)

Primary Efficacy Evaluation

¹ On at least one of PDE5 inhibitor / sGC inhibitor and/or endothelin receptor antagonist and/or prostacyclin
Clinicaltrials.gov NCT02736149
LIBERTY: Phase 2 Study
Open-Label Extension Study

A Randomized, Double-BLInf, Placebo-Controlled Study of UBenimex in Patients with Pulmonary ARTerial Hypertension

Months 1-6

- Standard of Care\(^1\) + Ubenimex 150 mg TID
- Standard of Care\(^1\) + PBO

Months 6+

- Standard of Care\(^1\) + Ubenimex 150 mg TID
- Standard of Care\(^1\) + PBO

Primary Endpoint:
Pulmonary Vascular Resistance

Secondary Endpoint:
Six Minute Walk Distance (6MWD)

Safety and Efficacy Follow-up

Primary Efficacy Evaluation

\(^1\) On at least one of PDE5 inhibitor / sGC inhibitor and/or endothelin receptor antagonist and/or prostacyclin

Clinicaltrials.gov NCT02736149
LIBERTY: North American Sites
45 Sites Activated
LIBERTY: Enrollment Complete
May 2017

- Planned enrollment: 45 – 60
- Actual enrollment: 61
- Patient Demographics
- Last patient out anticipated November 2017
- Topline data at JPM - January 2018
LIBERTY Study

Key Players

• Lead Investigator: Roham Zamanian, MD

• Steering Committee
  – Nicholas Hill, MD (Chair)
  – Marc Humbert, MD
  – James Seibold, MD

• Data Safety Monitoring Board
  – Bruce Brundage, MD (Chair)
  – Harold Palevksy, MD
  – Charles Davis, PhD (biostatistician)
Ubenimex in PAH Timeline
Phase 2 / Phase 3 Plan

2016

Enrollment

LIBERTY
Phase 2 Study
N = 61

2017

Dose

2018

Topline Data
JPM 2018

EOP2

Initiate Phase 3 Study
An Orphan Disease Company by Design

Discussion and Q&A Session