Updated Therapeutic Strategies in the Management of Pulmonary Arterial Hypertension

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Disclosure of Commercial Interest

Dr. Badesch has received grant/research support from the NIH, United Therapeutics / Lung Rx, Actelion / CoTherix, Gilead, Pfizer, Lilly, Bayer, Novartis, Ikaria, Bellerophon, Arena, and Reata.

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He has also provided consultation to legal counsel for Actelion.
Pulmonary Arterial Hypertension

Key Points:

- Non-specific symptoms → delayed diagnosis
- Poor prognosis without therapy
- Methodical evaluation, including catheterization required
- Evolving therapies → improved prognosis (but not yet normal)

A Disease of Decline and Deterioration: IPAH Survival if Untreated

- Poor prognosis in an era lacking therapy
- Therapeutic options and research efforts now offer more hope

PAH: Hemodynamic and Clinical Course

Adapted from Gaine S. JAMA. 2000;284:3160-3168.

Clinical Classification of Pulmonary Hypertension (Dana Point)

1. PAH
   - Idiopathic PAH
   - Heritable
   - Drug- and toxin-induced
   - Persistent PH of newborn
   - Associated with:
     - CTD
     - HIV infection
     - portal hypertension
     - CHD
     - schistosomiasis
     - chronic hemolytic anemia

2. PH Owing to Left Heart Disease
   - Systolic dysfunction
   - Diastolic dysfunction
   - Valvular disease

3. PH Owing to Lung Diseases and/or Hypoxia
   - COPD
   -ILD
   - Other pulmonary diseases with mixed restrictive and obstructive pattern
   - Sleep-disordered breathing
   - Alveolar hypoventilation disorders
   - Chronic exposure to high altitude
   - Developmental abnormalities

4. CTEPH

5. PH With Unclear Multifactorial Mechanisms
   - Hematologic disorders
   - Systemic disorders
   - Metabolic disorders
   - Others

The REVEAL Registry: WHO Subgroup at Enrollment

N=2525

N=1280


The REVEAL Registry: Mean Age and Gender Distribution at Enrollment

Age at Enrollment (years)  n=2525

Percent Female  n=2525

REVEAL: Observed 1-year Survival From Time of Enrollment According to Predicted Risk Strata


No. at risk:

- Low: 1374, 1368, 1364, 1359, 1356, 1352, 1351, 1346, 1341, 1336, 1311, 1304, 1303
- Average: 665, 659, 657, 653, 648, 647, 640, 628, 625, 618, 604, 602, 596
- Mod. high: 280, 277, 274, 269, 264, 263, 260, 259, 255, 254, 249, 244, 243
- Very high: 102, 100, 96, 89, 81, 74, 72, 69, 61, 59, 55, 52, 49

PAH Registries: Functional Class at Diagnosis Indicates Delayed Diagnosis

% Patients NYHA Functional Class III-IV at Diagnosis

- More common in women
- Spans broad age range
- Delay in diagnosis persists
- Most patients diagnosed with late symptoms
- Poor prognosis if untreated

**Is There a Reason to Suspect PAH?**

**Clinical Presentation**

<table>
<thead>
<tr>
<th>Common Initial Symptoms (N=187)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Syncope or near syncope</td>
<td>13</td>
</tr>
<tr>
<td>Chest pain</td>
<td>7</td>
</tr>
<tr>
<td>Palpitations</td>
<td>5</td>
</tr>
<tr>
<td>Leg edema</td>
<td>3</td>
</tr>
</tbody>
</table>


**Diagnostic Approach**

- RVE, RAE, ↑RVSP
- Left heart disease
- VHD
- CHD
- Echocardiogram
- Emphysema
- ILD
- Thoracic abnl
- Sleep disorder
- Sleep study
- Ventilation-perfusion scan, Contrast CT, Angiography
- HIV test
- Functional test
  - BNP
  - RH cath
- Vasodilator test
- Autoantibody tests
- Scleroderma
- SLE
- RA
- Vasculitis
- Chronic thrombo-embolism
- Portopulmonary hypertension
- LFTs and clinical evidence of cirrhosis and portal htn
- HIV
- Exam
- CXR
- ECG
- PFTs

Dana Point Hemodynamic Definition of PH/PAH

**PH**
Mean PAP ≥25 mm Hg

**PAH**
Mean PAP ≥25 mm Hg *plus* PCWP/LVEDP ≤15 mm Hg


PH: The Importance of Hemodynamics

Pulmonary venous hypertension
*Elevated PCWP, normal PVR*

- PAH
- PH with respiratory disease
- CTEPH

*Normal PCWP, elevated PVR*
Chronic Pulmonary Embolism

Ventilation Perfusion Lung Scan

Idiopathic Pulmonary Arterial Hypertension

Chronic Pulmonary Embolism

CTEPH: A “Curable” Form of PH Not to Be Missed
Cardiac Catheterization

- Exclude congenital heart disease
- Measure wedge pressure or LVEDP
- Establish severity and prognosis
- Test vasodilator therapy

*Catheterization is required when pulmonary hypertension is suspected*

PAH Treatment Goals

- Fewer/less severe symptoms
- Improved exercise capacity
- Improved hemodynamics
- Prevention of clinical worsening
- Improved quality of life
- Improved survival
What Is the Optimal Treatment Strategy?

Anticoagulate ± Diuretics ± Oxygen ± Digoxin

Acute Vasoreactivity Testing

- Positive
- Negative

Oral CCB

Sustained Response

Yes

Continue CCB

LOWER RISK
- No
- Gradual
- Longer (>400 m)
- Peak VO₂ >10.4 mL/kg/min

Minimal RV dysfunction
- RAP <10 mm Hg;
- CI >2.5 L/min/m²

Minimally elevated

Determinants of Risk
- Clinical evidence of RV failure
- Progression of symptoms
- WHO class
- 6MWD
- CPET

Echocardiography

Hemodynamics

BNP

Significantly elevated

Higher Risk
- Yes
- Rapid
- IV
- Shorter (<300 m)
- Peak VO₂ <10.4 mL/kg/min
- Pericardial effusion, significant RV enlargement/dysfunction; RA enlargement
- RAP >20 mm Hg;
- CI <2.0 L/min/m²

Other Management Issues

• Encourage exercise and activity within the limits of disease and ability to maintain O₂ levels
• Immunizations
• Contraception

What Is the Optimal Treatment Strategy?

Calcium Channel Blockers Only If “Vasodilator Responsive”

“Vasodilator Response”

- Fall in mPAP ≥10 mm Hg
- + PAPm (absolute) <40 mm Hg
- + Normal CO


Survival in IPAH

**Long-term CCB Responders**

\[p=0.0007\]

Subjects at risk, n

\[
\begin{array}{cccccccc}
\text{Years} & 0 & 2 & 4 & 6 & 8 & 10 & 12 & 14 & 16 & 18 \\
\text{Subjects at risk, n} & 38 & 33 & 30 & 22 & 13 & 8 & 3 & 2 & 1 & 0 \\
\end{array}
\]

Approved Therapeutic Targets


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Approved Therapeutic Targets

IV Epoprostenol in IPAH: Change From Baseline in 6MWD


IV Epoprostenol in PAH Due to Scleroderma: Change From Baseline in 6MWD

Survival Among Patients With IPAH: Epoprostenol vs Conventional Therapy

Subcutaneous Treprostinil: Change From Baseline in 6MWD Overall and by Dose Quartile

*Two-sided, by log-rank test.

*Hodges-Lehmann estimate
Treprostinil IV: 6MWD (TRUST)

* $p=0.022$. 6MWD values are mean+SE.


Inhaled Iloprost: Change From Baseline in 6MWD (AIR Trial)

$6MWD$ was not the primary end point in the AIR trial.

Inhaled Treprostinil: Median Change in 6MWD (TRIUMPH)

- **Hodges-Lehmann estimate of treatment effect.**
- **Peak:** between 10-60 min after dose. **Trough:** ≥ 4 hr after dose.


Prostanoid Side Effects

- **Flushing**
- **Headache**
- **Diarrhea, nausea, vomiting**
- **Jaw pain**
- **Leg pain**
- **Hypotension**
- **Dizziness**
- **Syncope**
- **Cough (inhaled)**
- **Delivery site complications**

*Vary according to drug and route of delivery*
Approved Therapeutic Targets


Bosentan*: 6-MWD (351 and BREATHE-1)


**p<0.05 vs baseline; p=0.021 vs placebo. Values are mean±SEM.
Bosentan: Time to Clinical Worsening (BREATHE-1 and EARLY)


Would Earlier Treatment Be Better?
The “EARLY” Study

Ambrisentan* in PAH: 6MWD (ARIES)

ARIES-1
- 10 mg ambrisentan
- 5 mg ambrisentan
- Placebo

ARIES-2
- 5 mg ambrisentan
- 2.5 mg ambrisentan
- Placebo


Ambrisentan in PAH: Time to Clinical Worsening (ARIES)

ARIES-1
- 5 mg ambrisentan
- 10 mg ambrisentan
- 5 and 10 mg ambrisentan
- Placebo

ARIES-2
- 2.5 mg ambrisentan
- 5 mg ambrisentan
- 2.5 and 5 mg ambrisentan
- Placebo

Endothelin Receptor Antagonists: Side Effects

• Nasal congestion
• Abnormal hepatic function
  – reversible transaminase elevations >3X ULN
  – may require dose adjustments or discontinuations
  – monthly LFTs required for bosentan
• Edema
  – lower extremity edema may require diuretic adjustment
• Use requires dual contraceptive methods (hormonal plus barrier)

Treatment of Pulmonary Arterial Hypertension (PAH)
Macitentan – “SERAPHIN”


Background:
• ERA’s, PDE5-I’s, and prostacyclins have been approved for the treatment of PAH
• The dual ERA macitentan was developed by modifying the structure of bosentan to increase efficacy and safety.
  – Macitentan is characterized by sustained receptor binding and enhanced tissue penetration.

Design:
• SERAPHIN was a multicenter, double-blind, randomized, placebo-controlled, event-driven, phase 3 trial.
• Investigated whether long-term treatment with macitentan reduces TTCW among patients with PAH.
• Patients with symptomatic PAH were randomized to receive placebo once daily, macitentan at a once-daily dose of 3 mg, or macitentan at a once-daily dose of 10 mg.
• Stable use of oral or inhaled therapy for PAH, other than ERA’s, was allowed at study entry.
Treatment of Pulmonary Arterial Hypertension (PAH)

Macitentan – “SERAPHIN”


Primary Endpoint:
• The composite primary end point was time from the initiation of treatment to the first event related to PAH, as defined by:
  – Worsening of PAH, defined by all 3 of the following:
    • Decrease in 6MWD of at least 15% from baseline
    • Worsening of symptoms of PAH
    • Need for additional treatment for PAH
  – Initiation of treatment with intravenous or subcutaneous prostanoids
  – Lung transplantation
  – Atrial septostomy
  – Death from any cause

Secondary Endpoints:
• Change from baseline to month 6 in 6MWD
• Percentage of patients with an improvement in WHO FC at month 6
• Death due to PAH up to end of treatment and up to end of study
• Safety endpoints included adverse events and laboratory abnormalities

With respect to safety, there seemed to be an increased occurrence of anemia with macitentan.
Approved Therapeutic Targets

Endothelin Pathway
- Pre-proendothelin → Proendothelin
- Endothelin-1
- Endothelin receptor A
- Exogenous nitric oxide

Nitric Oxide Pathway
- L-arginine → L-citrulline
- L-arginine
- Nitric Oxide
- Exogenous nitric oxide
- Phosphodiesterase type 5
- Vasodilation and antiproliferation

Prostacyclin Pathway
- Prostacyclin (prostaglandin I2)
- Prostacyclin derivatives

Effect of Sildenafil* on 6MWD (SUPER)


Placebo
- 20 mg of sildenafil
- 40 mg of sildenafil
- 80 mg of sildenafil

Change In 6MWD (m)

Week

*p<0.001
Sildenafil: Incidence of Clinical Worsening (SUPER)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=70)</th>
<th>20 mg tid (n=69)</th>
<th>40 mg tid (n=67)</th>
<th>80 mg tid (n=71)</th>
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</thead>
<tbody>
<tr>
<td>Clinical worsening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– death</td>
<td>7 (10)</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>– hospitalization for PAH</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>– initiation of prostacyclin</td>
<td>7 (10)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>– initiation of bosentan</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

\[p=NS\]. Clinical worsening defined as death, transplantation, hospitalization for PAH, or initiation of additional therapies for PAH.


Effect of Tadalafil* on 6MWD (PHIRST)

\[p<0.001\] \[p<0.05\] \[p<0.05\]

Effect of Tadalafil on Time to Clinical Worsening (PHIRST)


PDE-5 Side Effects

- Nose bleed
- Headache
- Dyspepsia
- Flushing
- Diarrhea
- Visual changes
- Contraindicated with use of nitrates
Background:

- Riociguat is a member of a new class of agents called soluble guanylate cyclase stimulators.
- It has a dual mode of action, directly stimulating soluble guanylate cyclase (sGC) independently of nitric oxide (NO), and increasing the sensitivity of sGC to NO.

Design:

- Phase 3, multicenter, randomized, double-blind, placebo-controlled
- 443 patients with symptomatic PAH were randomized to receive placebo, riociguat in individually adjusted doses of up to 2.5 mg three times daily
- Patients who were receiving no other treatment for PAH and patients who were receiving ERA’s or (nonintravenous) prostanoids were eligible.
Treatment of Pulmonary Arterial Hypertension (PAH)  
Riociguat – “PATENT”


**Primary Endpoint:**
- Change from baseline to the end of week 12 in 6MWD.

**Secondary Endpoints:**
- Changes from baseline in PVR, NT-proBNP level, WHO FC, TTCW, Borg dyspnea score, QOL, and safety.

**Results:**
- Riociguat significantly improved:
  - exercise capacity, as assessed by 6MWD
  - PVR, PAPm, CO
  - In the 2.5 mg maximum group,
    - NT-proBNP, WHO FC, Borg Score, and clinical worsening events also improved
- Adverse Events included:

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**Graph**

- Observed
- Imputed

0 2 4 6 8 10 12

Week

- Change from Baseline in 6-Minute Walk Distance (m)

- Day 0: 247, 243, 241, 235, 233
- Day 12: 121, 117, 116, 111, 126
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- Vascular disorder characterized by organized thrombotic obstructions in the pulmonary arteries
- Can be associated with small vessel vasculopathy indistinguishable from idiopathic PAH
- CTEPH is associated with increased risk of mortality
  - In one study, the 5-year survival rate in patients with CTEPH was 30% with mPAP >40 mm Hg, and 10% with mPAP >50 mm Hg
  - 62 out of 679 patients in a registry died in <10 months
  - Right ventricular heart failure is the most common cause of death


CTEPH Epidemiology

- ~600,000 individuals in the United States have an acute PE annually
- Incidence of CTEPH is ~4% within 2 years in patients with first episode of PE
- A significant proportion of patients have no history of clinically overt pulmonary embolism
- CTEPH may be under-recognized and under-diagnosed

Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)


Background:

• CTEPH is characterized by obstruction of the pulmonary vasculature by residual organized thrombi, leading to increased PVR, PH, and RVF.

• Patients with CTEPH have a poor prognosis without early treatment.

• Pulmonary thromboendarterectomy (PTE) is the standard treatment for CTEPH and the only potentially curative treatment.

• Surgery is not an option for all patients:
  – occlusion of distal vessels
  – coexisting conditions
  – some decline surgery
  – some do not have access to expert surgical centers.

• Operability should be assessed at an experienced PTE center.

• Some patients who undergo PTE have persistent or recurrent PH.

CTEPH Management

CTEPH Anticoagulation

Operable
- PEA is the treatment choice

Durable
- operative success

Non-operable
- PEA not possible owing to distal obstruction and/or comorbidities

Persistent/ recurrent PH

CTEPH patients who are appropriate candidates for medical therapy

Background:

- Riociguat is a member of a new class of agents called soluble guanylate cyclase stimulators.
- It has a dual mode of action, directly stimulating soluble guanylate cyclase (sGC) independently of nitric oxide (NO), and increasing the sensitivity of sGC to NO.

Design:

- Phase 3, multicenter, randomized, double-blind, placebo-controlled
- 261 patients with inoperable CTEPH or persistent or PH after PTE were randomized to receive placebo or riociguat.

Primary Endpoint:

- Change from baseline to the end of week 16 in 6MWD.

Secondary Endpoints:

- Changes from baseline in PVR, NT-proBNP level, WHO FC, TTCW, Borg dyspnea score, QOL, and safety.

Results:

- Riociguat significantly improved:
  - exercise capacity, as assessed by 6MWD
  - PVR in patients with CTEPH
  - NT-proBNP level.
- Adverse Events included:
  - Headache, dizziness, dyspepsia, hypotension.
Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)


What Is the Optimal Treatment Strategy?

5th World Symposium on PH, Nice, FR: 2013 PAH Treatment Algorithm

- Supervised exercise training (I-A)
- Psycho-social support (I-C)
- Avoid strenuous physical activity (I-C)
- Avoid pregnancy (I-C)
- Influenza and pneumococcal immunization (I-C)

General measures and supportive therapy

Expert Referral (I-C)

Acute vasoreactivity test (I-C for IPAH) (IIb-C for APAH)

VASOREACTIVE

WHO FC I-II
CCB (I-C)

Sustained response
(WHO FC I-II)

NO

INITIAL THERAPY WITH PAH-APPROVED DRUGS

NON-VASOREACTIVE

YES

Continue CCB

Oral anticoagulants:
- IPAH, heritable PAH, and PAH due to anorexigens (IIa-C)
- APAH (IIb-C)
- Diuretics (I-C)
- Oxygen (I-C)
- Digoxin (IIb-C)

5th World Symposium on PH: 2013 PAH Treatment Algorithm

INITIAL THERAPY WITH PAH-APPROVED DRUGS

YELLOW: Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined)
Level of evidence based on WHO-FC of majority of patients of studies

<table>
<thead>
<tr>
<th>Evidence</th>
<th>WHO FC II</th>
<th>WHO FC III</th>
<th>WHO FC IV</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>A or B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Iloprost IV*, Treprostinil IV
- Ambrisentan, Bosentan, Epoprostenol IV
- Iloprost inh
- Macitentan
- Riociguat
- Sildenafil
- Tadalafil
- Treprostinil SC, inh
- Ambrisentan, Bosentan, Iloprost inh and IV*
- Macitentan
- Riociguat
- Sildenafil, Tadalafil
- Treprostinil SC, IV, Inh*

5th World Symposium on PH: 2013 Treatment Algorithm Caveat

- Since 5th World Symposium, oral treprostinil has been approved by FDA for treatment of PAH (WHO Group 1) to improve exercise capacity
- Study that established effectiveness included predominantly patients with WHO FC II-III symptoms and etiologies of IPAH or heritable PAH (75%) or CTD-associated PAH (19%)
- As sole vasodilator, effect on exercise is small
- Oral treprostinil has not been shown to add to other vasodilator therapy

At time of 5th World Symposium, treatment working group had examined clinical evidence published at that time and noted:
- Oral treprostinil had been evaluated in 2 RCTs in PAH patients on background therapy with bosentan and/or sildenafil and, in both, primary endpoint of 6MWD did not reach statistical significance
- Additional RCT in PAH-naive patients showed improvement in 6MWD by 26 m at peak dose


5th World Symposium on PH: 2013 Treatment Algorithm

INITIAL THERAPY WITH PAH-APPROVED DRUGS

Sequential Combination Therapy (I-A)

- Prostanoids + PDE-5 I or SGCs
- ERAs

Inadequate Clinical Response

Consider Eligibility for Lung Transplantation

Referral for Lung Transplantation (I-C)

Inadequate Clinical Response on Maximal Therapy

Balloon Atrial Septostomy (IIa-C)

Combination Therapy

SGC Stimulators

PATENT-1*

Prostanoids

TRIUMPH
STEP

Endothelin
Receptor
Antagonists

PATENT-1*

PHIRST* SERAPHIN†

AMBITI0N
COMPASS-2

Phosphodiesterase
Inhibitors

TRIUMPH
PACES

*53% on background ERA for PHIRST, 50% on background ERA or prostanoid for PATENT-1
†64% on background PDE-5 I or prostanoid in SERAPHIN.

French Registry: Kaplan-Meier Survival Estimates According to Baseline NYHA Functional Class

Survival (%)

NYHA I/II NYHA III NYHA IV

Time (mo)

0 12 24 36

0 100

No. at risk:

NYHA I/II 12 15 19 23 24 26 27
NYHA III 37 48 70 79 86 88 89
NYHA IV 7 6 9 11 10 13 17

Combined idiopathic, familial, and anorexigen-associated PAH.
French Registry: Kaplan-Meier Survival Estimates According to Baseline 6MWD

Combined idiopathic, familial, and anorexigen-associated PAH.

Plasma BNP as a Prognostic Indicator in Patients With IPAH

By multivariate analysis, higher BNP at follow-up (RR=25.880, p=0.0243) was an independent predictor of mortality.
Sildenafil Added to Epoprostenol (PACES)


Combination Therapy: Other Ongoing or Recently Completed Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Current therapy</th>
<th>Added therapy</th>
<th>Patients (n)</th>
<th>Study duration</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREEDOM-C</td>
<td>Bosentan and/or sildenafil</td>
<td>Epoprostenol</td>
<td>300</td>
<td>16 weeks</td>
<td>6MWD</td>
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<tr>
<td>AMBITION</td>
<td>Ambrisentan/ treprostinil</td>
<td>Combo vs mono</td>
<td>300</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
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<tr>
<td>Pfizer</td>
<td>Epoprostenol</td>
<td>Sildenafil</td>
<td>106</td>
<td>12 weeks</td>
<td>6MWD</td>
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<td>COMPASS-1</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>45</td>
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<td>PVR</td>
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<td>COMPASS-2</td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>250</td>
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<td>ATHENA-1</td>
<td>Sildenafil or tadalafil</td>
<td>Ambrisentan</td>
<td>40</td>
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<td>PVR</td>
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<td>SERAPHIN</td>
<td>Naive/PGI/6PGL/comb</td>
<td>Macitentan</td>
<td>742</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
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<tr>
<td>PATENT</td>
<td>Naive/PGI/ERA</td>
<td>Riociguat</td>
<td>462</td>
<td>12 weeks</td>
<td>6MWD</td>
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<tr>
<td>IMPRES</td>
<td>≥2 current therapies</td>
<td>Imatinib</td>
<td>200</td>
<td>24 weeks</td>
<td>6MWD</td>
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<td>ATPAHSS</td>
<td>Ambrisentan/ tadalafil</td>
<td>Combo vs mono</td>
<td>63</td>
<td>36 weeks</td>
<td>RV mass/PVR</td>
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<td>GRIPHON</td>
<td>ERA, PDE5 or both</td>
<td>Selaxipag</td>
<td>670</td>
<td>Event-driven</td>
<td>Morbidity/mortality event</td>
</tr>
</tbody>
</table>
AMBITION Study – Initial ABS+TAD Combination (NEJM)

Study Design

Clinic Visits Every 12 Weeks
Safety Visits Every 4 Weeks

Randomized
(2:1:1)

Treatment-Naïve PAH Patients
(N = 610)*

Screening
Week 0
105
Clinical Failure Events
Primary Endpoint

ABS 10mg + TAD 40mg
n=302

ABS 10mg + TAD PBO
n=152

TAD 40mg + ABS PBO
n=151

ABS 10mg + TAD 20mg

ABS 5mg + TAD PBO

TAD 20mg + ABS PBO

ABS 5mg + TAD 20mg

ABS 5mg + TAD PBO

TAD 40mg + ABS PBO

ABS 5mg + TAD 40mg

ABS 5mg + TAD PBO

TAD 20mg + ABS PBO

ABS 5mg + TAD PBO

TAD 40mg + ABS PBO

ABS 5mg + TAD PBO

All randomized patients received 4 pills daily


AMBITION Study – Initial ABS+TAD Combination (NEJM)

Novel Primary Study Endpoint

Time to Clinical Failure (TTCF) = Time from randomization to first event* of:

- Death (all-cause)
- Hospitalization for worsening PAH
- Disease progression
- Unsatisfactory long-term clinical response

- Any hospitalization for worsening PAH
- Lung or heart/lung transplant
- Atrial septostomy
- Initiation of parenteral prostanoid therapy

- >15% ↓ 6MWD from baseline at 2 consecutive clinic visits
- WHO FC III or IV symptoms at 2 consecutive clinic visits
- Received at least one dose of randomized treatment and enrolled in the study for at least 6 months
- Any ↓ 6MWD from baseline at 2 consecutive clinic visits
- WHO FC III symptoms at 2 clinic visits separated by ≥ 6 months

Secondary Study Endpoints

- Change from Baseline at Week 24
  - NT-proBNP
  - Percentage of subjects with a satisfactory clinical response
    - 10% improvement in 6MWD compared to baseline
    - Improvement to or maintenance of WHO FC I or II symptoms
    - No events of clinical worsening prior to or at the Week 24
  - 6-Minute Walk Distance (6MWD)
  - WHO Functional Class
  - Borg Dyspnea Index (immediately following exercise)

AMBITION Study – Initial ABS+TAD Combination (NEJM)

Study Inclusion Criteria

<table>
<thead>
<tr>
<th>Demographics and PAH Classification</th>
<th>Diagnostic Tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 and ≤ 75 years</td>
<td>6MWD ≥ 125 m and ≤ 500 m</td>
</tr>
<tr>
<td>Weight ≥ 40 kg</td>
<td>mPAP ≥ 25 mmHg</td>
</tr>
<tr>
<td>Diagnosis with idiopathic or heritable, or PAH associated with CTD, drugs/toxins, HIV, or CHD</td>
<td>PVR ≥ 300 dyn·sec/cm²</td>
</tr>
<tr>
<td>WHO FC II and III symptoms</td>
<td>PCWP/LVEDP ≤ 12 or 15 mmHg</td>
</tr>
<tr>
<td></td>
<td>TLC ≥ 60% predicted</td>
</tr>
<tr>
<td></td>
<td>FEV₁ ≥ 55% predicted</td>
</tr>
<tr>
<td></td>
<td>SaO₂ ≥ 88%</td>
</tr>
<tr>
<td></td>
<td>Negative V/Q scan</td>
</tr>
</tbody>
</table>

*6MWD at screening visit (screening and baseline 6MWD must not vary by > 10%), hemodynamic values documented by right heart catheterization prior to screening, pulmonary function tests measured within 24 weeks of the screening visit, SaO₂ measured at the screening visit
†PCWP/LVEDP ≤ 12 mmHg if PVR ≥ 300 to 500 dyn·sec/cm²; PCWP/LVEDP ≤ 15 mmHg if PVR ≥ 500 dyn·sec/cm²
### Amended Study Eligibility Criteria

#### Original Protocol Criteria
- PVR ≥ 240 dyne•sec/cm
- PCWP or LVEDP ≤ 15 mmHg
- No exclusion of subjects with risk factors for left ventricular disease

#### Key Amendment Changes
- PVR ≥ 300 dyne•sec/cm
- PCWP lowered to ≤ 12 mmHg in subjects with PVR ≥ 300 but < 500 dyne•sec/cm
- Exclusion of subjects with ≥ 3 of the following risk factors for left ventricular disease:
  - BMI ≥ 30
  - History of essential hypertension
  - Diabetes mellitus (any type)
  - History of significant CAD

---

### Subject Disposition

**Intention-to-Treat**: N=610

**Modified Intention-to-Treat**: N=605

- **Primary Analysis Set (PAS)**: n=500
  - ABS+TAD Combination: n=253
  - Pooled Monotherapy: n=247
- **Ex-PAS**: n=105
  - ABS+TAD Combination: n=49
  - Pooled Monotherapy: n=56

- **Ambrisentan Monotherapy**: n=126
- **Tadalafil Monotherapy**: n=121
- **Ambrisentan Monotherapy**: n=26
- **Tadalafil Monotherapy**: n=30

*5 subjects randomized did not receive study drug*  
*PCWP requirement maintained at ≤ 15 mmHg in subjects with PVR ≥ 500 dyne•sec/cm*
**AMBITION Study – Initial ABS+TAD Combination (NEJM)**

**Time to First Adjudicated Clinical Failure (PAS)**

Combination vs. Pooled Monotherapy

- **AMBITION Study – Initial ABS+TAD Combination (NEJM)**
- **Time to First Adjudicated Clinical Failure (PAS)**
- **Combination vs. Pooled Monotherapy**

**Hazard Ratio = 0.50**

**95% CI = 0.35–0.72**

**p < 0.001**

---

**AMBITION Study – Initial ABS+TAD Combination (NEJM)**

**Time to First Adjudicated Clinical Failure (PAS)**

Combination vs. Ambrisentan Monotherapy

- **AMBITION Study – Initial ABS+TAD Combination (NEJM)**
- **Time to First Adjudicated Clinical Failure (PAS)**
- **Combination vs. Ambrisentan Monotherapy**

**Hazard Ratio = 0.48**

**95% CI = 0.31–0.72**

**p < 0.001**
AMBITION Study – Initial ABS+TAD Combination (NEJM)

Time to First Adjudicated Clinical Failure (PAS)
Combination vs. Tadalafil Monotherapy

Hazard Ratio = 0.53
95% CI = 0.34–0.83
\( p = 0.005 \)


AMBITION Study – Initial ABS+TAD Combination (NEJM)

Secondary Endpoint Results (PAS)

<table>
<thead>
<tr>
<th>Change from Baseline at Week 24</th>
<th>ABS+TAD Combination (n=253)</th>
<th>Pooled Monotherapy (n=247)</th>
<th>Ambrisentan Monotherapy (n=126)</th>
<th>Tadalafil Monotherapy (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD, m</td>
<td>+48.98</td>
<td>+23.80</td>
<td>+27.00</td>
<td>+22.70</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.63 – 85.75</td>
<td>-12.25 – 64.53</td>
<td>-14.00 – 63.25</td>
<td>-8.25 – 66.00</td>
</tr>
<tr>
<td>( p )-Value</td>
<td>-</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>WHO Functional Class, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>37% (94)</td>
<td>33% (81)</td>
<td>34% (42)</td>
<td>32% (39)</td>
</tr>
<tr>
<td>No Change</td>
<td>58% (146)</td>
<td>60% (147)</td>
<td>59% (73)</td>
<td>62% (74)</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>5% (12)</td>
<td>7% (16)</td>
<td>7% (9)</td>
<td>6% (7)</td>
</tr>
<tr>
<td>( p )-Value</td>
<td>-</td>
<td>0.24</td>
<td>0.30</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Forest Plot of TTCF by Subgroup (PAS)

### AMBITION Study – Initial ABS+TAD Combination (NEJM)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants</th>
<th>Combination Therapy</th>
<th>Pooled Monotherapy</th>
<th>Hazard Ratio (95%CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH/HPAH</td>
<td>279</td>
<td>25/134 (90)</td>
<td>46/145 (32)</td>
<td>0.54 (0.33, 0.87)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>PAH</td>
<td>221</td>
<td>21/120 (18)</td>
<td>31/120 (26)</td>
<td>0.45 (0.26, 0.78)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Baseline WHO FC II</td>
<td>155</td>
<td>6/76 (8)</td>
<td>17/79 (22)</td>
<td>0.21 (0.07, 0.63)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Baseline WHO FC III</td>
<td>345</td>
<td>42/177 (24)</td>
<td>60/184 (36)</td>
<td>0.58 (0.39, 0.86)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Age at Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 57 years</td>
<td>244</td>
<td>13/124 (10)</td>
<td>31/124 (26)</td>
<td>0.37 (0.19, 0.75)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>&gt;= 57 years</td>
<td>256</td>
<td>31/120 (26)</td>
<td>46/120 (38)</td>
<td>0.58 (0.37, 0.88)</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Baseline 6MWD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 363.7 m</td>
<td>250</td>
<td>25/120 (21)</td>
<td>51/120 (43)</td>
<td>0.54 (0.35, 0.83)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>&gt;= 363.7 m</td>
<td>250</td>
<td>11/120 (9)</td>
<td>26/120 (21)</td>
<td>0.39 (0.19, 0.77)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>226</td>
<td>22/114 (19)</td>
<td>34/122 (28)</td>
<td>0.51 (0.30, 0.87)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Rest of World</td>
<td>272</td>
<td>34/148 (23)</td>
<td>60/168 (36)</td>
<td>0.51 (0.31, 0.83)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>388</td>
<td>32/188 (17)</td>
<td>61/200 (31)</td>
<td>0.47 (0.21, 0.87)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>112</td>
<td>16/54 (32)</td>
<td>16/57 (29)</td>
<td>0.58 (0.28, 1.20)</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

### Adverse Events (PAS)

<table>
<thead>
<tr>
<th>Event</th>
<th>ABS+TAD Combination (n=253)</th>
<th>Ambrisentan Monotherapy (n=126)</th>
<th>Tadalafil Monotherapy (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Edema</td>
<td>115 (45%)</td>
<td>41 (33%)</td>
<td>34 (28%)</td>
</tr>
<tr>
<td>Headache</td>
<td>107 (42%)</td>
<td>41 (33%)</td>
<td>42 (35%)</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>54 (21%)</td>
<td>19 (15%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50 (20%)</td>
<td>29 (23%)</td>
<td>23 (19%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>50 (20%)</td>
<td>24 (19%)</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>44 (17%)</td>
<td>22 (17%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (17%)</td>
<td>18 (14%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Cough</td>
<td>40 (16%)</td>
<td>14 (11%)</td>
<td>21 (17%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>38 (15%)</td>
<td>18 (14%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>37 (15%)</td>
<td>8 (6%)</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>37 (15%)</td>
<td>26 (21%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>37 (15%)</td>
<td>14 (11%)</td>
<td>18 (15%)</td>
</tr>
</tbody>
</table>

### Adverse Events (PAS) Continued

<table>
<thead>
<tr>
<th>Condition</th>
<th>ABS+TAD Combination (n=253)</th>
<th>Ambrisentan Monotherapy (n=126)</th>
<th>Tadalafil Monotherapy (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>URTI</td>
<td>34 (13%)</td>
<td>20 (16%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>32 (13%)</td>
<td>17 (13%)</td>
<td>19 (16%)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>31 (12%)</td>
<td>13 (10%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>30 (12%)</td>
<td>17 (13%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>29 (11%)</td>
<td>5 (4%)</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>28 (11%)</td>
<td>20 (16%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (11%)</td>
<td>11 (9%)</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>27 (11%)</td>
<td>5 (4%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Non-Cardiac Chest Pain</td>
<td>27 (11%)</td>
<td>10 (8%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>23 (9%)</td>
<td>12 (10%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>UTI</td>
<td>18 (7%)</td>
<td>9 (7%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>12 (5%)</td>
<td>13 (10%)</td>
<td>9 (7%)</td>
</tr>
</tbody>
</table>


### Discontinuations Due to AEs and Serious AEs (PAS)

<table>
<thead>
<tr>
<th>Condition</th>
<th>ABS+TAD Combination (n=253)</th>
<th>Ambrisentan Monotherapy (n=126)</th>
<th>Tadalafil Monotherapy (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other AEs of Clinical Interest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>20 (8%)</td>
<td>9 (7%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>13 (5%)</td>
<td>7 (6%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>AEs Leading to Treatment Discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>31 (12%)</td>
<td>14 (11%)</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Most Common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (2%)</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>4 (2%)</td>
<td>3 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>92 (36%)</td>
<td>45 (36%)</td>
<td>50 (41%)</td>
</tr>
<tr>
<td>Most Common</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>11 (4%)</td>
<td>11 (9%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (4%)</td>
<td>7 (6%)</td>
<td>4 (3%)</td>
</tr>
</tbody>
</table>

Author Conclusions

- The risk for a first TTCF event was 50% lower among participants who received initial combination therapy with ambrisentan and tadalafil than among those who received monotherapy with either drug.
- The treatment effect on first TTCF event was driven mainly by a lower rate of hospitalization for worsening PAH in the combination therapy group.
- Most previous studies of combination therapy for patients with pulmonary arterial hypertension compared the addition of a therapy (investigational or approved) with placebo including a proportion of participants already receiving background treatment with approved drugs (sequential combination therapy).
- The AMBITION trial supports the rationale for targeting multiple pathways in pulmonary arterial hypertension and showed that early combination therapy can be beneficial.

Collaborative Care With PH Centers: Initial Steps

- Diagnostic dilemmas
- Diagnostic cath/vasodilator trial
- Complex comorbidities
- Failure to achieve Rx goals
- Considering prostanoids
- Considering combination Rx
- Clinical trials
Collaborative Care With PH Centers: Ongoing Care

- Symptom evaluation
- Titrate diuretics
- Monitor Rx
- Need to change Rx
- Manage SEs
- ? Transplant
- Evaluate acute issues
- Acute hospital care
- Emotional support

Local Care

PH Center

It Takes a Team

- Providers:
  - Todd Bull, MD
  - Jack Dempsey, MD
  - Brian Graham, MD
  - Steven Pugliese, MD
  - Debbie Zupanic, NP
  - David Badesch, MD

- Research Coordinators:
  - Holly del Junco, BA
  - Kelly Moulden, RN
  - Lisa Nicotera, RN
  - Elba Abaza
  - Sylwia Szuberla

- Nurses:
  - Robin Hohsfield, RN
  - Nikki Mann, RN
  - Ladean Marshall, RN

- Administrative Assistants and Volunteer:
  - Laura Sanchez
  - Alexandra Armitage
  - Bruce Hoskinson

- Cardiac and Vascular Center Administration:
  - Denise Cordova and Aryn Benton, RN
  - Lorna Prutzman

- Clinical Pharmacist:
  - Matthew Casciano, PharmD
It Takes a Team

A truly **multidisciplinary** approach:

- Pulmonary
- Cardiology
  - Cath Lab Team
  - Echo
  - Congenital Heart Disease
- Rheumatology
- Interventional Radiology
- Pharmacy
- Nursing
- Research
  - COMIRB
  - CCTSI
  - UCH Research Administration
- Respiratory Therapy
- Cardiothoracic Surgery / Lung Transplantation
- Hepatology / Transplant Surgery / Liver Tx
- Pediatric PH Program at Children's Hospital Colorado
- Basic and translational research