SATELLITE SYMPOSIUM OF MSD

sGC Stimulation for the treatment of PH

Real life management of PAH: case presentation

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Cardiologist
Onassis Cardiac Surgery Center
Conflict of interests

NAME OF COMPANIES WITH WHICH RELATIONSHIP EXISTS

Actelion Pharmaceuticals Ltd, Bayer Schering, Galenica, GlaxoSmithKline, Lilly, MSD, Pfizer Ltd

NAME OF RELATIONSHIP

Consultant, Honoraria, Advisory Board Member
Woman, 56 y.o.

2010 (49 y.o.)
IPAH diagnosis

2010: PASP (echo 50mmHg)
Bosentan 125 mg x 2

2013: WHO III

Drugs:
  Acenocumarol, Bosentan,
  Bisoprolol 2,5mg
  Furosemide 20mg

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Case

ECG:
Afib 85bpm, RVH

Spirometry:
FEV1: 90% pred
FVC: 98% pred
DLCO: 65%

Clinical signs
BP 120/70 mmHg
SaO2: 98% (pO2: 77.4 mmHg, pCO2: 31.2 mmHg)

RHC
C.I. (l/min/m2) 2,2
PVR (WU) 8,2
Evidence-Based Treatment Algorithm

Combination therapy and interventional procedures

Sequential combination therapy (I-A)
- ERAs
  - +
- Prostanoids
  - +
- PDE-5i or sGCS

Inadequate clinical response on maximal therapy

Inadequate clinical response

Consider eligibility for lung transplantation

Referral for lung transplantation (I-C)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2013</th>
<th>2014</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (mmHg)</td>
<td>10</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>PAPmean (mmHg)</td>
<td>44</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>C.I. (l/min/m2)</td>
<td>2,2</td>
<td>2,5</td>
<td>2,2</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>8,2</td>
<td>7,5</td>
<td>8,1</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>11</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>950</td>
<td>320</td>
<td>830</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>330</td>
<td>410</td>
<td>320</td>
</tr>
<tr>
<td>WHO class</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
</tbody>
</table>

Sponsored by MSD
### Risk Assessment in PAH

<table>
<thead>
<tr>
<th>Determinants of prognosis</th>
<th>Low risk (&lt;5%)</th>
<th>Intermediate risk (5–10%)</th>
<th>High risk (&gt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional syncope</td>
<td>Repeated syncope</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6MWD</td>
<td>&gt;440 m</td>
<td>165–440 m</td>
<td>&lt;165 m</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO₂ &gt;15 ml/min/kg (&gt;65% pred) VE/VCO₂ slope &lt;36</td>
<td>Peak VO₂ 11–15 ml/min/kg (35–65% pred) VE/VCO₂ slope 36–44.9</td>
<td>Peak VO₂ &lt;11 ml/min/kg (&lt;35% pred) VE/VCO₂ &gt;45</td>
</tr>
<tr>
<td>NT-proBNP plasma levels</td>
<td>BNP &lt;50 ng/l NT-proBNP &lt;300 ng/ml</td>
<td>BNP 50–300 ng/l NT-proBNP 300–1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm² No pericardial effusion</td>
<td>RA area 18–26 cm² No or minimal pericardial effusion</td>
<td>RA area &gt;26 cm² Pericardial effusion</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>RAP &lt;8 mmHg CI ≥2.5 l/min/m² SvO₂ &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 l/min/m² SvO₂ 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 l/min/m² SvO₂ &lt;60%</td>
</tr>
</tbody>
</table>

*Most of the proposed variables and cut-off values are based on expert opinion.

**Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

***Repeated episodes of syncope, even with little or regular physical activity.

EVALUATION OF SEVERITY AND CLINICAL RESPONSE TO THERAPY

Achievement/maintenance of a low-risk profile (Table 13) is recommended as an adequate treatment response for patients with PAH.

Achievement/maintenance of an intermediate-risk profile (Table 13) should be considered an inadequate treatment response for most patients with PAH.

ESC GUIDELINES 2015

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WHAT ARE THE OPTIONS?

- Parenteral / inhaled **prostanoid therapy**
- **Add selexipag** (first-in-class orally available selective prostacyclin IP receptor agonist)
- **Sildenafil dose**
- **Switch therapy**  
  Sildenafil to Tadalafil  
  Sildenafil to Riociguat  
  Bosentan To Macitentan  
  *Bosentan to Ambrisentan*  
  *Ambrisentan/Macitentan & Tadalafil/Riociguat*
## TARGETING THE PROSTACYCLIN PATHWAY

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Class</th>
<th>Route of Administration</th>
<th>Regulatory Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol</td>
<td>Prostanoid (synthetic prostacyclin)</td>
<td>Intravenous</td>
<td>US: 1995</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Selective IP receptor agonist (stimulates prostacyclin receptors)</td>
<td>Oral</td>
<td>US 2015</td>
</tr>
</tbody>
</table>

**GRIPHON TRIAL**

**Selexipag**

**PRIMARY End Point**

- Orally active, IP agonist, highly selective for the IP receptor
- Clinically relevant and highly robust primary EP
- At baseline, 80% of pts were on ERA and/or PDE-5i
## COMBINATION THERAPY OPTION FOR PAH

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macitentan added to sildenafil</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Riociguat added to bosentan</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Selexipag added to ERA and/or PDE-Si</td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Sildenafil added to epoprostenol</td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>Treprostinil inhaled added to sildenafil or bosentan</td>
<td>IIa</td>
<td>B</td>
<td>IIa</td>
</tr>
<tr>
<td>Iloprost inhaled added to bosentan</td>
<td>IIb</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td>Tadalafil added to bosentan</td>
<td>IIa</td>
<td>C</td>
<td>IIa</td>
</tr>
<tr>
<td>Ambrisentan added to sildenafil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan added to epoprostenol</td>
<td>-</td>
<td>-</td>
<td>IIb</td>
</tr>
<tr>
<td>Bosentan added to sildenafil</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Sildenafil added to bosentan</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other double combinations</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
<tr>
<td>Other triple combinations</td>
<td>IIb</td>
<td>C</td>
<td>IIb</td>
</tr>
</tbody>
</table>

GRIPHON, TITRATION AND SIDE EFFECTS OF ORAL PROSTANOIDS

Headache, jaw pain & in high doses nausea, vomiting and diarrhea

NEJM 2015; 373: 2522-2533
COMBINATION THERAPY

Prostacyclin Pathway

- cAMP

- Prostacyclin Derivatives
  - Prostacyclin

Endothelin Pathway

- Endothelin-1
  - Endothelin Receptor Antagonists
    - Endothelin Receptor A
    - Endothelin Receptor B

Nitric Oxide Pathway

- sGC stimulator
  - sGC
  - cAMP

- Phosphodiesterase Type 5
  - Endogenous Nitric Oxide
  - Exogenous Nitric Oxide

- Phosphodiesterase Type-5 Inhibitors

Targets Multiple Pathologic Processes

Establishes Synergy Among Agents

Overcomes Limitations of Monotherapy

Enhanced Efficacy and Improved Tolerability

**NEJM 2004;351: 142501436**

**Eur Respir Rev 2014; 23: 469-475**

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WHAT ARE THE OPTIONS?

• Monitor carefully

• Parenteral / inhaled prostanoid therapy

• Add selexipag (first-in-class orally available selective prostacyclin IP receptor agonist)

• Sildenafil dose

• Switch therapy  Sildenafil to Tadalafil  
  Sildenafil to Riociguat  
  Bosentan To Macitentan  
  **Bosentan to Ambrisentan**  
  **Ambrisentan/Macitentan & Tadalafil/Riociguat**

• ???

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Sildenafil improves exercise capacity, WHO functional class, and hemodynamics in patients with symptomatic pulmonary arterial hypertension.
WHAT ARE THE OPTIONS?

• Monitor carefully

• Parenteral / inhaled prostanoid therapy

• Add selexipag (first-in-class orally available selective prostacyclin IP receptor agonist)

• Sildenafil dose

• **Switch therapy**  Sildenafil to Tadalafil
  Sildenafil to Riociguat
  Bosentan To Macitentan
  **Bosentan to Ambrisentan**
  **Ambrisentan/Macitentan & Tadalafil/Riociguat**

• ???
EVENT-DRIVEN STUDIES AND SERIOUS CHRONIC DISEASES: ADDRESSING PLACEBO, DRUG EFFICACY, AND TREATMENT FAILURE IN PAH

New Approaches in the Therapy of Serious, Rare Diseases

Adaptive treatment strategy

An ATS is a set of rules for adapting a treatment plan to the changing state of an individual patient, taking into account both the history of previous treatments and the response to those treatments.

ATSs may be an essential component of PAH management, where individualized approaches to treatment are required, owing to the heterogeneity of responses across PAH patients.

WHAT ARE THE OPTIONS?

- Monitor carefully
- Parenteral / inhaled prostanoid therapy
- Add selexipag (first-in-class orally available selective prostacyclin IP receptor agonist)
- Sildenafil dose
- **Switch therapy**  
  - Sildenafil to Tadalafil  
  - Sildenafil to Riociguat  
  - Bosentan To Macitentan  
  - **Bosentan to Ambrisentan**  
  - **Ambrisentan/Macitentan & Tadalafil/Riociguat**

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Pharmacokinetic and Pharmacodynamic Comparison of Sildenafil-Bosentan and Sildenafil-Ambrisentan Combination Therapies for Pulmonary Hypertension

To elucidate whether the pharmacokinetics (PK) and pharmacodynamics (PD) of sildenafil are influenced differently when it is coadministered with bosentan (S+B) or with ambrisentan (S+A), we evaluated the PK and PD profiles of sildenafil before and after 4–5 weeks of S+A or S+B treatment in patients with pulmonary arterial hypertension. The area under the plasma concentration–time curve of sildenafil was significantly higher in S+A treatment than in S+B treatment (165.8 ng·h/mL vs. 396.8 ng·h/mL, $P = 0.018$) and the oral clearance of sildenafil was significantly lower after S+A treatment than after S+B treatment (120.6 L/h/kg vs. 50.4 L/h/kg, $P = 0.018$). In the PD study, incremental shuttle walking distance was superior during treatment with S+A than during treatment with S+B (S+B: 280 m vs. S+A: 340 m, $P = 0.042$). There were no concerns about safety with either combination therapy regime.

**Figure 2** Sildenafil concentration–time curves of the two coadministration therapies. The solid line shows the sildenafil concentration when coadministered with bosentan (S+B), and the dotted line shows the sildenafil concentration when coadministered with ambrisentan (S+A). Values are expressed as mean ± SD.

**Table 2** Difference in pharmacokinetic parameters of sildenafil between the two combination therapies

<table>
<thead>
<tr>
<th></th>
<th>S+B</th>
<th>S+A</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>0.5 (0.50–1.50)</td>
<td>1.0 (0.5–2.0)</td>
<td>0.336</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>58.3 (56.4–85.4)</td>
<td>120.2 (95.6–181.1)</td>
<td>0.018</td>
</tr>
<tr>
<td>AUC$_{0-8}$ (ng·h/mL)</td>
<td>165.8 (113.3–190.8)</td>
<td>396.8 (200.8–517.8)</td>
<td>0.018</td>
</tr>
<tr>
<td>CL/F (L/h/kg)</td>
<td>120.6 (104.8–176.6)</td>
<td>50.4 (38.6–99.6)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Data are expressed as the median (interquartile range). S+B, coadministration of sildenafil with bosentan; S+A, coadministration of sildenafil with ambrisentan; $t_{\text{max}}$, time to maximum plasma concentration; $C_{\text{max}}$, maximum plasma concentration; AUC$_{0-8}$, area under the plasma concentration-time curve from 0 to 8 hours; CL/F, oral clearance.
COMBINATION real-world

COMBINing bosentan and sildenafil in PAH patients failing mONotherapy: real-world insights

<table>
<thead>
<tr>
<th></th>
<th>Pre-combination</th>
<th>Post-combination</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III-IV (%)</td>
<td>49</td>
<td>35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>428 (339-496)</td>
<td>465 (380-545)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>9 (7-12)</td>
<td>8 (6-11)</td>
<td>0.003</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>62 (51-76)</td>
<td>57 (48-70)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.3 (1.9-2.6)</td>
<td>2.5 (2.2-2.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>13 (10-18)</td>
<td>11 (8-15)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

192 patients: Follow-up to 31st December 2013

SERAPHIN TRIAL

MACITENTAN ADD-ON BACKGROUND THERAPY SIGNIFICANTLY REDUCES MORBIDITY AND MORTALITY

SERAPHIN: Morbidity and mortality in patients on background PAH therapy (EOT)

Macitentan reduced the risk of a morbidity/mortality event* by 38% in patients on background PAH therapy (HR: 0.62; p-value = 0.009)

Seraphin Trial: Deaths at the end of double blind period

- All causes of deaths: 36% Risk Reduction (p = 0.20)
- Deaths due to PAH: 56% Risk Reduction (p = 0.07)


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Patients With PAH Can Switch From Bosentan to Macitentan & from Bosentan to Ambrisentan

Hemodynamic stability after transitioning between ERA’s in patients with PAH.

Twenty-eight patients were studied who switched from bosentan 125 mg orally twice a day or ambrisentan 10 mg daily to macitentan 10 mg orally daily between 2013 and 2015, when macitentan became available. Switching between ERA’s appears to be safe and sustains exercise capacity, maintains WHO functional class, and incurs no increased peripheral edema.

The Safely Change From Bosentan To Ambrisentan In Pulmonary Hypertension (SCOBA-PH) Study

Of the 30 patients transitioned (15 to ambrisentan, 15 to bosentan), 23 had complete hemodynamic data. Transitioning between ERAs in stable PAH patients does not result in hemodynamic or clinical deterioration during the first 4 months post transition. A minority of patients have developed increased cardiac filling pressures.

Published in Cardiology News · October 28, 2015

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TRANSITIONING SILDENAFIL TO TADALAFIL

20 clinically-stable pts
Well-tolerated in all pts but one developed myalgia
Clinical stability maintained when switched

Eur Respir J 2015; 46: PA3781

13 pts, clinically stable
in 6 pts: improvement in clinical course,
in 5 pts adverse events, discontinuation

Lung 2015; 192: 105-12

Conversion from sildenafil to tadalafil: results from the sildenafil to tadalafil in pulmonary arterial hypertension (SITAR) study no report in clinical improvement.

J Cardiovasc Pharmacol Ther 2014; 19: 5507
Primary Endpoint:
Time to
First Clinical Failure Event

50% Risk Reduction

95% CIs (using log-log transform method) are presented for each treatment group at weeks 4, 8, 16, 24, and then every 12 weeks up to week 96.

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Why might Riociguat Be effective when PDE5i has failed?

- **PDE5i: MOA**
  - Prolong vasodilatory effects of NO by preventing degradation of cGMP
  - Requires NO

- **sGC stimulator: dual mechanisms of action**
  - Sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding
  - Directly stimulates sGC via a different binding site, independently of NO

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By Week 12, increase of 30m

Hemodynamic variables:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary-artery pressure (mm Hg)</td>
<td>109</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>109</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>108</td>
<td>0.07</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>108</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary-capillary wedge pressure (mm Hg)</td>
<td>108</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Sponsored by MSD

Comparison of hemodynamic parameters in treatment-naïve and pre-treated patients

Overall population: 
-226 dyne-sec/cm²
(95% CI: -281 to -170)
$p < 0.0001$

Pretreated population: 
-186 dyne-sec/cm²
(95% CI: -252 to -120)
$p < 0.0001$

Treatment-naïve: 
-266 dyne-sec/cm²
(95% CI: -357 to -175)
$p < 0.0001$

Overall population: +0.6 liters/min/m²
(95% CI: 0.4 to 0.7)
$p < 0.0001$

Pretreated overall: +0.5 liters/min/m²
(95% CI: 0.3 to 0.7)
$p < 0.0001$

Cardiac index ±SEM (liters/min/m²)

<table>
<thead>
<tr>
<th></th>
<th>BL Week 12</th>
<th>BL Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (n = 232)</td>
<td>2.5 ± 0.2</td>
<td>2.7 ± 0.2</td>
</tr>
<tr>
<td>Placebo (n = 107)</td>
<td>2.8 ± 0.3</td>
<td>2.9 ± 0.3</td>
</tr>
</tbody>
</table>

Cardiac index ±SEM (liters/min/m²)

<table>
<thead>
<tr>
<th></th>
<th>BL Week 12</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (n = 233)</td>
<td>2.6 ± 0.2</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Placebo (n = 108)</td>
<td>3.0 ± 0.3</td>
<td>3.1 ± 0.3</td>
</tr>
</tbody>
</table>

Cardiac index ±SEM (liters/min/m²)

<table>
<thead>
<tr>
<th></th>
<th>BL Week 12</th>
<th>BL Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (n = 117)</td>
<td>2.3 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Placebo (n = 52)</td>
<td>2.6 ± 0.2</td>
<td>2.7 ± 0.2</td>
</tr>
</tbody>
</table>

Cardiac index ±SEM (liters/min/m²)

<table>
<thead>
<tr>
<th></th>
<th>BL Week 12</th>
<th>BL Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (n = 118)</td>
<td>2.4 ± 0.1</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Placebo (n = 53)</td>
<td>2.7 ± 0.2</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Case</td>
<td>SILDENAFIL $\rightarrow$ RIOCIGUAT</td>
<td>2013</td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>C.I. (l/min/m2)</td>
<td>2,2</td>
</tr>
<tr>
<td></td>
<td>PVR (WU)</td>
<td>8,2</td>
</tr>
<tr>
<td></td>
<td>PCWP (mmHg)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>SvO2 (%)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>NT-proBNP (pg/ml)</td>
<td>950</td>
</tr>
<tr>
<td></td>
<td>6MWT (m)</td>
<td>330</td>
</tr>
<tr>
<td></td>
<td>WHO class</td>
<td>III</td>
</tr>
</tbody>
</table>

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PATENT-2 STUDY

Kaplan-Meier plots for a) clinical worsening and b) survival in the overall population during the PATENT-2 study.

At 1 year, the estimated rate of clinical worsening-free survival was 88%

At 1 year, the estimated survival rate was 97%

RIOCIGUAT IN PAH

• As switch therapy

• As initial monotherapy

• As add-on therapy in ERA
RESpite trial: open-label, multicenter, uncontrolled phase 3b pilot study

Riociguat, a direct sGC stimulator, offers the potential for a new mode of action for PH treatment. Preclinical studies have shown that it stimulates sGC directly, increasing the activity of sGC independently of NO and increasing sensitivity to low levels of endogenous NO.

To investigate whether it is safe, feasible, and beneficial to replace PDE5i therapy with riociguat in patients with PAH who do not respond adequately to PDE5i

Eligibility -- patients assessed as not at goal on PDE5i met the following criteria:

- WHO FC III
- 6MWD 165 to 440 m
- CI < 3.0 L/min/m²
- PVR > 400 dyn·s·cm⁻⁵
- PAPm > 30 mm Hg

Sponsored by MSD
## Demographics at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Riociguat up to 2.5 mg tid (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>45 (74)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>56 (92)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)*</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Dana Point classification of PH, n (%)</td>
<td></td>
</tr>
<tr>
<td>1.1 Idiopathic PAH</td>
<td>56 (92)</td>
</tr>
<tr>
<td>1.2 Heritable PAH</td>
<td>1 (2)</td>
</tr>
<tr>
<td>1.3 Toxin induced</td>
<td>1 (2)</td>
</tr>
<tr>
<td>1.4.1 Connective tissue disease</td>
<td>1 (2)</td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Concomitant treatment with anticoagulants, n (%)</td>
<td>56 (92)</td>
</tr>
<tr>
<td>Concomitant treatment with ERA, n (%)</td>
<td>50 (82)</td>
</tr>
<tr>
<td>Pretreated with sildenafil, n (%)</td>
<td>40 (66)</td>
</tr>
<tr>
<td>Pretreated with tadalafil, n (%)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Mean time since first PH diagnosis, years (SD)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Mean 6MWD, m (SD)</td>
<td>357 (81)</td>
</tr>
<tr>
<td>WHO FC III, n (%)</td>
<td>61 (100)</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL (SD)</td>
<td>1190 (1828)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m² (SD)</td>
<td>73 (22)</td>
</tr>
</tbody>
</table>
## Change from baseline in hemodynamics at week 24

<table>
<thead>
<tr>
<th>Parameter, mean (SD)</th>
<th>n</th>
<th>Baseline</th>
<th>n</th>
<th>Week 24</th>
<th>Change from baseline to week 24&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVR, dyn·sec·cm&lt;sup&gt;−5&lt;/sup&gt;</td>
<td>61</td>
<td>835 (272)</td>
<td>49</td>
<td>753 (379)</td>
<td>−103 (296)</td>
</tr>
<tr>
<td>Cardiac index, L/min/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>61</td>
<td>2.3 (0.4)</td>
<td>48</td>
<td>2.6 (0.6)</td>
<td>+0.3 (0.5)</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>61</td>
<td>51.8 (11.9)</td>
<td>49</td>
<td>49.7(13.2)</td>
<td>−2.8 (8.8)</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>60</td>
<td>8.2 (4.9)</td>
<td>49</td>
<td>8.0 (4.3)</td>
<td>−0.83 (4.2)</td>
</tr>
<tr>
<td>SvO&lt;sub&gt;2&lt;/sub&gt;, %</td>
<td>57</td>
<td>64.8 (6.9)</td>
<td>48</td>
<td>65.0 (7.6)</td>
<td>+1.0 (6.3)</td>
</tr>
</tbody>
</table>
RESPITE trial demonstrated benefit

Improvement in 6MWD of approximately 30 m

Improvement in functional class:
- 48% of patients improved from FC III to FC II at week 12
- 52% of patients improved FC at week 24
  - 1 patient reached FC I
  - Remainder reached FC II
- Improvement (decrease) in plasma level of NT-proBNP about 30% from baseline

NT-proBNP levels: Transition to Riociguat

Mean Change From Baseline = (-347 pg/mL) at 24 Weeks, After Transient Increase in BNP of (+171 pg/mL)

Data courtesy of Marius Hoeger, MD, as presented at ERS, London, September 4, 2016
Transitioning to sGC stimulator

- Concomitant use of PDE5i and sGC stimulator not recommended (systemic hypotension)
- Recommendation for washout period varies according to half-life of the respective PDE5i
  - Sildenafil: 24 hours
  - Tadalafil: 72 hours
- Uptitration
  - Initiate riociguat at 1 mg 3 × daily
  - Increase every 2 weeks, as systemic BP allows
  - Maximum dose is 2.5 mg 3 × daily
SYSTEMIC BP. A limiting Factor?

Requires careful and frequent watching during uptitration

Phone calls to ensure that patients remain stable during transition

BP should be measured at least twice daily
If systolic BP < 90 mm Hg, then patient should call the center and discuss dosing
Decrease in BP similar to that seen with initiation and uptitration of other PAH treatment regimens
Once on maintenance dose, very seldom must riociguat dose be adjusted due to hypotension
In RESPITE, > 90% reached the maximum dose of 2.5 mg three × daily and the remainder were on 2 mg three × daily

Sponsored by MSD
RIOCIGUAT IN PAH

*Adempas* 0,5 mg/ 1 mg/ 1,5 mg/ 2mg/ 2,5 mg

- As switch therapy
- As initial monotherapy
- As add-on therapy in ERA
NEW STEP IN THE EVOLUTION OF MANAGEMENT OF PAH?

RIOCIGUAT AND SWITCH THERAPY

• RESPITE opens the perspective of a new treatment option for patients with an insufficient response to PDE5i treatment

REPLACE Trial

Riociguat replacing PDE-5i Therapy evaluated Against Continued PDE-5i therapy

Sponsored by MSD
### ROLE OF RIOCIGUAT FOR MONOTHERAPY & SEQUENTIAL THERAPY

<table>
<thead>
<tr>
<th>Measure/treatment</th>
<th>Class Level (^a)-Level (^b)</th>
<th>WHO-FC II</th>
<th>WHO-FC III</th>
<th>WHO-FC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endothelin receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambrisentan</td>
<td></td>
<td>I</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Bosentan</td>
<td></td>
<td>I</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Macitentan(^d)</td>
<td></td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td><strong>Phosphodiesterase type 5 inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td></td>
<td>I</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Tadalafil</td>
<td></td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td>Vardenafil(^d)</td>
<td></td>
<td>IIb</td>
<td>B</td>
<td>IIb</td>
</tr>
<tr>
<td><strong>Guanoylate cyclase stimulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riociguat</td>
<td></td>
<td>I</td>
<td>B</td>
<td>I</td>
</tr>
<tr>
<td><strong>Prostacyclin analogues</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostol Intraocular</td>
<td></td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td>Iloprost Inhaled</td>
<td></td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Intravenous(^d)</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
</tr>
<tr>
<td>Treprostinil Subcutaneous</td>
<td></td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Inhaled(^d)</td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Intravenous(^d)</td>
<td>-</td>
<td>-</td>
<td>IIa</td>
</tr>
<tr>
<td></td>
<td>Oral(^d)</td>
<td>-</td>
<td>-</td>
<td>IIb</td>
</tr>
<tr>
<td>Beraprost(^d)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>IIb</td>
</tr>
<tr>
<td>Selexipag (oral)(^d)</td>
<td>I</td>
<td>B</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

\(^a\) Class: \(1\) = strong evidence for efficacy, \(2\) = evidence for efficacy, \(3\) = evidence for ineffectiveness, \(4\) = no evidence of efficacy. \(^b\) Level: \(A\) = first-line, \(B\) = second-line, \(C\) = third-line.
Thank you for your attention
Riociguat:
Mode of Action and Clinical Development in Pulmonary Hypertension

Riociguat stabilizes NO binding to sGC and also directly stimulates sGC independently of NO, increasing generation of cGMP.

**Figure 2.** Summary of the mode of action and effects of riociguat. NT-proBNP = N-terminal pro-brain natriuretic peptide. Data are from Pulmonary Arterial Hypertension sGC-Stimulator Trial (PATENT)-1 and -2. See Figure 1 legend for expansion of other abbreviations...
RESPITE implications

- RESPITE opens the perspective of a new treatment option for patients with an insufficient response to PDE5i treatment

REPLACE Trial

Riociguat rEplacing PDE-5i Therapy evaLuated Against Continued PDE-5i thErapy

A Prospective, Randomized, International, Multicenter, Double-arm, Controlled, Open-label Study of Riociguat in Patients With PAH Who Are on a Stable Dose of Phosphodiesterase-5 Inhibitors (PDE-5i) With or Without Endothelin Receptor Antagonist (ERA), But Not at Treatment Goal.

ClinicalTrials.gov Identifier: NCT02891850
Cost Effectiveness

<table>
<thead>
<tr>
<th>Specific PAH oral drugs</th>
<th>PRICES Euro/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revatio</td>
<td>450,19</td>
</tr>
<tr>
<td>Adcirca</td>
<td>544,30</td>
</tr>
<tr>
<td><strong>Riociguat</strong></td>
<td><strong>1288,32</strong></td>
</tr>
<tr>
<td>Klimurtan</td>
<td>1350,60</td>
</tr>
<tr>
<td>Tracleer</td>
<td>2043,21</td>
</tr>
<tr>
<td>Volibris</td>
<td>2115,94</td>
</tr>
<tr>
<td>Opsumit</td>
<td>2762,18</td>
</tr>
</tbody>
</table>

**Greece, October 2016**

PARADIGM SHIFT IN PAH TREATMENT

4th World Symposium on PH at Dana Point Recommendation
- TTCW should be a primary endpoint for phase 3 or pivotal trials
- Trials with TTCW as primary endpoint will be of longer duration
- Adjudication of events should be mandatory

Dana Point Definition of TTCW
- All-cause mortality
- Nonelective hospital stay for PAH
- Disease progression

Predefined criteria usually for initiation of intravenous prostanoids, lung transplantation, or septostomy

Defined as ↓ from baseline in 6MWD by 15%, confirmed by 2 studies done within 2 weeks

Worsening FC (except for patients already in FC IV)

Short-term trials with goal-oriented outcomes (6MWD)

Long-term trials with event-driven outcomes (morbidity/mortality)
- SERAPHIN\textsuperscript{a}
- AMBITION\textsuperscript{b}
- GRIPHON\textsuperscript{c}

NEJM 2013; 369: 809-818
Eur Respir J 2014; 44S58: 2916
JACC 2009; 54:S97-107
JACC 2015; 65 10S
RESPITE Trial Limitations

- Size: 51 patients completed the study
- Design: uncontrolled open-label study
- Randomized controlled trial to start soon
Design of the RESPITE study

Open-label, multicenter, uncontrolled Phase 3b pilot study

Patients with PAH not at goal with PDE5i (n=61)

1- to 3-day PDE5i treatment-free period

Treatment phase

Dose adjustment

Maintenance

Safety follow-up

Right heart catheterization

Stop PDE5i

Screening (baseline)

Time (weeks)

0 8 12 24 28

Right heart catheterization

Patients may participate in an extended drug supply phase for 18 months or until reimbursement. Baseline = the last documented value while still receiving PDE5i.

Not at goal on PDE5i defined as: WHO FC III, 6MWD 165–440 m, cardiac index <3.0 L/min/m², PVR >400 dyn·sec·cm⁻⁵, mPAP >30 mmHg.

6MWD, 6-minute walking distance; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PVR, pulmonary vascular resistance; tid, three times daily; WHO FC, World Health Organization functional class.

Patient disposition

Discontinued\(^a\) (n=10) (16%)

- Adverse event 4 (7%)
- Death\(^b\) 1 (2%)
- Lack of efficacy 1 (2%)
- Physician decision 1 (2%)
- Withdrawal by patient 3 (5%)

Screened (n=79)

- Treated (n=61)

- Riociguat up to 2.5 mg tid (n=61)

- Completed 24 weeks of treatment (n=51) (84%)

PDE5i, phosphodiesterase type 5 inhibitor; tid, three times daily.

\(^a\)Primary reason for discontinuation.

\(^b\)Two patients died during the main study. Causes of death were subdural hematoma and pneumonia. The patient who died of pneumonia was recorded as withdrawal by patient. Prior PDE5i therapy for these patients was tadalafil for the patient who experienced a subdural hematoma and sildenafil for the patient who died of pneumonia.

## Hemodynamics at baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg) (n=60)</td>
<td>8.2 (4.9)</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>51.8 (11.9)</td>
</tr>
<tr>
<td>PAWP (mmHg)</td>
<td>9.4 (3.2)</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.3 (0.4)</td>
</tr>
<tr>
<td>PVR (dyn·sec·cm⁻⁵)</td>
<td>835 (272)</td>
</tr>
<tr>
<td>SvO₂ (%) (n=57)</td>
<td>64.8 (6.9)</td>
</tr>
</tbody>
</table>
RESPITE safety outcomes

- Adverse event profile as in PATENT, no new safety signals detected

- SAEs usually related to underlying disease or concomitant illness; only two SAEs rated as study drug-related by the investigators (1 right heart failure, 1 asthenia)

- Two deaths, both considered unrelated to study medication by the investigators and the sponsor
Change from baseline in 6MWD over time

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>61</th>
<th>36</th>
<th>53</th>
<th>34</th>
<th>54</th>
<th>52</th>
<th>51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean absolute values (m)</td>
<td>35</td>
<td>7</td>
<td>384</td>
<td>382</td>
<td>39</td>
<td>0</td>
<td>388</td>
</tr>
<tr>
<td>Change from baseline (m)</td>
<td>0</td>
<td>+13</td>
<td>+4</td>
<td>+16</td>
<td>+2</td>
<td>7</td>
<td>+24</td>
</tr>
</tbody>
</table>

Mean treatment change (n= 51): +31m
Change from baseline in WHO FC at weeks 12 and 24

- Baseline (n=61): 100%
- Week 12 (n=54): 48% WHO FC II, 2% WHO FC I, 50% WHO FC III
- Week 24 (n=52): 52% WHO FC II, 2% WHO FC I, 46% WHO FC III
Initiation of Riociguat

- Screening
- Start of Treatment
- Replace PDE5i With Riociguat

RHC, Washout Phase, Titrated phase, Maintenance phase

- 0 wk
- 8 wk
- 24 wk

Screening period approx 2 wk
24-wk treatment period
Safety follow-up period 4 wk

Patients with PAH
Treatment-naive or receiving background therapy with endothelin receptor antagonist or phosphodiesterase type-5 inhibitor (N = 1156)

Selexipag 200 to 1600 mcg twice daily (n = 574)
Placebo (n = 582)

Primary end point:
Time to first morbidity/mortality event
- Disease progression
- Hospitalization for PAH worsening
- Worsening PAH
- All-cause death

- 47% patients received monotherapy; 33% combination therapy
- 40% risk reduction for morbidity/mortality events vs placebo (HR, 0.60; 99% CI, 0.46-0.78; P < .0001)
- Treatment effect consistent across multiple subgroups, including type of background therapy
- Safety profile consistent with prostacyclin effects

AMBITION

Primary end point:
Time to clinical failure
- Death
- Hospitalization for worsening PAH
- Disease progression
- Unsatisfactory long-term response

Patients with PAH
Treatment naive (N = 500)

- Ambrisentan (target dose: 10 mg)
  (n = 253)
- Tadalafil (target dose: 40 mg)
  (n = 121)

- Ambrisentan (target dose: 10 mg)
  (n = 126)
- Tadalafil (target dose: 40 mg)
  (n = 121)

24 weeks

Ambrisentan/tadalafil reduced risk for clinical failure events (hospitalizations) by 63% vs ambrisentan or tadalafil alone (hazard ratio, 0.372; 95% confidence interval = 0.217-0.639; P = .0002)

DRUGS INTERACTION

Bosentan is an inducer of cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Plasma concentrations of drugs metabolised by these isoenzymes will be reduced when co-administered with bosentan.

Sildenafil is metabolised by cytochrome P450 isoenzymes CYP3A4 (major route) and CYP2C9 (minor route). There is an increase in sildenafil bioavailability and reduced clearance with CYP3A4 substrates and inhibitors and CYP3A4 substrates plus beta-adrenoceptor blockers.

Liver toxicity is still a problem, even if well-managed in the vast majority of our patients, but this is an issue with bosentan but not for ambrisentan and macitentan.

<table>
<thead>
<tr>
<th>Bosentan</th>
<th>CYP3A4 inducer</th>
<th>Sildenafil</th>
<th>Sildenafil levels fall 50%; bosentan levels increase 50%. May not require dose adjustments of either drug.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CYP2C9 inducer</td>
<td>Warfarin</td>
<td>Increases warfarin metabolism, may need to adjust warfarin dose. Intensified monitoring of warfarin recommended following initiation but dose adjustment usually unnecessary.</td>
</tr>
<tr>
<td>Tadalafil(44)</td>
<td>CYP3A4 substrate</td>
<td>Bosentan</td>
<td>Tadalafil exposure decreases by 42%, no significant changes in bosentan levels.(44) May not require dose adjustment.</td>
</tr>
</tbody>
</table>
PGI$_2$ Analogues and IP Agonists

- PGI$_2$ is produced predominantly by endothelial cells and induces potent vasodilation
- PAH is characterized by dysregulation of the PGI$_2$ metabolic pathway resulting in reduction of PGI$_2$ synthase expression in pulmonary arteries
- Analogues of PGI$_2$ extend (or "mimic") the effect of PGI$_2$
  - PGI$_2$ analogues (epoprostenol, treprostinil, iloprost)
- Agonists act selectively on IP, resulting in vasodilation and inhibition of proliferation of smooth muscle cells
  - Nonprostanoid receptor agonists (selexipag)

The potentially increased risk of pulmonary bleeding with riociguat in some patients is reflected as a warning in the local prescribing information (summary of product characteristics) and should be considered as drug-related. However, the risk of haemoptysis and pulmonary haemorrhage may be influenced by other factors, such as age, severity of disease, deterioration in pulmonary haemodynamics and concomitant treatment with anticoagulants [12, 14]. The mechanism of how riociguat could cause haemoptysis and pulmonary haemorrhage is unclear. One hypothesis is that the observation may be related to the vasodilatory effects of riociguat on the bronchial arterial circulation, which is hypertrophied and associated with angiogenesis in the systemic circulation i.e. bronchial arteries, in PH [13, 15], increasing the flow and favouring haemoptysis.
Riociguat for the treatment of PAH associated CTD: results from PATENT-1 and PATENT-2

Kaplan–Meier survival curves for patients with PAH-CTD in PATENT-2

2-year survival rates

- Idiopathic/familial PAH: 93% (95% CI 89–96%)
- PAH-CTD: 93% (95% CI 85–97%)
- PAH-SSc: 94% (95% CI 82–98%)
- PAH-other defined CTD: 94% (95% CI 78–98%)

Number of patients at risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>0</th>
<th>250</th>
<th>500</th>
<th>750</th>
<th>1000</th>
<th>1250</th>
<th>1500</th>
<th>1750</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic/familial PAH</td>
<td>254</td>
<td>244</td>
<td>225</td>
<td>179</td>
<td>116</td>
<td>69</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>PAH-CTD</td>
<td>94</td>
<td>87</td>
<td>79</td>
<td>63</td>
<td>43</td>
<td>29</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>PAH-SSc</td>
<td>55</td>
<td>49</td>
<td>44</td>
<td>34</td>
<td>20</td>
<td>16</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PAH-other defined CTD</td>
<td>34</td>
<td>34</td>
<td>31</td>
<td>26</td>
<td>21</td>
<td>13</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Time since start of study drug in extension study (days)

2-year data cut-off March 2014
Mean±SD treatment duration (months): PAH-CTD, 31±14; PAH-SSc, 29±15; PAH-other defined CTD, 35±12.

CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with CTD; SSc, systemic sclerosis.

Sponsored by MSD

Riociguat dose and duration

- Mean±SD duration of treatment: 154±44 days
- Cumulative treatment exposure: 25.7 patient years (n=61)
Transition From Inhaled Treprostinil to Oral Selexipag

TRANSIT-1
Study to Assess the Tolerability and the Safety of the Transition From Inhaled Treprostinil to Oral Selexipag in Patients With Pulmonary Arterial Hypertension

ClinicalTrials.gov: NCT02471183