MACITENTAN DEVELOPMENT IN CHILDREN WITH PULMONARY HYPERTENSION (PAH)

ORPHAN DRUG AND RARE DISEASE

11 MAY 2017

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AGENDA

- Pulmonary Arterial Hypertension (PAH) in children
- Management of pediatric PAH
- Challenges to design a global trial in pediatric PAH
- Macitentan pediatric plan
- Next steps
PAH IN CHILDREN
PULMONARY ARTERIAL HYPERTENSION

- PAH is a class of pulmonary hypertension
  - precapillary PH
- PAH results from an unknown trigger that leads to vascular injury
- Pathophysiological changes in the pulmonary vasculature in PAH include:
  - abnormal vasoconstriction
  - remodeling of blood vessel layers
  - disease-specific lesion formation (plexiform lesions)
- Changes lead to increased pulmonary vascular resistance, right ventricular hypertrophy, right heart failure and death
CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION (PH) - 2015

1. PAH
   1.1 Idiopathic PAH (iPAH)
   1.2 Heritable PAH
   1.3 Drugs and toxin induced
   1.4 Associated with (APAH):
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital Heart Disease (CHD)
      1.4.5 Schistosomiasis

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1”. Persistent pulmonary hypertension of the newborn

2. PH due to left heart disease
3. PH due to lung disease and/or hypoxia
4. Chronic thromboembolic PH and other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms

Galiè et al. Eur Heart J 2015
CHILDREN WITH PAH

- PAH is a rare disease:
  - 0.5-0.7/1 Mio children are diagnosed with iPAH every year
  - 2.2/1 Mio children are diagnosed with aPAH-CHD every year

In Europe:
  - ~ 60 children with iPAH, and
  - ~ 230 children with aPAH-CHD
  are newly diagnosed every year

- Prior to availability of PAH targeted therapies, median survival ~ 4 years
- Currently, survival rate continues to improve ~ 70% at 5 years
- Disease characteristics and response to treatment similar to adults
MANAGEMENT OF PAH IN CHILDREN
2015 ESC/ERS GUIDELINES: RISK ASSESSMENT IN PAH SHOULD BE MULTIFACTORIAL
## Pediatric PAH – Determinants of Risk

<table>
<thead>
<tr>
<th>Lower Risk</th>
<th>Determinants of Risk</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Clinical evidence of RV failure</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Progression of symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Syncope</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Growth</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>I,II</td>
<td>WHO functional class</td>
<td>III,IV</td>
</tr>
<tr>
<td>Minimally elevated</td>
<td>SBNP/NTproBNP</td>
<td>Significantly elevated Rising level</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td>Severe RV enlargement/dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pericardial Effusion</td>
</tr>
<tr>
<td>Systemic CI &gt;3.0 l/min/m²</td>
<td>Hemodynamics</td>
<td>Systemic CI &lt;2.5 l/min/m²</td>
</tr>
<tr>
<td>mPAP/mSAP &lt; 0.75</td>
<td></td>
<td>mPAP/mSAP &gt; 0.75</td>
</tr>
<tr>
<td>Acute vasoreactivity</td>
<td></td>
<td>RAP &gt;10 mm Hg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVRI &gt;20 WU-m²</td>
</tr>
</tbody>
</table>

D. Ivy, Pediatric Pulmonary Hypertension, JACC 2013
PATHWAYS TARGETED WITH ADVANCED THERAPIES


cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; NO: nitric oxide; sGC: soluble guanylate cyclase
TREATMENT ALGORITHM IN CHILDREN WITH PAH

Figure 3: World Symposium on Pulmonary Hypertension 2013 Consensus Pediatric IPAH/FPAH Treatment Algorithm*

*Use of all agents is considered off-label in children aside from sildenafil in Europe. **Dosing recommendations per European approved dosing for children. See text for discussion of use of sildenafil in children in the United States. CCB = calcium channel blocker; ERA = endothelin receptor antagonist; HPAH = hereditary pulmonary arterial hypertension; inh = inhalation; IPAH = idiopathic pulmonary arterial hypertension; IV = intravenous; PDE-5i = phosphodiesterase 5 inhibitor; SQ = subcutaneous.
MANAGEMENT OF PAEDIATRIC PAH IS HETEROGENEOUS

- Adults medications are used to treat children, although evidence is very limited in paediatric patients
- No PAH drug approved globally for children with PAH, none in the US
- Since first approval of epoprostenol in adults with PAH in the US (1995), only 2 drugs are available for children with PAH:
  - Sildenafil is approved in Europe but is not recommended in the US
  - Bosentan has dosing recommendations and a paediatric-specific formulation in Europe only
MACITENTAN: A DUAL ERA

Macitentan is the result of an extensive medicinal chemistry program

Optimized physicochemical properties favoring tissue penetration\(^1\)

Enhanced affinity for ET receptors, long-lasting receptor occupancy\(^2\)

Superior pre-clinical in vivo efficacy compared with other ERAs\(^3,4\)

Potential for favorable safety and tolerability\(^5,6\)

\(^1\)Iglarz et al. J Pharmacol Exp Ther 2008; \(^2\)Gatfield et al. PLoS ONE 2012;  
\(^3\)Iglarz et al. Am J Respir Crit Care Med 2011; \(^4\)Iglarz et al. Eur Respir J 2012;  

ERA: endothelin receptor antagonist; ET: endothelin
SERAPHIN STUDY DESIGN

- **Macitentan 10 mg**
- **Macitentan 3 mg**
- **Placebo**

**Time (months)**
- Screening: 28 days
- Randomization
- Variable treatment period: 3, 6, 12 months
- EOT (discontinuation of study drug)
- EOS (285 confirmed morbidity/mortality events)

**Additional assessments**
- Assessment of primary endpoint
- Additional survival assessment

EOS: end of study; EOT: end of treatment

**PRIMARY ENDPOINT: MACITENTAN SIGNIFICANTLY REDUCED THE RISK OF A MORBIDITY OR MORTALITY EVENT**

![Graph showing patient outcomes](chart)

- **Macitentan 10 mg**, 45% RR, $p < 0.0001^*$
- **Macitentan 3 mg**, 30% RR, $p = 0.0108^*$
- **Placebo**

 Patients without the event (%)

<table>
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<tr>
<th>Time from treatment start (months)</th>
<th>Patients at risk:</th>
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<tr>
<td>0</td>
<td>250</td>
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<tr>
<td>6</td>
<td>188</td>
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<td>30</td>
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<td>36</td>
<td>41</td>
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</tbody>
</table>

RR: risk reduction; *Log-rank

DEVELOPING A DRUG IN CHILDREN WITH PAH
CHALLENGES FOR A RARE DISEASE
DRUG DEVELOPMENT IN PAEDIATRIC PAH CHALLENGES

- PAH is a rare disease
  - Paediatric PAH represents a very small population of patients

- Design
  - Placebo is an issue unless adequate background / rescue measures
  - no global drug approved (none in the US)
  - off label use of all drugs approved in adults
  - SoC varies across countries

- Only global studies can provide substantial evidence. A paediatric development is not mandatory for orphan diseases in the US contrary to Europe
  - Required Level of Evidence is not similar
    - FDA requires conclusiveness to satisfy a written request
    - EMA (PIP) requires sufficient data leading to medical interpretation
5th World symposium (NICE 2013)

- Primary outcome measure should be consistently and reliably measurable, minimising missing data. It should be a clinically meaningful endpoint.
- No longer acceptable to use invasive procedure, e.g. right heart catheterisation.
  - FDA position since 2012
- While a recognised endpoint in addendum on developing drugs in PAH for children
- It is recognised that there is no validated surrogate endpoint (biomarker, exercise test)
- Composite endpoints may more comprehensively reflect clinically meaningful effects.
MACITENTAN PEDIATRIC PLAN
Two double-blind, randomized, multicentre, placebo-controlled (add-on to standard of care) study to evaluate the efficacy, safety, tolerability and PK of macitentan in children with PAH.

Main objectives:
- Demonstrate efficacy of macitentan on PVRi
- Demonstrate efficacy of macitentan on exercise capacity
- Evaluate safety and tolerability

92 patients randomized 1:1 to maci or placebo (on top of standard of care)

24 week treatment

Primary EP: change from baseline to week 24 in PVRi at rest, assessed by RHC
REVISED PLAN OF MACITENTAN IN PEDIATRIC PAH PATIENTS

OBJECTIVES

- Add pediatric PAH indication and formulations to the Opsumit® label.

- Develop one global clinical study, accepted by HAs, that
  - Has a clinically meaningful non-invasive endpoint; in-line with the most recent guidelines
  - Covers all age ranges
  - Results in conclusive efficacy outcome
  - Provides long-term safety information

- Has impact on the future pediatric patient management /guidelines
CONCLUSIONS:

– Clinical Worsening (CW) occurred with a high event incidence and each of the soft end-point components was predictive of death or Lung Transplantation. This supports the usefulness of CW as a study endpoint in clinical trials in pediatric PAH.
PROSPECTIVE, MULTICENTER, OPEN-LABEL, RANDOMIZED, CONTROLLED, PARALLEL GROUP, EVENT-DRIVEN STUDY TO EVALUATE EFFICACY SAFETY AND PK OF MACITENTAN IN CHILDREN

187 Events

Macitentan as monotherapy or add-on to PDE-5 inhibitor

1:1 Randomization

Standard of Care with up to 2 PAH-specific treatments

- Approximately 300 subjects
- Males or females between ≥ 2 years and < 18 years of age

Announcement of Study Closure
DISEASE PROGRESSION: COMPOSITE ENDPOINT

Time to 1st disease progression event

- Death (all cause)
  - OR
  - Atrial septostomy or Pott’s anastomosis
    - OR
    - Registration on lung transplant list
      - OR
      - Hospitalization due to worsening PAH
        - OR
        - Clinical worsening of PAH

All events adjudicated by a blinded clinical events committee
PRIMARY ENDPOINT

- Previous PIP: haemodynamics, consistent with paediatric addendum of the PAH guidelines foreseen for agents like ERAs, for which efficacy and safety are already established in adults, but
  - Risks inherent to this invasive procedure done for the sole purpose of a clinical trial
  - Not acceptable for FDA

- No component with measure of exercise capacity (versus adult study / CHMP guideline)
  - Accelerometry (exploratory measure)
SCIENTIFIC ADVICE DISCUSSION

DESIGN

- OPEN-LABEL
  - A double-blind placebo-controlled study Would exclude patients on ERA and therefore limit the population to be enrolled
  - A double-blind active control study (Standard of Care - SoC) is not feasible
    - SoC varies across regions / countries
    - Use of some drugs (inhaled) makes blinding not possible

- COMPARATOR: SOC
  - Leads to relevant information for the physicians
OTHER ASSESSMENTS

- PANAMA WHO FC
- NT-PROBNP
- ECHO
- ACCELEROMETRY
- GROWTH, PUBERTY
- QUALITY OF LIFE
- PALATABILITY AND ACCEPTABILITY
A Study to Find Out Whether the Medicine Macitentan Works in Children With Pulmonary Arterial Hypertension (PAH)

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified April 2017 by Actelion

Sponsor: Actelion

Information provided by (Responsible Party): Actelion

ClinicalTrials.gov Identifier: NCT02932410

First received: October 12, 2016
Last updated: April 25, 2017
Last verified: April 2017

Purpose

This is a prospective, multicenter, open-label, randomized, controlled, parallel group, group-sequential, event-driven Phase 3 study to evaluate efficacy, safety and PK of macitentan in children.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Arterial Hypertension</td>
<td>Drug: Macitentan Other: Standard-of-care</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: No masking
Primary Purpose: Treatment
FUTURE WAYS FORWARD

- Rare pediatric disease
  - Recruitment challenges
  - Off label use

- Need for development of alternative trial methodology
  - Extrapolation
  - Use of registries
  - Alternative statistical approach

- Endpoint harmonisation and validation agreed with both Agencies

→ Increase the rate of completed and conclusive studies
THANK YOU.