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EMA/FDA/Health Canada Workshop on Paediatric PAH






Industry Perspective

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Public

Industry perspective on partnering with academia and agencies in drug development for children with PAH

On behalf of Pharmaceutical Industry working group

James Strait M.D., Ph.D.

Cardiovascular Therapeutic Area Head, European Clinical Development
Merck Sharp & Dohme

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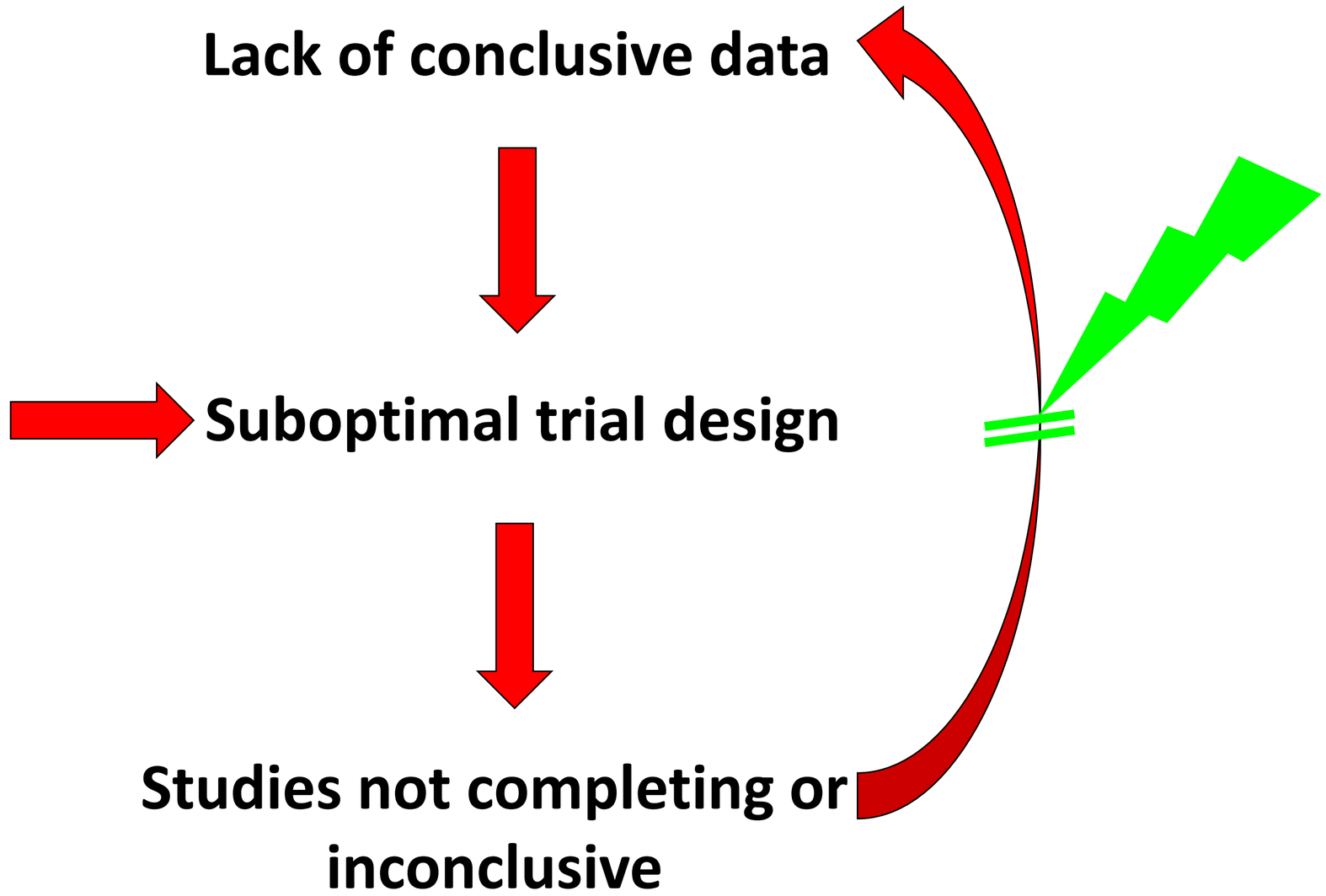
Multiple challenges have resulted in a lack of approved pediatric PAH (pPAH) treatment options long after the development of adult treatment options

- Rare paediatric disease
- Recruitment challenges
- Lack of accepted and feasible methodology / guidance (e.g Level of evidence (LoE), endpoints)
- Simultaneous development of multiple treatments, even when MOA is already established



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Barriers to Successful Trial Completion
Small population with heterogeneous aetiology and SOC

- Recruitment challenges:
    - Orphan disease + heterogenous aetiology; necessary exclusion criteria to enroll a more homogeneous population further limits eligible patients
    - Number of competing trials
    - New treatments assessed on top of background standard of care (SoC) medications; (available) SoC not uniform in different regions
    - Lack of equipoise after marketing authorization for new investigational drugs in adults
        - E.g. parents/investigators unwilling to randomize patients to placebo/SOC controlled trials when drugs have demonstrated efficacy in adults and are already being used in pPAH patients
    - Specialist centres are needed to perform complex endpoint assessments
        - Utilising small sites adds heterogeneity to these assessments and add considerable expense to conducting the trials.
- Feasibility assessments overestimate enrollment projections as it is difficult to predict the proportion of patients/parents who are willing to consent

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There are a number of ongoing trials in pPAH

Active substance	Study	# of Patients in protocol (# of enrolled patients)	Planned Start date/end date (Duration of recruitment)	Number of sites/ Countries	Approximate recruitment rate	Comments
Riociguat	Ongoing: OL, dose titration, safety, tol, PK	20 (3)	Oct 2015 – Jun 2018 (32 months)	36/13	0.03 pts/site/month	First in class No controlled efficacy Extrapolation; M&S
Tadalafil	Ongoing: Pbc controlled, safety and efficacy (TTCW/6MWD)	134 (29)	Jul 2013 – present (46 months to date)	59/17	0.01 pts/site/month	Placebo arm (background ERA)
Tadalafil	Ongoing: PK, safety	At least 15 (19, fully enrolled)	Dec 2011 – Jan 2017 (61 months)	21/6	0.01 pts/site/month	
Ambrisentan	Ongoing: OL, 2 dose, safety, efficacy	66 (35 EEA)	Jan 2011 – May 2016 (64 months)	34/?	0.03 pts/site/month	Study recruitment suspended No controlled efficacy
Macitentan	OL, AC, event driven efficacy safety, PK	300	Approx 6 years (72 months)	Unknown	4.2 pts/mon (sites unknown)	Not yet initiated
Completed studies for comparison:						
Bosentan	Completed: OL, PK, tol, safety, efficacy	64	Mar 2011 – Feb 2013 (23 months)	48	0.06 pts/site/month	First in class No controlled efficacy
Sildenafil	Completed: Pcb-controlled, dose ranging	234	Aug 2003 – Jun 2008 (58 months)	41	0.1 pts/site/month	First in class
Sildenafil	Completed: Long-term, open-label ext.	220	Jan 2004 - Dec 2012	31	NA	

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Ongoing pPAH trials are challenged by imperfect endpoints

STATE-OF-THE-ART

Reliable and developmentally appropriate study end points are needed to achieve drug development for treatment of pediatric pulmonary arterial hypertension

H Sun[1], N Stockbridge[2], RL Ariagno[3,4], D Murphy[1], RM Nelson[1] and W Rodriguez[1]

Table 1. Summary of efficacy end points used in the PAH trials submitted to the FDA

End points used	*Types of end points*	*Study population and numbers of products approved (n)*	*Products approved*	*Suitability for pediatric trials*	*Major limitations*
Increase in 6 min walking distance	Pri		Bosentan; ambrisentan; denafil; tadalafil; treprostinil, iloprost, epoprostenol; riociguat	Partial	Not reliable in children ⩽5 years No normal ref < 4 years Not applicable in infants
A composite of time to the 1st morbidity or mortality event	Pri		Macitentan	Yes	Need to optimize and define relevant components of clinical worsening in pediatric PAH patients
Reduction in initiation of ECMO treatment	Primary end point	Neonates ($n=1$)	INOmax	No	No similar standard of the care in children
Increase in O_2 consumption at peak exercise via CPET	Primary end point	Pediatrics ($n=1$)	Sildenafil*	Partial	51% of children were developmentally unable to perform CPET in this trial
ΔPVRi or ΔmPAP assessed by RHC	S				Two death and three severe adverse events were observed during RHC

Abbreviations: CPET, cardiopulmonary exercise testing; ECMO, extracorporeal membrane oxygenation; FDA, Food and Drug Administration; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; ΔPVRi, change in pulmonary vascular resistance index; ΔmPAP, change in mean pulmonary arterial pressure. *Not approved for use in pediatric PAH.

Downside

Opportunity

High variability; sample size +

N=300?!

Acceptability?

Approximation by cMRI?

Journal of Perinatology (2016) 00, 1–5

Table 2. Evaluation of five promising noninvasive biomarkers as potential surrogate end points for pediatric PAH trials

Noninvasive biomarkers	*Measurement function*	*Drug effect detection*	*Correlation with 6MWD or RHC mPAP/PVRi*	*Validation in definitive RCT*	*Major potential limitations*
Echocardiography	Diagnosis tool for heart function and shape; cardiopulmonary hemodynamics	Not studied	Tricuspid Em and mPAP correlation: $r=-0.67$, $P<0.001$; RV peak strain and PVR correlation: $r=0.73$, $P<0.001$	Not studied	
MRI	Cardiopulmonary Hemodynamic Measure	Yes	Correlation between RHC and MRI derived mPAP: $r=0.92$ Average blood velocity had the best correlation with RHC mPAP and PVRi: $r=-0.86$, $P<0.001$	Not adequate	Sedation in young children; Long scan time and incompatibility with metal compounds such as the delivery pump
PET	RV function and myocardial glucose metabolism	Not studied	Not well established	Not studied	Less suitable for pediatric patients due to radio-active isotope exposure
Electrical Velocimetry	Cardiac Output Measure	Not studied	Comparable with left ventricular output measured by echocardiography	Not studied	Not studied in PAH condition
NT-proBNP	RV failure	Yes	mPAP ($r=0.47$, $P<0.001$); PVR ($r=0.66$, $P<0.001$); 6MWD ($r=0.6$, $P<0.001$)	Not adequate	Impacted by demographic characteristics, renal insufficiency and etiology of PAH.

Abbr[illegible]walking distance; mPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; NT-pro-BNP, N-terminal pro-B-type [illegible]ar resistance; RHC, right heart catheterization; RV, right ventricular; Tricuspid Em, Tricuspid early diastolic myocardial

High variability; sample size +

Role of activity tracking?

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CHALLENGE

How can drug development processes (e.g. overall trial design, endpoint selection, statistical methodology, regulatory discussions, etc.) be re-imagined to improve the rate of success in developing effective therapies for pPAH?

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Potential Solutions

- Endpoint validation and harmonisation
- Alternative trial design and analysis options
- Data Pooling and validation of a PD parameter to enable extrapolation

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Endpoint validation and harmonisation

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What are the indicators of risk in pPAH patients that could guide endpoint selection?

Determinants of Risk in Paediatric Pulmonary Vascular Disease (PHVD)

Lower Risk	Determinants of Risk	Higher Risk
No	Clinical evidence of RV failure	Yes
No	Progression of symptoms	Yes
No	Syncope	Yes
	Growth	Failure to thrive
I,II	WHO functional class	III,IV
Minimally elevated	Serum BNP/ NT-proBNP	Significantly elevated Rising level
	Echocardiography	Severe RV enlargement/ RV dysfunction Pericardial effusion
CI >3.0 l/min/m2 mPAP/mSAP <0.5 Acute vasoreactivity	Hemodynamics	CI <2.5l/min/m2 mPAP/mSAP >0.75 mRAP >15 mm Hg PVRi >15 WU x m2

1,2

1

Systemic CI >3.0 l/min/m^2 mPAP/mSAP <0.75 Acute vasoreactivity	Hemodynamics	Systemic CI <2.5 l/min/m^2 mPAP/mSAP >0.75 RAP >10 mm Hg PVRI >20 WU·m^2

2

1) Hansmann G, Apitz C. Heart 2016;102:ii67–ii85

2) Ivy, DD et al., J Am Coll Cardiol 2013;62:D117–26

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Strengths/weaknesses of HCP identified non-invasive endpoints

Endpoint	Strengths	Limitations
ECHO	• Non-invasive procedure • Widely used for monitoring in patient population	• High operator variability • Sample likely to be larger • No consensus on which echo endpoint should be used as a primary outcome
Cardiac MRI	• Good correlation between RHC and MRI derived mPAP • Requires smaller sample size • Less variability than ECHO	• Requires sedation in young children (long scan time) • Limitation on compatibility • Need experienced centre
NT-proBNP	• Simple procedure (plasma) • seems to be a predictor of PAH prognosis	• Not a specific indicator for PAH only • Impacted by etiology of PAH • The normal value of NT-proBNP in children can vary with age

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Alternative Trial Designs & Analysis

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Data Pooling and Extrapolation

CHALLENGE:

- In common diseases, summary **and** subject/patient level meta-analyses are a possible approach to guide trial design, but in rare diseases only the compilation of patient level databases is helpful to provide the necessary evidence to deal with the heterogeneity across trials
  - This requires high level of industry sharing and collaboration to address e.g. 6MWD, PVR and PVO2 relationships
- Extrapolation from adult data about new drugs with similar MOA can be particularly helpful but one must be mindful of heterogeneity of some elements and lack of accepted PD parameters

POTENTIAL SOLUTION:

- Work across industry by sharing available data, e.g. placebo data, to contribute to endpoint evaluation and validation
- Utilize available supportive data, e.g. from other products with the same MOA, registry or open label data.

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Methodological Advances for Rare Diseases

FP7 Small-population research methods projects and regulatory application workshop (March 2017)

- Selected Topics
  - Leveraging multiple endpoints in small clinical trials. Extension of standard co-primary endpoint test with a fall-back option, if the main goal is not reached. Adds decision rules, and controls α. [1]
  - Skepticism factor: how to relax the standard significance level for pivotal trials in children, taking into account that the drug will have been approved for adults? [2]
  - … others applicable to pediatric PAH, to be discussed.

[1]: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/04/WC500226122.pdf
[2]: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/04/WC500226111.pdf

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Randomised withdrawal design considerations

Data on the relationship between withdrawal period and clinical outcomes measured by various endpoints is needed before a randomized withdrawal study can be appropriately designed to detect a difference between treatments.

- PAH is a chronic disease and treatment is generally continued uninterrupted unless there is a strong rationale to stop (such as a concern for drug tolerance).
- Utilizing a withdrawal design does not overcome the key challenge in pediatric PAH research – lack of consensus on a reliable and sensitive endpoint that serves as a marker of clinical worsening that can be used to define a “Responder” vs. “Non-Responder”
- It is unknown how long a withdrawal period would need to be in order to observe the clinical event. If it is too short the evaluation is inadequate, if it is too long then potentially irreversible disease progression for the patient may take place.
- **Randomized withdrawal design and placebo-controlled design share a similar limitation – a proportion of patients will not receive the study drug for a period of time. Parents and health care providers may be reluctant for their children/patients to have a therapy that they view as beneficial “taken away”**

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Summary of Industry Perspective

1. **Paediatric PAH patient numbers are very small – each patient should contribute to a conclusive study outcome**
2. **To support optimal trial conduct, global regulatory harmonisation is key**
3. **Potential approaches to improve therapeutic development**
   - Endpoint clarification, harmonisation, composite endpoint construction, and validation to enable conclusive studies (e.g. Echo, cMRI, NT-proBNP, etc.)
   - Data Pooling: Utilization of registry data, open-label data, and supporting data from approved compound with same MOA.
     - Extrapolation [of efficacy] from adult data or from one paediatric population to the other, in appropriate situations, could permit streamlining of drug development programs and improve success in a reasonable time

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BACK UP

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