# Report on the Expert Group Meeting of Paediatric Heart Failure, London 29 November 2010

## Clinical trials in Paediatric Heart Failure

**List of participants:**

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**Aim**

A Paediatric Heart Failure Expert Group Meeting was held at the European Medicines Agency in London on 29 November 2010 to identify priorities and optimal design of studies for development of drugs for heart failure in children for the purpose of Paediatric Investigation Plans evaluation.

**Introduction**

The introduction of participants was followed by a declaration of their conflict of interests. The chair of the meeting Gylfi Oskarsson gave an outline of the current situation. It is characterised by:

- Heterogeneous aetiology of paediatric heart failure
- Recruitment difficulties
- Lack of organised co-operation (existing network)
- Lack of well defined and validated end-points
- Lack of data on efficacy of current therapy
- Lack of funding

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# Conclusions

## *Drug classes for paediatric heart failure*

## Drugs currently used

- Chronic heart failure (CHF):

Angiotensin converting enzyme inhibitors (ACEI) should be the first line treatment for CHF. They could be used from the neonatal age for as long as needed. There is a need, however, for evaluation of long-term safety data with this class of medicines.

Diuretics are recommended when fluid overload is present. Risks with long term use include hypokalaemia and resistance.

Beta-blockers could be used in children whose systemic ventricle is a left ventricle, unless contraindicated or not tolerated.

Angiotensin receptor blockers (ARBs) have little beneficial effect over ACEI in adults, but pharmacokinetic/pharmacodynamic (PK/PD) and safety data are needed anyway. It is possible to obtain PK data from hypertension trials with ARBs.

Aldosterone antagonists improve prognosis in CHF.

Digoxin reduces hospitalisations and improves symptoms. It has, however, a controversial benefit in CHF.

- Acute heart failure (AHF):

There are many studies in children showing evidence of acute benefit with the use of IV inotropic drugs, including catecholamines (dopamine, dobutamine, epinephrine, and noradrenaline), phosphodiesterase (PDE) inhibitors (milrinone) and loop diuretics (furosemide) in AHF.

## New drug classes in the pipeline

| **Systolic blood pressure (BP)** | **Current** | **Investigational** |
|---|---|---|
| **Normal or Normal/High systolic BP + Congestion** | Diuretics<br>Vasodilators<br>NTG<br>Nitroprusside<br>Nesiritide<br>ACE inhibitors<br>Beta-blockers | Endothelin Antagonists<br>Vasopressin Antagonists<br>Adenosine Antagonists<br>Natriuretic peptides (Ularitide etc.)<br>Metabolic Modulators<br>Direct Renin inhibitors (Aliskiren) |

| Systolic blood pressure (BP) | Current | Investigational |
|---|---|---|
| **Normal/Low or Low systolic BP** | Inotropes (dopamine/ dobutamine)<br>PDE inhibitors<br>Digoxin IV or oral<br>Levosimendan | Metabolic Modulators<br>sGC activators<br>Istaroxime<br>Cardiac Myosin activators |

- Priority list for drugs to be studied for paediatric heart failure:
- Beta-blockers
- Levosimendan
- ACE inhibitors
- Aldosterone antagonists, including new specific aldosterone receptor antagonists

The ideal medicine for paediatric heart failure should possess safety, efficacy, multilevel blockade of renin-angiotensin-aldosterone system (RAAS), plus anti-remodelling, improving endothelial function, and vasodilatation properties; anti-inflammatory, anti-arrhythmic and diuretic effects.

## *Types of paediatric HF – indications to be studied*

Aetiological subtypes of paediatric heart failure, recommended to be studied, include dilated cardiomyopathy, post-operative, low cardiac output heart failure, and failing Fontan procedure. Ventricular septal defect (VSD) with significant left-to-right shunt could not be studied in Europe as these patients are operated early in life.

There is a consensus that safety data should not be extrapolated from adult population to children and from older to younger children as there is a high potential for errors. PK studies for heart failure drugs are needed for all ages before determining safety. Efficacy is considered difficult to be extrapolated due to feasibility limitations of fully powered trials using hard end-points.

## *Overall development plan – required and feasible studies*

All experts consider pharmacokinetic and pharmacodynamic studies required but only some of them consider them feasible. PK studies should be conducted to achieve systemic exposures similar to those in adults in all cases. PD studies should be performed if it is not reasonable to assume similar disease progression and response to treatment in adults and children.

Safety and efficacy studies are required, but difficult due to the larger number of patients required to perform such studies.

## *Study design issues*

The heterogeneity of paediatric heart failure complicates the assessment of pharmacotherapy in this population which is further compounded by the low number of children affected by heart failure. The population should be as homogeneous as possible and feasible. Age subgroups (newborns, infants and younger children) and acute heart failure (more important) versus chronic one should be taken into account.

Patients with unmet needs (those who deteriorate despite therapy) may be more likely to complete studies and less likely to drop out.

Baseline assessment may comprise:

- Clinical scores – New York Heart Association (NYHA) Functional Classification, the Ross Heart Failure Classification or PHFI (New York University Pediatric Heart Failure Index)
- Biochemical evaluation – level of natriuretic peptide, inflammatory markers, N-terminal pro B-type natriuretic peptide, haemoglobin
- Echocardiographic parameters – left ventricular (LV) dimensions, end-diastolic volume, LV systolic function
- Quality of life score

Placebo-controlled studies in children are always a major issue, especially in the context of a severe and acute clinical condition. In severe and acute disease the placebo-controlled studies should be ethically acceptable. In AHF milrinone should be the standard active comparator.

The optimal (composite) primary end-point may include:

- Death caused by cardiovascular event
- Heart transplantation
- Hospitalisation for aggravation of HF
- LV assist device placement

Composite end-points are challenging and/or are difficult to use in Europe due to country and/or centre specific differences of care. Mortality and hospitalisation rates are not useful end-points for short-term studies. Renal failure could be a safety end-point. It may be better to perform trials using an imperfect, but clinically important end-point than to reach a hard end-point during a study which may never occur. The former endpoint could be left ventricular end-diastolic dimension or volume or a composite of other echo parameters such as end-systolic dimension or volume, shortening fraction or ejection fraction.

Secondary end-points may include:

- Quality of life score
- Weight gain/growth
- Drop-out rate
- Natriuretic peptide is the best end-point to be used as a surrogate one; other biomarkers are more difficult to measure.
- Selected echocardiographic parameters of diastolic and/or systolic dysfunction (e.g. LV dimensions, end-diastolic volume) permit robust assessment of left ventricular function. It is important that one and the same laboratory adjudicates readings and standardised training is provided to the participating technicians.
- Other secondary end-points could be MRI for school-age children, heart rate (HR) variability, cardiac output, and exercise score.
- In acute heart failure the duration of hospitalisation or ICU stay could also be secondary end-points.

## *Paediatric Cardiology Network for drug studies*

The need for establishment of European Paediatric Cardiology Network for drug studies was discussed. It should include existing research centres and investigators with recognised expertise in performing clinical studies in children with cardiovascular diseases and will help bring up high-quality, ethical research of medicines in children with heart failure.

The experience of the Pediatric Heart Network (PHN) in the USA, created and funded in 2001 by the National Heart, Lung and Blood Institute, was debated. Now 10 years old, the PHN has developed into a strong organisation capable of performing multicentre trials in patients with paediatric and congenital heart disease.

Academia representatives, especially the Association for European Paediatric Cardiology (AEPC) in partnership with industry, interested in such trials, have an important role to play in this process.