EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Drug Development in Paediatric Heart Failure

## The EMA Paediatric Committee Approach

M-CERSI Workshop: Drug Development in Paediatric Heart Failure

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Paediatric Medicines Office, EMA

# Introduction

- Treatment of heart failure (HF) in children is based mainly on indirect evidence from adult studies.
- Some clinical studies in children with HF have shown mixed results, e.g. studies with β-blockers.
- Carvedilol trial failed to show benefit in children with HF and ventricular dysfunction due to larger placebo improvement response than expected.
  Shaddy R et all, Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA. 2007;298(10):1171
- A subsequent clinical trial in 89 paediatric HF patients also found no difference in clinical improvement with carvedilol compared with conventional treatment.
  Huang M et all, The effect of carvedilol treatment on chronic heart failure in pediatric patients with dilated cardiomyopathy: a prospective, randomized-controlled study. Pediatr Cardiol. 2013;34(3):680

# Introduction

- This presentation is based on the current experience with PIPs for heart failure, on the outcome of Expert Group Meeting of Paediatric Heart Failure in London, November 2010 and on the Paediatric Addendum on the CHMP Guideline on clinical investigation of medicinal products for the treatment of acute heart failure.
- Topics for discussion:
  - selection of patients
  - clinical trial designs
  - primary and secondary endpoints
  - safety endpoints
  - extrapolation, modelling & simulation
  - what needs to be done

# PIPs for cardiovascular diseases, including heart failure (2007-2015)

Cardiovascular PIPs represent 6% of all agreed PIPs.

| Therapeutic area | Number of agreed PIPs | PIPs with age-appropriate formulation | Number of completed PIPs | Number of MAs with paediatric indications |
|---|---|---|---|---|
| All areas | 808 | 353 | 98 | 71 |
| Cardiovascular diseases | 48 | 24 | 9 | 6 |
| Heart failure | 10 | 8 | 1 | 3 |
| Heart failure in neonates | 6 | 8 | 1 | 3 |

Source: 10-year Report to the European Commission

# Limitations for conducting clinical trials in paediatric heart failure

- Heterogeneous aetiology of paediatric heart failure
- Low patient numbers leading to recruitment difficulties
- Lack of consensus regarding the optimal study design
- Absence of well-defined and validated endpoints
- Lack of data on efficacy of current therapy
- No existing European Paediatric Cardiology Network

# Patient selection

- Diagnostic criteria of HF based on baseline evaluation of functional or clinical scoring systems (NYHA, Ross Classification or PHFI), combined with imaging (echocardiography or cardiac MRI)
- Echocardiographic parameters – left ventricular (LV) dimensions, end-diastolic volume, LV systolic function
- Patients with heart failure secondary to either high or low output disease included
- Patients with systolic hypotension, ventricular dysrhythmias, renal dysfunction excluded
- Stratification by aetiology or stratified randomisation to maximise the information from the trial. It is recognised that separate studies in different aetiologies are not possible due to the small patient numbers.

# Clinical trials design

- Human Pharmacology studies – data from the adult heart failure population defines the studies required in the paediatric population. Where possible, use of PK/PD modelling based on adult data to explore the PK behaviour in children.
- Exploratory Therapeutic studies – separate dose titration studies are sometimes required.
- Confirmatory Therapeutic studies:

- placebo-controlled with add-on design to the best standard of care is the preferred option by the PDCO to demonstrate superiority in terms of efficacy and safety.

- when placebo-controlled studies are not feasible, approved active comparators should be used.

# Efficacy evaluation

- Composite endpoints or ranked composite endpoints preferred, which could include:

  - mortality

  - time to events (transplantation, referral for transplantation, duration of intensive care or hospital stay)

  - left ventricular function assessment (ejection fraction, dimensions, volumes)

  - clinical scores (NYHA, Ross Classification or PHFI)

  - biochemical parameters (B-type natriuretic peptide, inflammatory markers)

- The endpoint components should capture the spectrum of relevant clinical parameters and point in the same direction (concordance).

- As a rule composite endpoints are defined at high level and have to be agreed by the PDCO before the trial start.

# Evaluation of safety

Safety evaluation in paediatric population expected to be similar to adults with additional endpoints relevant to children, including:

- Systolic hypotension
- Organ hypoperfusion
- Ventricular arrhythmias
- Failure to thrive, growth retardation / developmental delay
- Renal function assessment (creatinine or glomerular filtration rate)

# Extrapolation, Modelling & Simulation

- Phase I studies not expected, information extrapolated from studies in adults.
- PK/PD data from the adult heart failure population guide the level of PK information and studies required in the paediatric population.
- PK/PD modelling based on data derived from adult populations requested in 3 PIPs.
- Systematic literature review, extrapolation of clinical efficacy data from adults / adolescents requested in 3 PIPs.

# What needs to be done?

- Identification of areas of highest unmet medical need and prioritisation, e.g. patients with Duchenne muscular dystrophy, PAH and single ventricle defects with heart failure.
- Registries on natural history and long-term safety data.
- Maximising use of available data, e.g. use of PK/PD modelling based on data derived from adult populations to explore the pharmacokinetic behaviour in children and validation of the models.
- Development of appropriate study designs and validated endpoints with definition of a clinically meaningful difference.
- Discussion and alignment of clinical study designs with the FDA.
- Establishment of an European Paediatric Cardiology Network similar to the Pediatric Heart Network (PHN) in the USA.

# Any questions?

## Further information

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