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Human Medicines Development and Evaluation

# Standard acute myeloid leukaemia paediatric investigation plan

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Comments should be provided using this template. The completed comments form should be sent to paediatrics@ema.europa.eu.


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| Keywords | *Child, medicine development, acute myeloid leukaemia, haematology, paediatric investigation plan* |


Note:

Comments are sought in particular on the clinical strategy and methodological aspects of clinical trials as well as on the following questions:

- How can the processes by which priorities are proposed for patient subsets, targets, pathways and mechanisms of action be made transparent and integrated with the objectives of this standard PIP?
- How to balance the unmet therapeutic needs of paediatric patients with newly-diagnosed acute myeloid leukaemia with those at first or subsequent relapse or a progression of acute myeloid leukaemia and those of specific subsets such as Down syndrome?

## 1. Background

The standard PIP for acute myeloid leukaemia (AML) was prepared by the Paediatric Committee with external experts in the Paediatric oncology task force of the EMA. The aim is to highlight the persistent unmet therapeutic needs for AML in children, to propose plausible targets / mechanisms of action that could address the needs, to set out the principal features of trials in children with AML as well as to make transparent the possible requirements for a PIP for AML. The standard paediatric investigation plan is a starting point for discussions on paediatric AML development. The intention is to support


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pharmaceutical companies to propose a PIP that is scientifically adapted to the medicine. The document will be reviewed and updated as needed.

The annual incidence of AML in the paediatric population in the EU is about 700 patients, based on projections, accruals into trials and accruals into European registries; about 10 % of patients are under the age of 1 year at diagnosis; about 50 patients have Down's syndrome.

The underlying biology of AML overall and within its subtypes seems similar in children and young adults. However, not all biological characteristics are similar (e.g., NPM1 mutations). Moreover, the therapeutic settings and uses of medicines often cannot be compared across all ages (curative intention pursued with intensive front-line and first relapse treatment in young patients, in contrast to choices for palliation with low-toxicity treatment in the elderly), and the previous treatment exposure is largely different in advanced disease stages (relevant for medicines with late toxicities such as anthracyclines).

The overall prognosis declines with increasing age, even when looking only at children and young adults (5-year event free survival (EFS) 54% in young children, 43% children from 13 years to less than 21 years and 28% in young adults from 21 years to less than 30 years) (Creutzig et al. 2008) and this impacts options for clinical development; further prognostic factors include cytogenetics and gene mutations (Creutzig et al. 2012; Pui et al. 2011). Although the prognosis of AML in children has improved children over the last decades, it has remained much inferior to the prognosis in acute lymphoblastic leukaemia.

Relationship to other relevant diseases: Myelodysplastic syndrome (MDS) should be specifically addressed by collecting specific robust paediatric data, whether in separate paediatric studies or in stratified studies jointly recruiting MDS and AML, for medicines that are developed for AML and also MDS treatment.

# 2. Priority medicines to be developed, and patient subsets with high unmet needs

Reference is made to the academic community's clinical priorities or inventories for medicines for this disease, including currently known "druggable" targets of relevance. Available references may not represent the latest information on priority medicines and targets / pathways:

- Arsenic trioxide (Vassal 2009), cladribine, clofarabine, liposomal daunorubicine, gemtuzumab ozogamicin, dasatinib, midostaurin, multityrosine kinase inhibitors (FLT3, KIT, VEGF), farnesyltaransferase inhibitors (Kaspers and Zwaan 2007).

There are still unmet therapeutic needs in paediatric patients with newly-diagnosed AML (suboptimal prognosis with current best treatment) as well as in those with refractory or with recurrent disease (even worse prognosis, unchanged since long). All subsets of the paediatric population with AML should be discussed in the PIP documentation and the PIP indication should target 2 or 3 of the following subsets, selected based on a scientific rationale for the medicine and with the objective to improve the overall outcome in AML.

- Patients with newly-diagnosed high-risk AML: need for a more efficacious treatment as part of a first-line induction regimen, in particular when there is a good rationale for use during first-line treatment, such as the individual disease biology (e.g., FLT3 mutations with high allelic ratio etc.) or the potential for reduction of toxicity.

- Patients with AML that is resistant to first or to second line induction treatment: need for an efficacious treatment as part of a re-induction regimen.
- Patients at the time of diagnosis of relapse after HSCT / second or subsequent relapse: need for an efficacious treatment that is not overly toxic in this subset of patients who likely had high cumulative previous treatment exposure, likely including at least one prior transplant procedure.
- Patients with secondary AML: need for an efficacious treatment.
- Patients at the time of diagnosis of early first relapse: need for a more efficacious treatment as part of a treatment regimen.
- Patients at the time of diagnosis of first relapse (other than early): need for a more efficacious treatment as part of a treatment regimen.
- Patients with APL: need for safer treatment to be used during induction.
- Patients with AML in Down syndrome: Needs may exist, specifically for non-cytotoxic or "targeted" medicines to reduce treatment toxicity. Needs may be less in patients younger than one year of age and in those with FAB M6 or M7, compared to other patients with AML in Down syndrome.
- Congenital AML, extramedullary AML.

# 3. Criteria for evaluation of PIP proposal

The EMA with the PDCO want to address public health needs by addressing the highest unmet needs in a timely fashion and by generating robust data, recognising that acute myeloid leukaemia is malignancy that occurs in the paediatric and adult population, albeit some notable differences exist in terms of disease features and outcome. The Appendix 2 to the Guideline on the evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3) on Confirmatory studies in Haematological Malignancies applies also to the paediatric population, in particular the general principles, as well as the Addendum on Paediatric Oncology (CPMP/EWP/569/02). In addition, the following aspects in a PIP proposal for acute myeloid leukaemia will be particularly evaluated by the EMA / PDCO:

- How exactly can data from literature, non-clinical and adult studies support and inform the paediatric development, decision on paediatric studies and conclusions for efficacy (and perhaps dose) in children, respectively? On the similarity of the medicine for treatment of AML in adults and children, which data are needed? How robust is the plan to search for and model any differences (e.g., age-related difference in response, different treatment regimens) in joint analyses of studies in children and in adults? Are possibilities explored to recruit paediatric and young adult patients together into clinical trials?
- Are paediatric patient subsets well defined and do they represent paediatric patients with AML and high unmet needs (see above)? A priori, it is equally important to prevent a relapse as to develop salvage treatments for AML. Do the paediatric studies progressively cover the relevant age range, generating some data in the youngest patients (infants)?
- Method and robustness of dose-finding and early trials, for example, optimum biological dose versus maximum tolerable dose, or a combination thereof, and how the choice is informed by data; how are pharmacokinetic assessments informed by predictions from models of Pk and / or Pk/PD to which then paediatric data are added; dose-finding in younger children; supportive pharmacodynamic data; establishing a relationship to adult data. Pharmacokinetic, safety and dose-escalating dose-finding studies with cytotoxic medicines should probably not define

haematological toxicity as dose-limiting (DLT) for AML, or should differentiate between haematological and non-haematological DLT.

- Does dose-finding appropriately reflect that single-agent studies may not be justified because therapeutic benefit cannot be expected to be sufficient for a treatment effect on AML?

# 4. Non-clinical studies

Currently few paediatric AML cell lines and xenografts seem to be available for non-clinical pharmacology (efficacy) studies (Kang et al. 2011; Drexler 2010); fresh material from children with AML could be used. Studies in a PIP should contribute to establishing more paediatric AML models for non-clinical pharmacology (efficacy) studies. Non-clinical data may be needed to investigate pharmacodynamic interactions and to analyse impacts on the activity of used and established medicines, for example anthracyclines and cytarabine.

# 5. Clinical studies

## *5.1. Clinical study overview*

1. Dose-finding trial in paediatric (and possibly young adult) patients with AML, preferably including testing a rational combination, limited to identify unexpected paediatric toxicity and / or unexpected pharmacokinetic profile, allowing as soon as possible to progress with subsequent studies.
2. Therapeutic-exploratory trial in paediatric (and possibly young adult) patients at diagnosis of first relapse of AML, unless data show relevant activity in adults with AML so that this study is not necessary and the next study should be started.
3. Randomised trial in paediatric (and possibly young adult) patients with AML to evaluate safety and efficacy of the medicine, added to standard of care or active-controlled when used in rational combination, in target subset(s).

## *5.2. Methodological aspects for studies*

Paediatric trials should be initiated not later than preliminary dosing, safety and activity data are available from a study(ies) in adults with AML or another malignant disease.

Trials may recruit both paediatric and young adult populations (e.g., up to 30 years of age, depending on trial objectives) provided that the trial is driven by the paediatric therapeutic use of the medicine. Trials with paediatric patients at first relapse should be stratified by time of relapse and by early treatment response. Patients with CNS involvement should be included.

Patients with Down syndrome should be studied separately from other paediatric patients with AML, or at least be analysed as a separate subset, if the safety profile of the medicine being studied suggests that they could be included alongside other paediatric patients.

Reporting of paediatric trial results to include sensitivity analyses by cytogenetics and by age as well as descriptive comparison of the results in paediatric and any adult patients.

Definitions accepted in internationally established paediatric oncology groups should be used for describing risk factors and endpoints. However, some variation in such definitions is recognised. Working definitions could be as follows:

- "High risk AML": An example is, unfavourable cytogenetics or bone marrow blast proportion exceeds 15% on day 15 of induction therapy (or whatever other blast percentage and timing of this assessment is selected), but no favourable cytogenetics.
- Favourable cytogenetics: Examples are, t(15;17), t(8;21)(q22;q22)/RUNX1-CBFA2T1, inv(16)(p13q22)/t(16;16)(p13;q22)/CBFB-MYH11, and others to be included.
- "Resistance" to, "refractory to", progression on front-line treatment: It may be possible to group patients with such AML disease together, if they have received appropriately intensive treatment.
- "APL": acute promyelocytic leukaemia; for this and other AML subtypes refer to (Vardiman 2010); APL may need to be studied or analysed specifically.
- "Early relapse": relapse when first complete remission duration is less than one year
- "Secondary AML": encompasses AML developing after preceding myelodysplastic syndrome or as a second malignancy after previous malignancy and treatment.
- Endpoint definitions according to Creutzig and Kaspers (2004) for CRi and according to Cheson et al. (2003) for other endpoints, for example criteria for "phase I or II" trials.

### *5.3. Extrapolation of efficacy*

Based on the data of similarities and dissimilarities, extrapolation of efficacy from adults may be justifiable, in well-defined subsets of adult and paediatric patients based on the similarity of risk factors, stage and previous treatment if any. The PIP should discuss strengths and weaknesses of this approach, based on the pharmacological rationale, non-clinical and clinical data, in order to explore opportunities for extrapolation of efficacy. The requirements for acceptability of extrapolation of efficacy include that relevant data are, or will be available from studies in similar adult AML populations exposed to similar treatments. Where extrapolation of efficacy is a relevant part of the proposed paediatric development, the extrapolation exercise should be systematically planned and described (see EMA templates).

## 6. General requirements

Pharmaceutical development (age-appropriate pharmaceutical form[s]), non-clinical studies (pharmacokinetics/ metabolism, toxicology and pharmacology) and issues for long-term follow-up of safety and / or efficacy (after completion of a PIP) need to be proposed as for any other paediatric anti-cancer medicine.

The number of patients to be evaluable should be proposed and put into context by providing: a tabulation of a range of patient numbers, treatment effect sizes and study power; a plan for synthesis / meta-analysis of all relevant data; a discussion of the trade-off between sample size and the quality of data-driven conclusions.

Plans for collecting data on long-term safety and efficacy including on other uses of the medicine being explored, after first authorisation, in controlled environments such as a clinical trial(s); plans for integrating with scientific communities for this data collection.

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