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Human Medicines Development and Evaluation

Standard rhabdomyosarcoma paediatric investigation plan

Adopted by Paediatric Committee for release for consultation	7 December 2012
Start of public consultation	21 February 2013
End of consultation (deadline for comments)	5 May 2013

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

Keywords	*Child, medicine development, rhabdomyosarcoma, tumour, oncology, paediatric investigation plan*

Note:

Comments are sought in particular on the clinical strategy and details of the 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 address unmet therapeutic needs of children with "standard-risk" rhabdomyosarcoma?
- In which way could different "standard" treatments that are used in different regions of Europe impact the development of new medicines for rhabdomyosarcoma?

1. Background

The standard PIP for rhabdomyosarcoma was prepared by the Paediatric Committee with external experts of the Paediatric oncology task force of the EMA. The aim is to highlight the persistent unmet therapeutic needs for rhabdomyosarcoma 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 rhabdomyosarcoma and to make transparent the possible requirements for a PIP for rhabdomyosarcoma. The standard paediatric investigation plan is a starting point for discussions on rhabdomyosarcoma development. The intention is to support pharmaceutical companies to propose a

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

Rhabdomyosarcoma is the most common subtype of the condition soft tissue sarcoma in children less than 15 years of age, representing about 50% of all soft tissue sarcomas in this age range. Rhabdomyosarcoma also occurs in adults, in whom it represents less than 5 % of soft tissue sarcomas. In the European Member States, there are about 400-500 children who are newly-diagnosed with rhabdomyosarcoma each year, 50 % of them are 5 years or younger at diagnosis; a first relapse is diagnosed in about 150-200 paediatric patients and about 115-155 die from the disease each year.

The rhabdomyosarcoma is chemosensitive (80% show at least a partial response after 2 months). Local control is essential for cure: modalities include surgery and radiotherapy. Outcome: Upfront treatment (neoadjuvant) chemotherapy followed by local treatment results in complete remission in 90 % of patients with localised disease. In newly-diagnosed metastatic rhabdomyosarcoma (non-localised disease), the 3-year event-free survival probability is 27 %. Among all patients with a relapse of initially localised rhabdomyosarcoma, 75 % have local/locoregional disease. The different biological features of the two types of rhabdomyosarcoma, alveolar and embryonal rhabdomyosarcoma, may be relevant for the development programme and this question should be addressed.

2. Priority medicines to be developed

A workshop on development strategies and priorities for medicines to treat rhabdomyosarcoma in children took place in April 2010 with experts from paediatric and adult oncology study groups in Europe.[1] Based on data available at the time, medicines that target / inhibit / modify the following molecules / pathways were considered priorities for rhabdomyosarcoma studies, these examples are not exclusive:

ALK, cMET, FGFR1/2/3/4, G2M kinases, HSP90, IGF1R*, KIT, MET, NOTCH, PDGFR, PIK3CA/mTOR including SPRY1, PTEN, Raf1, SrC, VEGF(R)* (alphabetical order; * some paediatric trials have been completed and should be taken into account).

Conclusions from other consensus finding meetings should also be considered. Not all targets are relevant in both biological types of rhabdomyosarcoma. Other targets may be relevant and proposals are welcome.

3. Criteria for evaluation of PIP proposal

The EMA and the PDCO want to address public health needs by addressing the highest unmet needs in a timely fashion and by generating robust data. The "Guideline on the evaluation of anticancer medicinal products in man (CHMP/205/95 Rev. 4)" applies also to the paediatric development, in particular its appendix 1 on "Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials (EMA/CHMP/27994/2008/Rev.1)" and its "Addendum on Paediatric Oncology (CPMP/EWP/569/02)". In addition, because rhabdomyosarcoma is primarily a paediatric malignancy and is unrelated to other soft tissue sarcoma subtypes such as those frequent in adults, in a PIP proposal the following aspects will be particularly evaluated by the EMA / PDCO:

- The understanding of the medicine's mechanism of action and relevance for rhabdomyosarcoma, for example, available and expected biological data of importance regarding the target and the specificity and potency of the medicine with respect to the target; off target effects, in particular

[1] Conticanet, Connective Tissue Cancer Network; ITCC, Innovative treatments for children with cancer consortium / KCK, Kids' cancer kinome project; EpSSG, European paediatric soft tissue sarcoma group.

those that cannot be expected in adults; data and plans for developing a biomarker(s) and using it to optimise the paediatric development.

- 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; dose-finding in younger children; supportive pharmacodynamic data; combination with another medicine with rationale for rhabdomyosarcoma; establishing a relationship to adult data.
- Relevant populations / subsets to be included with high unmet needs, as indicated for rhabdomyosarcoma (table section 4). In particular for targeted medicines, in which types of tumours can activity and potential benefit be expected; in later studies, are patient subsets well-defined with respect to preceding treatment, baseline risk factors etc. (Chisholm et al. 2011).
- If a surrogate endpoint is proposed, then there should be some pre-existing data establishing a correlation of the treatment effect on the surrogate (e.g., progression-free survival) with that on the desired clinical efficacy endpoint (e.g., overall survival) (for a methodological example see Buyse et al. 2007).
- Building up of data on safety, activity and efficacy for rhabdomyosarcoma: Because efficacy cannot be extrapolated from adult data, the plan is to describe a complete paediatric development, under the assumption that accumulating paediatric data and other evolving scientific data support to progress the development. Early paediatric trial(s) in children with rhabdomyosarcoma and possibly other malignancies with a rationale for the medicine, and later paediatric trial(s) in the target population are needed to generate data on safety and activity and / or efficacy that well inform the benefit / risk assessment for using the medicine in children. This likely includes a study(ies) with a controlled design; single-arm designs such as those based on two-stage calculations may not be appropriate for this objective.
  Regarding the sample size of later trials in children with rhabdomyosarcoma, an overall small population, the PIP should clearly explain and discuss the degree of certainty and the precision of estimates, including the strengths and the limitations of this aspect of the proposal.
  The need for interim futility analyses and possible consequences for a paediatric use of the medicine should be discussed.

4. Clinical studies

This standard PIP suggests addressing as a priority the highest needs in identified subsets, rather than in so-called standard risk rhabdomyosarcoma. Some medicines may however be of most advantage to patients with standard risk rhabdomyosarcoma, and this may be proposed to the EMA / PDCO.

In addition to studies 1 and 2, either study 3 or 4 should be included in a PIP, together with a rationale for the choice. The rationale as well as advantages and limitations of proposed design choices also need to be provided.

Study	**1**	**2**	**3**	**4**
Objective(s): To evaluate ...	Single-agent dose-finding (maximum tolerable dose and / or biologically optimal dose) and tolerability	Safety and dose-refinement in combination	Activity, efficacy and safety (benefit/risk)	Activity, efficacy and safety (benefit/risk)
Design	Single arm, successive cohorts, e.g., rolling six design or continual reassessment method	• In combination with standard of care, or • In combination with novel medicine	Randomised add-on to multi-agent chemotherapy, futility interim analysis	Randomised, in combination with a front-line treatment regimen

Study	1	2	3	4
		Selection of combination partner(s) based on biological and perhaps adult data. Design depending on activities.		
Design – alternatives	Combination use, in the case that single-agent activity is likely to be low (non-clinical and adult wide dose-ranging)	Run-in phase to later study or extension phase of earlier study		
Population	Solid malignant tumours potentially susceptible to mechanism of action and for which no effective therapy is known. Second or subsequent relapse. Possibly after at least one (failed) treatment attempt using active anti-cancer medicines for the following situation: • Refractory* rhabdomyo-sarcoma with no local therapy option** • First relapse of localised rhabdomyosarcoma with unfavourable prognostic factors • Metastatic rhabdomyosarcoma Possibly paediatric and (young) adult patients	• Refractory* rhabdomyosarcoma with no local therapy option** • First relapse of localised rhabdomyosarcoma with unfavourable prognostic factors • Metastatic rhabdomyosarcoma Possibly restricted to presence or function of marker (biomarker, pharmacogenomic marker, ...)	• First, untreated relapse of rhabdomyosarcoma, perhaps groups of patients with certain risk factors (Chisholm et al. 2011) in particular refractory rhabdomyosarcoma with no local treatment option	• Newly-diagnosed untreated high risk rhabdomyosarcoma • Newly-diagnosed untreated very high-risk rhabdomyosarcoma
Population - alternatives	Only rhabdomyo-sarcoma, if mechanism of action is relevant only for subtype of rhabdo-myosarcoma	Defined with a view to mechanism of action (e.g., anti-angiogenesis medicines for metastatic disease) or in relation to subtype of rhabdomyosarcoma	Based on presence or function of marker (biomarker, pharmacogenomic marker, ...)	
Dose	Dose-escalation, with intra-individual escalation when no adult maximum tolerated dose. Duration as long as clinical benefit	• Starting from study 1 • Up- and down-titration of either medicine • Different administration schedule(s)	Based on preceding study(ies)	Based on preceding study(ies)
Dose - alternatives	Fixed (normalised) dose based on adult data (=extrapolation of dose)			
Endpoints***	• Acute toxicities	• Pharmaco-	Time-to-event	Time-to-event

Study	1	2	3	4
	• Cumulating toxicity • Activity	dynamic activity on targets and related pathways • Anti-tumour activity (WHO and RECIST)	(failure-free, progression-free, event-free survival) with supportive overall survival	(failure-free, progression-free, event-free survival) with supportive overall survival
Analyses	• Pharmaco-kinetics • Pharmacodynamics as potential biomarkers • Modelling of dose including adult data	• Pharmaco-dynamics and any interaction • Pharmacokinetics and any interaction	• Interim analysis (blinded) on response rates (futility) • Subset analysis of treatment effect homo-geneity in embryonal vs alveolar histology	• Interim analysis (blinded) on response rates (futility) • Subset analysis of treatment effect homo-geneity in embryonal vs alveolar histology
Number of evaluable patients – **order of magnitude** (see section 3 above)	~15	~15-75	~100-200	~100-200

* „refractory" = not having achieved at least a partial response after about 8 weeks of standard of care, intensive multi-agent treatment

** „no local therapy option" = surgical resection would result in residual disease or in important functional or cosmetic consequences and radiation therapy is not an option

*** Studies of anti-cancer medicines in patients with a malignant disease capture signs of anti-tumour activity (response and duration, progression-free survival), tumour-related events (progression, relapse) and survival.

5. 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.

6. References

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