

## **CDDF-ITCC -SIOPE 4th Paediatric Oncology Conference**

**Accelerating the development of new oncology drugs for children and adolescents:**

**Brussels, Belgium 20-21 January 2016**

*Conference Chair:* Gilles Vassal

*Present:* See attached list of participants

**Abbreviations:** ALK: anaplastic lymphoma kinase; BPCA: Biologics Price Competition & Innovation; CDDF: Cancer Drug Development Forum; EMA: European Medicines Agency; ENCCA: European Network for Cancer Research in Children and Adolescents; FDA: Food and Drug Agency; IMI: Innovative Medicine Initiative; ITCC: Innovative Therapies for Children with Cancer; LTFU: long-term follow-up; MA: marketing authorisation; MoA: Mechanism of Action; PDCO: the Paediatric Committee [of the EMA]; PIP: Paediatric Investigation Plan; PK: pharmacokinetic; PPoC: paediatric proof of concept; PREA: Pediatric Research Equity Act; PRINTO: Paediatric Rheumatology International Trials Organisation; SIOPE: European Society for Paediatric Oncology; US[A]: United States [of America]; TYA: teenagers and young adults; WG: Working Group; WR: written requests

**This document summarises the discussions and conclusions of the meeting, and reflects the personal views of the participants, not the opinions of their organisations (industry, PDCO, EMA or academia).**

## Summary

The goal of the CDDF-ITCC-SIOPE multi-stakeholder, Paediatric Oncology Platform, created in 2013, is to improve oncology drug development for children and adolescents in Europe; it comprises three Working Groups (WG). Their overall objectives for 2016 are to take three proposals to the EU Commission for the Revision of the Paediatric Regulation in 2017. The WGs' progress was discussed in the context of presentations underlining and examining their remits, and the details and potential problems arising from the WGs' Review proposals were explored.

WG1 continues work on implementation of MoA drug development, prioritisation of drugs across company pipelines and inclusion of TYA in early phase adult clinical trials. The principles of MoA development were agreed and WG1 will publish a position paper in 2016; it will also define the implementation of MoA development from a regulatory and reward perspective by building a business case, and harmonise language with the US. Secondly, exploration of the concept of multi-stakeholder prioritisation was agreed, and two forums will be held over 2016: to prioritise development of ALK inhibitors in ALK positive paediatric malignancies and to prioritise development of new agents for B cell malignancies. Thirdly, it was agreed that there is no additional risk and no regulatory limitation for TYA in early phase adult trials, and deliverables for 2016 will include a position paper and include TYA in five such studies. Alongside these plans, the development of an aggregated database of paediatric tumour targets and an aggregated pipeline of drugs continues; a target database will be made available in 2016 and a proposal will be built for an IMI2 comprehensive 'paediatric pre-clinical proof of concept platform' to enable clinical molecule development for children with cancer. WG1 will work with WG2 on proposed changes to the Regulation in 2017.

WG2's proposals for new incentives for paediatric oncology drug development – early, segmented and transferable – and repositioning of adult drugs were endorsed. The incentives, providing additional and transferable patent exclusivity at different stages of the drug development programme, will be ~~fine-tuned~~ fine-tuned, and their implementation and a business plan will be worked up to support the proposals for the 2017 Review. The group will also define a strategy to access Policy Makers. In 2016, they will publish 2 papers; one on the new incentives and a second on the refinement of these proposals supported by a business case.

WG3 gained a consensus on two proposals for LTFU – one, to better define its content, i.e., which data and for what purpose (e.g., health care, regulatory/pharmacovigilance, academic research) and second to define its implementation (when, how, for how long). Its objectives for 2016 are to build a pilot proposal and publish a white paper on its proposals.

The Platform itself continues to develop, and in 2016 its members will finalise the terms of reference, launch a website, and decide on a name. The next CDDF-ITCC- -SIOPE Paediatric Oncology Conference will be in early 2017.

## Introduction

This 4th CDDF-ITCC-SIOPE paediatric conference examined and shared the progress of the three Paediatric Platform Working Groups (WGs) in 2015, and aimed to identify firm proposals to take to the EU Commission for the Revision of the European Paediatric Regulation in 2017.

The meeting was divided into four sections:

- Accelerating drug development for children with life-threatening diseases
- Prioritisation through mechanism of action – why and how?
- Long term follow up of patients receiving innovative oncology drugs
- New incentives for specific paediatric oncology drug development

## Session 1: Accelerating drug development for children with life-threatening diseases

Chairs: Martin Schrappe (SIOPE President, Germany) and Heinz Zwierzina (CDDF President, Austria)

### Presentations

*'Working together – a report from The CDDF–SIOPE–ITCC multistakeholder paediatric platform'* [Gilles Vassal, Gustave Roussy, France]

*'Unite2Cure – mobilizing the general public and decision makers'* [Debbie Binner, Create for Chloe Foundation, UK & Nicole Scobie, Zoé4Life, Switzerland]

*'Improving the implementation of the Paediatric Medicine Regulation – recent changes made by the PDCO'* [Dirk Mentzer, Paul-Ehrlich-Institut, Germany & PDCO at the EMA, UK]

*'Improving the regulatory environment in the US'* [Gregory Reaman, FDA, USA]

**Discussion:** The consensus was that interaction and discussion between all stakeholders had increased and become more positive, but that actual progress was difficult to evaluate. Certainly, the options for children and young people have not dramatically increased.

Even with recent changes to its implementation (revision of the class waiver list issued by EMA in July 2015) waivers are still given for drugs developed for adult indications, where the drug's MoA is relevant to one or more cancers in children. Though these recent changes necessitate pharma applying and discussing waiver applications, the PDCO cannot still mandate paediatric development.

*At the same time, changes are currently being proposed to PREA. Currently the FDA can "request" a company carry out paediatric development, pursuant to Best Pharmaceuticals for Children Act, and can mandate certain trials pursuant to the Pediatric Research Equity Act (PREA). However, PREA requirements are almost always waived in the case of oncology drug products because PREA obligations only extend when the paediatric population has the same indication as the adult population. However, proposals recently taken to Congress will propose that PREA obligations will not be waived for oncology drug products when the cancer of the paediatric population has the same mechanism of action as the adult cancer. This could significantly increase the number of earlier paediatric studies under PREA. It is hoped this will come into force in the next 1-2 years. However, this will lead to a discrepancy between the operations of the FDA and the EMA. The*

European situation is different and not ideal, because the EMA cannot request or require a paediatric drug development even if there is an identified need through the MoA.

Voluntary PIPs are rare and some people believe this is partly because of the high attrition rate of drugs in development. Funding would be therefore difficult to achieve for paediatric development with compelling reasons needed to take a drug forward. From the industry perspective a useful tool would be a one-stop shop with the EMA to discuss PIP content and design. Were industry to begin work on a compound with academia, start a trial, and then discuss PIP possibilities with the EMA, it might enable funding of the early phase work. The EMA is currently running a pilot to provide such scientific advice, dialogue and evaluation. In the US this facility exists in the form of early review meetings with the FDA to get scientific advice and can be used by large and small companies. Parents would like to see increased interaction between the EU and US in order to explore such possibilities.

Opportunities to change the Regulation are available in 2017. If the MoA requirements are not implemented, the consequences for the treatment of children with cancer are dire. The EMA wants to move forward and provide support and information, but it cannot initiate action, this must be undertaken by industry and academia.

Although both waivers and MoA based development affect the speed of paediatric drug development, the question of acceleration itself also plays a part, with delay often caused by practicalities: lack of incentives for industry to start work early on a potential paediatric compound and irrelevant and unimaginative trial design. It is estimated that only 10% of PIPs are submitted by companies at the end of adult phase I / pharmacological studies, as prescribed by the regulation. Most PIPs are submitted late during the development in adults, even very shortly before filing the adult dossier for marketing authorisation.

Additionally, academia needs early access to high priority drugs and resources. The example of PD1 was cited, where drug development and approval took place before the drug had become available for paediatric development. With a system that is clinically and scientifically based, drugs could be prioritised and would be available earlier in the paediatric arena.

## **Session 2: WG1: Prioritisation through mechanism of action – why and how?**

Chairs: Nicole Scobie (Zoé4Life, Switzerland) and Jeffrey Skolnik (TetraLogic Pharmaceuticals, USA)

### **Presentations**

*'Prioritisation through mechanism of action in paediatric malignancies: the CDDF-ITCC-SIOPE proposal'* [Andy Pearson, Institute for Cancer Research, UK]

*'Prioritising drug development for children with rheumatologic diseases'* [Nicola Ruperto, PRINTO, Italy]

*'How to evaluate the relevance of a drug target for paediatric malignancies?'* [Stefan Pfister, German Cancer Research Center, DKFZ, Germany]

*'Is it safe to recruit teenagers in adult early drug trials?'* [Nathalie Gaspar, Gustave Roussy, France]

*'Prioritising through multistakeholder forums: the CDDF-ITCC-SIOPE proposal'* [Koen Norga, Antwerp University Hospital, Belgium & vice-chair PDCO at the EMA, Belgium]

**Discussion:** Prioritisation is a complex situation that should take place in a non-competitive arena looking for the *best* in class, and examining efficacy, toxicity, and ease of administration; however, limited resources both in patients and drugs, and the complication of some drugs being deprioritised complicates this. The situation will become more complex with time and 4 to 5 times as many drugs and the same resources.

Although prioritisation is ongoing in industry, it is not for paediatric oncology. Data should be shared, discussed, and assessed in order to prioritize. Two situations were highlighted: i) when several drugs with the same mechanism of action are developed in adults by several companies; ii) when many drugs with different mechanisms of action are developed by several companies in an adult malignancy occurring rarely in children. In addition prioritisation could allow that drugs that would otherwise be abandoned within the industry context can be taken forward if they show potential in the paediatric oncology arena. Who would make such final decisions is a major conundrum. It was agreed to pilot the concept of a 'prioritisation forum' involving all stakeholders, to agree which drugs to take forward, with no penalty for deprioritised drugs and sharing of pre-clinical data that would lead to non-legally binding ways forward.

The goal of academia is to rapidly undertake early phase paediatric studies of new drugs, especially first-in-class compounds, as this is the most valuable way to gain knowledge. Early phase trials do not necessarily mean full development but can feed the prioritisation process with relevant clinical and pharmacological data. Academia is essentially in agreement that collection of early data is the best way to accelerate development, providing data for the regulatory process and PIPs at the same time.

New levels of discussion, interaction and evaluation are needed in the planning of PIPs and the EMA is happy to respond to needs. Greater transparency is needed and the involvement of paediatric oncologists. PIPs need to be evaluated for feasibility, availability of patients, and numbers of studies being carried out for an indication. To pilot the concept of prioritisation, academia suggested ALK inhibitors as a first class of drug to take forward for MoA development with the buy-in of industry and B cell malignancies as a disease to prioritise.

TYA should not be barred from adult studies; there is neither scientific nor regulatory reason to do so and complex industry systems should not be a barrier.

### **Session 3: WG3 Long term follow up of patients receiving innovative oncology drugs**

Chairs: Peter Adamson (The Children's Hospital of Philadelphia, USA) and Jaroslav Sterba (University Hospital Brno, Czech Republic)

## Presentations

*'Being a childhood cancer survivor in daily life'* [Jaap den Hartogh, Dutch Childhood Cancer Parent Organization, the Netherlands]

*'Toxicology of innovative oncology drugs and new European pharmacovigilance provisions'* [Jacqueline Carleer, Federal Agency for Medicines and Health Products, Belgium, and PDCO at the EMA, Belgium]

*'Setting up long term follow up measures: the industry perspective'* [Jürgen Maares, Novartis, Switzerland]

*'Long term follow up and quality of survivorship – a major goal'* [Lars Hjorth, Lund University, Sweden]

*'Proposals from Working Group 3'* [Raphaël Rousseau, Genentech/Roche, USA]

**Discussion:** A proposed model for LTFU envisaged collaboration between academia and industry, working with a survivor passport-based programme, which could be used via a web portal or app by patients with data held in registries. Financially such LTFU would need both industry and payor buy-in, with follow-up embedded in patient care and producing data for industry in order to acquire some industry funding. Discussion centred around the feasibility of various models and aspects of those models to enable LTFU to take place. It was recognised that the implementation and funding of LTFU would be complex whether carried out through registries or by other means. Currently plans are for LTFU for patients treated with new drugs only and data would thus be prospective.

Social media was seen as a way to collect data and encourage TYA involvement, whilst also recognising potential issues for privacy. LTFU clinics are distressing and not popular particularly if young patients have long-term treatment sequelae. Where patients are no longer part of a clinical trial, data collection would pose problems unless there was a mandatory framework. Additionally, drugs, companies and development programmes are not stable entities and this could also present challenges with transferability of data, patients and programmes. A way to protect the privacy of patients and industry data was therefore needed.

Collaboration between academia and industry would be an imperative; academic follow up of patients has been the norm for decades, and the academic platform could therefore provide the necessary infrastructure. Regulatory expectations would also need to be discussed with the possibility of influencing content and the framework of the project.

In the future, increasing numbers of patients undergoing treatment with new compounds and surviving cancer will need LTFU, and disentangling population, disease and drug effects, particularly with combination therapies becoming the norm and sub-sets of patients becoming smaller, will be problematic. However, if LTFU became the natural follow-on from a clinical trial the data produced would provide invaluable data for future clinical trials. Nevertheless the initial model proposed may be too ambitious and it was suggested that the use of national Health Authorities and data collection registers might be a good starting point and would solve many infrastructure problems.

Essentially a framework for survivorship is needed across the board. The survivorship passport, developed by ENCCA, feeds into LTFU, and is not only a side-effects and sequelae record, but could also be used as a good health initiator and provide support for other problems and difficulties suffered by survivors, such as employment, relationships, isolation; this might provide the necessary buy-in for patients. Although the initial intention is for LTFU of patients treated with new compounds, it is hoped that maybe in the longer term the model might be extended to current survivors. Overall, the CDDF with its multiple stakeholders was seen as a good platform for further discussion to take this forward.

#### **Session 4: WG2: New incentives for specific paediatric oncology drug development**

Chairs: *Ralf Herold (European Medicines Agency, UK) and Pamela Kearns (University of Birmingham, UK)*

##### **Presentations**

*'Paediatric rewards, incentives and obligations: How they work and how their impact is assessed?'* [Florian Schmidt, European Commission, Belgium]

*'Creating Hope Act in the US – where are we after 2 years'* [Nancy Goodman, Kids v Cancer, USA]

*'Is the Orphan regulation working for paediatric malignancies?'* [Gilles Vassal, Gustave Roussy, France]

*'Orphan Drug Regulation, Paediatric Medicine Regulations and Paediatric cancer: the industry perspective'* [Jeffrey Skolnik, TetraLogic Pharmaceuticals, USA]

*'Results of the Platform survey and Proposals from Working Group 2'* [Patricia Blanc, Imagine for Margo, France]

**Discussion:** Current rewards come late in the drug's life cycle, at the end of the supplementary protection certificate lifespan i.e. after approximately 7 years of marketing. Incentives proposed by WG2 would provide early, segmented incentives and transferable incentives. The former would see PIPs rewarded in sections, e.g., end of phase 1 and later; in the latter, PIPs completed but not associated with an adult indication, would receive a transferable voucher. From the regulatory standpoint the potential consequences of operating segmented incentives would need to be carefully examined; e.g., PIPs may not get beyond phase 1 and the first part incentive, or may be delayed. The second proposal of transferable incentives would also need careful examination of the effect of moving an incentive from one item of public health interest to another and of whether the US voucher scheme has actually produced significant numbers of new paediatric oncology drugs.

From the industry perspective, earlier incentives to offset upfront costs and greater flexibility in PIPs would be beneficial and help to bring paediatric drug development forward in the overall process. However, although there was agreement that incentive segmentation might be a disincentive to continuing with phases 2 and 3, the first part of the development reveals the value, or not, of a drug and enables paediatric development to go forward.

Historically, with the US Best Pharmaceutical for Children Act and PREA, the reward system initiation led to a lot of new data/new labels driven by incentives, but now it is largely driven

through requirement. The Creating Hope Act addresses the different sector of developing drugs for children first. Recent successes show the relevance of early and transferable reward. In Europe a different situation sees obligation through the implementation of the Paediatric Regulation driving development.

Examining the current situation shows that paediatric drugs are very slow to be developed, and there are many reasons for this. Of 900 drugs in the oncology pipeline, 850 will be abandoned, but some of those might be beneficial to children. If development programmes all started with a paediatric component, an early signal might show a drug's potential usage for children. Thus when the adult development ceases those drugs might be taken forward, repurposed by a small biotech company under a transfer/licensing agreement.

An early incentive would derisk paediatric development and two months exclusivity for another marketed product could be a trigger for paediatric development.

With these incentive models, academia can help to accelerate development and pharma will have patients earlier. Proposed incentives need to be fine-tuned, costs must be examined, the link between the development and the reward must be underlined; and it must be affordable.

#### **'Wrap up and further development of the multistakeholder paediatric oncology platform'**

[Gilles Vassal]

The Platform continues to develop and its members to work on terms of reference, a website, and a name. The overall objectives of the Working Groups for 2016 resulted in three main proposals to take forward to the EU Commission for the Review of the Paediatric Regulation in 2017: Mechanism of Action based paediatric oncology drug development [WG1]; prioritisation of such drugs [WG1], and new incentives for their development [WG2]. With these proposals, the Platform will engage with the EU Commission and Parliament in the run-up to the Review. These three proposals will be fine-tuned by the Working Groups and a communication group will be created to publicise the aims and work of the Platform. WG3 will build a pilot proposal for LTFU of patients treated with new therapies. In addition a baseline of PIP timelines will be created, so that 'acceleration' within paediatric drug development can be seen and measured.