November 15, 2019

Mark Turner, Chair
European Network of Paediatric Research
European Medicines Agency
PO Box 71010
1008 BA Amsterdam
The Netherlands

Re: Preparedness of medicines' clinical trials in paediatrics: Recommendations by the Enpr-EMA working group on trial preparedness

Sent electronically to enpremasurveys@ema.europa.eu.

Dear Mark Turner:

On behalf of the Cystic Fibrosis Foundation and the Cystic Fibrosis Foundation Therapeutics Development Network (TDN), we write to provide comments on the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) draft framework entitled *Preparedness of medicines' clinical trials in paediatrics: Recommendations by the Enpr-EMA working group on trial preparedness* (September 2019). We appreciate that the EMA has signaled the importance of well-designed clinical studies for vulnerable populations like pediatric patients in this draft framework.

Background on cystic fibrosis and the CF Foundation

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis – a rare genetic disease that affects over 30,000 people in the United States and 70,000 worldwide. Although many people with CF now live into adulthood, approximately 47% of those with CF are still under the age of 18. The CF Foundation actively works to improve treatment options and standards of care for both adults and children living with the disease.

CFF has significant experience with the process of rare disease drug research and development. When the Foundation was formed in 1955, no CF-specific drugs existed. However, by raising and directing funds needed to fuel CF drug development programs, the Foundation has encouraged pharmaceutical companies to invest in rare disease research. Additionally, with the Foundation's Therapeutics Development Network (TDN) – the largest CF clinical trials network in the world – we have been able to spur clinical trial designs that work for the CF community. Today, there are 14 therapeutic products available in the United States to treat people with CF, four of which treat the underlying cause of the disease. CFF is also engaging globally on clinical trial studies. We are working with our CF clinical trial network peers in other countries, and we are deeply interested in furthering our engagement on issues

impacting global clinical trials. Our comments provided below reflect our substantial experience and observations in the rare disease drug development space.

Clinical trials for rare patient populations are more frequently global

Clinical trials for both adults and children need to draw on global patient populations with increasing frequency. This is especially true for rare disease populations like CF, where trials may need to access populations of patients from around the world in order to overcome small patient pools in any given country. As a result, it is imperative that clinical trial designs, endpoints, and the timing of studies are coordinated between global regulatory agencies such as the EMA and the US Food and Drug Administration.

Coordination between regulatory agencies on the timing of pediatric program plans

Currently, the EMA requires a pediatric investigation plan (PIP) at the end of phase 1 of development. However, the FDA requires submission of an initial pediatric studies plan (iPSP) much later in development – at the end of phase 2 of development or at least 210 days prior to NDA/BLA submission. This discrepancy in timing can create additional challenges for drug developers. A plan submitted too early may likely be agreed to prior to establishing a prospect of direct benefit to children, which is typically drawn from phase 2 study results in adults. As a result, the plan may end up being irrelevant or require multiple revisions as clinical data in adults become available. Conversely, a submission or agreement that is completed too late can result in major delays for evaluation and approval of important disease-modifying therapies for children. Better coordination between regulatory agencies on the timing of pediatric plans, such as through the current monthly Pediatric Cluster Conference, is needed to avoid unnecessary barriers during the pediatric drug development process.

More consensus is needed on appropriate designs for pediatric clinical studies

Given that pediatric patients are a vulnerable population, there is a heightened need to ensure clinical trials involving children are conducted in an efficient manner and are held to the highest ethical standards. We wanted to bring attention to two key issues impacting the ethics and efficiency of pediatric clinical trials conducted globally: the use of placebos and trial endpoint selection.

Use of placebos in pediatric studies

We recognize that placebo-controlled studies are the gold standard for any research program and are ideal when feasible. However, regulatory agencies should strongly consider whether the utility of placebo-controlled trials outweighs the potential risk for pediatric populations. Denying beneficial treatments to pediatric study subjects where disease burden is high may result in significant undue harm, especially for children with serious and life-threatening conditions. Instead, regulatory agencies should carefully consider whether extrapolating efficacy from adult populations with the same disease is sufficient for a given product and population as well as other alternatives to using placebo arms.

Appropriate selection of endpoints for pediatric studies

Lack of coordination in the past between regulatory agencies on the designs of pediatric studies has resulted in largely duplicative pediatric phase 3 studies in children with cystic fibrosis. Once a prospect of direct benefit has been established, such as from positive data in adults, alternative efficacy endpoints such as from biomarkers should be considered to expedite a clinical study where appropriate.

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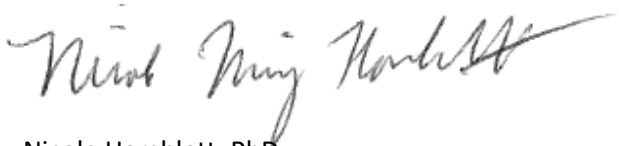
Once again, we thank the Enpr-EMA working group for its request for comments on this draft framework. The international regulatory community's efforts to improve clinical trial design practices will be critical for advancing rare disease drug development, especially for vulnerable populations like pediatric patients. We look forward to seeing the Enpr-EMA continue its engagement in this arena.

Sincerely,

Anthony Durmowicz, MD
Vice President of Clinical Development
Cystic Fibrosis Foundation



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