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On behalf of PeDRA and multiple organizations involved in caring for children and adolescents with atopic dermatitis and involved in research for the prevention, management and cure of atopic dermatitis (AD) and its associated comorbidities, we are submitting this position document and background materials to the DODAC in preparation for discussion of the pediatric development of systemic products for the treatment of atopic dermatitis with inadequate response to topical prescription therapies.

Position:

Given the high unmet need for effective and safe therapies in atopic dermatitis in children, pediatric studies with systemic therapies should be initiated as soon as possible in the drug development process, as long as there are no safety signals that would raise particular concern in pediatric age patients.

As of the submission date of February 23, 2015, this statement has been endorsed by:

The Pediatric Dermatology Research Alliance (PeDRA)
The American Academy of Dermatology (AAD)
The Society for Investigative Dermatology (SID)
The Atopic Dermatitis-Expert Resource Group (AD-ERG)
The National Eczema Association Scientific Advisory Committee (NEA-SC)
The Society for Pediatric Dermatology (SPD)
The International Eczema Council (IEC)

Background and Rationale:

There is evidence that there is a high unmet medical need in the US for safe and effective therapy for treating children and adolescents suffering from moderate to severe AD that is refractory to topical therapy.

Prevalence of AD is very high in the pediatric age group, with 10-20% of children in the US and 2-10% of adults affected, similar to other industrialized countries.

- *Prevalence of AD in children in US is similar to that seen in other industrialized countries (Laughter et al., 2000)*
- *Reported prevalence ranges from 10-20% (Eichenfield et al., 2012)*
- *Using data from National Survey of Children's Health (NSCH), the overall prevalence in US in children aged 17 years and under was found to be 10.7% (Shaw et al., 2011)*

A significant proportion of children with AD suffer with a severe form of the disease.

- *Results from International Study of Asthma and Allergies in Childhood (ISAAC) showed that children with severe atopic eczema accounted for 6-25% of all those with atopic eczema (Williams et al, 1999)*
- *Seven percent of children in the U.S. with AD were labelled as having severe disease in the population-based National Survey of Children's Health (NSCH) (Silverberg, et al. 2013)*

AD is has a negative impact on Quality of Life (QoL) of affected patients and caregivers

- *Pruritus is a universal finding in AD and may result in sleep disruption, irritability and generalized stress (Kemp, 2003. Kim et al., 2012)*
- *The impact on QoL of children was found to be higher for AD as compared to other common skin disorders like psoriasis and acne (Lewis-Jones et al., 1995), and equivalent to type I diabetes.*
- *Even mild disease negatively impacts a child's quality of life, and more generalized disease can affect a child and family to a similar degree as having type I diabetes. (Ben-Gashir et al., 2004)*

Comorbidities and complications add to the burden of disease

- *Approximately one half of AD patients will develop asthma and two thirds will develop allergic rhinitis as part of 'atopic march' (Spergel and Paller, 2003)*
- *More severe skin disease is directly correlated with a higher risk of*

developing comorbidities (asthma, allergic rhinitis, food allergy, and mental health disorders) and is associated with more severe comorbidities (Silverberg et al., 2013)

- *Patients with more severe AD are more prone to develop asthma, allergic rhinitis, and food allergy. (Simpson et al., 2005; Boguniewicz et al., 2003)*

- *ADHD, psychological disturbances, and hypertension are associated comorbidities (*Schmitt J et al., 2009; Yaghmaie et al., 2013)

- *Staphylococcal infections and eczema herpeticum are common in children with AD and occur more frequently in patients with severe skin disease. (Eichenfield et al., 2014).*

AD is an economic burden in the US

- *US economic burden of AD has been estimated at overall annual costs between $364 million and $3.8 billion (Mancini et al., 2008)*

- *Costs include direct (treatment fees, hospitalization) and indirect (pain and suffering, work or school performance)* (*Carroll et al., 2005; Ellis et al., 2002*)

A significant number of patients have inadequately controlled disease, and there are no approved systemic agents for children or adolescents with AD in the US.

- *Approved treatment options are mostly limited to topical therapies such as emollients, Topical Corticosteroids (TCS) and Topical Calcineurin Inhibitors (TCIs)*

- *Systemic agents are used (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, prednisone) with known side effects and toxicities, and little guidance or evidence basis. (Sidbury et al., 2014)*

- *Systemic agents available for off-label use have significant side effects including stunted growth, diabetes, hypertension, and osteoporosis (corticosteroids), myelosuppression and hepatotoxicity (methotrexate), nephrotoxicity and hypertension (cyclosporine), gastrointestinal disturbances and leukopenia (azathioprine and mycophenolate mofetil).*

    - *There is little guidance and minimal evidence basis for the use of these systemic agents in children, making their use problematic for patients, families and physicians.*

    - *A high proportion of patients in which disease is initially controlled by systemic agents suffer from relapse once therapy is discontinued (Granlund et al., 1995; Schmitt et al., 2009)*

    - *In a study of atopic dermatitis care of children in the U.S. from 1997-2004 (utilizing the National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey databases) oral corticosteroids were prescribed in 1.1 million (17%) of the 6.7 million AD visits (with asthma cases excluded from this analysis, and 130,000 prescriptions for children younger than age two. (Horli et al., 2007)*

- In a recent survey of more than 130 pediatric dermatologists (the Treating Atopic Dermatitis Taskforce US and Canada (TREAT US & Canada), administered by the Pediatric Dermatology Research Alliance) **86.5% utilized systemic therapy** for severe pediatric AD (45% with cyclosporine as first line therapy). The main reported factors discouraging use of systemic agents were the side effect

profiles (82%) and suspected risks of long term toxicity (80%) of presently available agents.

- *Thus there are many, many children being treated with potentially dangerous medications for which there has been minimal safety data generated. And many are being inadequately treated because safety data, approval, and guidelines are lacking.*

There is precedence of approval for initiation of clinical trials in children with AD in other countries, such as EU, Japan, and Canada.

Patients, families and patient advocacy groups (such as the National Eczema Association) are supportive of early inclusion of children into clinical studies**,** as long as there are no safety signals that would raise particular concern in pediatric age patients (personal communication).

We respectfully submit this letter with the hope that the committee will recognize the clinical need for better research and treatments for pediatric atopic dermatitis, and accelerate the inclusion of adolescents and children into the clinical study of new therapeutic agents.

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