Developing Drugs for Treatment of Atopic Dermatitis in Pediatric Patients (≥3 months to <18 years of age)

DRAFT GUIDANCE FOR INDUSTRY

TO BE SUBMITTED FOR CONSIDERATION BY FDA

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I. INTRODUCTION

The purpose of this guidance is to assist in and encourage the development of safe and effective drugs[1] for the treatment of atopic dermatitis (AD) in pediatric patients, ≥3 months to <18 years of age. Specifically, this guidance addresses the overall development program and clinical trials to support the development of drugs with a variety of mechanisms of action targeted for the treatment of AD. This proposed draft guidance is intended to serve as a focus for continued discussions among the Division of Dermatology and Dental Products (DDDP), pharmaceutical sponsors, the academic community, clinicians, and the public.[2] Development plans should be discussed with the review division before initiating trials to ensure that the trial design meets defined objectives.

This document was prepared by a consensus committee of stakeholders, including patient advocates, parents/caregivers, clinical trialists, clinicians, nurse practitioners, physicians, basic scientists, dermatologists, allergists/immunologists, pediatricians, psychiatry/psychology specialists, statisticians, and industry representatives. The consensus committee was formed in partnership with the Pediatric Dermatology Research Alliance (PeDRA), the National Eczema Association (NEA), and the International Eczema Council (IEC) in response to the March 2015 FDA Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) decision that supported earlier inclusion of children in clinical trials for moderate-to-severe AD (ANA [Guttman Krader, 2015]; Minutes of the Dermatologic and Ophthalmic Drugs Advisory Committee, March 9, 2015). This proposed draft guidance is being submitted to the FDA by the consensus committee based on a provision in the *Federal Register (Good Guidance Practices)* and the FDA is asked to consider adopting it in whole, or in part.

This proposed draft guidance does not contain discussion of more general issues of statistical analysis, clinical trial design, or pediatric clinical trials. These topics are addressed in ICH guidances *E9 Statistical Principles for Clinical Trials*, *E10 Choice of Control Group and Related Issues in Clinical Trials*, and *E11 Clinical Investigation of Medicinal Products in the Pediatric Population,* respectively. This proposed draft guidance also does not contain discussion of chemistry, manufacturing, and controls issues. It

[1] For the purposes of this guidance, all references to drugs include small molecule medications and biologic agents administered topically or systemically unless otherwise specified.

[2] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs used to treat AD.

focuses on drug development and trial design issues that are unique to the study of AD in pediatric patients.

In general, FDA guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

AD (a form of eczema) is the most common chronic skin disease and primarily affects children. With a pediatric prevalence of up to 25% (Eichenfield, et al., 2014b), studies in the pediatric population are required by Pediatric Research Equity Act (PREA).

Eczema bears the highest impact on the global burden-of-skin disease (Hay, et al., 2014). Topical and systemic corticosteroids have been used to treat AD since the 1950s. Ironically, until 2016 systemic corticosteroids were the only non-topical medication with FDA approval for this indication, despite published guidelines of care that recommend against this option (Eichenfield, et al., 2014a; Eichenfield, et al., 2014b; Schneider, et al., 2013; Sidbury, et al., 2014a; Sidbury, et al., 2014b).This has led to wide-spread off-label use of medications to treat AD, which increases the risk for adverse events (Lowenthal, et al., 2016).

More recent approvals of corticosteroid-sparing agents have allowed a treatment paradigm for short-term control of mild-to-moderate AD with topical corticosteroids and long-term maintenance with newer topical non-steroid medications. The first systemic drug was approved for severe AD in adults in 2017, but no high-level studies that have defined optimal therapy for severe disease in the pediatric age group.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. General Considerations for Pediatric Clinical Trials in AD

Every effort should be made to minimize patient distress resulting from clinical trial participation. This includes ensuring investigators are trained and experienced in studying the pediatric population, invasive procedures are limited to only those that are necessary, and that protocols are designed with pediatric patients in mind (not just re-worked from adult protocols). It may also be helpful to consult experts in pediatric behavioral health. See ICH guidance *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* for additional details.

2. Timing of Pediatric Development Plans, Pediatric Studies Plans, and Pediatric Studies

Because AD is primarily a disease of childhood, pediatric development plans for new drug entities under investigation for the treatment of AD should be addressed as early as possible in negotiations with the FDA. Sponsors are encouraged to submit a pediatric development plan (including timelines, proposed juvenile toxicology studies, and clinical study designs) as part of a pre-investigational new drug application (IND) briefing document for discussion at the pre-IND meeting. Because AD affects a significant number of infants, pediatric studies waivers for patients ≤2 years of age should be granted only after careful consideration and demonstration that the potential risks outweigh the benefits to evaluating a drug in this age group.

Pediatric Study Plans should be submitted soon after adult efficacy and safety data are available, but no later than 60 days after the end of phase 2 meeting as required by PREA. See FDA guidances *How to Comply With the Pediatric Research Equity Act* and *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* for more information.

Pediatric studies should commence as soon as sufficient preclinical data are collected, but no later than the initiation of phase 3 studies in adults.

3. Importance and Timing of Stakeholder Involvement

Sponsors are encouraged to initiate open dialogue as early in the development process as possible with clinicians who have pediatric dermatology and/or pediatric immunology expertise regarding patient-centered clinical and investigational aspects of clinical trial design. This dialogue should continue throughout the product lifecycle.

The FDA encourages patient involvement in drug development as required by the *Food and Drug Administration Safety and Innovation Act of 2012* and the fifth authorization of the *Prescription Drug User Fee Act*. Sponsors are encouraged to solicit and incorporate patient-provided information (including information provided by caregivers, patient advocates, and patient advocacy organizations) as part of the overall drug development process to ensure that new products meet the needs of patients and to help the FDA assess the benefit-risk ratio of products under review.

Sponsors should collect patient-provided information about patient preferences and treatment goals early in development and in a general, non-promotional, and ongoing manner. At a minimum, patient-provided information should be used to develop clinical trial protocols that are minimally burdensome to patients and caregivers. Input from patient advocacy organizations may be especially helpful when evaluating the heterogeneity of AD or a specific subset of patients with AD. See *Patient-Focused Drug Development –*

Recommended Language for Use in Guidance Document Development (2017) for more information on this topic.

4. Extrapolation of Efficacy to the Pediatric Population

Discussion with FDA about extrapolation of efficacy using data from older age groups should begin as early in drug development programs as possible. While there are some data to suggest differences in pathobiology between adult and pediatric patients with AD,[1] risk factors, primary skin inflammatory infiltrates, and response to currently available therapies suggest that pediatric patients will respond similarly to therapies that are effective in adults (Lan, et al., 2003; Lübbe, et al., 2006; Tan, et al., 2004).

Similar exposure-response relationships with regards to efficacy are expected for systemic drugs in AD. Therefore, extrapolation of efficacy from adults to children for systemic drugs should be generally acceptable. In many cases, performing pharmacokinetic (PK) and safety studies should be considered adequate to extend the indication of systemic drugs for AD to all pediatric age groups. An incremental approach may also be used, ie, extrapolating adult data to adolescent data, then extrapolating adolescent data to children, and data in children to infants.

However, because pediatric patients have a greater body surface area-to-weight, extrapolation for topical drugs may not be suitable for pediatric patients. Furthermore, systemic absorption of topical medications, even when detectable, often does not correlate with local bioavailability or efficacy, so exposure-response relationship calculations required for extrapolation are generally not possible for topical medications. There is precedent, however, for allowing full extrapolation for topical drugs for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (topical mometasone, topical betamethasone dipropionate) and treatment of ichthyosis/xerosis (Lac-Hydrin topical [Dunne, et al., 2011]).

See ICH guidance *E11 Clinical Investigation of Medicinal Products in the Pediatric Population,* proposed draft guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* and Dunne, et al., (2011) for more information on extrapolation.

B. Preclinical Development

It is anticipated that patients with AD may be exposed long-term maintenance treatment for up to 52 consecutive weeks during a single year. Another approach may be exposure to short-term, intermittent treatment to manage flares. Thus, chronic toxicity and carcinogenicity studies that support long-term continuous or intermittent exposure to the investigational drug should be performed as specified by ICH guidances *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S1A The Need for Long-Term Rodent Carcinogenicity Studies of*

Pharmaceuticals. Furthermore, these guidances suggest that developmental studies using juvenile animal studies should be performed.

At the time of writing, there are no ideal animal models for AD; the choice of an AD animal model should be based on the best science available at the time of the study. If this model is defined, the FDA should consider it for qualification via the Animal Model Qualification Program (https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284078.htm).

1. Considerations for Biologic Drugs

Anti-drug antibodies (ADAs) should be characterized (ie, binding site) and titers should be assessed at baseline and regular intervals thereafter beginning in preclinical studies (see III.E.3.bImmunogenicity for more information).

2. Considerations for Topical Drugs

In vivo assessments should be conducted using the planned marketed formulation and proposed strength under conditions that reflect that planned application frequency, duration of treatment, amount applied, size of application site, and method of application. Vehicle and sham controls should be employed whenever possible to evaluate any adverse or beneficial effects of topical formulation ingredients. Vehicle-control animals should receive the same excipients and formulation as are in the test product formulation, without the active agent. Sham control animals should be manipulated in the same manner as the vehicle control animals, but should not receive the vehicle or the active agent.

Due to a higher body surface area-to-weight ratio and reduced skin barrier function for developmental and AD-related reasons, systemic exposure to topical drugs may be greater in pediatric patients (especially infants and young children) than in adult patients. The differential distribution of AD lesions between age groups also affects the extent of percutaneous absorption. Many of the body areas most affected by AD in infants and children (flexural surfaces, face, neck) allow incrementally greater percutaneous absorption and systemic exposure than areas such as the back where topical drugs are often applied during in vivo testing.

Precautions should be taken to ensure that study animals do not ingest the topical drug (via licking or biting themselves or other animals) as this could affect both PK and pharmacodynamic results. The potential toxicity of inadvertent mucosal exposure or ingestion should also be considered. Alternatively, if these precautions are not feasible, systemic exposure data from these preclinical studies should be interpreted with the potential for enteral absorption in mind. In addition, topical products should be

assessed for dermal and ocular toxicity. Products that will be delivered in an aerosol or powder formulation should be evaluated for ocular and pulmonary toxicity.

C. Early Clinical Development

1. Formulation

Formulations that foster accurate dosing and promote patient compliance within the pediatric population should be developed. For systemic drugs, oral administration (versus injection) is preferred in order to minimize patient discomfort.

For oral drugs, formulations such as liquids, suspensions, chewable tablets, and tablet/capsule formulations that allow grinding up and/or sprinkling on food (eg, applesauce), will make dosing in even the youngest patients feasible. Multiple formulations may be required to accommodate different age groups within the pediatric patient population (ie, liquids/suspensions are more appropriate for infants and toddlers; liquids/suspensions and chewable tablets are more appropriate for children; tablets/capsules may be appropriate for adolescents). Liquids and suspensions, however, allow for more precise dosing in younger children.

For injectable formulations, the subcutaneous route is preferred as this route is more comfortable for patients and allows for safer patient/caregiver administration. Use of a pH-adjusted formulation and autoinjectors will also minimize patient discomfort. Appropriate drug concentrations should be developed to allow accurate, safe, and convenient administration of the dose. Autoinjector design considerations should include contact site padding, ergonomics, calibrated injection speed, and automatic needle retraction for patient safety and comfort (SHL Group, 2015).

Because patients with AD are more susceptible to burning and stinging reactions, local tolerability should be considered when formulating new topical drugs. Sponsors should also consider patient preferences for the tactile acceptability of different formulations. Cream, gel, and foam formulations are often preferred by patients over ointments and oils. Of note, many clinicians prefer ointment or oil formulations because they are typically better emollients and less likely to contain excipients that might lead to contact reactions.

For more information on pediatric formulations, see ICH guidance *E11 Guideline for Clinical Investigation of Medicinal Products in the Pediatric Population*.

2. Dosage

Dosage determinations may be indication-specific because effective dosages may vary by disease state (ie, patients with atopic dermatitis may require a higher dosage than patients with psoriasis or vice versa).

Age-based dosing is limited by the wide range of body sizes within pediatric age subgroups. Weight range-based dosing is less accurate, but may be required for tablet, capsule, or autoinjector formulations.

Weight-based oral and injectable dosing should be considered, as it yields the greatest accuracy; however, there is potential for dosing error. Weight-based dosing guidelines should be pediatric-specific or age group-stratified (ie, pediatric weight-based dosing should be considered separately from adult weight-based dosing), because drug pharmacokinetics and safety may differ based on developmental differences. For obese patients, dosing may be based on actual weight or ideal weight depending on the bioavailability of a drug and the observed dose-response relationship.

For all routes of administration, patient adherence may be improved with a uniform dosing interval (eg, once daily or once weekly rather than twice weekly). If different concentrations are available, the concentration that minimizes the number of units given (eg, less volume/injections with an injectable/fewer pills with an oral) while maximizing the interval between doses should be chosen.

a. Considerations for Topical Drugs

In phase 2 trials, efforts should be made to standardize and quantify the amount of drug to be applied. Dosages should be specified, eg. grams per application, grams per day, or grams per week or month and quantified by change in package weight or other appropriate measure. Terms like ‘thin layer’ and ‘fingertip unit’ are insufficiently standardized to support phase 2 trials.

Phase 3 trials can be more reflective of the variability observed in clinical practice for how topical drugs are applied, and practical measurement such as ‘fingertip unit’ can be utilized, with quantification of maximum use in grams per month.

D. Phase 1 Clinical Development

Care should be taken to obtain sufficient PK data in patients of all ages within the target population. In general, pediatric PK studies should be conducted in patients with AD.

For all age groups, consideration should be given to alternative PK methods that minimize the number blood draws and/or the amount of blood drawn including population PK, physiologically-based PK (Edginton, 2011), biomarker-supported PK (Bruin, et al., 2017), and cumulative whole blood drug concentrations. Institutional review boards may review and limit the number of draws and/or the amount drawn. See ICH guidance *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* for more information on pediatric PK study considerations and FDA guidance *Population Pharmacokinetics* for more information on population PK.

1. Considerations for Topical Drugs

Because of the inherent variability of topical dosing and the potential that local skin reactions/toxicity may only develop with chronic use, PK studies should be conducted under *maximal use conditions* using the planned marketed formulation and proposed strength using conditions that reflect the planned application frequency, duration of treatment, amount applied, size of application site, and method of application (emollients/wet wraps/occlusion). In addition, trials should be conducted in an adequate number of patients at the upper end of the target range of AD severity as absorption may be higher for patients with greater epidermal barrier dysfunction and/or more skin inflammation and excoriations. Furthermore, trials should be conducted in an adequate number of patients in each pediatric age group to determine how developmental differences may affect absorption. Safety and PK studies for topical products should be conducted in pediatric subjects with AD, since absorption through intact skin of a healthy volunteer would not necessarily predict absorption in an inflamed AD lesion.

E. Phase 2 and Phase 3 Clinical Development

1. Drug Development Population

a. Disease Definition

Although newer criteria have been developed, those developed by Hanifin and Rajka (1980) remain the gold standard on which most other criteria have been based. The Hanifin-Rajka criteria, however, were developed with a predominantly adult population in mind. A suitable alternative, though not formally validated, is the American Academy of Dermatology (AAD) Consensus Criteria for pediatric AD (Eichenfield, et al., 2014b), which were developed using the Hanifin-Rajka criteria as the foundation with modifications to address the pediatric population specifically. The UK Working Party criteria (Williams, et al., 1994) were developed using a systematic approach and are commonly used, but were designed to use a minimum set of criteria and lack the specificity needed for clinical trials involving investigational agents.

b. Disease Severity

Severity in AD may be measured using a variety of approaches and there is no standardized definition for overall disease severity. Factors involved in determining disease severity include lesion intensity (disease signs), location of lesions (head and neck predominant vs other areas), extent of disease (body surface area involved; BSA), symptoms, and impact on quality of life (QoL). Harmonising Outcome Measures for Eczema (HOME) initiative has defined four domains (clinical signs, symptoms, QoL, and long-term control) that should be measured in all clinical trials (Schmitt, et al., 2012) and thus far reached consensus on the instruments that best measure the signs and symptom domains (Schmitt, et al., 2014).

At a minimum, baseline severity should be defined via a combination of the following:

- An investigator-based objective measure of clinical signs:
    - The Eczema Area and Severity Index (EASI) is recommended. This instrument was identified by the HOME initiative through a systematic review of the literature and consensus voting process to be the best instrument for measuring the signs of AD (Schmitt, et al., 2014).
    - The objective portion of the Scoring of Atopic Dermatitis (SCORAD) tool was also found to be a valid instrument for signs (Schmitt, et al., 2014). The full SCORAD instrument (including objective and subjective domains) provides a more global approach than EASI as it incorporates patient-reported sleep loss and pruritus.
- Investigator Global Assessment of Signs (IGA). There is no standard instrument to measure IGA and significant variability exists in the literature (Futamura, et al., 2016). Instruments most commonly utilize a 5-point scale and incorporate at least erythema and papulation, while some scales also include oozing and crusting. However, a measure of extent (ie, percent BSA) is not included in most IGAs; which is an important morbidity factor (Chopra, et al., 2017).
- Patient/caregiver-reported symptoms. The Patient-Oriented Eczema Measure (POEM) was identified by the HOME initiative as the best patient/caregiver-reported instrument for measuring signs and is recommended for all clinical trials in AD (Chalmers, et al., 2016).
- Measurement of BSA affected. The extent of the disease as measured by BSA does correlate with overall severity of AD and should be measured at baseline to help stratify patients into severity categories; however, there is no standard stratification for disease severity. BSA is also useful as an inclusion criterion to ensure patients have a minimal level of disease activity at baseline.
- Quality of life (QoL) measurement. The HOME initiative also recommended utilizing a QoL instrument in all trials of AD, although a consensus of which instrument to be used has not been reached (Chalmers, et al., 2016; Heinl, et al., 2016). With these knowledge gaps, sponsors should choose a QoL instrument appropriate to the age of their study population.

c. Lower Age Limit

There is a high prevalence of AD in children of all age groups down to 3 months of age (Hanifin, et al., 2007). For this reason, efforts should be made to evaluate children of all ages to ≥3 months in the clinical program. If younger children and infants (≥3 months) are not included in clinical studies, then the risk of off-label use of medications in these age groups increases (Lowenthal, et al., 2016).

There is evidence that renal and hepatic systems mature by 2 years of age. Thus, if a study medication undergoes renal and/or hepatic clearance or has potential renal and/or hepatic toxicity, it would be reasonable to exclude children under 2 years of age in early clinical studies. In situations in which the

study medication may have a hormonal effect, then stratification by Tanner stage (Marshall, et al., 1969; Marshall, et al., 1970) may be indicated. For drugs with potential central nervous system effects, then the sponsor may consider excluding children younger than 12 years of age in early clinical studies.

Further information on age stratification can be found in the ICH guidance *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*.

2. Efficacy Considerations

If certain criteria are met, partial or full extrapolation of adult efficacy data to pediatric patients may be allowed for systemic drugs (see III.A.4. Extrapolation of Efficacy to the Pediatric Population). For drugs that have not been previously investigated in adults, drugs for which extrapolation has not been allowed, and topical drugs sponsors should conduct two adequate, well controlled, phase 3 superiority trials to support the intended indication(s): short-term intermittent or long-term maintenance treatment. Because AD is a disease marked by intermittent flares, reduction in the number of flares is an endpoint of interest. When a uniform definition of flare has been developed, this should be included. (see **III.E.4.b Efficacy Endpoints**). Two single adequate, well controlled, phase 3 superiority trials should be performed for each indication sought. Data from these trials may be submitted together to provide sufficient evidence for approval for both indications. See FDA guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* for more information. If superiority trials are not feasible, noninferiority trials may be acceptable to support approval, especially if some other aspect of a drug is expected/considered to be an advantage over currently available treatment (ie, patient preferences for formulation/drug delivery system, better safety profile, reduced costs).

3. Safety Considerations

During development, as much safety data as possible should be collected from patients across the spectrum of disease severities, including (whenever possible) patients who discontinued treatment. Systemic safety and, for topical drugs, local safety (for topical drugs) information should be collected during clinical trials.

Given the chronic nature of AD, drugs used to treat AD have the potential for chronic use. Therefore, long-term safety should be addressed in clinical trials and applied to labeled indications. See FDA guidance *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (ICH-E1A)* for general information on the extent of exposure required for drug approval. Pediatric-specific exposure requirements have not been defined. Durations of follow-up in pediatric clinical trials should be determined for each individual drug based on target indication (ie, severe AD will require longer follow-up than less severe AD), clearance rates, anticipated duration of action, and possible side effects. There is precedent to recommend 1 additional

month of specific pediatric safety data for oral drugs and 3 additional months for intranasal drugs (FDA guidance *Allergic Rhinitis: Developing Drug Products for Treatment)*.

Since the potential for rebound effects or AD worsening (which is distinct from relapse [off-treatment], is well known for certain AD treatments (eg, systemic corticosteroids), safety evaluations should include an off-treatment follow-up. The duration of the follow-up should extend at least to the anticipated duration of effect.

Trials in AD generally should be conducted under the oversight of a drug safety monitoring board (DSMB) that has access to real-time unblinded safety data. The DSMB should ideally include representatives from pediatric dermatology and, pediatric allergy/immunology, as well as an expert on statistical analysis. The DSMB should evaluate potential safety signals at regular intervals and, if necessary, take appropriate measures to ensure that patients are not placed at unreasonable risk of harm. See FDA guidance *Establishment and Operation of Clinical Trial Data Monitoring Committees* for more information.

a. Adverse Events of Interest

It will be important to ensure that any new treatment does not exacerbate or increase the risk for AD comorbidities (see **II.E.4.e. Specific Populations** for more information). Those of concern are new-onset or frequent eczema herpeticum, contact dermatitis, and staphylococcal or streptococcal infection. Several potential safety issues have been identified for drugs already approved for AD treatment or other immune-mediated skin diseases (eg, psoriasis). These include cutaneous eruptions and malignancy (especially lymphoma or cutaneous malignancy). Phase 2 and 3 trials should assess these AEs of interest carefully and perform analyses of these results to ensure there is no excess of these events in the test article treatment arm. Any potential safety signal identified in preclinical testing or in clinical trials in other indications should also be considered as an AE of interest. These AEs of special interest should be included in the proposed safety monitoring plan submitted to the FDA. See FDA guidance *Allergic Rhinitis: Developing Drug Products for Treatment* for information on corticosteroid-specific issues.

- Because the skin of most patients with AD is colonized with *Staphylococcus aureus*, positive culture alone does not confirm cutaneous infection. On the other hand, recovery of group A streptococcus from the skin more often marks infection than colonization. An AE of cutaneous infection should be defined as skin changes marked by tenderness, increased erythema, and other clinical signs of infection (eg, oozing, crusting, pustules) that requires antibacterial treatment.
- Because the signs of eczema herpeticum may be indistinguishable from cutaneous bacterial infection, the presence of herpes simplex virus should be confirmed by polymerase chain reaction (PCR) and/or culture.
- Because allergic and/or irritant contact dermatitis frequently complicates AD, investigators should be educated to recognize persistent patterned dermatitis as a sign of contact dermatitis. In these cases of suspected allergic contact dermatitis, patch-testing should be provided, especially if a reaction to the topical investigational drug is implicated.

Because depression and suicidal ideation are potential comorbidities of AD, including in pediatric patients (Yaghmaie, et al., 2013), monitoring for suicidal ideation should be included in all phase 2 and 3 studies for systemic/biologic AD treatments in children and/or adolescents (cognitive developmental limitations preclude assessment in infants). See FDA guidance *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials* for more information.

For topical drugs, assessments of local tolerability (including adjacent skin) should be performed, including evaluations of skin atrophy/thinning and worsening erythema, edema, freckling, excoriations, and oozing, crusting, or pustules that are not associated with an AD flare. Many of these local reactions may only manifest after chronic use, therefore, safety monitoring should include serial examinations beginning at baseline.

b. Immunogenicity

The immunogenicity of a biologic drug may be related to circulating levels of anti-drug antibodies (ADAs). However, the pathophysiology of this observation is not well-understood. ADA levels may develop or increase over time in subjects receiving a biologic agent, but they have also been detected in a minority of subjects at baseline and the placebo arm. So, measurable ADA titers may represent reactivity to the biologic agent, non-specific binding in the assay, cross-reacting epitopes or preexisting memory response. The molecular binding site of the ADA, target pathway, dosing interval and treatment duration can all affect ADA titers and anti-neutralizing effects, as well as subsequent pharmacodynamics, efficacy and toxicity (Jullien, et al., 2015)

Specific issues:

- Detection of ADAs is highly variable and dependent on sample processing and assay sensitivity and specificity, development of ADAs should be longitudinally assessed with an effort to define and distinguish between transient versus persistent and neutralizing versus non neutralizing ADAs.
- Hyperimmunizing effects of intermittent dosing may increase ADA titers, leading to more potent pathologic effects. This mechanism may also reduce the likelihood of regaining a good clinical response in patients resuming treatment after discontinuation. Consideration should be given to incorporating a challenge-rechallenge phase with ADA monitoring into late-phase trials (See **III.E.3.b Immunogenicity**).
- The association between systemic hypersensitivity reactions and ADAs is unclear. However, it is important to recognize the role of ADAs in triggering more serious hypersensitivity reactions (eg, anaphylaxis, serum sickness, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms), including the target molecule, ADA binding sites, ADA titers, and clearance.
- Until the impact of ADAs is more well-understood, the risk of developing these specific antibodies should be monitored via surrogate anti-nuclear antibody (ANA [Pink, et al., 2010]), anti-double-stranded DNA (Hoffmann, et al., 2014) and ADAs (Jullien, et al., 2015) at baseline and throughout trials of biologic agents.

c. Immunizations

The great majority of children in the US receive a routine series of immunizations (Centers for Disease Control and Prevention). Children with moderate-severe AD may have immune defects as suggested by increased susceptibility to some skin infections (Gao, et al., 2009) and impaired immunologic response to some vaccines (eg, hepatitis B [Sigurgeirsson, et al., 2015]). Another concern is that some forms of primary immunodeficiency present with severe eczema that may be misdiagnosed as AD. These patients are at risk for serious adverse effects from live, even attenuated viral vaccines. So, vaccine safety and efficacy monitoring should be considered for children with AD participating in clinical trials of systemic immunomodulating agents. For practical purposes, these children should be considered to have 'limited immune deficits' (Centers for Disease Control and Prevention, 1993) which may be especially important for cutaneous modes of efficacy induced by vaccination (Leung, et al., 2017). Important issues include: minimizing the risks of vaccine administration, optimizing vaccine responses, and preventing transmission of infection and disease associated with public health risks.

- **Minimizing the Risk of Vaccine Administration**

Immunization history should be recorded for all subjects at enrollment. Every effort should be made to administer 'catch up' vaccines that have not been received on schedule, prior to receiving study drug. For optimal safety and efficacy, live and killed vaccines should be administered at least 4 weeks prior to receiving study drug.

- **Optimizing Vaccine Response**

Optimal response to immunization is influenced by several factors, including age, degree of atopy, primary immune deficiency and the targeted pathway of the investigational drug. Administration of live vaccines (measles, mumps, rubella, oral polio, typhoid, yellow fever, vaccinia, varicella) should be avoided during active treatment, unless the targeted pathway is considered unlikely to increase vaccination risks. For investigational drugs warranting disruption of routine childhood vaccinations,, these may be administered a minimum of 3 months after treatment is discontinued (https://www.cdc.gov/mmwr/preview/mmwrhtml/00023141.htm)

Killed, subunit, and toxoid vaccines may be received on schedule before, during and after trial participation. Consider evaluating effect of study drug on immunization efficacy by measuring responses to killed vaccines most likely to be impacted by the investigational agent. For example, a study drug targeting T-cell responses should be assessed using T-cell–dependent vaccines (eg, conjugated pneumococcal vaccine). Hemagglutinin inhibition assay response to influenza vaccine may be a good model to reflect impact of a study agent on CD4 and B cell mediated vaccine responses.

- **Preventing Transmission of Infections Associated with Public Health Risks**

Effort should be made to screen study subjects at baseline for potential to increase the risks associated with preexisting infection and transmission of diseases with significant public health risks. These diseases include human immunodeficiency virus, Epstein-Barr virus, varicella zoster virus, hepatitis B, hepatitis C, and tuberculosis (TB). Screening for these diseases should be considered based on the immunologic target of the study agent and the likelihood that it will impact susceptibility to the specific infection. For example, drugs targeting pathway-specific Th1 immune responses are likely to increase the risk of acquiring or reactivating latent TB. So, for study agents targeting these pathways, it is necessary to screen for latent infection. Interferon-gamma release assay (IGRA; eg, QuantiFERON-TB Gold) may be preferred over a purified protein derivative (PPD) test based on its greater specificity and convenience (ie, no 2- to 3-day read). In cases of indeterminate results by IGRA, medical history and a chest x-ray are critical for assessing TB risk in nonendemic areas.

4. Specific Efficacy Trial Considerations

a. Minimum Trial Duration

The recommended minimum duration for phase 2 and 3 clinical trials is 1 month for topical drugs and 3 months for systemic drugs.

b. Efficacy Endpoints

The FDA has historically required IGA score as the primary endpoint for AD trials, because they map to terms the public will understand (clear through severe for a 5-point Likert scale). However, the IGA scoring system currently lacks standard nomenclature, scale size, definitions, outcome description, and analysis and in many cases does not adequately assess all the relevant signs and symptoms or extent of disease (ie, body surface area affected by AD [Futamura, et al., 2016]). AD is increasingly being recognized as a systemic disease (Brunner, et al., 2017); therefore, evaluation of a target lesion may not be appropriate.

Until a standardized, validated IGA is available that includes measures of extent, the HOME initiative's recommendations for EASI score as the primary instrument for the measurement of clinical signs for efficacy should be used (with SCORAD as an alternative [Schmitt, et al., 2014]). EASI assesses severity as well as extent of skin lesions. It can be learned quickly (Hanifin, et al., 2001) and administered reliably (Zhao, et al., 2015a) and rapidly (Leshem, et al., 2015). Training materials for EASI are available (http://www.homeforeczema.org/resources.aspx). EASI score ranges have been interpreted by Leshem, et al. (2015) using a 6-point IGA scale (see below), which are more understandable to patients and caregivers. Despite this, absolute concordance between IGA and EASI scores is not expected and Investigators should not bias their evaluations in attempting to achieve it.

EASI Score	**IGA**
0	Clear
0.1-1.0	Almost Clear
1.1-7.0	Mild
7.1-21.0	Moderate
21.1-50.0	Severe
50.1-72.0	Very Severe

Regardless of endpoints utilized, assessments should be standardized and investigators should be trained on their use. As new endpoints are developed and validated by groups such as the IEC and/or recommended by the HOME initiative, they should be implemented in pediatric AD clinical trials as appropriate.

Timepoints below are suggested MINIMUMS, additional timepoints can and should be included to determine onset of action and/or relapse.

- **Primary Endpoints**

Mean AD severity as assessed by mean EASI score (or SCORAD) at a predefined window of time is the recommended primary efficacy endpoint. If EASI is utilized, SCORAD could be included as a secondary endpoint and vice versa.

- **Secondary Endpoints**

Secondary endpoints may include:

- Proportion of patients achieving IGA success, defined as IGA score of 0 'clear' or 1 'almost clear' with ≥2-point improvement from the baseline.
- Proportion of patients achieving ≥2-point improvement in IGA from baseline
    - A static 5-point IGA is preferred. See below for an example, which has been used in clinical trials but has not been validated.
        - At the time of writing, a 5-point IGA is being developed by the IEC and is under consideration by the FDA.
    - The exact IGA scale should be pre-specified in the protocol and investigators should be adequately trained on its use. The full exact IGA scale should also be included in any publications related to the study to allow adequate evaluation by clinicians.
    - Photographic examples of each grade, as agreed upon with the FDA, may be provided to investigators.
    - When a standardized IGA is developed, development of a uniform training module (including with photographs and/or video demonstrations, by groups such as the IEC) would be optimal for use across all trials. This module should be freely available for use.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
1 – Almost clear	Barely perceptible erythema, barely perceptible papulation and/or barely perceptible lichenification that is limited in extent
2 – Mild	Slight erythema (pink), slight papulation and/or slight lichenification that may be limited or widespread in extent
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible papulation and/or clearly perceptible lichenification that may be limited or widespread in extent
4 – Severe	Marked erythema (deep or bright red), marked papulation and/or marked lichenification that is widespread in extent

- Change from baseline in AD severity as assessed by mean and/or percent change in EASI (or SCORAD).
- EASI 50, EASI 75, and/or EASI 90 responder rates, defined as proportions of patients achieving ≥50%, ≥75%, and ≥75% improvement in EASI score from baseline, respectively.
- Change from baseline in extent of disease as assessed by % change in BSA (if not already assessed as part of SCORAD).
    - The method for determining BSA should be clearly described in the protocol. Methods include the 'hand method', the 'palmar method', and the 'rule of 9s'. Extent of disease may be a factor in choosing a method. The 'rule of 9s' may be more accurate for higher BSA affected (>50%).
- All studies should include, at a minimum, a unidimensional assessment of change from baseline in itch.
    - Assessment of itch should NOT be included as a primary endpoint, unless the drug is specifically targeted to treat itch and assessed by a validated, standardized instrument.
    - While no standard exists, the International Forum on Itch recommends a 24-hour recall of the average pruritus.
    - There is currently no preferred method for assessing itch and a number of options and several tools are currently available including the visual analog scale, numeric rating scale, ItchyQoL, and individual items from subjective SCORAD, Patient-Oriented SCORAD (PO-SCORAD), Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM). A validated pediatric itch tool and parent-reported proxy should be used once one is available. Age-group specific or parent-proxy tools may be required.

- Itch also mediates sleep quality, so assessments of sleep may also be included. Available measures of sleep include an individual item from PO-SCORAD and the Pittsburgh Sleep Quality Index.

- Assessment of pain using a validated pain scale may also be considered, especially for moderate-to-severe AD.

• Other Endpoints

Other endpoints may include the following:

- Number of days without rescue medication
- Change from baseline in QoL.
  - If QoL is assessed, at least two measures should be included: one symptom/disease-specific measure to detect small changes AND a more general measure to maximize ability to compare across trials (and potentially across indications).
    - AD-specific QoL measures include PO-SCORAD, POEM; POEM is recommended by the HOME initiative (Chalmers, et al., 2016).
    - Skin-specific QoL measures include DLQI and Skindex.
    - Age-group specific tools may be required.
- As new noninvasive biomarkers are validated, they should be included as appropriate for the mechanism of action of the test article.

• Additional Endpoints for Long-Term Studies

The following endpoints should be considered for long-term studies, as appropriate for test article mechanism of action.

On-Treatment Endpoints

On-treatment endpoints are measured from start of maintenance treatment (after AD and dose are stabilized during initial treatment).

- Reduction of flares as assessed by number of flares and/or time to flare.
  - Definitions of flare that have been used in AD clinical trials have been highly varied and largely unvalidated (Langan, et al., 2014; Langan, et al., 2006; Thomas, et al., 2015). Langan, et al. (2006) proposed defining flares as 'an episode requiring escalation of treatment of seeking of additional medical advice,' or, following the asthma example, 'totally controlled weeks and well-controlled weeks.' Thomas, et al. (2015) found 'escalation of treatment' and 'days of topical anti-inflammatory medication use' both to be good proxy indicators of AD worsening of disease/flare.
  - Flares beyond what could be considered as a normal fluctuation should be recorded as AEs.

    - Future flare definitions as evaluated and recommended by the HOME initiative, should be implemented.
- Number of days without rescue medication, quantity of rescue medication, and/or time to rescue medication.
- Improvement in atopic comorbidities (ie, asthma, food allergy, allergic rhinitis, and/or blepharitis/conjunctivitis) or other AD-associated comorbidities (see **III.E.4.e. Specific Populations**).
    - New onset or worsening of comorbidities should be recorded as AEs.
- Number of disease-free days, which has been defined as no or almost no AD symptoms with no topical corticosteroid treatment (Schneider, et al., 2016).
- Change in concomitant medications.

Off-Treatment Endpoints

Off-treatment endpoints are measured from end of treatment/treatment withdrawal. These endpoints should be used with caution in trials for drugs with potential for immunogenicity following treatment withdrawal.

- Time to relapse, generally defined as time to regaining ≥100% of baseline disease severity by EASI score.
- Time to re-treatment.

c. Trial Population

Sponsors should endeavor to include pediatric patients in clinical trials from the full age range of patients affected by AD including patients from 3 months of age to 18 years of age. Of note, this includes 17-year old patients, who are sometimes excluded from trial participation due to ambiguity in the FDA's definitions of the pediatric age group (FDA defines adolescents as 12 to 16 or 18 years of age). Sponsors may approach this age range incrementally, (eg, conducting trials in children after confirmation of safety and efficacy in adolescents; conducting trials in infants, only after confirmation of safety and efficacy in children).

Trial populations should also include sufficient numbers of patients at the upper threshold of AD severity for the target indication. Considerations should also be made to include sufficient representation in phase 3 trials of US patients, rural patients (vs urban), patients from a variety of ethnic groups, and patients with higher Fitzpatrick skin types.

d. Inclusion and Exclusion Criteria

- **Inclusion Criteria**

Inclusion criteria should specify a minimum level of disease as defined by EASI/SCORAD, IGA, and BSA thresholds that are appropriate for AD severity for the target indication (eg, mild AD, moderate-to-severe AD). See **III.E.1.b. Disease Severity** for additional details. In addition, inclusion criteria should incorporate the following:

- Clinical diagnosis of AD according to the Hanifin and Rajka criteria (Hanifin, et al., 1980).
- AD should be present for at least 3 months for patients ≥2 years of age, although the disease activity may wax and wane during this time with periods of clearance.
- Note: At the time of writing, no reliable biomarkers for AD diagnosis, severity, or treatment effect are available, although reduction in total IgE levels and TARC levels have been used to reflect disease control (Krause, et al., 2016). Once biomarkers are discovered and validated, they should be implemented as inclusion criteria as appropriate.

- **Exclusion Criteria**

Exclusion criteria should include the following:

- Pregnant or lactating women.
    - Measures to reduce the risk for pregnancy should also be employed for subjects who are of childbearing age, defined as Tanner stage 3 or menarche
- History of current or past malignancy for systemic therapies that modulate the immune system.
- History of immunodeficiency syndrome. See Error! Reference source not found. for clinical features of well-defined immunodeficiency syndromes and other pathologies that may mimic AD. Atypical rash morphology, failure to thrive or significant skin, severe viral skin infections, sinopulmonary, or opportunistic/recurrent infections should alert the investigator to diseases that may not be AD. (Note: rheumatoid arthritis, vitiligo, and alopecia areata are generally not a reason for exclusion, unless there is reason to believe one of these disease processes could be affected by the mechanism of action of the drug or poses an undue risk to the participant).
- Concurrent skin disease that significantly interferes with the accurate assessment of AD outcomes, such as irritant contact dermatitis, allergic contact dermatitis, infestations (ie, scabies), or psoriasis (see below for information about contact dermatitis and psoriasis-eczema overlap).
- Active cutaneous or extracutaneous infection (bacterial, viral, or fungal) requiring systemic treatment within 2 weeks of baseline (note: localized molluscum contagiosum with <20 lesions and viral warts are generally not a reason for exclusion).

- For drugs with Th1 helper cell pathway-specific immunosuppressant potential, it may be necessary to exclude patients previously exposed to tuberculosis (TB) or with latent TB. See **III.E.3.a** for more information.

See **III.E.4.f. Washout Periods** and **III.E.4.g. Concomitant Treatments** for lists of prohibited and allowed medication suggestions

e. Specific Populations

Assessing patients for AD phenotype/endotype and AD-associated comorbidities at baseline will allow for subgroup analysis, as appropriate for the mechanism of action of the drug. The immunogenicity of the drug may also impact efficacy and/or safety and should be assessed in clinical studies of biologic products.

- **Considerations for AD Phenotype or Endotype**

Like asthma, various phenotypes and endotypes of AD have been considered in efforts to provide a more individualized approach to patient care (Leung, et al., 2014; Muraro, et al., 2016). However, evidence to support the idea that various AD phenotypes have significantly different pathophysiological mechanisms is sparse. Depending on the mechanism of action of the drug under study, sponsors may consider stratifying analyses or randomization based on potential disease phenotypes (See **APPENDIX B)**. It is important to note that, to date, these phenotypes have not been convincingly associated with differential treatment effects.

- **Considerations for AD-Associated Comorbidities**

Although AD can present as what is sometimes called the 'intrinsic' type—having no major related allergies or clear triggers, most commonly characterized by elevated allergen-specific IgE levels—there are many comorbidities that frequently accompany it and are important considerations when designing clinical studies. There are some data to suggest that therapy that addresses inflammation may have positive benefits on comorbid diseases in AD. Appropriate measurement of selected comorbidities allows for evaluation of the effect of new therapies on common comorbid diseases.

The classically associated morbidities include: asthma, allergic rhinitis, allergic conjunctivitis/blepharitis, nasal polyposis, food allergies, bacterial infections (especially *Staphylococcus aureus),* and viral infections (eczema herpeticum, eczema vaccinatum, eczema coxsackium, molluscum dermatitis, viral warts). More recently described potential comorbidities in epidemiologic studies include: extracutaneous infections, conduct problems/disorder, attention deficit hyperactivity disorder, emotional problems, anxiety, depression/suicidal ideation, epilepsy, obesity, cardiovascular disease, irritable bowel disease (Crohn's disease/ulcerative colitis), celiac disease, alopecia areata, and cancer (lymphoma).

- **Considerations for Fitzpatrick Skin Types**

While the morphology of AD varies based on Fitzpatrick skin types (Fitzpatrick, 1988), an accurate diagnosis of AD can still be made utilizing the Hanifin-Rajka criteria (Hanifin, et al., 1980) or the AAD consensus criteria (Eichenfield, et al., 2014b). However, investigators should be made aware that patients with more pigmented skin/higher Fitzpatrick skin type often have less visibly apparent erythema, more lichenification, greater follicular prominence, and more areas of dyspigmentation. Data are conflicting with regards to the performance of current scoring systems (including EASI and SCORAD) for patients with highly pigmented skin (Zhao, et al., 2017; Zhao, et al., 2015b).

f. Washout Periods

Washout requirements pose barriers to participation in clinical trials and may bias study results, therefore, washout requirements should be applied only to drugs that have the potential to directly influence the efficacy evaluation or have a potential for adverse drug-drug interactions with the test article. This will also ensure that trials results will reflect clinical practice as closely as possible. Furthermore, emphasis should be placed on standardization of washout requirements, rather than specific durations of washout periods.

Trials of new topical drugs may not require washout at all (Sandoval, et al., 2014). However, if there is potential for contact dermatitis-AD overlap, washout periods may need to be extended beyond the expected duration of the reaction (some reactions may take a month or more to clear).

The following washout periods are recommended. This list is by no means exhaustive and the mechanism of action of the investigational drug should be considered when determining which drugs should be washed out prior to randomization.

Medication Class	Suggested Washout Period (If Indicated)
Emollients	
Emollients containing additives such as ceramides, hyaluronic acid, urea, or filaggrin degradation products	1 week
Device creams (Atopiclair, MimyX, EpiCeram)	1 week
Other topical emollients	1 day (ie, no application on study visit days)
Bleach baths	No washout required if used regularly, unless assessments of microbiome are among the clinical endpoints studied
Anti-inflammatories	
Low potency topical corticosteroids	No washout required if dose is stable[a]
Medium to high potency topical corticosteroids	1 to 2 weeks; however, for moderate-to-severe disease, no washout may be required if dose is stable[a]
Topical immunomodulators (tacrolimus ointment, pimecrolimus cream)	1 to 2 weeks
Systemic corticosteroids	4 weeks[a]
Inhaled corticosteroids	For asthma, no washout required if used regularly at stables doses that do not exceed the maximum approved
Apremilast	1 week
Leukotriene inhibitors (montelukast)	4 weeks
Anti-infectives	
Topical antibiotics	For cutaneous infection: 1 week; For acne: no washout required if dose is stable
Systemic antibiotics	2 to 4 weeks
Phototherapy/tanning booths	4 weeks
Biologics	
Non-cell–depleting (etanercept, ustekinumab, dupilumab, infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, anakinra, omalizumab)	16 weeks or 5 half-lives, whichever is longer
Cell-depleting agents (rituximab)	6 months or until lymphocyte and CD19 lymphocyte counts return to normal, whichever is longer
IVIG[b]	5 half-lives (many have a 6-week half-life, but this varies by product)
Antihistamines	
Sedating antihistamines (hydroxyzine, diphenhydramine)	No washout required if dose is stable; often used for their sedating effects allow for more restful sleep without scratching and should not impact scoring/grading of AD
Nonsedating antihistamines (cetirizine)	No washout required if dose is stable
Systemic immunosuppressants (cyclosporine, oral methotrexate, mycophenolate mofetil, azathioprine)	4 weeks
Other investigational treatments	4 to 8 weeks or 5 half-lives (if known), whichever is longer

[a]If washout is required, corticosteroid dose should be tapered; [b]Can impact presence of anti-drug antibodies

g. Concomitant Treatments

Medications for other medical problems should be continued throughout trials. Specifically:

- Inhaled corticosteroids: continue pre-study practice
- Sedating and nonsedating antihistamines: continue pre-study practice, capture indication
- Antibiotics and antivirals: continue pre-study practice, capture indication
  - Infection prior to enrollment: treat prior to enrollment
  - Infection after enrollment: allow treatment

- **Standard-of-Care Skin Care**

Except where the target indication precludes it, standard-of-care skin care (including use of emollients, gentle skin cleansing, and trigger avoidance [Eichenfield, et al., 2015]) should be implemented for every clinical trial regardless of route of administration of the test product. Standardization of skin care routines will be critical in phase 2 studies. For phase 3 studies, the variability in routines seen in daily clinical practice should be reflected, therefore, standardization is not needed; however, changes in skin care routine during a trial should be excluded.

- **Rescue Medications**

Use of concomitant rescue medications should be carefully considered and well defined in study protocols. Data regarding use of rescue medication should be captured and reported for subjects in both active and placebo/vehicle arms (see **III.E.4.a Efficacy Endpoints**). For investigational systemic medications, options for rescue drugs can include topical drugs with FDA approval for AD (eg, topical corticosteroids or calcineurin inhibitors) and/or those in common use off-label for AD (eg, cyclosporine, methotrexate, azathioprine, mycophenolate).

For investigational topical medications, options for rescue drugs can include topical drugs with FDA approval for AD.

h. Randomization, Blinding, and Stratification

Given the subjective nature of endpoints utilized in trials of new AD treatments, sponsors should implement randomization and double-blinding. These methods must be specified in trial protocols, but need not be uniform for all studies.

For trials of topical drugs, it is critical that vehicle controls resemble the active treatment as closely as possible due to the potential for benefit (ie, moisturizing effect) and decrement (ie, irritating solubilizers) with vehicle. If an active topical comparator in utilized, double-blinding may not be feasible. In such cases, efforts should be made to implement an evaluator blind. The appearance of the test product and

comparator, and their respective packaging, should be included in the protocol to assist evaluations of adequacy of the blind.

If an active comparator that uses a route of administration that is different from the test article, double blinding may still be possible by utilizing two placebo controls or a placebo control and a vehicle control. Options to maintain double-blinding when matching placebos or vehicles are not available from the manufacturer include over-encapsulation.

To ensure adequately powered trials, randomization strata should be limited to only critical factors, which may vary by route of administration and mechanism of action of the treatment under investigation. Stratification may be based on FDA-defined age ranges, but weight (especially relevant for adolescents who may be 'adult-like' in size) and BSA involved (although this parameter may be difficult to determine) may be more appropriate. Stratification by geographic area or season of enrollment (to account for seasonal variations) may also be appropriate.

i. Choice of Comparator

Since AD is not a life-threatening disease, inclusion of a placebo/vehicle arm is not unethical; however, for the pediatric population, it should be kept in mind that an extended duration of placebo treatment may have a disproportionately greater detrimental effect on pediatric patients, including potential for psychosocial and/or developmental risks.

- **Trials for Systemic Drugs**

After superiority to placebo is established in phase 2, if a suitable active comparator is available, sponsors are encouraged to utilize active controls in phase 3 trials of systemic medications with the following considerations: adequate measures should be taken to maintain the blind; the goal should be demonstration of superiority over active comparator to obviate need to establish assay sensitivity. There is FDA precedent for requiring an active comparator to have labeling for the indication being studied (see FDA guidance *Head Lice Infestation: Developing Drugs for Topical Treatment*), but other FDA guidance does not require this (see FDA guidance *Non-Inferiority Clinical Trials to Establish Effectiveness)* if there is adequate comparator efficacy data (see FDA guidance *Non-Inferiority Clinical Trials to Establish Effectiveness)*.

Because there are several different disease mechanisms that can be targeted to treat AD (eg, skin inflammation, pruritus), appropriate choice of an active comparator is critical. For example, an anti-inflammatory would not be an appropriate active comparator for a trial of an antipruritic drug, and vice versa.

If active control is not feasible, sponsors should consider study design modifications such as add-on, early escape, or randomized withdrawal rather than allowing rescue medication use, which can complicate analysis.

- **Trials for Topical Drugs**

Vehicle controls should be used in short-term (ie, less than 3 months) trials of topical medications when possible. Because topical drugs are generally intended to treat limited, mild-to-moderate disease, utilizing a placebo control for short-term trials in this population is not expected to adversely impact patient recruitment. However, for long-term trials (longer than 3 months), use of an appropriate active topical comparator or use of rescue medication is suggested.

Unlike placebo controls for systemic drugs, vehicle comparators for trials of topical drugs are likely to have physiologic effects in the skin. In the vast majority of cases, these are beneficial effects due to skin hydration and skin barrier repair (see Paller, et al., 2016). However, there are examples where vehicle controls exacerbated AD due to irritant excipients whose impact was mitigated by the active pharmaceutical ingredient in the test product (see Abramovits, et al., 2006). So, vehicle controls should be formulated as closely as possible to the test product not only to maintain the blind, but also to mitigate any amplification or diminution of the observed treatment effect due to the physiologic effects of the vehicle on skin.

Of note, trial designs in which subjects serve as their own control have been used to study topical products to minimize the heterogeneity characteristic of this patient population. However, this approach compromises the evaluation of systemic toxicity, necessitating additional controls or studies to collect adequate safety data.

j. Trial Procedures

- **Timing of Assessments**

At least 3 study visits should be included – 1 at screening/randomization/baseline, 1 at end of treatment, and 1 at end of follow-up (which can be conducted via phone, etc). Throughout the trial, sponsors should consider alternative mechanisms for data capture (electronic diaries, mailed questionnaires, etc) and follow-up (phone call, telemedicine, etc) that may reduce the burden of study participation on patients and caregivers.

Depending on the overall length of the study, in-office study visits should occur approximately every 1 to 3 months at a minimum, then progress to once every 6 months. Consideration should be given to the number and duration of required in-office visits to not be burdensome.

- **Considerations for Laboratory Assessments**

Age-appropriate, normal laboratory values should be used for standard laboratory assessments. The volume of blood withdrawn should be minimized in pediatric studies (ie, Microtainer® technology) and blood volumes should be justified in protocols.

- **Injection Volumes**

To maximize comfort, the volume of injections, the injection site, and needle size should be considered. The smallest needle size should be implemented and the use of autoinjectors should be considered. The duration of injection should be a quick as possible to minimize discomfort and topical anesthetics/analgesia or distraction techniques may also be useful for minimizing distress.

The injection amounts listed here are maximum amounts based on expert opinion. If a more concentrated formulation of the test article is available, the concentration that minimizes the number of injections and maximizes the interval between injections should be used, taking solubility, stability and viscosity into consideration.

Subcutaneous Injection Route

The subcutaneous route is often used to deliver long-term, self-administered, and biologic therapies.

For all ages, volumes of 2.0 mL (2.0 cc) or less are recommended as the volume of fluid injected subcutaneously in one site. The smallest volume necessary should be given, especially for younger age groups, as volumes greater than 1.5 mL may be associated with injection site pain and/or reactions.

Intramuscular Injection Route

For infants (birth to 12 months of age) and young children (>12 to 36 months of age), the maximum volume of fluid recommended for intramuscular injection is 1.0 to 2.0 mL in one site.

For the neonate, the maximum volume of fluid recommended for intramuscular injection is 0.5 mL in one site.

Older children (>36 months of age) with good muscle mass may receive up to 2.0 mL (or 2.0 cc) of fluid intramuscularly.

- **Primary Care Provider/Referring Physician Communication and Disposition Plans**

It may be helpful to include tools in the protocol/clinical report form that will encourage investigators to follow-up with a patient's primary care physician/referring physician (ie, form letter, business card). This will help to reduce protocol deviations (ie, prescribing prohibited medications/immunizations), encourage prompt AE reporting, and improve the continuum of care for patients.

Other Resources

Sponsors should be aware of the NEA as a resource for subject recruitment and education/support. It may be also helpful to include NEA contact information for subjects (https://nationaleczema.org).

k. Adverse Event Reporting

All subjects should be evaluated for safety as a minimum, at the time of each trial visit or assessment, regardless of whether the investigational drug has been discontinued for safety. Generally, all AEs should be followed until resolution, even if time on clinical trial would otherwise have been completed.

In clinical trials, individual case narratives may be of interest to the FDA for information regarding AEs or SAEs. MeDRA nomenclature (http://www.medra.org/) is preferred for AE reporting in clinical studies.

l. Endpoint Adjudication

Generally, development of AD treatments should be based on the endpoints listed above (see **III.E.4.a. Efficacy Endpoints**). However, there may be instances where central endpoint adjudication based on photographic evidence is warranted. Photographs may be useful to validate new evaluation tools.

If photographs are used, photographic parameters should be standardized (lighting, distance, exposure, and camera type) along with consent forms.

Photographs used in publications, clinical study reports, or other documentation of study results should be representative of the overall patient population that participated in the study. It should also be kept in mind that photographic evidence may less accurately reflect some clinical parameters for patients with darker skin/higher Fitzgerald skin types.

m. Open-Label Treatment Eligibility

For phase 2 trials, an opportunity for open-label use of study drug at a dose that is being moved forward in development should be offered to patients who did not improve during the blinded phase if safety has been established. For phase 3 trials, an opportunity for open-label use of study drug should be offered to all patients in the form of an open-label extension. Minimal criteria should be established that allows for transition from double-blind treatment to open-label treatment with as little gap as possible; however, a delay until the blind can be broken after last patient-last visit may be required to ensure that patients are not unduly exposed to a treatment to which they were unresponsive). Patients who switch to open-label treatment should continue to be followed; however, data should be censored for the primary analysis. At the time of enrollment, patients and/or caregivers must be fully informed about opportunities for open-label use of study drug, and this must be clearly distinguished from use of a noninvestigational rescue medication. The opportunity for open-label use in phase 3 studies should not be modified or withdrawn by the sponsor unless there is a safety concern. However, sponsors should be careful to avoid

presentations of such opportunities as an incentive to enhance recruitment, unless there is clear and direct benefit to the pateint.

A long-term extension of a clinical study is highly desirable for pediatric studies to extend the potential benefit to this underserved population, especially since FDA approval of the pediatric indication often lags the adult indication. It may also help to increase recruitment and retention in clinical trials and allows sponsors to gather additional information about long-term efficacy and safety. These scientific objectives should be clearly stated in the protocol.

n. Risk-Benefit Considerations

As for all medications, clinically meaningful benefits of treatment should outweigh potential risks. In the case of AD, the potential for reducing the risk of developing AD-associated comorbidities (see **III.E.4.e. Specific Populations**) will substantially outweigh the risk of treatment for many treatments. Of note, in the context of these potentially serious, life-long comorbidities, potential safety signals should be adjudicated against background epidemiology with input from experts in the field.

There are currently few FDA-approved systemic treatments are available for severe AD. Few FDA-approved treatments are available for mild AD and those that are available are limited to short term use (topical corticosteroids) or chronic intermittent use (topical calcineurin inhibitors). Furthermore, use of long-term topical corticosteroids is not recommended by treatment guidelines (Eichenfield, et al., 2014a; Eichenfield, et al., 2014b; Schneider, et al., 2013; Sidbury, et al., 2014a; Sidbury, et al., 2014b) and access to topical calcineurin inhibitors is limited by a boxed warning (Siegfried, et al., 2015). So, new medications are needed to treat the full spectrum of AD.

F. Other Considerations

1. Risk Management Considerations

Parents/caregivers should be made aware of all potential safety issues as part of the informed consent process. Patients should also be made aware as much as is feasible, using age-appropriate language, of the risks of participating in a clinical trial. Older children and adolescents may be able to assent to participation in addition to parent/guardian consent. See ICH guidance *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* for more information on informed consent/assent in the pediatric population.

2. Accelerated Approval (Subpart H) Considerations

AD is not a ‘life-threatening condition’; therefore, accelerated approval is not appropriate.

3. Labeling Considerations

Safety concerns, especially with respect to use in the pediatric age group (eg, accidental ingestion, misapplication), should be included in product labelling.

Suggestions for minimizing pain and discomfort from injections can be included in the Medication Guide.

For topical products, labelling should reflect typical use and specify maximal use (as assessed in phase 3 studies). For products that have complex application procedures, FDA-approved instructions for use should be included in the Medication Guide. In addition, approximate amounts to dispense may be included in a Medication Guide as a resource for physicians to ensure that they prescribe, and insurers reimburse, for adequate amounts of topical medication.

4. Packaging Considerations

The safest possible packaging should be utilized for all pediatric formulations, such as blister packs for tablets, safety caps for bottles, and autoinjectors for injectable medications.

Liquid formulations with (<2 mL/dose) should be packaged in premeasured aliquots to avoid dispensing errors. Packaging injectable drugs that require more than one injection per dose as a single unit will help to reduce reimbursement hurdles.

Topical products should be packaged in adequate amounts to support typical use (as assessed in phase 3 studies) for at least one month. This will also help to reduce reimbursement hurdles.

5. Trial Setting

Specialty-based trials (university-based or private) are preferred if inclusion/exclusion criteria define a patient population that would generally require a specialist and/or study assessments require a specialty trained expert. However, if a primary care-based investigator can demonstrate training and experience to fulfill these requirements, that primary-care based site can be considered.

Primary care-based trials may be considered if inclusion/exclusion criteria define a patient population that is commonly seen at the primary care level with disease severity that is appropriately treated by a primary care physician, and the primary care physician can demonstrate the expertise required to complete study procedures.

Conducting a trial in a setting that is already familiar to patients may minimize distress. Regardless of setting, investigators should be skilled in dermatologic assessments as well as issues and concerns specific to the pediatric population. All individual sites and investigators will require a complete assessment by the sponsor to ensure compliance with regulatory requirements.

6. Postmarketing Considerations

Sponsors should consider postmarketing/phase 4 studies or registries to assess long-term effects on growth/development and comorbidities in consultation with the FDA.

REFERENCES

Abramovits W and Boguniewicz M. 2006. A Multicenter, Randomized, Vehicle-Controlled Clinical Study to Examine the Efficacy and Safety of MAS063DP (Atopiclair) in the Management of Mild to Moderate Atopic Dermatitis in Adults. J Drugs Dermatol. 5(3):236-44.

Bruin G, Loesche C, Nyirady J and Sander O. 2017. Population Pharmacokinetic Modeling of Secukinumab in Patients with Moderate to Severe Psoriasis. J Clin Pharmacol. doi: 10.1002/jcph.876.

Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, Luger TA, Deleuran M, Werfel T, Eyerich K and Stingl G. 2017. Increasing Comorbidities Suggest That Atopic Dermatitis Is a Systemic Disorder. J Invest Dermatol. 137(1):18-25.

Chalmers JR, Simpson E, Apfelbacher CJ, Thomas KS, von Kobyletzki L, Schmitt J, Singh JA, Svensson A, Williams HC, Abuabara K, Aoki V, Ardeleanu M, Awici-Rasmussen M, Barbarot S, Berents TL, Block J, Bragg A, Burton T, Bjerring Clemmensen KK, Creswell-Melville A, Dinesen M, Drucker A, Eckert L, Flohr C, Garg M, Gerbens LA, Graff AL, Hanifin J, Heinl D, Humphreys R, Ishii HA, Kataoka Y, Leshem YA, Marquort B, Massuel MA, Merhand S, Mizutani H, Murota H, Murrell DF, Nakahara T, Nasr I, Nograles K, Ohya Y, Osterloh I, Pander J, Prinsen C, Purkins L, Ridd M, Sach T, Schuttelaar ML, Shindo S, Smirnova J, Sulzer A, Synnove Gjerde E, Takaoka R, Vestby Talmo H, Tauber M, Torchet F, Volke A, Wahlgren CF, Weidinger S, Weisshaar E, Wollenberg A, Yamaga K, Zhao CY and Spuls PI. 2016. Report from the Fourth International Consensus Meeting to Harmonize Core Outcome Measures for Atopic Eczema/Dermatitis Clinical Trials (HOME Initiative). Br J Dermatol. 175(1):69-79.

Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, Kantor R, Hsu DY and Silverberg JI. 2017. Severity Strata for EASI, Measi, Oscorad, Scorad, Adsi and Bsa in Adolescents and Adults with Atopic Dermatitis. Br J Dermatol. doi: 10.1111/bjd.15641.

Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, Lewis LL, Sachs HC, Sheridan PH, Starke P and Yao LP. 2011. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. Pediatrics. 128(5):e1242-9.

Edginton AN. 2011. Knowledge-Driven Approaches for the Guidance of First-in-Children Dosing. Paediatr Anaesth. 21(3):206-13.

Eichenfield LF, Boguniewicz M, Simpson EL, Russell JJ, Block JK, Feldman SR, Clark AR, Tofte S, Dunn JD and Paller AS. 2015. Translating Atopic Dermatitis Management Guidelines into Practice for Primary Care Providers. Pediatrics. 136(3):554 -65.

Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, Bergman JN, Chamlin SL, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Feldman SR, Hanifin JM, Margolis DJ, Silverman RA, Simpson EL, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W and Sidbury R. 2014a. Guidelines of Care for the Management of Atopic Dermatitis: Section 2. Management and Treatment of Atopic Dermatitis with Topical Therapies. J Am Acad Dermatol. 71(1):116-32.

Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W and Sidbury R. 2014b. Guidelines of Care for the Management of Atopic Dermatitis: Section 1. Diagnosis and Assessment of Atopic Dermatitis. J Am Acad Dermatol. 70(2):338-51.

Fitzpatrick TB. 1988. The Validity and Practicality of Sun-Reactive Skin Types I through Vi. Arch Dermatol. 124(6):869-71.

Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC and Simpson EL. 2016. A Systematic Review of Investigator Global Assessment (IGA) in Atopic Dermatitis (AD) Trials: Many Options, No Standards. J Am Acad Dermatol. 74(2):288-94.

Guttman Krader C. May 21, 2015. Pediatric Trials for AD Systemic Treatments. Dermatology Times.

Hanifin JM and Rajka G. 1980. Diagnostic Features of Atopic Dermatitis. Acta Derm Venereol. Suppl 92:44-7.

Hanifin JM and Reed ML. 2007. A Population-Based Survey of Eczema Prevalence in the United States. Dermatitis. 18(2):82-91.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ and Graeber M. 2001. The Eczema Area and Severity Index (EASI): Assessment of Reliability in Atopic Dermatitis. EASI Evaluator Group. Exp Dermatol. 10(1):11-8.

Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, Marks R, Naldi L, Weinstock MA, Wulf SK, Michaud C, Murray CJL and Naghavi M. 2014. The Global Burden of Skin Disease in 2010: An Analysis of the Prevalence and Impact of Skin Conditions. J Invest Dermatol. 134(6):1527-34.

Heinl D, Prinsen CA, Sach T, Drucker AM, Ofenloch R, Flohr C and Apfelbacher C. 2016. Measurement Properties of Quality-of-Life Measurement Instruments for Infants, Children and Adolescents with Eczema: A Systematic Review. Br J Dermatol. doi: 10.1111/bjd.14966.

Krause L, Mourantchanian V, Brockow K, Theis FJ, Schmidt-Weber CB, Knapp B, Mueller NS and Eyerich S. 2016. A Computational Model to Predict Severity of Atopic Eczema from 30 Serum Proteins. J Allergy Clin Immunol. 138(4):1207-1210.e2.

Lan CC, Huang CC, Chen YT, Wang LF, Lin CT and Chen GS. 2003. Tacrolimus Ointment for the Treatment of Atopic Dermatitis: Report of First Clinical Experience in Taiwan. Kaohsiung J Med Sci. 19(6):296-304.

Langan SM, Schmitt J, Williams HC, Smith S and Thomas KS. 2014. How Are Eczema 'Flares' Defined? A Systematic Review and Recommendation for Future Studies. Br J Dermatol. 170(3):548-56.

Langan SM, Thomas KS and Williams HC. 2006. What Is Meant by a "Flare" in Atopic Dermatitis? A Systematic Review and Proposal. Arch Dermatol. 142(9):1190-6.

Leshem YA, Hajar T, Hanifin JM and Simpson EL. 2015. What the Eczema Area and Severity Index Score Tells Us About the Severity of Atopic Dermatitis: An Interpretability Study. Br J Dermatol. 172(5):1353-7.

Leung DY and Guttman-Yassky E. 2014. Deciphering the Complexities of Atopic Dermatitis: Shifting Paradigms in Treatment Approaches. J Allergy Clin Immunol. 134(4):769-79.

Lowenthal E and Fiks AG. 2016. Protecting Children through Research. Pediatrics. 138(4):e20162150.

Lübbe J, Friedlander SF, Cribier B, Morren MA, Garcia-Diez A, Gelmetti C, Hofmann H, Houwing RH, Kownacki S, Langley RG, Virtanen M, Wolff K, Wisseh S, McGeown C, Abrams B and Schneider D. 2006. Safety, Efficacy, and Dosage of 1% Pimecrolimus Cream for the Treatment of Atopic Dermatitis in Daily Practice. Am J Clin Dermatol. 7(2):121-31.

Marshall WA and Tanner JM. 1969. Variations in Pattern of Pubertal Changes in Girls. Arch Dis Child. 44(235):291-303.

Marshall WA and Tanner JM. 1970. Variations in the Pattern of Pubertal Changes in Boys. Arch Dis Child. 45(239):13-23.

Minutes of the Dermatologic and Ophthalmic Drugs Advisory Committee, March 9, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM446396.pdf.

Muraro A, Lemanske RF, Jr., Hellings PW, Akdis CA, Bieber T, Casale TB, Jutel M, Ong PY, Poulsen LK, Schmid-Grendelmeier P, Simon HU, Seys SF and Agache I. 2016. Precision Medicine in Patients with Allergic Diseases: Airway Diseases and Atopic Dermatitis-PRACTALL Document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol. 137(5):1347-58.

Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, Eichenfield LF, Forsha DW, Rees WC, Simpson EL, Spellman MC, Stein Gold LF, Zaenglein AL, Hughes MH, Zane LT and Hebert AA. 2016. Efficacy and Safety of Crisaborole Ointment, a Novel, Nonsteroidal Phosphodiesterase 4 (PDE4) Inhibitor for the Topical Treatment of Atopic Dermatitis (AD) in Children and Adults. J Am Acad Dermatol. 75(3):494-503.e4.

Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, [Document prepared by the National Health Council and Genetic Alliance with the intent of submission to the Food and Drug Administration to encourage adoption, wholly or in part, by the Agency]. http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf. Published February 2017.

Sandoval LF and Feldman SR. 2014. Are Wash Outs Needed in Clinical Trials of Topical Agents? J Dermatolog Treat. 25(1):1.

Schmitt J, Spuls P, Boers M, Thomas K, Chalmers J, Roekevisch E, Schram M, Allsopp R, Aoki V, Apfelbacher C, Bruijnzeel-Koomen C, Bruin-Weller M, Charman C, Cohen A, Dohil M, Flohr C, Furue M, Gieler U, Hooft L, Humphreys R, Ishii HA, Katayama I, Kouwenhoven W, Langan S, Lewis-Jones S, Merhand S, Murota H, Murrell DF, Nankervis H, Ohya Y, Oranje A, Otsuka H, Paul C, Rosenbluth Y, Saeki H, Schuttelaar ML, Stalder JF, Svensson A, Takaoka R, Wahlgren CF, Weidinger S, Wollenberg A and Williams H. 2012. Towards Global Consensus on Outcome Measures for Atopic Eczema Research: Results of the HOME II Meeting. Allergy. 67(9):1111-7.

Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, Dohil M, Apfelbacher C, Singh JA, Chalmers J and Williams HC. 2014. The Harmonising Outcome Measures for Eczema (HOME) Statement to Assess Clinical Signs of Atopic Eczema in Trials. J Allergy Clin Immunol. 134(4):800-7.

Schneider L, Hanifin J, Boguniewicz M, Eichenfield LF, Spergel JM, Dakovic R and Paller AS. 2016. Study of the Atopic March: Development of Atopic Comorbidities. Pediatr Dermatol. doi: 10.1111/pde.12867.

Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, Novak N, Bernstein D, Blessing-Moore J, Khan D, Lang D, Nicklas R, Oppenheimer J, Portnoy J, Randolph C, Schuller D, Spector S, Tilles S and Wallace D. 2013. Atopic Dermatitis: A Practice Parameter Update 2012. J Allergy Clin Immunol. 131(2):295-9, 299.e1-27.

SHL Group. 2015. Auto Injectors & Pen Injectors: A User-Centric Design Approach. OnDrugDelivery.Com. (58):6-9.

Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, Chamlin SL, Cooper KD, Feldman SR, Hanifin JM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Simpson EL, Tom WL, Williams HC, Elmets CA, Block J, Harrod CG, Begolka WS and Eichenfield LF. 2014a. Guidelines of Care for the Management of Atopic Dermatitis: Section 3. Management and Treatment with Phototherapy and Systemic Agents. J Am Acad Dermatol. 71(2):327-49.

Sidbury R, Tom WL, Bergman JN, Cooper KD, Silverman RA, Berger TG, Chamlin SL, Cohen DE, Cordoro KM, Davis DM, Feldman SR, Hanifin JM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Simpson EL, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W and Eichenfield LF. 2014b. Guidelines of Care for the Management of Atopic Dermatitis: Section 4. Prevention of Disease Flares and Use of Adjunctive Therapies and Approaches. J Am Acad Dermatol. 71(6):1218-33.

Siegfried EC, Jaworski JC and Hebert AA. 2015. Request for Consistency in Boxed Warnings. Pediatrics.

Tan J and Langley R. 2004. Safety and Efficacy of Tacrolimus Ointment 0.1% (Protopic) in Atopic Dermatitis: A Canadian Open-Label Multicenter Study. J Cutan Med Surg. 8(4):213-9.

Thomas KS, Stuart B, O'Leary CJ, Schmitt J, Paul C, Williams HC and Langan S. 2015. Validation of Treatment Escalation as a Definition of Atopic Eczema Flares. PLoS One. 10(4):e0124770.

Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, Bingham EA, Finlay AY, Pembroke AC, Graham-Brown RAC, Atherton DA, Lewis-Jones MS, Holden CA, Harper JI, Champion RH, Poyner TF, Launer J and David TJ. 1994. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a Minimum Set of Discriminators for Atopic Dermatitis. Br J Dermatol. 131(3):383-96.

Yaghmaie P, Koudelka CW and Simpson EL. 2013. Mental Health Comorbidity in Patients with Atopic Dermatitis. J Allergy Clin Immunol. 131(2):428-33.

Zhao CY, Hao EY, Oh DD, Daniel BS, Martin LK, Su JC, Rodrigues M and Murrell DF. 2017. A Comparison Study of Clinician-Rated Atopic Dermatitis Outcome Measures for Intermediate- to Dark-Skinned Patients. Br J Dermatol. 176(4):985-992.

Zhao CY, Tran AQ, Lazo-Dizon JP, Kim J, Daniel BS, Venugopal SS, Rhodes LM, Law MG and Murrell DF. 2015a. A Pilot Comparison Study of Four Clinician-Rated Atopic Dermatitis Severity Scales. Br J Dermatol. 173(2):488-97.

Zhao CY, Wijayanti A, Doria MC, Harris AG, Jain SV, Legaspi KN, Dlova NC, Law MG and Murrell DF. 2015b. The Reliability and Validity of Outcome Measures for Atopic Dermatitis in Patients with Pigmented Skin: A Grey Area. Int J Womens Dermatol. 1(3):150-4.