

FDA Briefing Document

**Dermatologic and Ophthalmic Drugs Advisory Committee
Meeting**

March 9, 2015 Afternoon Session

**Background Package for Open Session on Clinical
Development for the Pediatric Use of Systemic Products in
the Treatment of Atopic Dermatitis Inadequately Responsive
to Topical Therapies**

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS

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Division Director Memorandum



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Date: February 10, 2015

From: Kendall A. Marcus, MD
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To: Chair, Members and Invited Guests
Dermatologic and Ophthalmologic Drugs Advisory Committee
(DODAC)

Subject: Overview of the March 9, 2015 DODAC Afternoon Meeting

The Division of Dermatology and Dental Products (DDDP) seeks input from the Advisory Committee regarding the timing of pediatric trials during the development of systemic drugs for the treatment of atopic dermatitis that responds inadequately to topical treatment.

Because atopic dermatitis primarily affects the pediatric population, DDDP has historically requested applicants to provide data on the use of their products in pediatric populations prior to initial product approval. For example, pimecrolimus cream was approved for the treatment of mild to moderate atopic dermatitis in adult and pediatric populations based on pivotal trials conducted in pediatric subjects. All of the topical products approved for the treatment of atopic dermatitis have had some pediatric labeling at the time of initial approval.

Novel systemic products are in development for the treatment of atopic dermatitis inadequately responsive to topical therapies. These novel systemic products present a different risk benefit assessment than approved topical products. This background document summarizes the currently available therapy for atopic dermatitis that is inadequately responsive to topical treatment, provides an example of a product under development for this population, and outlines a regulatory framework for pediatric drug development.

Draft Points To Consider

Please address the timing and inclusion of pediatric subjects in trials of systemic treatments for atopic dermatitis in the context of an ongoing adult development program. Specifically, please address the following issues:

- (1) how much preliminary evidence of treatment effect and safety should be obtained in adults prior to studying treatment of children with atopic dermatitis with novel agents
- (2) how much uncertainty about the potential risks and benefits of novel agents is tolerable when initiating a pediatric trial, given the nature of the disease and the available alternative treatments
- (3) the appropriate pediatric population in whom to study systemic treatments (e.g., severity of disease, lack of response to topical agents) such that the risks and potential benefits of the investigational agent would be comparable to alternative treatments
- (4) the importance of having sufficient data to label the product for use in some or all pediatric subpopulations at the time of an adult approval in order to avoid the risks of “off-label” use in children
- (5) whether older pediatric subpopulations should be studied prior to or concurrently with younger pediatric subpopulations.

1. ATOPIC DERMATITIS THAT IS INADEQUATELY RESPONSIVE TO TOPICAL TREATMENT: CLINICAL CONSIDERATIONS

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that predominantly affects the pediatric population but also occurs in adults. Clinical manifestations include erythematous papules and plaques with oozing, scale, crust, excoriations, and lichenification. The face and flexures are areas of predilection (distribution varies by age), but involvement can be generalized. Pruritis is the primary symptom. While the disease can range from mild to severe, the advisory committee meeting will focus on the sub-population of patients with atopic dermatitis that does not respond adequately to topical treatment.

In a population-based survey, the prevalence of AD in the US was found to be 6%, of which 30% reported mild disease, 53% moderate disease and 18% severe disease¹. Disease onset is typically in early childhood; approximately 45% of patients develop skin manifestations by 6 months of age, 60% by one year of age, and 85% by five years of age². Of those who develop AD in childhood, approximately one third will continue to have the disease into adulthood³.

The therapeutic armamentarium for AD includes i) non-pharmacologic measures such as bathing practices, moisturizers and device creams; ii) topical drugs such as corticosteroids and calcineurin inhibitors, and iii) phototherapy and systemic products such as corticosteroids for injection and various immunosuppressant drugs used off-label. This therapeutic approach is loosely hierarchical in that treatment often begins with non-pharmacologic measures and sequentially adds, depending on response and disease severity, topical corticosteroids, topical calcineurin inhibitors, and either phototherapy or systemic agents. Compliance with topical products, including non-pharmacologic agents, can be challenging due to the time required for application and the cosmetic awkwardness of some preparations (e.g., stickiness, greasiness, messiness). For caregivers of children with AD, the time costs can be substantial.

For AD patients and their caregivers, the disease burden can significantly impact on quality of life. Patients have to cope with sleep loss and psychosocial stress as well as the physical aspects of the disease, including treatment adverse effects. Atopic dermatitis can have a considerable impact on patients' emotional health and ability to function.^{4,5} In a survey of members from the National Eczema Society, work was adversely affected due to eczema in 54% of 1,972 adults.⁶ In children, itching and loss of sleep negatively affect their school performance as well as their

¹ Hanifin J, Reed M, the Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. *Dermatitis* 2007;18: 82-91.

² Bieber T. Atopic Dermatitis. *N Engl J Med* 2008;358:1483-94.

³ Garmhausen D, Hagemann T, Bieber T, et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy*. 2013;68:498-506.

⁴ Higaki Y, Kawamoto K, Kamo T, et al. Measurement of the impact of atopic dermatitis on patients' quality of life: a cross-sectional and longitudinal questionnaire study using the Japanese version of Skindex-16. *J Dermatol*. 2004;31:977-82.

⁵ Herd RM, Tidman MJ, Ruta DA, et al. Measurement of quality of life in atopic dermatitis: correlation and validation of two different methods. *Br J Dermatol*. 1997;136:502-7.

⁶ Ahmed A, Leon A, Butler DC, et al. Quality-of-life effects of common dermatological diseases. *Semin Cutan Med Surg*. 2013;32:101-9.

social and sports activities.^{7, 8} Embarrassment as a result of their appearance can lead to social isolation.⁵ Such effects, if not addressed early with effective treatments, may lead to low self-esteem, mood changes, and depression.⁵ Beattie et al⁴ compared QOL of children (ages 5 to 16 years) with chronic skin diseases to children (ages 5 to 16 years) with other chronic medical conditions using the CLQI measurement scale. The study showed that cerebral palsy has the worst QOL score, followed by generalized atopic dermatitis, renal disease, cystic fibrosis, urticaria, asthma, psoriasis, epilepsy, enuresis, diabetes, alopecia and acne.

Parents caring for children with atopic dermatitis are also impacted in multiple ways; including sleep disturbance, altered social and holiday plans, and effect on personal relationships.⁹ Frequently reported difficulties for parents include increased daily tasks such as special food preparation and increased house cleaning, the need for special clothing and detergents, as well as frequent healthcare provider visits. These difficulties equate to lost time from work and increased financial burden. Another reported difficulty for parents is psychological stress:¹⁰ A majority of the parents reported anxiety, depression, guilt, and frustration when caring for a child with atopic dermatitis.⁶

2. AVAILABLE THERAPIES FOR AD INADEQUATELY RESPONSIVE TO TOPICAL THERAPIES

The majority of patients achieve disease control with standard non-systemic treatments, including local skin care, environmental modification, and topical prescription products. , However, due to disease severity, treatment-related adverse reactions, or other factors, some are not. For these patients, systemic drugs or phototherapy may be used.

In 2014, the American Academy of Dermatology (AAD) published guidelines for the management of AD; Sections 3 of these guidelines address treatment with phototherapy and systemic agents¹¹. The following Table is a summary of recommendations for systemic therapies from the AAD guidelines. The use of the majority of these products in AD is off-label.

⁷ Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol*. 2006;155:145-51.

⁸ Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol*. 1995;132:942-9.

⁹ Lawson V, Lewis-Jones MS, Finlay AY, et al. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol*. 1998;138:107-13.

¹⁰ Warschburger P, Buchholz HT, Petermann F. Psychological adjustment in parents of young children with atopic dermatitis: which factors predict parental quality of life? *Br J Dermatol*. 2004;150:304-11.

¹¹ Sidbury R, Davis D, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol* 2014;71:327-49.

AAD Guideline Recommendations for Systemic Therapies for AD¹³

Table VII. Recommendations for the use of systemic immunomodulatory agents

Systemic immunomodulatory agents are indicated for the subset of adult and pediatric patients in whom optimized topical regimens and/or phototherapy do not adequately control the signs and symptoms of disease.
Systemic immunomodulatory agents are indicated when the patient's skin disease has significant negative physical, emotional, or social impact.
All immunomodulatory agents should be adjusted to the minimal effective dose once response is attained and sustained. Adjunctive therapies should be continued to use the lowest dose and duration of systemic agent possible.
Insufficient data exist to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication.
Treatment decisions should be based on each individual patient's AD status (current and historical), comorbidities, and preferences.
Cyclosporine is effective and recommended as a treatment option for patients with AD refractory to conventional topical treatment.
Azathioprine is recommended as a systemic agent for the treatment of refractory AD.
Methotrexate is recommended as a systemic agent for the treatment of refractory AD. Folate supplementation is recommended during treatment with methotrexate.
Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory AD.
Interferon gamma is moderately and variably effective and may be considered as an alternative therapy for refractory AD in adults and children who have not responded to, or have contraindications to the use of, other systemic therapies or phototherapy.
Systemic steroids should be avoided if possible for the treatment of AD. Their use should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapy.

AD, Atopic dermatitis.

A summary of the regulatory status and the recommendations in the AAD guidelines, by product, follow:

2.1 Corticosteroids

Several systemic corticosteroids are approved for control of severe or incapacitating AD intractable to adequate trials of conventional treatments. The labeling for these products does not contain study results in AD or pediatric labeling for the treatment of AD.

The AAD guidelines recommend general avoidance of use of systemic corticosteroids in adults and children with AD because the potential short- and long-term adverse effects may outweigh the benefits. The guidelines allow consideration for short-term use in individual cases when other systemic or phototherapy regimens are being initiated and/or optimized. Labeled adverse reactions include hypertension, reversible hypothalamic-pituitary-adrenal axis suppression, increased susceptibility to infection, exacerbation of infection, reactivation of latent disease, glucose intolerance, gastritis, decreased bone density, cataracts and glaucoma,. Children and adolescents can experience decreased linear growth while on these medications, and may need revised immunization schedules due to the contraindication for co-administration of live or attenuated vaccines. The AAD guidelines state that systemic corticosteroids are not recommended for children with AD unless they are used to manage comorbid conditions (e.g., asthma exacerbations), or as part of a short-term transition protocol to nonsteroidal systemic immunomodulatory agents.

2.2 Cyclosporine A (CSA)

CSA is not approved in the US for the treatment of AD.

Per the AAD Guidelines¹³, both pediatric and adult patients treated with CSA experience a reduction in signs and symptoms of AD. Patients treated with CSA may see a decrease in disease activity within 2 to 6 weeks of treatment initiation. In one study, patients who received CSA had both a decrease in surface area of involvement and in the degree of inflammation of the remaining dermatitis at 6 weeks, with mean decrease in total body severity assessment of 55%, compared with an increase of 4% in patients taking placebo. The mean score for the extent of disease, decreased by 40% in patients taking CSA, compared with an increase of 25% in those taking placebo¹². Dosage and monitoring is shown in Table VIII from the guidelines¹³. Product labeling includes a boxed warning for risks of infection, malignancy, hypertension, nephrotoxicity, and structural renal damage. In pediatric patients, both continuous long-term (up to 12 months) and intermittent short-term dosing schemes (3- or 6-month courses) have been used¹³.

2.3 Azathioprine

Azathioprine is not approved for the treatment of AD.

Per the AAD Guidelines¹³, many patients treated with azathioprine experience a reduction in AD disease activity. In one placebo-controlled study of patients with moderate to severe AD, the azathioprine-treated group reported a 37% improvement in their dermatitis, as compared to 20% in the placebo-treated group after 12 weeks¹³. Another placebo-controlled study showed 26% improvement in azathioprine-treated patients compared to 3% in the placebo-treated group¹⁴. Both studies based improvement on the reduction of the Six Area, Six Sign AD (SASSAD) scoring system. For dosage and monitoring, see Table VIII from the AAD guidelines¹³.

Product labeling includes a boxed warning for malignancy, including lymphoma and hepatosplenic T-cell lymphoma, mutagenicity, and hematologic toxicities. Labeled warnings include risk of malignancy, skin malignancy, lymphoma, severe leukopenia, thrombocytopenia, pancytopenia, severe bone marrow suppression, and serious infection. Labeled adverse reactions include nausea, vomiting and gastrointestinal hypersensitivity reaction.

In pediatric patients, the AAD guidelines recommend azathioprine for those with recalcitrant disease or when the disease causes significant psychosocial impact. However, the guidelines note that there are not sufficient data to support optimal dosing, duration of therapy, or

¹² van Joost T, Heule F, Korstanje M, et al. Cyclosporin in atopic dermatitis: a multicenter placebo-controlled study. *Br J Dermatol* 1994; 130:634-40.

¹³ Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomized controlled trial. *Lancet* 2006;367:839-46.

¹⁴ Berth-Jones J, Takwale A, Tan E, Barclay G, Agarwal S, Ahmed I, et al. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 2002;147:324-30.

prediction of relapse rate upon discontinuation¹³. The most common dosage is 2.5 mg/kg/d, with a maximum of 4 mg/kg/d recommended in the AAD guidelines (adult maximum 3 mg/kg/d). The AAD guidelines also suggest monitoring thiopurine methyltransferase levels in patients for prediction of response and toxicity.

2.4 Methotrexate

Methotrexate is not approved for the treatment of AD.

The treatment effect associated with MTX in refractory AD is unclear. One pediatric study reported a slower onset of effect compared with low-dose cyclosporine, but increased time before relapse on discontinuation¹⁵. Dosage and monitoring is shown in Table VIII from the guidelines¹³. Product labeling includes a boxed warning for bone marrow, liver, kidney and lung toxicities, fetal death and congenital anomalies, methotrexate-induced lung disease, hemorrhagic enteritis, lymphoma, severe skin reactions, and opportunistic infections.

¹⁵ El-Khalawany MA, Hassan H, Shaaban D, et al. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013;172:351-6.

AAD Guideline Recommendations for Dosing and Monitoring for CSA, Methotrexate and Azathioprine in the Treatment of AD¹³

Table VIII. Dosing and monitoring guidelines for the use of selected systemic agents

Drug	Dosing	Baseline monitoring	Follow-up monitoring	Miscellaneous
Cyclosporine	150-300 mg/d Pediatric: 3-6 mg/kg/d	Blood pressure $\times 2$ measurements Renal function Urinalysis with microscopic analysis Fasting lipid profile CBC/differential/platelets Liver function Mg+, K+, Uric acid TB testing HIV if indicated HCG if indicated	Blood pressure every visit Every 2 wk for 2-3 mo, then monthly: renal function, liver function, lipids, CBC/differential/platelets, Mg+, K+, uric acid If dose increased, check laboratory results 2-4 wk after HCG if indicated Annual TB testing	If Cr increases $> 25\%$ above baseline, reduce dose by 1 mg/kg/d for 2-4 wk and recheck; stop CSA if Cr remains $> 25\%$ above baseline; hold at lower dose if level is within 25% of baseline Whole-blood CSA trough level in children if inadequate clinical response or concomitant use of potentially interacting medications
Azathioprine	1-3 mg/kg/d Pediatric: 1-4 mg/kg/d	Baseline TPMT CBC/differential/platelets Renal function Liver function Hepatitis B and C TB testing HIV if indicated HCG if indicated	CBC/differential/platelets, liver function, renal function twice/mo $\times 2$ mo, monthly $\times 4$ mo, then every other month and with dose increases HCG if indicated Annual TB testing	Dosing may be guided by TPMT enzyme activity
Methotrexate	7.5-25 mg/wk Pediatric: 0.2-0.7 mg/kg/wk Consider test dose: 1.25-5 mg Check CBC in 5-6 d; if normal, increase dose gradually to desired therapeutic effect	CBC/differential/platelets Liver function Renal function Hepatitis B and C TB testing HIV if indicated HCG if indicated Pulmonary function tests if indicated	CBC/differential/platelets, liver function weekly for 2-4 wk and 1 wk after each major dose increase, then every 2 wk for 1 mo and every 2-3 mo while on stable doses Renal function every 6-12 mo Annual TB testing HCG as indicated	Liver enzymes transiently increase after MTX dosing; obtain laboratory results 5-7 d after the last dose Significant elevations of liver enzymes: - Exceeding $\times 2$ normal, check more frequently - Exceeding $\times 3$ normal, reduce the dose and recheck - Exceeding $\times 5$ normal, discontinue Avoid in patients at risk for hepatotoxicity Liver biopsy may be considered at 3.5-4.0 g of cumulative MTX in adults No standard liver biopsy recommendations for children Consider pulmonary function tests before initiation and during therapy in consultation with a pulmonologist for patients with asthma or chronic cough, or consider alternative therapies CXR if respiratory symptoms arise

2.5 Mycophenolate Mofetil (MMF)

MMF is not approved for the treatment of AD.

MMF is considered by the AAD guidelines as an alternative therapy for patients with AD. Reports of treatment effect among patients with refractory AD has been variable. Studies suggested that the initial response to MMF is delayed, with improvement as drug levels increase. Clinical remission lasted longer for patients treated with MMF relative to those treated with CSA upon medication discontinuation¹⁶. Dosing ranged from 0.5 to 3 g/d, but insufficient data exist to make recommendations regarding optimal dosing or duration of therapy. Product labeling includes a boxed warning about embryofetal toxicity, malignancies, lymphoma, and serious infections. Labeled warnings include lymphoma, skin and other malignancies, serious infection, reactivation of latent infection including progressive multifocal leukoencephalopathy (PML), severe neutropenia, and pure red cell aplasia.

¹⁶ Haeck IM, Knol MJ, Ten Berge O, et al. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011;64:1074-84.

Labeled adverse reactions include gastrointestinal bleeding leading to hospitalization; administration of live or attenuated vaccines is not recommended, and other vaccines may be less effective.

Per the AAD guidelines, MMF "...should be considered a relatively safe alternative systemic therapy for pediatric patients with refractory AD."¹³ There are reports about use in children with AD for up to 24 consecutive months¹⁷.

2.6 Phototherapy

The medical devices used for phototherapy are cleared under the 510(k) pathway and include AD in labeling.

The AAD guidelines¹³ note that numerous studies demonstrate the efficacy of phototherapy for AD. It is not possible to designate one or more forms of phototherapy as superior, given limited head-to-head trials and lack of comprehensive comparative studies. Most studies involve small sample sizes, and the dosing parameters vary widely. Adverse effects include actinic damage, erythema and tenderness, pruritus, nonmelanoma and melanoma skin cancer, lentigines, photosensitive eruptions, and herpes simplex virus reactivation. Cost and inconvenience are pragmatic concerns.

For pediatric patients, the AAD guidelines have this recommendation on phototherapy¹³:

Several studies document the safe and effective use of both UVA and UVB phototherapy in children and adolescents. Additional psychosocial factors must be anticipated and addressed to successfully treat younger patients, as lamps and machines can appear intimidating, and caregivers often have many questions and concerns. There are no known studies that report the long-term consequences of phototherapy use in children with AD. An increased risk of non-melanoma skin cancer has been reported in children receiving PUVA treatment for psoriasis. Centered on 311 to 313 nm, NB-UVB is safe and effective for a number of photoresponsive dermatoses in children and is often considered as a first-line agent because of its ease of administration and safety profile relative to PUVA. Thus, phototherapy as a treatment for children with AD unresponsive to multimodal topical measures is appropriate.

Psoralens used in PUVA are not labeled for use in children, as the safety in this population has not been established.

¹⁷ Heller M, Shin HT, Orlow SJ, et al. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007;157:127-32.

3. INVESTIGATIONAL SYSTEMIC PRODUCTS IN DEVELOPMENT FOR AD

Although there are systemic products under investigation for the treatment of AD, the published literature contains few adequate and well controlled studies in AD patients not responding adequately to topical therapy. Several such studies have been reported in the literature for dupilumab, a human monoclonal antibody intended to block drivers of type 2 helper T-cell (Th2)-mediated inflammation, interleukin-4 and interleukin-13. They have been described in one publication as discussed below:

In 2014, Beck et al reported randomized, double-blind, placebo-controlled trials of dupilumab administered subcutaneously once a week in adults with moderate-to-severe atopic dermatitis not responding adequately to topical glucocorticoids and calcineurin inhibitors¹⁸. There were two 4-week trials and one 12-week trial in which dupilumab was used as monotherapy, as well as in a 4-week study used in combination with topical glucocorticoids:

- Phase 1 Sequential Dose-Escalation: Studies M4A (U.S.) and M4B (Multinational)
- Phase 2 Dupilumab Monotherapy: Study M12 (Europe)
- Phase 2 Dupilumab Combination Therapy with Topical Corticosteroids: Study C4 (Europe)

In these studies, study subjects were 18 years of age or older, with moderate-to-severe atopic dermatitis, as defined by an investigator's global assessment score of 3 or more. Inclusion criteria included duration of AD for at least 3 years in the monotherapy studies and at least 2 years in the combination study.

Disease severity was assessed with commonly used indices for AD, including the Eczema Area and Severity Index¹⁹ (EASI, on which scores range from 0 to 72, based on clinical signs and body surface area of involvement), and the Scoring Atopic Dermatitis²⁰ (SCORAD) score (on a scale from 0 to 103, based with weighting on intensity of clinical signs, disease extent and subjective symptoms), percent body surface area involvement, a 6-point investigator global assessment scale (0 for clear to 5 for very severe), and an 11-point pruritus scale (0 for no itch to 10 for worst imaginable itch)²¹.

¹⁸ Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med*. 2014;371:130-9.

¹⁹ Hanifin JM, Thurston M, Omoto M, et al. The Eczema Area and Severity Index (EASI): assessment of reliability in atopic dermatitis. *Exp Dermatol* 2001;10:11-8.

²⁰ Kunz B, Oranje AP, Labrèze L, et al. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;195:10-9.

²¹ Phan NQ, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol*. 2012;92:502-7.

Other features of these studies are shown in the following Table²⁰:

Study	Baseline Disease Severity		Number of Subjects Randomized	Study Duration	Primary Objective
	BSA	Disease Scoring			
M4A	≥10	EASI≥12	P:d75:d150:d300=6:8:8:8	4 weeks	Safety
M4B	≥15	EASI≥12	P:d150:d300=10:14:13	4 weeks	Safety
M12	≥10	EASI≥16	P:d300=54:55*	12 weeks	Safety/Efficacy
C4	≥10	SCORAD≥20	P:d300=10:21	4 weeks	Safety

BSA=body surface area involvement, EASI= Eczema area and severity index, SCORAD= SCORing Atopic Dermatitis, P=placebo, d75= dupilumab 75 mg, d150= dupilumab 150 mg, d300= dupilumab 300 mg. *randomization in M12 stratified by serum IgE level (cutoff at 150 kU/L).

For the Phase 2 safety and efficacy study (M12), efficacy was evaluated at week 12 and for the combination therapy trial (C4), at day 29.

Reported Results of Dupilumab Clinical Trials²⁰

- In the 4-week monotherapy studies, M4A and M4B, treatment with dupilumab was reported to result in rapid and dose-dependent improvements in clinical indexes, and certain biomarker levels.
- In the 12-week study, M12, 85% of patients in the dupilumab group, as compared with 35% of those in the placebo group, were reported to have a 50% reduction in the EASI score (EASI-50) ($P<0.001$); 40% of patients in the dupilumab group, as compared with 7% in the placebo group, had a score of 0 to 1 (clearing or near-clearing of skin lesions) on the investigator's global assessment ($P<0.001$); and pruritus scores decreased by 55.7% in the dupilumab group versus 15.1% in the placebo group ($P<0.001$).

The treatment effect in the above three studies is summarized in the following figure²⁰.

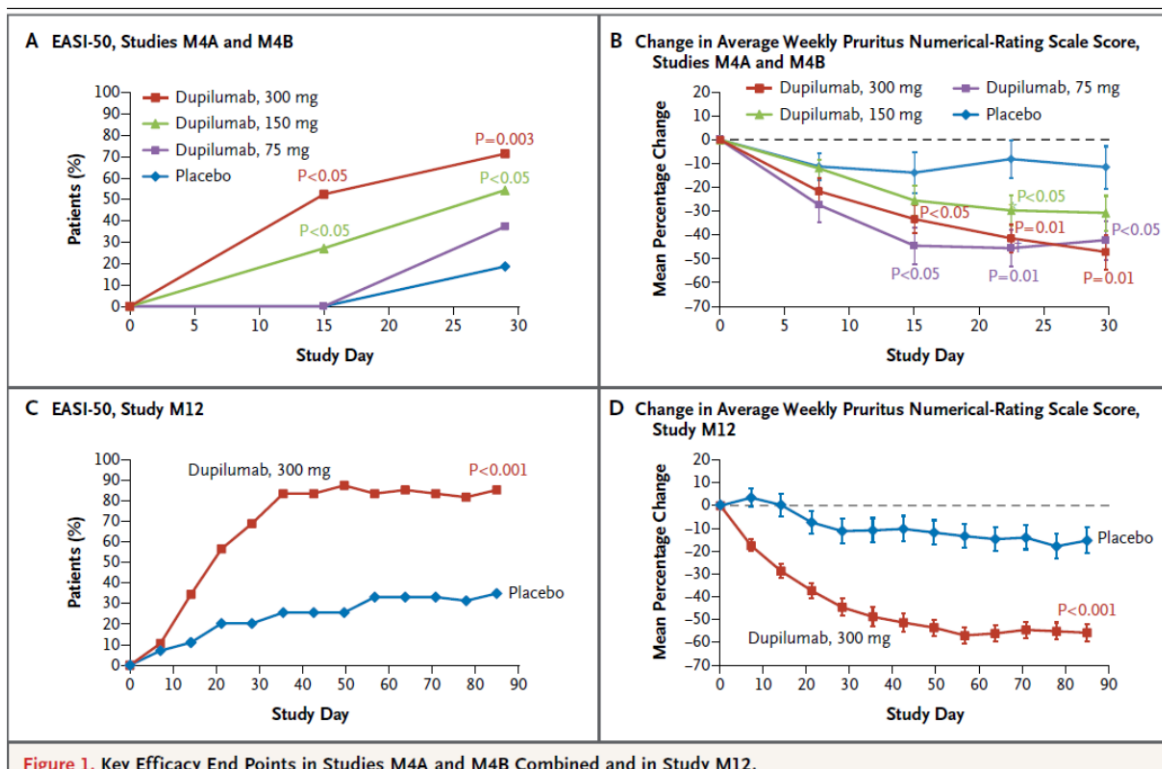


Figure 1. Key Efficacy End Points in Studies M4A and M4B Combined and in Study M12.

- In the 4-week combination study with topical corticosteroids (C4), 100% of the patients in the dupilumab group, as compared with 50% of those who received topical glucocorticoids with placebo injection, were reported to meet the criterion for 50% reduction in the EASI score (EASI-50) ($P=0.002$). Of note, patients who received dupilumab plus glucocorticoids used less than half the amount of topical glucocorticoids used by those who received placebo plus the topical medication ($P=0.16$)²⁰.

Reported adverse events, such as skin infection, occurred more frequently with placebo; nasopharyngitis and headache were the most frequent adverse events with dupilumab. Injection-site reactions were observed at a higher frequency in the dupilumab group in the 12-week monotherapy study than in any treatment group in the other studies. Clinically significant values for clinical laboratory tests, vital signs, and electrocardiographic assessments were balanced between treatment groups in each of the studies, and no trends were reported²⁰.

4. PEDIATRIC DRUG DEVELOPMENT

Current labeling for many drugs marketed in the United States lack information on dosing, safety and effectiveness in some or all pediatric age groups. Product labeling of many drugs in widespread use in the pediatric population include the disclaimer that safety and effectiveness in pediatric patients has not been established. The absence of adequate pediatric use information in labeling poses potentially significant risks for children. Drug clearance can be highly variable in

the pediatric population and is not readily predictable based on information from adults. In response to written requests for pediatric studies, pediatric doses inferred from adults have both over- and under-estimated the effective pediatric exposure.²² The absence of pediatric safety data may expose pediatric patients to inappropriate use and age-specific adverse reactions that were not predictable from the adult experience. The absence of adequate pediatric labeling may deny pediatric patients therapeutic advances because of insurance coverage issues or physicians choosing to prescribe alternate and less effective medications due to a paucity of use data in pediatric populations. Failure to develop an age-appropriate pediatric formulation of a drug may also deny pediatric patients access to important new therapies, or may result in pediatric patients taking extemporaneous formulations that may be poorly or inconsistently bioavailable.

For these reasons, FDA strongly encourages and in some circumstances has authority to require applicants to conduct clinical studies to appropriately label drugs and biological products²³ for use in relevant pediatric populations as discussed in the next section.

4.1 Pediatric Research Equity Act (PREA)

PREA requires that all applications (or supplements to an application)²⁴ submitted for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment²⁵ unless the assessment is either waived or deferred.²⁶ Although PREA is often regarded as applying to drugs intended for use in adults, PREA also applies to drugs developed for use in pediatric populations. A requirement for pediatric clinical studies was first established as the Pediatric Rule²⁷ in 1998 and later codified under the Pediatric Research Equity Act (PREA) in 2003.²⁸ PREA was substantially revised in 2007 under the Food and Drug Administration Amendments Act (FDAAA) as FDA and industry gained experience in the implementation of the laws and in pediatric drug development in general. In 2012, the Food and Drug Administration Safety and Innovation

²² Rodriguez W, Selen A, Avant D, Chaurasia C, Crescenzi T, Gieser G, Di Giacinto J, Huang SM, Lee P, Mathis L, Murphy D, Murphy S, Roberts R, Sachs HC, Suarez S, Tandon V, Uppoor RS. Improving pediatric dosing through pediatric initiatives: what we have learned. *Pediatrics*. 2008 Mar;121(3):530-9.

²³ References to *drugs* and *drug and biological products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological drug products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262).

²⁴ Section 505B(a)(1) of the FD&C Act.

²⁵ See section 505B(a)(2) of the FD&C Act.

²⁶ Section 505B(a)(3) and (4) of the FD&C Act.

²⁷ The Pediatric Rule was codified at 21 CFR 314.55 and 601.27, with additional amendments to 21 CFR parts 201, 312, 314, and 601. Under the Pediatric Rule, approval actions taken or applications approved on or after April 1, 1999, for changes in active ingredient, indication, dosage form, dosing regimen, or route of administration were required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred. On October 17, 2002, the U.S. District Court for the District of Columbia held that FDA had exceeded its statutory authority when issuing the Pediatric Rule and the court suspended its implementation and enjoined its enforcement (*Association of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204 (D. D.C. 2002)).

²⁸ Section 505B of the FD&C Act (21 U.S.C. 355c).

Act (FDASIA) permanently reauthorized PREA, which was amended to require sponsors to submit initial pediatric study plans earlier in development.²⁹

Under PREA, a pediatric assessment must contain sufficient data to assess the safety and effectiveness of the drug for the claimed indication in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective³⁰. The appropriate pediatric age ranges to be studied may vary, depending on the pharmacology of the drug, the incidence and the manifestations of the disease in various age groups, and the ability to measure the response to therapy. If FDA determines that the course of the disease and the effect of the drug are sufficiently similar in adults and pediatric patients, pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults.³¹

Full or Partial Waiver of Requirement for a Pediatric Assessment

In certain circumstances it may not be appropriate to conduct pediatric studies in some or all pediatric age groups. PREA authorizes FDA to waive the requirement to submit pediatric assessments for some or all pediatric age groups if the applicant provides a written justification, with supporting evidence, and FDA determines that at least one of the following criteria apply:

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small, or the patients are geographically dispersed, or the disease does not occur).
- There is evidence strongly suggesting that the drug would be ineffective or unsafe in some or all pediatric age groups. In this case, labeling must reflect the safety concern and/or lack of efficacy in the relevant pediatric population.
- The drug (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, *and* (2) is not likely to be used in a substantial number of pediatric patients.

In addition to the above criteria, a waiver for certain pediatric subpopulations may also be granted if an applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed.³²

²⁹ See draft *Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* available on the internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

³⁰ Section 505B(a)(2)(A) of the FD&C Act.

³¹ Section 505B(a)(2)(B).

³² If a waiver is granted on the grounds that it is not possible to develop a pediatric formulation, the sponsor is required to submit documentation detailing why a pediatric formulation cannot be developed. This information is made publicly available by the FDA. See Section 505B(a)(4)(C) of the FD&C Act.

Deferral of Requirement for a Pediatric Assessment

FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug. A deferral acknowledges that a pediatric assessment is required, but permits the applicant to submit the pediatric assessment after the approval of an NDA, a BLA, or a supplemental NDA or BLA. To request a deferral, an applicant must provide a justification for deferring the assessment, a plan for the deferred pediatric studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time and a timeline for completion of such studies.

FDA may defer some or all required pediatric studies if the Agency finds one or more of the following:

- The drug is ready for approval for use in adults before pediatric studies are complete.³³
- Pediatric studies should be delayed until additional safety or effectiveness data have been collected.³⁴
- There is another appropriate reason for deferral³⁵ (e.g., discussion of appropriate study designs or clinical endpoints for pediatric studies are ongoing with FDA).

Plans for waivers and/or deferrals of pediatric studies should be discussed at key meetings between the review division and the sponsor (e.g., at the End-of-Phase 2 or before the initiation of any adult Phase 3 studies). These plans must be included in an initial pediatric study plan (iPSP) and an iPSP must be submitted to FDA within 60 days of an End-of-Phase 2 meeting.³⁶

The intent of the pediatric study plan, as required under PREA, is to identify needed pediatric studies early in drug development and begin planning for these studies. As stated above, an initial pediatric study plan must be submitted within 60 days of an End-of-Phase 2 meeting. However, sponsors are strongly encouraged to seek advice or submit pediatric study plans to FDA earlier in development, when appropriate. Earlier consultation may be particularly helpful in situations in which endpoints for pediatric trials are not clearly established or when general concordance between multiple regulatory agencies is desirable. Sponsors may also consider early consultation with FDA when further guidance is required to assess when pediatric investigations are ethically or scientifically appropriate.

In general, sponsors are encouraged to carefully consider the condition(s) to be investigated, the drug under study, and the population(s) of children for whom such a drug would represent a meaningful therapeutic option before initiating a pediatric development program.

³³ Section 505B(a)(3)(A)(i)(I) of the FD&C Act.

³⁴ Section 505B(a)(3)(A)(i)(II) of the FD&C Act.

³⁵ Section 505B(a)(3)(A)(i)(III) of the FD&C Act.

³⁶ See draft *Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* available on the internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

The information needed to approve a drug for pediatric use includes nonclinical studies, and clinical dosing, safety, and effectiveness information³⁷. As noted earlier, in some cases, pediatric efficacy information can be partially or fully extrapolated from studies in adults or other pediatric populations. Finally, existing data from humans or animal models may be used to support both the safety and proof-of-concept regarding potential benefit of the drug sufficiently to initiate pediatric studies.

4.2 Necessary Data in Support of Approval of Drugs in Pediatrics

Nonclinical Information

Nonclinical data to support the initiation of clinical studies in different pediatric age groups may be needed in addition to traditional toxicology studies and/or data from adult clinical development programs. In certain cases, data from clinical studies in adults, supported by nonclinical studies in adult animals, have been used to support the initiation of studies in pediatric patients. However, these types of studies may not always assess possible drug effects on developmental processes that occur at specific ages in pediatric patients. Developmental processes in pediatric patients may also differentially affect drug pharmacokinetics and pharmacodynamics, compared to these parameters in adult therapeutic use. Juvenile animal studies may assist in identifying postnatal developmental toxicities that are not adequately assessed in reproductive toxicity testing, and that may not be adequately and safely evaluated in pediatric clinical trials. If human safety data and previous animal studies are insufficient to determine the likely safety profile of the drug in the intended pediatric age group, or if the mechanism of a drug's action or its pharmacokinetic profile suggests that it may impact growth or developmental processes, juvenile animal studies may be necessary to address these developmental concerns.³⁸

Clinical Pharmacology

Rigorous early phase dosing studies are critical to a successful pediatric development program. Inadequate dosing studies in the past have contributed to failed efficacy studies and an inability to expand marketing approval to include pediatric age groups. Modeling and simulation, when appropriate, should be used to inform dose selection and/or trial design. Confirmatory pharmacokinetic (PK) studies remain critical, particularly in younger children, in whom dosing is not necessarily predictable based on the experience in adults or adolescents. General guidance on the clinical pharmacology information (e.g., exposure-response, pharmacokinetics, and pharmacodynamics) that supports effectiveness and safety

³⁷ For purposes of section 505A of the FD&C Act, the term *pediatric studies* or *studies* is defined as at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of the Secretary, may include preclinical studies (21 U.S.C. 355a(a); for example, see 21 CFR 50.3(c) for the definition of clinical investigation)

³⁸ Additional information can be found in *Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products* available on the internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

and helps select appropriate doses in the pediatric population is provided in other guidance.³⁹ Depending on the approach, PK and/or pharmacodynamic (PD) studies may be needed when extrapolating efficacy from adult to pediatric patients, between different pediatric age groups, or between formulations and to establish dosing recommendations.

Safety Information

Safety information from adult human studies and animal models may provide preliminary information regarding the expected safety profile of a product in pediatric populations, but safety information from administration of the product to children is nearly always required. In a substantial proportion of cases, adverse effects of a drug or biological product in pediatric populations are not predictable based on the adult experience, particularly related to behavior, cognition, or growth. However, there may be circumstances in which pediatric safety information that is available from different formulations of a product, or from other closely related products within the same class, as appropriate, may be used to provide support for a new application. In addition, because some effects may be measureable only in children of a certain age or maturity level, long-term follow-up studies, particularly for products tested in infants or young children, may be necessary to assess the effects of the drug.

Extrapolation

One approach to simplify pediatric product development is the use of extrapolation, when appropriate. In certain cases, if the course of the disease and the effects of the drug are sufficiently similar in adult and pediatric patients FDA may conclude that pediatric effectiveness may be extrapolated from adequate and well-controlled studies in adults.⁴⁰ Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, similar exposure-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Similarly, effectiveness data from one pediatric age group may be extrapolated to another pediatric age group.⁴¹ For examples of the use of extrapolation, FDA has published a review of 370 pediatric studies submitted between 1998 and 2008 in response to 159 Written Requests.⁴²

The need for pediatric studies can be assessed by asking a series of questions about the similarity of the adult and pediatric disease, response to intervention, drug exposure-response, and pharmacokinetic and pharmacodynamic measurements that could be used to predict efficacy. Full extrapolation refers to situations in which no confirmatory evidence of effectiveness from pediatric studies is required. Partial extrapolation refers to situations in

³⁹ Additional information can be found in *Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biologic Products* available on the internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

⁴⁰ Section 505B(a)(2)(B)(i) and (ii) of the FD&C Act.

⁴¹ PREA further provides, "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group" (section 505B(a)(2)(B)(ii) of the FD&C Act).

⁴² Dunne J, WJ Rodriguez, MD Murphy, et al., *Pediatrics* 2011;128:e1242-e1249.

which pediatric clinical data are required to support extrapolation of effectiveness, and may range from a corroborative change in an appropriate biomarker, pharmacodynamic or clinical endpoint to a single adequate and well-controlled trial absent other supporting data. If extrapolation from adult effectiveness data is not supported by existing data, or PK and/or PD measures to determine pediatric exposure and dosing are not available; adequate and well-controlled trials to establish effectiveness in the pediatric population would likely be required (i.e., no extrapolation). Additionally, a study may not be needed in each pediatric age group if data from one pediatric age group can be extrapolated to other pediatric age groups. Thus, the extent of effectiveness data required to support substantial evidence of a product in any or all pediatric populations will depend, in part, on the ability to extrapolate from adult or other pediatric populations.

Historically, DDDP has extrapolated efficacy for the treatment of atopic dermatitis between adult and pediatric populations. For example, pimecrolimus cream was approved for the treatment of mild to moderate atopic dermatitis in adult and pediatric populations based on pivotal trials conducted in pediatric subjects. Some topical corticosteroid products have obtained extension of their initial approved indication to younger age groups based on extrapolation of efficacy from older children and adults and safety studies in the younger age groups. All of the topical products approved for the treatment of atopic dermatitis have had some pediatric labeling at the time of initial approval.

Although effectiveness may be extrapolated in certain cases, dosing and safety information may not be extrapolated. Therefore, studies are typically needed to determine the appropriate dose and provide an assessment of the safe use of the product in the pediatric population. Safety information gathered for the product from clinical studies in pediatric patients for one indication may be used to support the safety of the product for another indication or the same indication if there is a similar or lower dose/exposure of the product, and the patient populations are not significantly different as to affect the response to the product,. The appropriateness of such an inference of safety would be evaluated by FDA on a case-by-case basis.

4.3 Timing of Pediatric Studies in Support of Pediatric Approval

From a scientific and ethical perspective, the timing of when to initiate pediatric trials is grounded in the Additional Safeguards for Children in Clinical Investigations (21 CFR 50 subpart D). FDA-regulated clinical trials that enroll children as subjects may be initiated when sufficient data from animal models and/or adult human subjects are available to support either 1) an acceptably low risk of the experimental intervention or procedure absent any prospect of direct benefit (21 CFR 50.53)⁴³ or 2) a sufficient prospect of direct benefit to justify the risks (21 CFR 50.52).

⁴³ Although approval of low risk studies not offering a prospect of direct benefit may also be considered under 21 CFR 50.51 (minimal risk), FDA generally views the administration of an FDA-regulated drug or biological product as presenting more than minimal risk.

Studies involving the administration of novel systemic products are most often considered under the latter pathway (21 CFR 50.52). Stated more fully, clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects (21 CFR 50.52 may proceed if the risk is justified by the anticipated benefit to the subjects, and that the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches. For example, an investigational product may hold out a prospect of direct clinical benefit to children with a particular disorder if preliminary proof-of-concept or efficacy data are available in adults with the same disorder to substantiate that the product may have a favorable treatment effect in children. The risks and benefits of the investigational product are also explicitly compared to the risks and benefits of other therapeutic options for the selected pediatric population.

Apart from issues regarding assent and permission, the explicit requirements regarding risks and benefits specified in the Additional Safeguards for Children do not vary based on the age of the child. However, in some situations, the safety or effectiveness of products may be expected to be substantially different in children of different age groups. Some differences may be significant enough to delay or altogether prohibit studies in specific pediatric subpopulations. Practical considerations may also mandate the sequential conduct of studies in progressively younger age groups, such as when dosing information from older pediatric populations is necessary to inform PK or PK/PD studies in younger age groups, or when additional time is required to develop endpoints for certain pediatric subpopulations.

If substantial data on the safety and potential benefit of a product already exist (e.g. from a previously approved indication, or a different formulation), pediatric studies may be conducted concurrently with the adult development program. For many novel products with little previous human exposure, the dose-finding stage of pediatric development (i.e., Phase 1) might begin after the adult Phase 2 studies have established evidence of a sufficient prospect of direct benefit to justify exposing children to the risks of the product. Dosing, safety and efficacy studies then may be performed in children concurrently with the efficacy trial in adults. If the efficacy of the drug may be extrapolated to some or all pediatric subgroups, sufficient pediatric data may be available at the conclusion of the Phase 3 adult studies to support approval for both the adult and pediatric populations concurrently.

Pediatric studies of drugs for life-threatening diseases for which approved treatment is not available should also be considered earlier in development than might occur for less serious diseases.⁴⁴ For example, pediatric studies of some oncology products have begun as early as adult Phase 1 or Phase 2 studies, after initial safety data in adults were available. Initiation of pediatric studies under 21 CFR 50.52 still requires that the prospect of direct benefit to the enrolled children would be sufficient to justify exposure to the risks of the experimental product. Absent substantial adult human data, the nonclinical evidence of benefit and risk from an appropriate *in vitro* and/or animal model is particularly important. When evaluating the strength of nonclinical evidence, data on structural changes are considered weaker than

⁴⁴ Additional information can be found in *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics* available on the internet at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

appropriate functional changes based on the mechanism of action (e.g., molecular targets, biomarkers, physiologic pathways), which in turn is considered weaker than evidence from a clinical disease animal model (using either surrogate or clinical endpoints). FDA encourages sponsors to discuss the pediatric plan for the development of such products as early as possible (e.g., pre-IND and/or End-of-Phase 1 meetings).

The Agency recognizes that in certain cases, scientific and ethical considerations will dictate that pediatric studies should not begin until after adequate safety and efficacy data are available in adults. This approach may be considered, for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit of the novel product is likely to be low, or the risks of exposing pediatric patients to the new product are not considered justified absent additional safety information in adults. However, if substantial pediatric use may be anticipated once the drug is approved in adults, early initiation of pediatric studies may be necessary. It may be falsely reassuring to delay the initiation of pediatric trials if substantial pediatric off-label use exposes children to the risks of a product in an uncontrolled setting, and absent the possibility of collecting systematic safety or effectiveness information to inform future pediatric use.