Integrated Exposure-Response Analyses of Dupilumab in Pediatric, Adolescent, and Adult Patients with Atopic Dermatitis

by

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Dedication

To my dear family and friends, but mostly to Watson

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Abstract

Atopic dermatitis is a chronic skin disease characterized by inflammation and pruritis, which affects 20 percent of children and 10 percent of adults globally. Atopic dermatitis' complex pathology includes epithelial-barrier defects, increased T_H2 immune activity, and microbiome dysbiosis. The most prominent assessments for measuring disease severity are the Eczema Area and Severity Index (EASI) and the Investigator Global Assessment (IGA), a continuous bounded outcome score assessment and a five-point ordered categorical assessment, respectively.

Dupilumab, trade name Dupixent® (Regeneron Pharmaceuticals), is a fully human monoclonal antibody that is an interleukin-4 receptor alpha antagonist, blocking interleukin-4 and interleukin-13 signaling. Dupilumab has been shown to significantly reduce measures of disease severity in moderate-to-severe atopic dermatitis after subcutaneous injections.

The objective of this work was to develop an integrated population exposure-response model, using pooled data from six clinical trials to predict the efficacy of dupilumab in adults, adolescents, and children after adjusting for confounding factors.

Indirect response models were applied to link measures of efficacy and functional dupilumab concentrations, which characterize temporal delays in drug effect. A latent variable methodology was used to apply the indirect response model for the categorical efficacy measure IGA. Final parameters in both models were well-estimated, with relative standard errors < 4% for structural parameters and < 30% for covariate effects. Numerical and graphical diagnostics were

assessed at every step of the model development process. Simulation diagnostics utilized visual predictive checks (VPCs) on the final models and demonstrated the model predictability.

Based on half-life estimates of drug onset (2.0 weeks for EASI; 2.8 weeks for IGA), the full effect of dupilumab would be reached after approximately 2 months for EASI and 3 months for IGA (~ 4-5 half-lives). Drug concentrations achieving half the maximum effect (IC_{50}) were estimated as 20.3 and 27.1 mg/L for the EASI and IGA analyses, respectively. Each model had a placebo component indicating some improvement in response measures with time for patients receiving sham SC injections.

Several patient factors were assessed as potential sources of variability in efficacy response. In simulations evaluating each potential covariate in isolation, subjects with body weights ≤ 40 kg demonstrated a larger dupilumab effect relative to reference subjects with body weight of 70 kg. Higher baseline TARC was associated with higher baseline EASI score, leading to a larger predicted dupilumab EASI change from baseline in patients with higher baseline TARC.

Modeling and simulation provided an integrated assessment of dupilumab exposure-response across relevant clinical conditions and patient age groups, facilitating a comprehensive assessment of relative efficacy between adults, adolescents, and young children. For all efficacy predictions at Week 16 (EASI-75, EASI-90, IGA-0/1 and percent change from baseline in EASI score), on average, dupilumab performed better in young children than in adults and adolescents when given FDA-approved dupilumab dose regimens for moderate to severe atopic dermatitis by weight and age.

The predictive models developed in this dissertation provide conclusive evidence that may justify full extrapolation (i.e., pharmacokinetic bridging) to pediatric patients for other type 2 inflammatory diseases in scenarios in which conducting prospective, randomized, controlled trials

may not be feasible. The full extrapolation method would provide direct ethical benefits to pediatric populations, such that young children would not need to be unnecessarily enrolled in clinical trials, as the exposure-response relationship of dupilumab in type 2 inflammatory diseases has already been characterized.

Chapter 1 – Research Objectives

Atopic dermatitis, also known as eczema, is a chronic skin disease characterized by inflammation and pruritis that affects approximately 20 percent of children and 10 percent of adults in high-income countries [1]. The pathophysiology of atopic dermatitis involves the combination of genetic factors (i.e., mutations in filaggrin), epithelial-barrier defects, skin microbiome abnormalities and increased type 2 immune responses [2-4]. Typically, in patients with atopic dermatitis, allergen infiltration through the epidermal barrier activates an immune response in which T-helper 2 (T_H2) cells release cytokines, interleukin-4 (IL-4) and interleukin-13 (IL-13) into the skin that increases inflammation and pruritis [5]. Disease severity is measured using multiple subjective scales. Some of the most prominent assessments are the Eczema Area and Severity Index (EASI) and the Investigator Global Assessment (IGA) – a continuous bounded outcome score assessment and a five-point ordered categorical assessment, respectively [6, 7].

Dupilumab, a first-in-class fully human monoclonal antibody, is an IL-4 receptor alpha antagonist that blocks IL-4 and IL-13 signaling [8]. Currently, dupilumab is approved in the United States to treat a wide range of type 2 inflammatory diseases such as, moderate-to-severe atopic dermatitis, moderate-to-severe asthma, patients with inadequately controlled chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis [9]. Dupilumab (Dupixent®, Regeneron Pharmaceuticals) is administered via subcutaneous injection following a dose regimen of 300 mg every other week (Q2W) for adults and weight-tiered dosing (e.g., 200 mg Q4W [5 - < 15 kg], 300 mg Q4W [15 - <30 kg], 200 mg Q2W [30 - <60 kg], and 300 mg Q2W [60+ kg]) for pediatric

patients 6 months and older with moderate-to-severe atopic dermatitis after receiving an initial loading dose of twice the maintenance dose [9].

Onset of atopic dermatitis is typically seen during childhood, as early as six months, extending into adulthood; however, late-onset or adult-onset atopic dermatitis has been described in the literature as a prevalent population [10]. The heterogeneity of disease onset and duration, suggests, as described by the FDA guidance for industry, that a full pediatric development program in addition to the typical adult new drug application pathway be completed in order to evaluate the efficacy and safety across a wide range of age groups [11]. Sanofi and Regeneron Pharmaceuticals went through the rigorous process of conducting clinical trials in adults, adolescents, children 6 to 11 years, and children 6 months to 5 years in a stepwise manner [9].

Although dupilumab was studied across age groups, a direct comparison of observed efficacy between adults, adolescents, and children was not possible due to confounding factors such as study design differences. Phase III clinical trials in adults included dupilumab administered as monotherapy or in combination with topical corticosteroids (TCS) in both moderate and severe patients with atopic dermatitis [12, 13]. The Phase III adolescent study, on the other hand, administered dupilumab as monotherapy only in both moderate and severe patients with atopic dermatitis [14]. Additionally, the data Phase III study conducted in children (6 years and up) administered dupilumab as a combination therapy with TCS and was only conducted in only severe atopic dermatitis patients [15]. In addition to the study design differences across age groups, a varied placebo response from study-to-study made placebo-corrected comparisons difficult to interpret.

The efficacy of dupilumab is being investigated in pediatric patients with other type 2 inflammatory diseases including, but not limited to, eosinophilic esophagitis and asthma. A

comprehensive understanding of the exposure-response (E-R) relationship across age groups would not only provide a greater understanding of atopic dermatitis across age groups, but could also be used to justify full extrapolation (i.e., pharmacokinetic bridging) to pediatric patients in scenarios where conducting prospective, randomized, controlled trials may not be feasible [11].

One strategy to directly compare the exposure-response relationship between adults, adolescents, and children would be to perform an integrated analysis using a non-linear mixed effects methodology. We hypothesize that children with moderate-to-severe atopic dermatitis, will perform similarly in both IGA and EASI assessments to adolescents and adults in similar clinical scenarios (i.e., under concomitant medication and baseline disease severity).

To address our hypothesis, the following specific aims are proposed:

1) To develop a population exposure-response model to quantitatively determine the ability of subcutaneously administered dupilumab to improve atopic dermatitis as determined by an Eczema Area and Severity Index (EASI) in adult, adolescent, and pediatric populations.
2) To develop a population exposure-response model to quantitatively determine the ability of subcutaneously administered dupilumab to improve atopic dermatitis as determined by an Investigator Global Assessment (IGA) in adult, adolescent, and pediatric populations.
3) To evaluate both clinical efficacy endpoints, (i.e., EASI and IGA), in adults, adolescents, and children via exposure-response simulations under equivalent trial conditions

References

[1] Laughter, M.R., et al., *The Global Burden of Atopic Dermatitis: Lessons from the Global Burden of Disease Study 1990–2017**. British Journal of Dermatology, 2021. **184**(2): p. 304-309.

[2] Langan, S.M., A.D. Irvine, and S. Weidinger, *Atopic Dermatitis.* The Lancet, 2020. **396**(10247): p. 345-360.

[3] Bieber, T., *Atopic Dermatitis.* New England Journal of Medicine, 2008. **358**(14): p. 1483-1494.

[4] Nowicka, D. and E. Grywalska, *The Role of Immune Defects and Colonization of Staphylococcus Aureus in the Pathogenesis of Atopic Dermatitis.* Anal Cell Pathol (Amst), 2018. **2018**: p. 1956403.

[5] Ständer, S., *Atopic Dermatitis.* New England Journal of Medicine, 2021. **384**(12): p. 1136-1143.

[6] Hanifin J.M., T.M., Omoto M., Cherill R., Tofte S.J., Graeber M., EASI Evaluator Group, *The Eczema Area and Severity Index (Easi): Assessment of Reliability in Atopic Dermatitis.* Experimental Dermatology, 2001. **10**(1): p. 11-18.

[7] Simpson, E., et al., *The Validated Investigator Global Assessment for Atopic Dermatitis (Viga-Ad): The Development and Reliability Testing of a Novel Clinical Outcome Measurement Instrument for the Severity of Atopic Dermatitis.* Journal of the American Academy of Dermatology, 2020. **83**(3): p. 839-846.

[8] Gooderham, M.J., et al., *Dupilumab: A Review of Its Use in the Treatment of Atopic Dermatitis.* Journal of the American Academy of Dermatology, 2018. **78**(3, Supplement 1): p. S28-S36.

[9] *Dupixent (Dupilumab). Highlights of Prescribing Information.*, FDA, Editor. 2021: USA.

[10] Bannister, M.J. and S. Freeman, *Adult-Onset Atopic Dermatitis.* Australasian Journal of Dermatology, 2000. **41**(4): p. 225-228.

[11] *Fda Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.*, FDA, Editor. 2014.

[12] Thaçi, D., et al., *Efficacy and Safety of Dupilumab Monotherapy in Adults with Moderate-to-Severe Atopic Dermatitis: A Pooled Analysis of Two Phase 3 Randomized Trials (Liberty Ad Solo 1 and Liberty Ad Solo 2).* Journal of Dermatological Science, 2019. **94**(2): p. 266-275.

[13] Thaçi, D., et al., *Efficacy and Safety of Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis Inadequately Controlled by Topical Treatments: A Randomised, Placebo-Controlled, Dose-Ranging Phase 2b Trial.* Lancet, 2016. **387**(10013): p. 40-52.

[14] Simpson, E.L., et al., *Efficacy and Safety of Dupilumab in Adolescents with Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial.* JAMA Dermatology, 2020. **156**(1): p. 44-56.

[15] Paller, A.S., et al., *Efficacy and Safety of Dupilumab with Concomitant Topical Corticosteroids in Children 6 to 11 years Old with Severe Atopic Dermatitis: A Randomized, Double-Blinded, Placebo-Controlled Phase 3 Trial.* Journal of the American Academy of Dermatology, 2020. **83**(5): p. 1282-1293.

Chapter 2 – Background and Literature Review

2.1 Atopic Dermatitis

The term “atopic disorders” was originally introduced into the literature by Coca and Cooke with the term *atopy*, derived from the Greek word atopia (a-without, topos-place), to describe hay fever and asthma as strange diseases, later adding atopic dermatitis to the group [1, 2]. These “strange diseases” would later be described as genetically mediated allergic diseases that are characterized by an overexpression of immunoglobulin E (IgE) to protect against allergens which are generally harmless and lead to hypersensitive reactions [3].

2.1.1 Epidemiology

Approximately 230 million people, 20 percent of children and 10 percent of adults, have symptoms of atopic dermatitis [4]. The Global Burden of Disease Study is conducted annually to summarize the disease burden in terms of disability-adjusted life-years (DALY). Atopic dermatitis is ranked 15^{th} in global DALY rate and was the highest-ranking skin disease [5]. The bimodal distribution of atopic dermatitis by age showed that patients develop symptoms in early childhood or later into adulthood, with the majority of cases developing in children [5, 6]. The heterogeneity of atopic dermatitis is seen not only in disease onset and disease duration, but also differences in pathophysiology between ethnicities. All ethnic groups display strong T-helper (T_H) 2 activation; however, Asian patients have been shown to have stronger T_H17/T_H22 activation than black and Caucasian patients [7].

2.1.2 Pathophysiology

The pathophysiology of atopic dermatitis is complex and depends on a multitude of factors, including, genetic factors, immune dysregulation, and skin microbiome imbalances [8].

2.1.2.1 Genetic Factors

Genetics have been known to play an important role in the development of atopic dermatitis. The odds of having atopic dermatitis are approximately three times higher if both parents have atopic dermatitis compared to neither parent [9]. Filaggrin is a protein encoded by the FLG gene that is involved in the formation and maintenance of the skin barrier and plays a key role in atopic dermatitis [10]. Mutations in the FLG gene are distinct between European and Asian populations [10]. Should a filaggrin deficit occur, the skin surface would have a more basic pH, leading to the proliferation of staphylococci (microbiome imbalance –*Section 2.1.2.2*), and the corneal layer would have lower concentrations of natural moisturizing factors and an abnormal extracellular lipid matrix, leading to increased exposure to allergens (immune response – *Section 2.1.2.3*) [11]. Mutations in the FLG gene are important genetic risk factors for atopic dermatitis, although not all patients with atopic dermatitis have FLG mutations [10, 12].

2.1.2.2 Skin Microbiome

Healthy skin contains a symbiotic microbiome with bacteria, viruses, and fungi. After performing sequencing surveys in healthy adults to minimize bias from cultures, it was found that fungi and viruses were present, but bacteria was definitely dominant, with *Propionibacterium* species found in sebaceous sites near hair follicles and *Staphylococcus* and *Corynebacterium* species found in moist areas [13]. In patients with atopic dermatitis, there is usually an imbalance in the skin microbiome, with a large presence of *Staphylococcus aureus* (*S. aureus*) bound to atopic skin induced by Interleukin(IL)-4 [14]. Seen in more than 90% of patients with atopic dermatitis.

S. aureus has been shown to exaggerate skin disorders because it is able to infiltrate the skin barrier and further trigger immune responses [13, 15].

2.1.2.3 Immune Dysregulation

The skin is the largest organ of the body, and plays a critical role as the barrier between internal organs and the outside world. The skin, as described in *Section 2.1.2.2*, has a microbiome that can become imbalanced or be infiltrated by allergens and activate an immune response. Langerhans cells (LC) are spread throughout the epidermis and interact with foreign particles on the skin and determine the appropriate immune response [16].

T_H1 mediated immune response is present in psoriasis, another inflammatory skin disease. Atopic dermatitis, meanwhile, involves a complex pathology that is driven mainly by a T_H2 immune response [17]. Activated T_H2 cells produce cytokines – IL-4, IL-5, and IL-13 – that instruct B cells to produce IgE and increase the number of eosinophils, and eventually exacerbate symptoms of itchiness and inflammation [12, 18-20]. Additionally, the disruption of the epidermal barrier increases thymus and activation-regulated chemokine (TARC) through keratinocytes, and has been suggested as a biomarker of atopic dermatitis [12, 21]. In addition to TARC as a biomarker of disease severity, blood eosinophil levels have been shown to correlate with atopic dermatitis disease severity [22]. A detailed mechanism of action illustrated by Weidinger *et al* is show in Figure 2.1.

2.1.3 Clinical Characteristics

Generally, atopic dermatitis, more commonly known as eczema, is characterized by dry, leathery, itchy skin lesions that can develop on different areas of the body. Atopic dermatitis presents differently depending on age, race and disease severity [23].

Babies with atopic dermatitis can exhibit yellowish crust on their scalp, and the accompanying itching sensations can make the baby restless and lose sleep, but will heal in about 20-30% of cases by two years of age [24]. Areas including face, neck, trunk, groin and limbs are typically shows symptoms of atopic dermatitis in children [8]. IgE-mediated sensitization is not evident in about half of cases in babies with atopic dermatitis [24]. During childhood, symptoms can present for the first time or as continuous symptoms from infancy, with redness and dry skin on areas of the body that have a fold or curve, i.e., neck, the top of the feet and hands. Again, children tend to grow out of atopic dermatitis, happening in approximately 60% of cases [24]. Adults with atopic dermatitis have lesions on hands and feet at a higher rate than children [25]. Regardless of age, pruritis is a common symptom that usually worsens at night and impacts quality of sleep.

Presentation of symptoms were not only age-dependent, but also found to have regional differences. For example, in a systematic review and meta-analysis, flexural involvement was less commonly reported in the Americas and Iran. In East Asia, symptoms reflected more emotional and environmental factors, such as increased pruritis after sweating. African studies reported more dry skin (xerosis) and orbital darkening. The authors were not able to determine whether regional differences in environment also impacted differences in presentation of symptoms; however, heterogeneity of symptoms was clearly present across regions [25].

2.1.4 Measures of Disease Severity

2.1.4.1 Eczema Area and Severity Index

The eczema area and severity index (EASI) is a validated method used to assess the severity of atopic dermatitis. In determining a patient's EASI score, an expert must first provide a sub score in four body areas. These areas include the head and neck, upper extremities, trunk, and lower extremities.

An area score is determined for each region, and describes the percentage of skin affected by eczema. The area score is a value between 0-6 such that 0 = 0%, 1 = 1-9%, 2 = 10-29%, 3 = 30- 49%, 4=50-69%, 5=70-89% and 6=90-100% [26]. A severity score is based on the sum of four symptoms – erythema (E), induration/papulation (I), excoriation (X), and lichenification (L). Each symptom is assigned a score between 0-3, which indicated the average intensity of each symptom (0 = none, 1 = mild, 2 = moderate, 3 = severe) [26]. Half scores are allowed for the severity score.

For each of the four regions the EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI with sections weighted for ages ≥ 8 years: 10% = head and neck, 20% = upper extremities, 30% = trunk, and 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72, where a higher score indicates increased extent and severity of atopic dermatitis [26]

The formula is as follows:

$$EASI = \sum_{i \in B} (E_i + I_i + X_i + L_i) \cdot A_i w_i$$

The sum is taken over the set of body regions (B = [head and neck, upper extremities, trunk, lower extremities]) with corresponding set of weights of W = (w_h, w_u, w_t, w_l) = (0.1, 0.2, 0.3, 0.4) for ages ≥ 8 years and W = (w_h, w_u, w_t, w_l) = (0.2, 0.2, 0.3, 0.3) for ages <8 years [27]. A diagram on the method to calculate an EASI score is show in Figure 2.2.

In a systematic review, EASI score was one of three methods of disease severity assessments that were found to perform adequately and were recommended for clinical trial use [28]. EASI score is a co-primary aim required by the European Medicines Agency (EMA) [29].

2.1.4.2 Investigator's Global Assessment

The investigator's global assessment (IGA) score is a five-point scale used by physicians to assess atopic dermatitis disease severity. The assessment is easy to perform and frequently used in atopic dermatitis clinical studies. Furthermore, the IGA assessment provides an easy understanding of disease severity for the patient because severity is ordered by point value, with 0 being clear and 4 being severe disease. Descriptions of each point for the IGA scale are shown in Table 2.1.

The IGA assessment uses clinical characteristics, such as erythema, lichenification, and oozing, to assess disease severity [30]. While developing the validated IGA scale for atopic dermatitis, dermatology experts considered regulatory needs of a clear, distinct categorization of disease severity [31]. The Food and Drug Administration (FDA) currently recommends that new drug applications of atopic dermatitis include IGA assessment as a primary endpoint [32].

2.1.5 Disease Management

Given the complexity of the pathology of atopic dermatitis, there are a wide range of therapies available that target different factors. Although there are management options outside of topical and systemic therapies, i.e., ultraviolet light treatments, the focus will be on drug products used for the treatment of atopic dermatitis.

2.1.5.1 Topical Therapies

Topical corticosteroids (TCS) are considered the first-line therapy for atopic dermatitis, but chronic use of steroids presents risks of adverse events and is generally not recommended [33]. Topical calcineurin inhibitors such as, pimecrolimus and tacrolimus, suppress early phase of T-cell activation, but have received a "black box" warning from the FDA and "red-hand letter" from the EMA for the potential of developing malignant neoplasms, and are suggested to be used as a second line of therapy [24].

Topical therapies also target phosphodiesterase 4 (PDE4), which is involved in regulating cytokine production and thought to decrease proinflammatory responses. PDE4 inhibitors have been introduced in the treatment of atopic dermatitis as a non-steroidal anti-inflammatory alternative; however, the efficacy has been disputed in the literature [34]. One study found that PDE4 inhibitor E6005 did not have a statistically significant difference in efficacy compared to the vehicle treatment [35].The FDA has approved crisaborole ointment, a PDE4 inhibitor, in 2016 for patients with mild-to-moderate atopic dermatitis [36].

In an effort to restore the skin microbiome, Union therapeutics has developed ATx201 ointment, a niclosamide and synthetic antibiotic, that has been shown to effectively reduce *S. aureus* colonization in seven days compared to a matching vehicle in most recent Phase 2 study [37]. Janus kinases (JAKs) are important components of the immune response in atopic dermatitis.

JAK inhibitors have been suggested as a promising therapeutic option and are being developed as topical and systemic formulations for the treatment of atopic dermatitis [38, 39]. In 2021, the FDA approved ruxolitinib cream, a JAK1 and JAK2 inhibitor, for short-term topical use in patients with mild-to-moderate atopic dermatitis [40].

2.1.5.2 Systemic Therapies

In addition to topical treatments, systemic therapies have also been developed for the treatment of atopic dermatitis. Immunosuppressants, such as cyclosporine or methotrexate or azathioprine, were standard systemic treatments if topical therapies were not sufficient; although, only cyclosporin is approved for the indication of atopic dermatitis. Cyclosporin has been shown to provide fast relief to inflammation; however, it was not suitable for long lasting treatment [41].

Dupilumab is the first biologic approved for systemic treatment of atopic dermatitis and provided new hope for patients regarding therapeutic options. Dupilumab is a monoclonal antibody developed by Regeneron Pharmaceuticals and Sanofi Genzyme, and is the focus of this dissertation. More details of structure, mechanism of action, and clinical pharmacokinetics are in *Section 2.2.* Tralokinumab is a fully human monoclonal IgG4 antibody that blocks IL-13 and is administered as a subcutaneous injection. It is approved by the FDA for moderate-to-severe atopic dermatitis after showing long-term efficacy and tolerability in a Phase III trial [42]. Lebrikizumab, developed by Lilly, also blocks IL-13 and showed dose-dependent efficacy in adult patients; it is under fast-track designation status by the FDA [43]. Nemolizumab targets IL-31, which plays a role in pruritis, and showed a decrease in itchiness compared to placebo, but did not show significant decrease in the disease severity assessment, EASI (described in *Section 2.1.4.1*), compared to placebo [44].

2.2 Dupilumab

2.2.1 Biologics – Monoclonal Antibodies

Biologic therapies are derived from living cells or through biological processes and include monoclonal antibodies, bispecific antibodies, fusion proteins, growth factors and many others [45]. Compared to small molecules, biologics tend to have high molecular weights and are typically unstable [46]. A comparison between biologics and small molecules is shown in Table 2.2.

Monoclonal antibodies are molecules that mimic that natural function of immunoglobulins, antibodies produced by plasma B cells, in the body [47]. Monoclonal antibodies can be chimeric, fully humanized, or fully human, with the latter being developed from human sources such as transgenic mice [48]. There are five primary classes of immunoglobulins —immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), immunoglobulin D (IgD), and immunoglobulin E (IgE) [49]. These glycoproteins contain at least one unit of four polypeptide chains – two identical heavy chains and two identical light chains. Heavy chains are held together by disulfide bonds.

The most common class of immunoglobulins, and the class to which dupilumab belongs dupilumab, is IgG [47, 50]. Within an IgG monoclonal antibody there are constant domains (CH and CL) and variable domains (VH and VL), as shown in Figure 2.3 [51]. The IgG class is a monomer that has a molecular weight around 150 kD and constitutes about 75% of the total serum immunoglobulin [52]. Within the IgG primary classification there are 4 IgG subclasses, the most common subclass for pharmaceuticals being IgG1. Each subclass of IgG differs in the number of disulfide bonds in the hinge region, which affects the flexibility and length. IgG4 does not bind to polysaccharides and is usually less than 4% of the total IgG [53].

2.2.2 Structure and Properties

Dupilumab, trade name Dupixent, is a fully human monoclonal antibody of the IgG4 subclass (molecular weight = 147 kD) developed by Regeneron Pharmaceuticals and Sanofi Genzyme [50]. Dupilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture [54]. Biologics are typically limited to either subcutaneous (SC) or intravenous (IV) dosage forms because of instability and size [45]. Dupilumab is administered via subcutaneous injection as a preservative-free, colorless to pale yellow solution with a pH of 5.9 [50]. Other properties such as melting point or partition coefficient did not have data available in the label.

Storage of biologics is also important to prolong stability, and it is recommended that dupilumab be stored in the refrigerator, with a shelf-life of 3 years in 2-8°C or 14 days at room temperature. There are three available injections approved by the FDA: 1) 300 mg/2mL solution in a single-dose pre-filled syringe with needle shield or pre-filled pen, 2) 200 mg/1.14mL solution in a single-dose pre-filled syringe with needle shield or pre-filled pen, and 3) 100 mg/0.67 mL solution in a single-dose pre-filled syringe with needle shield [54]. The pre-filled pen and pre-filled syringe available are shown in Figure 2.4.

Although not nearly as simple as applying topical creams or ointments, patients may learn how to self-inject dupilumab, making dose administration more convenient. Furthermore, dosage frequencies described in *Section 2.2.4* are at most administered once a week and may be administered in addition to topical corticosteroids if needed for patients with moderate-to-severe atopic dermatitis[55].

2.2.3 Mechanism of Action

Dupilumab is fully human VelocImmune®-derived monoclonal antibody that is an interleukin-4 (IL-4) receptor alpha antagonist, blocking both IL-4 and interleukin-13 (IL-13) signaling [29]. Dupilumab specifically binds to the IL-4rα subunit that is connected to IL-4 and IL-13 receptor complexes. The binding to this subunit prevents IL-4 and IL-13 signaling, which in turn decreases the release of pro-inflammatory cytokines, chemokines, and immunoglobulin E, all of which are involved in the mechanism of atopic dermatitis and other T_H2 inflammatory diseases [56]. The mechanism of action is shown in Figure 2.5.

2.2.4 Approved Indications

The FDA has approved dupilumab for a multitude of Type 2 inflammatory diseases. Namely, dupilumab is approved for 1) patients 6 months and older with moderate-to-severe atopic dermatitis whose disease is not controlled by topical therapies; 2) patients 6 years and older with moderate-to-severe asthma as an add-on maintenance treatment; 3) adults patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) as an add-on maintenance treatment; 4) patients 12 years and older, at least 40 kg, with eosinophilic esophagitis (EoE) [54]. A table of approved dose regimens by indication is shown in Table 2.3.

The EMA has also approved dupilumab for a multitude of Type 2 inflammatory diseases, but for slightly different populations. For moderate-to-severe atopic dermatitis, dupilumab is approved for 12 years and older. Children 6 to 11 years are able to use dupilumab with severe disease. Dupilumab is approved only for patients 12 years and older with severe asthma. Dupilumab is also approved for adults with severe CRSwNP, but is not approved for EoE indication in Europe [57].

2.2.5 Clinical Pharmacokinetics

2.2.5.1 Absorption

Dupilumab's bioavailability following a subcutaneous dose was reported as 64% for patients with atopic dermatitis, with a time to maximum concentration (Tmax) following a single subcutaneous dose as one week after injection of 600 mg [58]. Figure 2.6 shows mean functional dupilumab concentration over time from IV and SC single dose [59]. No major differences in bioavailability between patients with atopic dermatitis, asthma, CRSwNP, and EoE were observed [54]. Maximum concentrations increased by greater than dose proportional and reached steady-state by Week 16 [58, 59].

2.2.5.2 Distribution

The apparent volume of distribution is approximately 4.8±1.3 L [54].

2.2.5.3 Metabolism and Excretion

The metabolic pathway of dupilumab has not been formally characterized. Most monoclonal antibodies are eliminated via intracellular catabolism by lysosomal degradation to amino acids [51]. No dose adjustments were needed for patients with renal or hepatic impairment [60]. Median times to non-detectable concentrations are 9-13 weeks for patients 12 years and older, 1.5 times longer in children 6 to 11 years, and 2.5 times longer in 6 months to 5 years after steady-state injections [54]. Population pharmacokinetic analyses indicate the median times to non-detectable concentration for children less than 12 years.

2.2.5.4 Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics [54]. AUC_{last}/Dose ratio after single IV and SC dupilumab dose is shown in Figure 2.7 [59].

2.2.6 Population Pharmacokinetics

A population pharmacokinetic (PK) model was developed to describe functional dupilumab concentrations over time. The population PK model was developed with data from 197 participants and 2518 concentration samples from two healthy volunteer studies (Phase I) and four atopic dermatitis studies (Phase II) [61]. Dosage forms included in the analysis were single intravenous infusions and subcutaneous injections. IV infusions had weight-based doses including 1, 3, 8, and 12 mg/kg. Subcutaneous injections included doses of 75, 100, 150, and 300 mg. Table 2.4 describes the clinical studies included in the population PK analysis as well as descriptions of dosing regimens and sample times.

A two-compartment disposition model with parallel linear and nonlinear elimination was found to fit the data best, typical of monoclonal antibodies [51]. Covariates included in the model were baseline body weight (kg) on the central volume of distribution [61]. A diagram of the population PK model is shown in Figure 2.8.

The central volume of distribution was estimated as 2.74 L (2.61, 2.97). The linear clearance, 0.126 L/day with the Michealis-Menten constant, Km, in the nonlinear elimination was fixed to 0.01 mg/L, which was well below the lower limit of quantification (LLOQ) for all studies (0.078 mg/L) [61]. Inclusion of below limit of quantification (BLQ) data estimated Km to values smaller than 0.01 mg/L with large relative standard error and thus the estimate was fixed to 0.01 mg/L.

Parameter estimates from the final population PK model, goodness-of-fit plots, and contribution of linear and nonlinear clearance are summarized in Table 2.5, Figure 2.9, and Figure 2.10, respectively.

Overall, the PK parameters are well estimated; however, the goodness-of fit plots show a difference between the population predicted concentrations and the individual predicted concentrations, suggesting possible model misfit. No significant differences were found between healthy adults and adults with moderate-to-severe atopic dermatitis. Baseline body weight had a significant impact on dupilumab concentration.

The target-mediated pharmacokinetics was described using an empirical Michaelis-Menten equation, and the parallel linear clearance represents nonspecific cellular uptake of monoclonal antibodies through pinocytosis/proteolysis [62]. The contribution of nonlinear clearance at therapeutic concentrations is minimal, suggesting saturation of target and that the main source of elimination is nonspecific cellular uptake.

2.3 Population Exposure-Response Modeling

2.3.1 Prior Modeling Experience

A dose-response relationship was not clear when directly comparing 300 mg QW and 300 mg Q2W treatment. Dupilumab concentration quartile analyses were performed to determine whether higher dupilumab concentrations were associated with greater drug effect in patients with atopic dermatitis as measured by the Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA). Exposure-response analysis of the relationship between quartile of dupilumab concentration at the end of a dosing interval (Ctrough) and the percentage of patients achieving IGA 0 or 1 (primary efficacy endpoint) showed a trend of increasing drug effect with increasing quartile of dupilumab Ctrough over time, with the proportion of patients reaching IGA 0 or IGA 1 increased from 37.1% to 56.6% between the lowest and highest quartile [63]. Similar E-R relationships were observed for other efficacy endpoints including EASI percent change from baseline, with an increase in response from 70% to 80% change from baseline between the lowest and highest quartile [63].

Statistical analyses from clinical trials in adolescents (12-17) and children (6-11) have also shown significant improvement after dupilumab treatment in both proportion of patients reaching at least a 75% reduction in EASI (EASI-75) and proportion of patients reaching IGA 0 or 1 (IGA0/1) compared to placebo [29, 64]. Graphical results from both clinical trials conducted in adolescents and children are shown in Figure 2.11 and Figure 2.12, respectively.

2.3.2 Exposure-Response Modeling Approach

2.3.2.1 Data Assembly

Source data will be provided from six studies (5 Phase III and 1 Phase IIb). These data include dose records from individual patients with the amount given (mg) and the time of injection. These data will also include IGA scores for each individual at multiple time points throughout the study duration. Baseline covariates will be provided in the data. Data from each study will be derived into a NONMEM® ready dataset for pharmacokinetic-pharmacodynamic modeling.

2.3.2.2 Exploratory Analysis

After the completion of the NONMEM® derived dataset, a thorough exploratory analysis will be performed. Summaries of covariates of interest will be expressed using descriptive summary statistics (mean, standard deviation, median, min, and max) for continuous covariates such as body weight. Categorical covariates will be summarized by the number of observations and percentage of the total observations. These summaries will be done for the overall dataset and for subgroups such as by age group (i.e., adults, adolescents, and children) and treatment group (i.e., placebo and dupilumab).

Exploratory plots will be drawn illustrating the relationship of the proportion of subjects at an IGA ≤ 1 vs. nominal week. Other IGA thresholds will be drawn, such as IGA ≤ 2 and IGA ≤ 3. Plots will be drawn by age group and treatment type. Missing IGA observations will not be included in the analysis, and IGA information after the use of rescue medication will also be excluded from the analysis.

2.3.2.3 Software and Estimation Methods

Originally developed by Lewis Sheiner and Stuart Beal, NONMEM® is a computer program that is designed to address pharmaceutical statistical problems [65]. NONMEM® is often

used for population pharmacokinetic and population pharmacokinetic-pharmacodynamic models. It has the ability to incorporate fixed effects, inter-individual variability, and intra-individual variability [66]. NONMEM® provides the flexibility to develop a variety of models with different data types. The first-order conditional estimation method with interaction was used in the EASI analysis, and the Laplacian conditional estimation method was used in the IGA analysis [65].

2.3.2.4 Model Development Overview

A sequential population pharmacokinetic/pharmacodynamic modeling approach will be applied – i.e., PK parameters will not be estimated simultaneously. Separate population PK models were developed for dupilumab in adults, adolescents and children, and PK parameters (typical value, variability) and PK-related covariates were estimated. The general compartmental structure of the dupilumab population PK model is described in *Section 2.2.6*. Using the Bayesian method, which allows for the posterior distribution – estimated using observed data – to serve as a prior distribution, individual PK parameters can be derived [67]. The individual PK parameters will then be incorporated when fitting the exposure-response models, along with actual dosing histories of each patient. Exposure-response parameters will be estimated using predicted PK data and efficacy observations.

2.3.2.5 Structural Model

Separate population exposure-response analyses will be conducted for EASI and IGA endpoints. For each clinical efficacy endpoint, a base (or structural) model will be developed. In the first step of base model development, a non-drug model component will be evaluated using placebo data only. In clinical trials, placebo subjects were shown in improve over time, but varied in magnitude of response across studies [29, 68-71]. Once a suitable non-drug effect component is identified, non-drug and drug effects will be simultaneously evaluated using combined data from

both placebo and active treatment groups. Model structures for random effects will also investigated at this stage.

2.3.2.6 Indirect-Response Models

Population pharmacokinetic-pharmacodynamic modeling attempts to characterize the relationship between plasma concentrations and pharmacodynamic response. The relationship with plasma concentrations and pharmacodynamic responses can be described in a direct or indirect manner. A direct relationship between exposure and response is observed with an immediate change of the measured variable after a dose is given. An indirect relationship between exposure and response is observed when there is a delay in the change of the measured variable. This may be due to the mechanism of action of the drug product that takes time to develop. Graphical analyses of response vs. exposure show a hysteresis loop for endpoints that require an indirect response model (Figure 2.13) [72].

For continuous variables, such as EASI, an indirect response model is appropriate to model the lag time of response. Indirect response models can take four main forms [73]. The general equation of the indirect response model is

$$\frac{dR}{dt} = k_{in}^{0} - k_{out} * R$$

where k_{in}^{0} represents the apparent zero-order rate constant for production of response, and k_{out} represents the first-order rate constant for the loss of response. R is the response variable (i.e., EASI score) and the baseline response R_0 is defined as $\frac{k_{in}^{0}}{k_{out}}$. From this equation, inhibition or stimulation of each rate constant using a sigmoid function (i.e., *I(t)* or *S(t)*) describes the four general indirect response models (Figure 2.14).

2.3.2.7 Latent Variables

A similar method to model a response delay can be used for a categorical variable (i.e., IGA score); however, the indirect-response method described for a continuous response variable is not sufficient for an ordered categorical variable [74]. The standard statistical approach to modeling ordered categorical variables utilizes logistic or probit regressions [75]. These types of models link the probabilities of achieving a response level, i.e., IGA =1, to the predictor R(t) as

$$P(Z(t) \leq k) = h(\beta_k - R(t))$$

Where k is the categorical response level that ranges from 0 to m-1, and $\beta_0 < \beta_1 < \ldots < \beta_{m-1}$ are intercepts, and h(x) is a link function forcing the probability to be between 0 and 1. Usually, the link functions are logistic or probit models. For the probit model, $h(x) = \phi(x)$ where ϕ is the cumulative distribution function of the standard normal distribution [75].

An extension of the indirect-response model method may be the most appropriate in providing a semi-mechanistic model to describe ordered categorical response variables. This extension of the indirect-response model uses an unobservable latent variable, which is a continuous variable that can be mapped into a categorical response using a threshold.

For a continuous response, the model can be represented as

$$y = R(t) + \epsilon$$

Where y is the measured response variable and ϵ is the residual error. R(t) is model predicted response.

For an indirect latent variable response model (ILVRM), the latent variable is a function of the indirect-response portion.

$$z^* = R(t) + \sigma\epsilon$$

Where z^* is the unobservable latent variable, R(t) is the model prediction of the latent variable response, σ is the error standard deviation, and ϵ is the error.

In order to interpret the output of an ILVRM, the results must be converted to a probability of response [74]. To do this, let's use IGA observations as an example. If we let the observable event, z, be an IGA score ≤ 1, then as the unobservable latent variable, z^*, falls below some threshold, γ, IGA tends to be less than or equal to 1. Finally, with the assumption that the error is normally distributed with mean of 0 and variance equal to 1 (i.e., $\epsilon \sim N(0,1)$), the probability that IGA ≤ 1 is expressed by

$$P(z \leq 1) = P(z^* < \gamma) = \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\gamma} e^{-\frac{z^* - R(t)^2}{2\sigma^2}} dz^* = \Phi\left[\left(\gamma - \frac{R(t)}{\sigma}\right)\right]$$

Where $\Phi(\circ)$ is the cumulative normal distribution, σ = 1 (assumed, since σ cannot be separately identifiable) [74]. Then we can write the equation corresponding to the probit regression as

$$\Phi^{-1}[\mathrm{P}(\mathrm{z} \leq 1)] = \gamma - \mathrm{R}(\mathrm{t})$$

Using the ILVRM, inhibitory and stimulatory functions can be applied the indirect response corresponding to the latent variable, thus allowing for a semi-mechanistic model application to an ordered categorical variable [74].

2.3.2.8 Covariate Model

In the development of a covariate model, a full model approach will be used by simultaneously adding pre-specified covariate effects to the model. The full model will undergo a backward elimination process to find a parsimonious model that provides similar information to the full model with the fewest number of covariates. Numerical diagnostics and graphical diagnostics will be assessed at every step of the model development process.

Numerical diagnostics include successful convergence and completion of the covariance step; objective function value (OFV) and Akaike Information Criterion (AIC) changes; relative precision of parameter estimates; and model stability [76]. Inspection of the covariance matrix of estimates at every stage of model development will be performed in order to verify that extreme pairwise correlations ($\rho > 0.95$) of the parameters is not encountered. The condition number of the correlation matrix of the parameter estimates (i.e., the ratio of the largest to smallest eigenvalues) will also be assessed to ensure values less than 1000, above which indicates a severely ill-conditioned model [77].

2.3.2.9 Model Validation

In order to evaluate the predictive nature of a model, simulation-based diagnostics are needed, in particular, visual predictive checks (VPCs) will be conducted prior to the declaration of a final model [78]. VPC plots will be stratified by study, age groups, and dose regimen. The observed 5^{th}, 50^{th}, and 95^{th} percentiles of the EASI efficacy endpoint will be binned by nominal time and compared to the 5^{th} and 95^{th} percentiles (90% confidence interval [CI]) of the simulated efficacy measures at corresponding percentiles (5^{th}, 50^{th}, and 95^{th}) of the simulated data in order to provide a visual assessment of the predictive performance of the exposure-response model. For the categorical endpoint, IGA, proportion of IGA responders will be compared to the simulated 90% prediction interval of IGA responders. If systematic and major deviations occur in the model validation process, model refinement will be performed as necessary until the predictive performance is adequate. Once confirmed, appropriate simulations will be conducted to address specific aims described in *Chapter 1*.

Tables and Figures

Table 2.1 Investigator's Global Assessment Score Description

IGA Score	Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost Clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Table adopted from [30]

Table 2.2 Major Differences between biologics and small molecules

Biologics	Small Molecules
Produces by living cell cultures	Produces by chemical processes
High molecular weight	Low molecular weight
Complex, heterogeneous structure	Well-defined structure
Process-dependent	Mostly process independent
Not entirely characterizable	Completely Characterizable
Unstable	Stable
Immunogenic	Nonimmunogenic
Approved in USA through biologics license application (BLA)	Approved in USA through new drug application (NDA)
8 out of 10 global best-selling drugs	2 out of 10 global best-selling drugs

Adopted from [46, 79].

Table 2.3 FDA Approved Dosing Regimens for Dupilumab by Indication

Indication	Age Group	Body Weight	Initial Dose	Maintenance Dose
Atopic Dermatitis	Adults	Any	2 x 300 mg	300 mg Q2W
Atopic Dermatitis	6 – 17 years	60 kg +	2 x 300 mg	300 mg Q2W
Atopic Dermatitis	6 – 17 years	30 to < 60 kg	2 x 200 mg	200 mg Q2W
Atopic Dermatitis	6 – 17 years	15 to < 30 kg	2 x 300 mg	300 mg Q4W
Atopic Dermatitis	0.5 – 5 years	15 to < 30 kg	No LD	300 mg Q4W
Atopic Dermatitis	0.5 – 5 years	5 to < 15 kg	No LD	200 mg Q4W
Asthma	12 years +	Any	2 x 200 mg	200 mg Q2W
			2 x 300 mg	300 mg Q2W
Asthma[i]	12 years +	Any	2 x 300 mg	300 mg Q2W
Asthma	6 – 11 years	30 kg +	No LD	200 mg Q2W
Asthma	6 – 11 years	15 to < 30 kg	No LD	100 mg Q2W 300 mg Q4W
CRSwNP	Adults	Any	No LD	300 mg Q2W
EoE	12 years +	40 kg +	No LD	300 mg QW

CRSwNP = chronic rhinosinusitis with nasal polyposis; EoE = eosinophilic esophagitis; LD = loading dose; Q2W = every other week; QW = every week; Q4W = every four weeks

[i] Patients with corticosteroid-dependent asthma or with co-morbid atopic dermatitis or adults with comorbid CRSwNP

Table adapted from [54]

Table 2.4 Descriptions of Studies Included in Published Population Pharmacokinetic Analysis

Study Name	Dosing Regimen	Subjects (N)	# Samples and Collection Times
NCT01015027 (R668-AS-0907): Ascending dose study of the safety and tolerability of REGN668 (SAR231893) in normal healthy volunteers	Single IV infusions of 1, 3, 8, and 12 mg/kg, Single SC injections of 150 and 300 mg	36	508 samples Days 1 (hours 0, 1, 2, 4, 8), 2, 4, 8, 11, 15, 22, 29, 43, 57, 85
NCT01259323 (R668-AD-0914): Sequential ascending dose study to assess the safety and tolerability of REGN668 (SAR231893) in patients with atopic dermatitis	4 SC injections of 75, 150, or 300 mg qw	24	279 samples Days 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85
NCT01385657 (R668-AD-1026): Safety and tolerability of REGN668 (SAR231893) in patients with moderate to severe atopic dermatitis	4 SC injections 150 or 300 mg qw	27	312 samples Days 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85
NCT01484600 (R668-HV-1108): Study of the safety, tolerability, pharmacokinetics, and immunogenicity of REGN668 administered subcutaneously to healthy volunteers	Single SC injections of 300 mg	36	564 samples Days 1 (hours 0, 1, 2, 4, 8, 12), 2, 4, 8, 11, 15, 22, 29, 36, 43, 50, 57, 64
NCT01548404 (R668-AD-1117): Study of REGN668/SAR231893 in adult patients with extrinsic moderate-to-severe atopic dermatitis	12 SC injections of 300 mg qw	53	693 samples Days 8, 15, 22, 29, 43, 57, 71, 78, 85, 99, 113, 127, 141, 155, 169, 183, 197
NCT01639040 (R668-AD-1121): Study to assess the safety of REGN668 (SAR231893) administered concomitantly with topical corticosteroids (TCS) in patients with moderate-to-severe atopic dermatitis (AD)	4 SC injections of 100 or 300 mg qw	21	162 samples Days 8, 15, 22, 29, 36, 50, 64, 78
SC = subcutaneous; IV = intravenous, qXw = given every X weeks			

Table adapted from [61].

Table 2.5 Final Published Population Pharmacokinetic Model Parameter Estimates

	Parameter estimate (bootstrap 5th, 95th percentiles)	
Parameter name	**BLQ data included**	**BLQ data excluded**
PK parameter (unit)		
V2 (L)	2.74 (2.61, 2.97)	2.60 (2.46, 2.79)
ke (1/d)	0.0459 (0.0403, 0.0503)	0.0488 (0.0422, 0.0566)
k23 (1/d)	0.0652 (0.0431, 0.0917)	0.104 (0.0755, 0.150)
k32 (1/d)	0.129 (0.101, 0.166)	0.173 (0.133, 0.234)
ka (1/d)	0.254 (0.226, 0.315)	0.261 (0.223, 0.303)
Vm (mg/L/d)	0.968 (0.836, 1.09)	1.06 (0.946, 1.20)
Km (mg/L)	0.01 (fixed)	0.01 (fixed)
F (unitless)	0.607 (0.537, 0.665)	0.623 (0.572, 0.678)
Covariate influence		
V2 ~weight (reference 75 kg)	0.705 (0.576, 0.840)	0.737 (0.588, 0.914)
Inter-individual variability		
ω^2(V2)	0.0225 (0.0152, 0.0285)	0.0295 (0.0189, 0.0419)
ω^2(ke)	0.131 (0.0738, 0.191)	0.131 (0.0733, 0.181)
ω^2(ka)	0.251 (0.187, 0.345)	0.230 (0.169, 0.293)
ω^2(Vm)	0.0428 (0.0215, 0.0663)	0.0379 (0.0120, 0.0705)
Residual variability (unit)		
σ^2proportional (CV%)	24.2 (22.1, 27.0)	18.2 (15.1, 21.1)
σ^2additive (mg/L)	0.03 (fixed)	0.871 (0.579, 1.32)
Derived parameters		
CL (L/d)[a]	0.126	0.127
Q (L/d)	0.179	0.270
V3 (L)	1.38	1.56
[a]Linear clearance calculated as $V_2 \cdot k_e$.		

Adopted from [61].

Figure 2.1 Stage-Based Pathogenesis and Main Mechanisms of Atopic Dermatitis

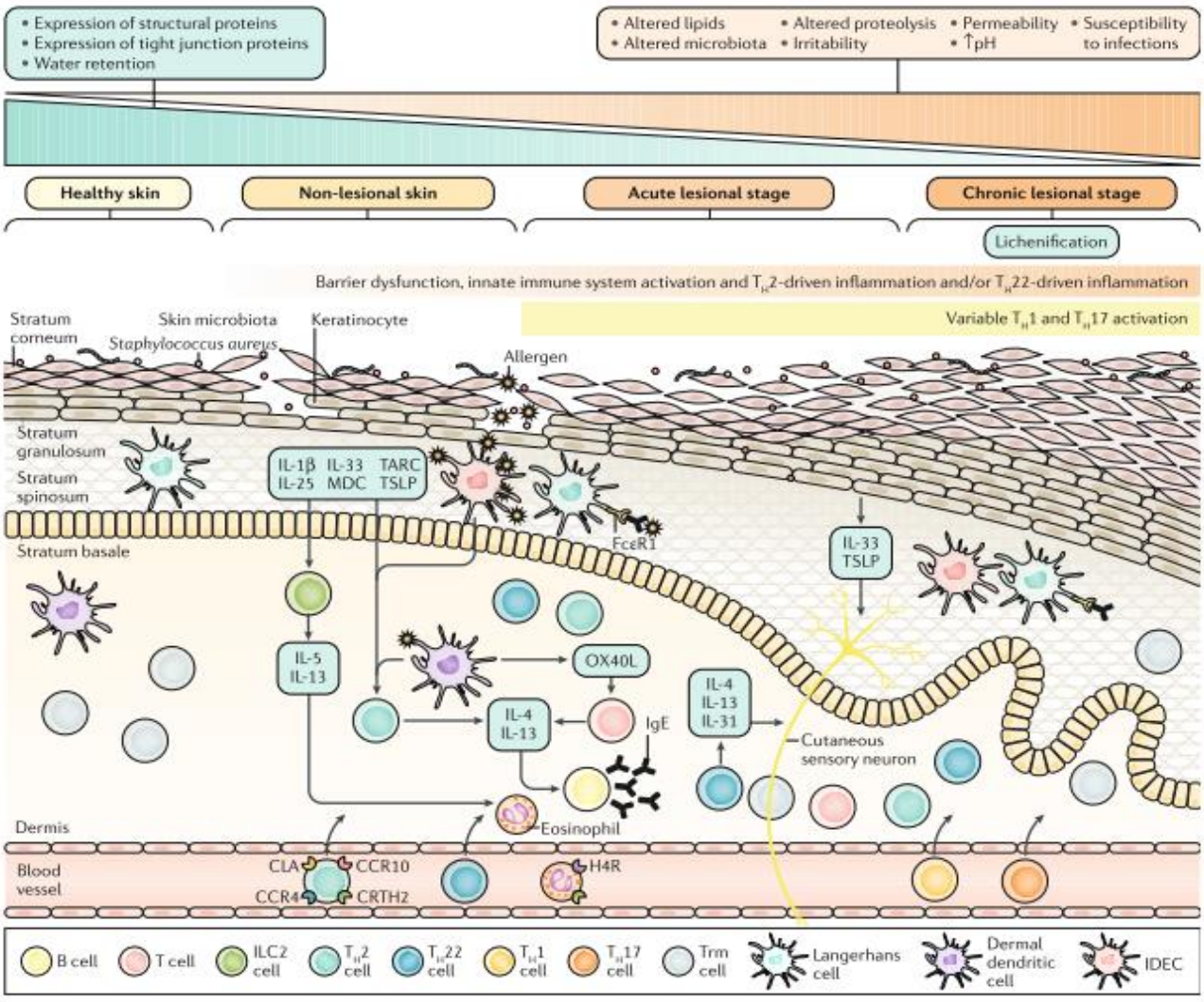
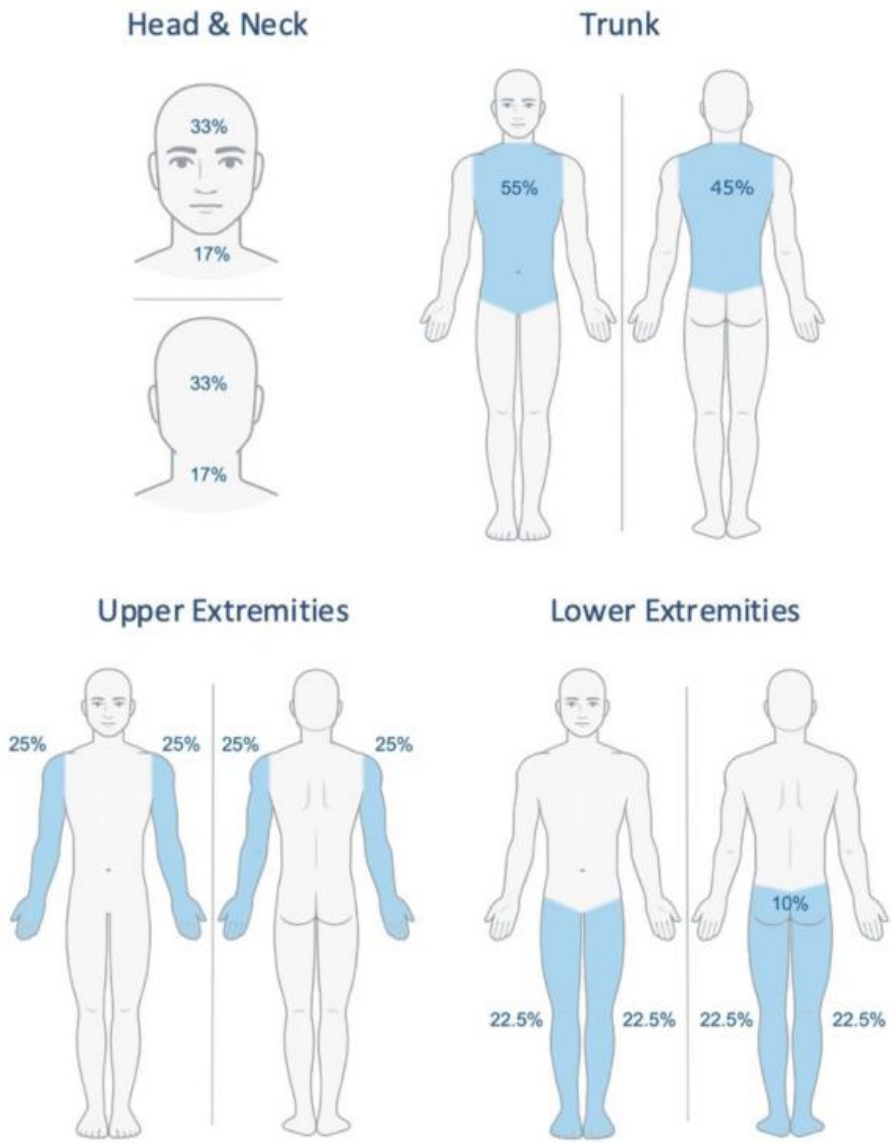
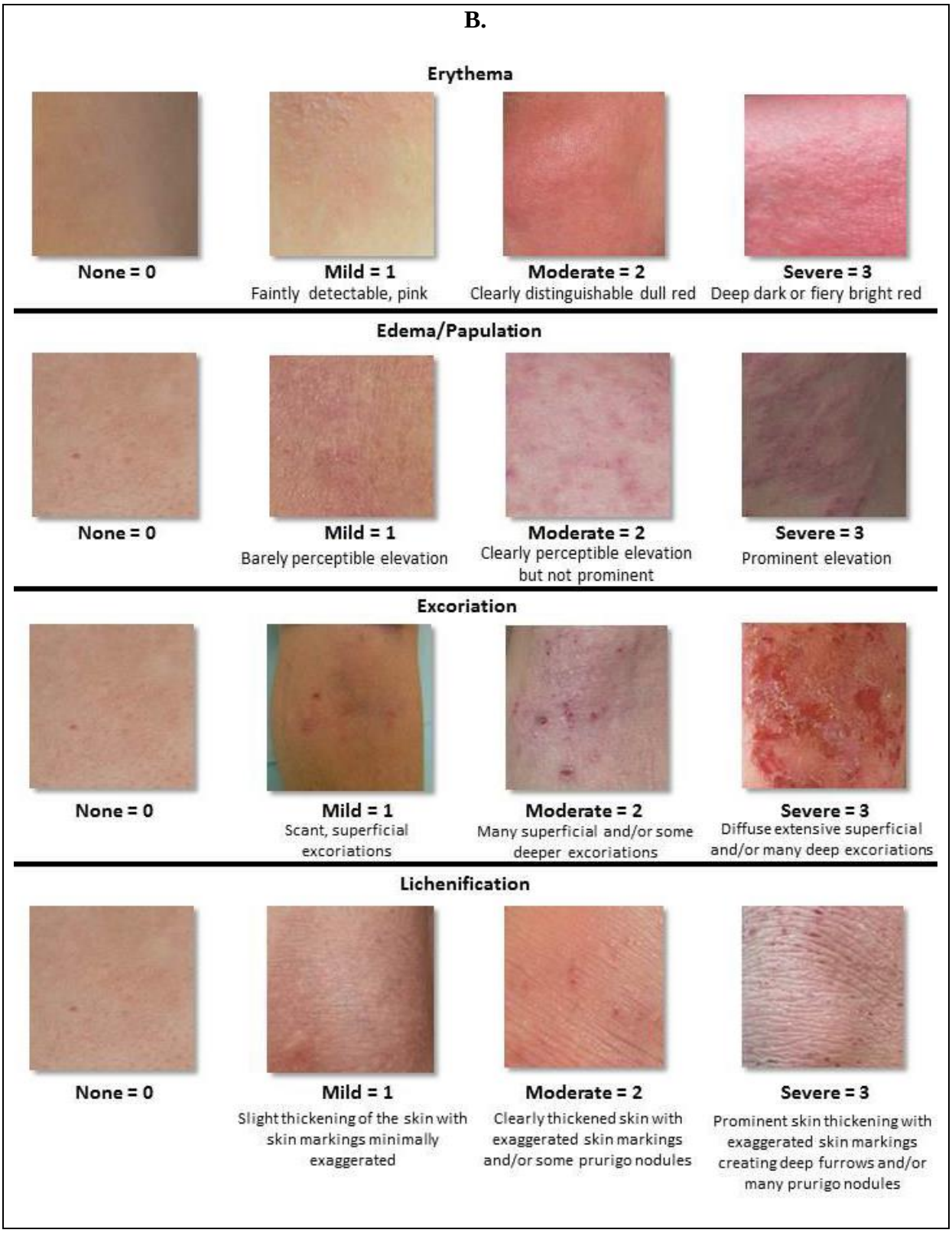


Figure adopted from [12].

Figure 2.2 Eczema Area and Severity Index Score Assessment and Calculation

A.





Panel **A** illustrates the Area of Involvement; Panel **B** illustrates examples of severity

Figures adopted from [27, 80].

Figure 2.3 Monoclonal antibody structure

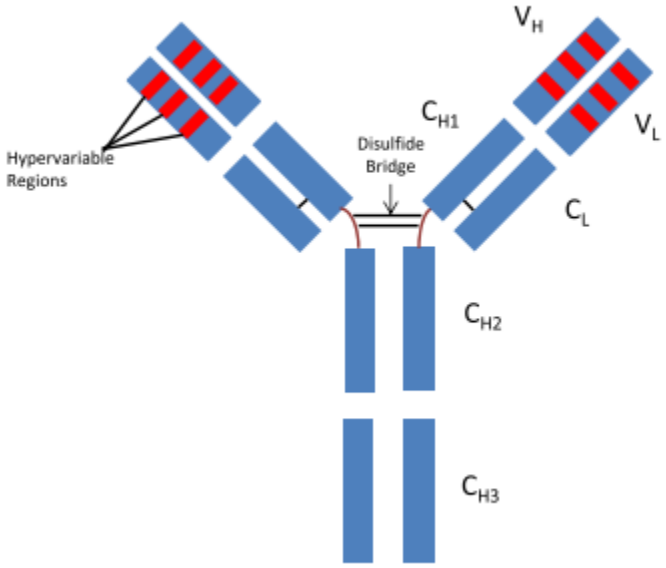
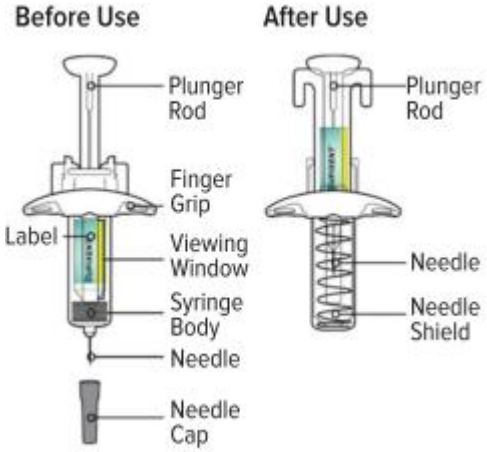


Figure adopted from [51].

Figure 2.4 Approved Dosage Vehicles of Dupilumab by the FDA – Pre-Filled Syringe with Needle Shield and Pre-filled Pen.

A. Pre-Filled Syringe with Needle Shield



B. Pre-filled Pen

Figure adopted from [56] (Panel A) and [81] (Panel B).

Figure 2.5 Dupilumab Mechanism of Action

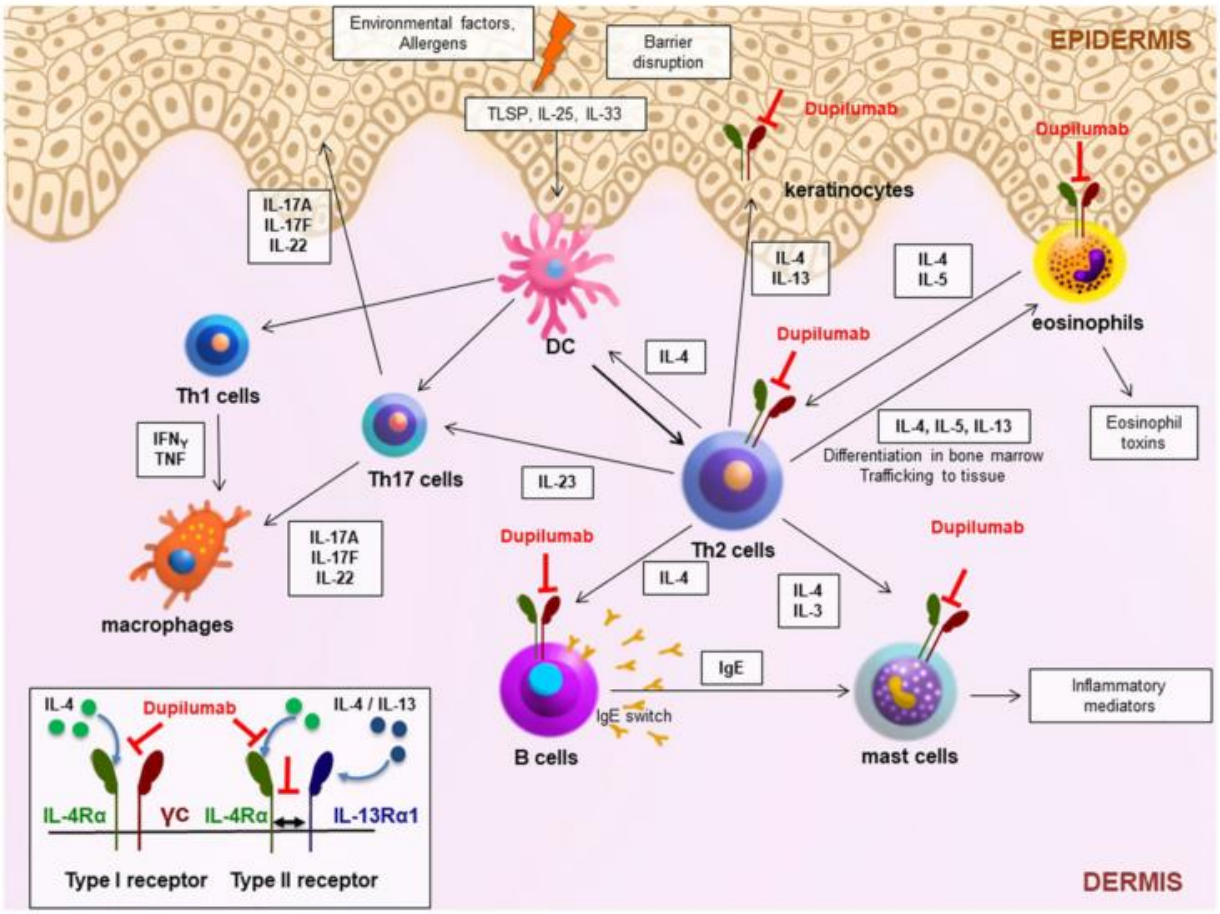
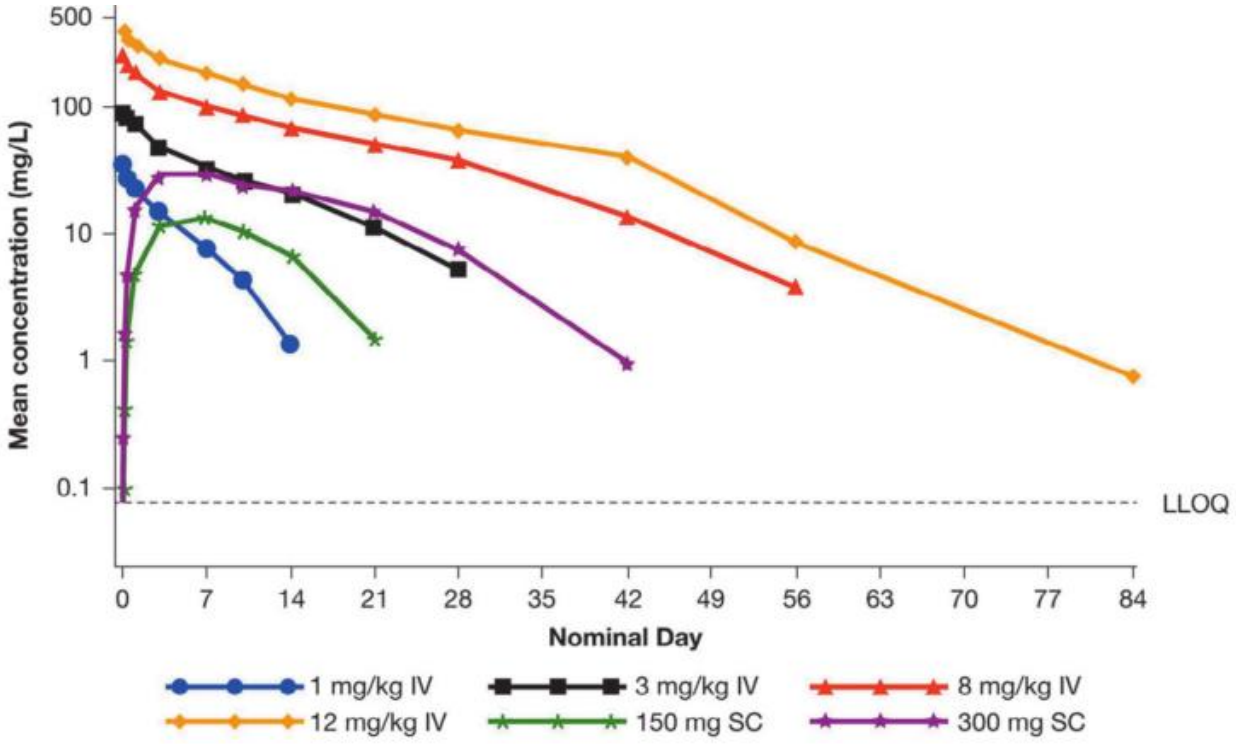


Figure shows dupilumab binding to IL-4 and IL-4Rα that can be found on B cells, mast cells, T_H2 cells, eosinophils, and keratinocytes.

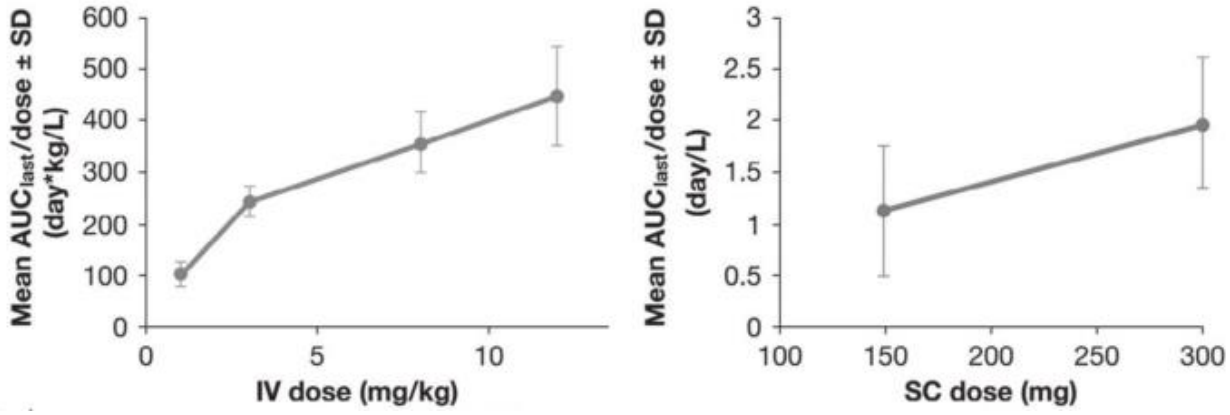
Adopted from [82].

Figure 2.6 Concentration-Time Profiles after Subcutaneous (SC) or Intravenous (IV) Single Dose from First in Human Study (R688-AS-0907)



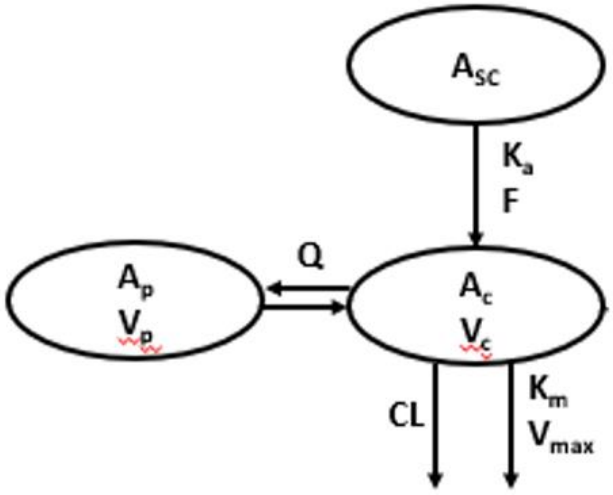
Adopted from [59].

Figure 2.7 AUC_{last}/Dose Ratio after Subcutaneous (SC) or Intravenous (IV) Single Dose from First in Human Study (R688-AS-0907)



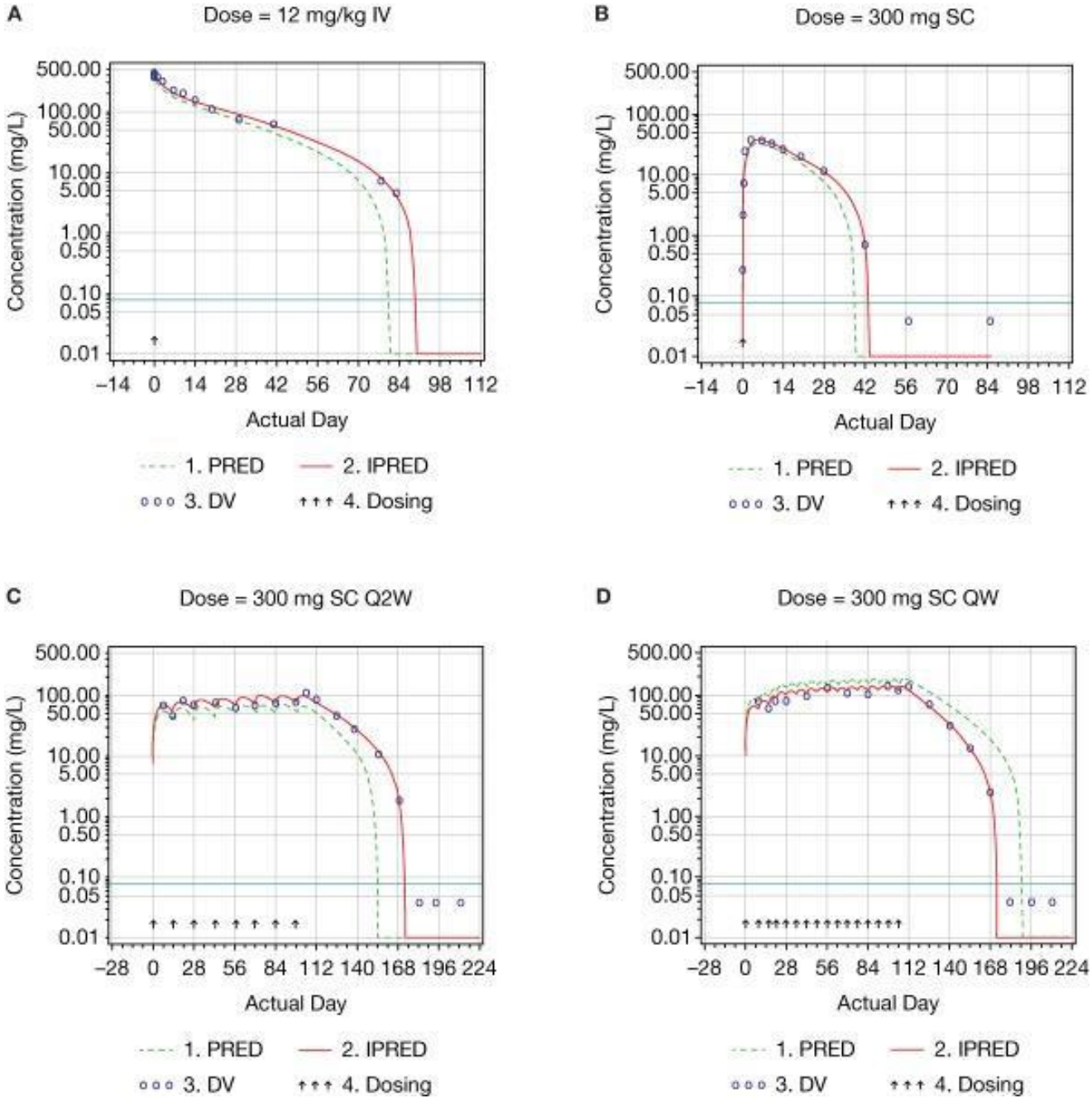
Adopted from [59].

Figure 2.8 Published Population Pharmacokinetic Model Diagram



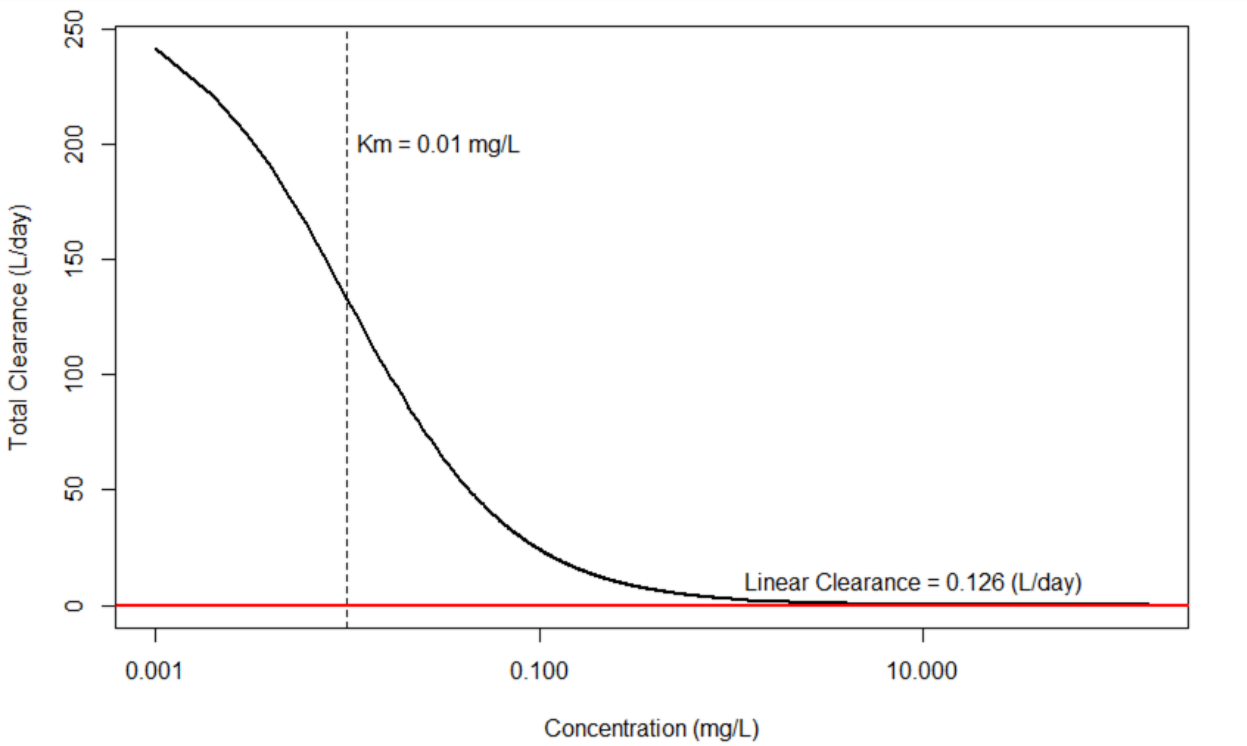
A_c, amount in central compartment; A_{sc}, amount in subcutaneous depot compartment; A_p, amount in peripheral compartment; CL, linear clearance; F, bioavailability; K_a, absorption rate constant; K_m, the concentration at which the rate of elimination is half of the maximum value; Q, inter-compartmental clearance; Vmax, the maximum rate of elimination via the nonlinear pathway; V_c, volume of distribution in central compartment; V_p, volume of distribution in peripheral compartment.

Figure 2.9 Published Population Pharmacokinetic Model Goodness-of-Fit



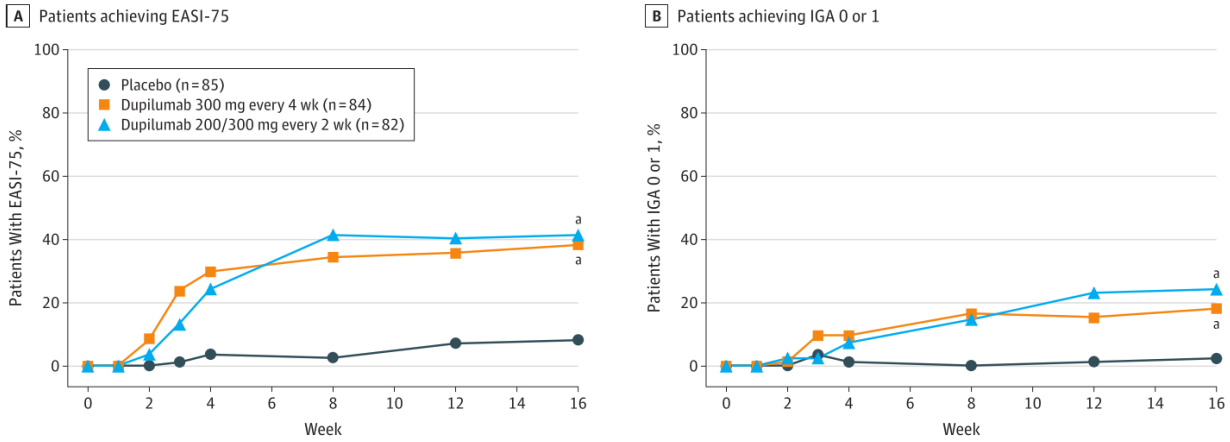
Log-scaled concentration-time profiles of dupilumab at different doses. PRED= population predicted concentration; IPRED = Individual predicted concentrations; DV = observed data. Adopted from [61].

Figure 2.10 Published Population Pharmacokinetic Model Comparison of Linear and Nonlinear Clearance Contribution



Red line depicts linear clears and black line displays total clearance across dupilumab concentration range using parameter estimates from Table 2.5.

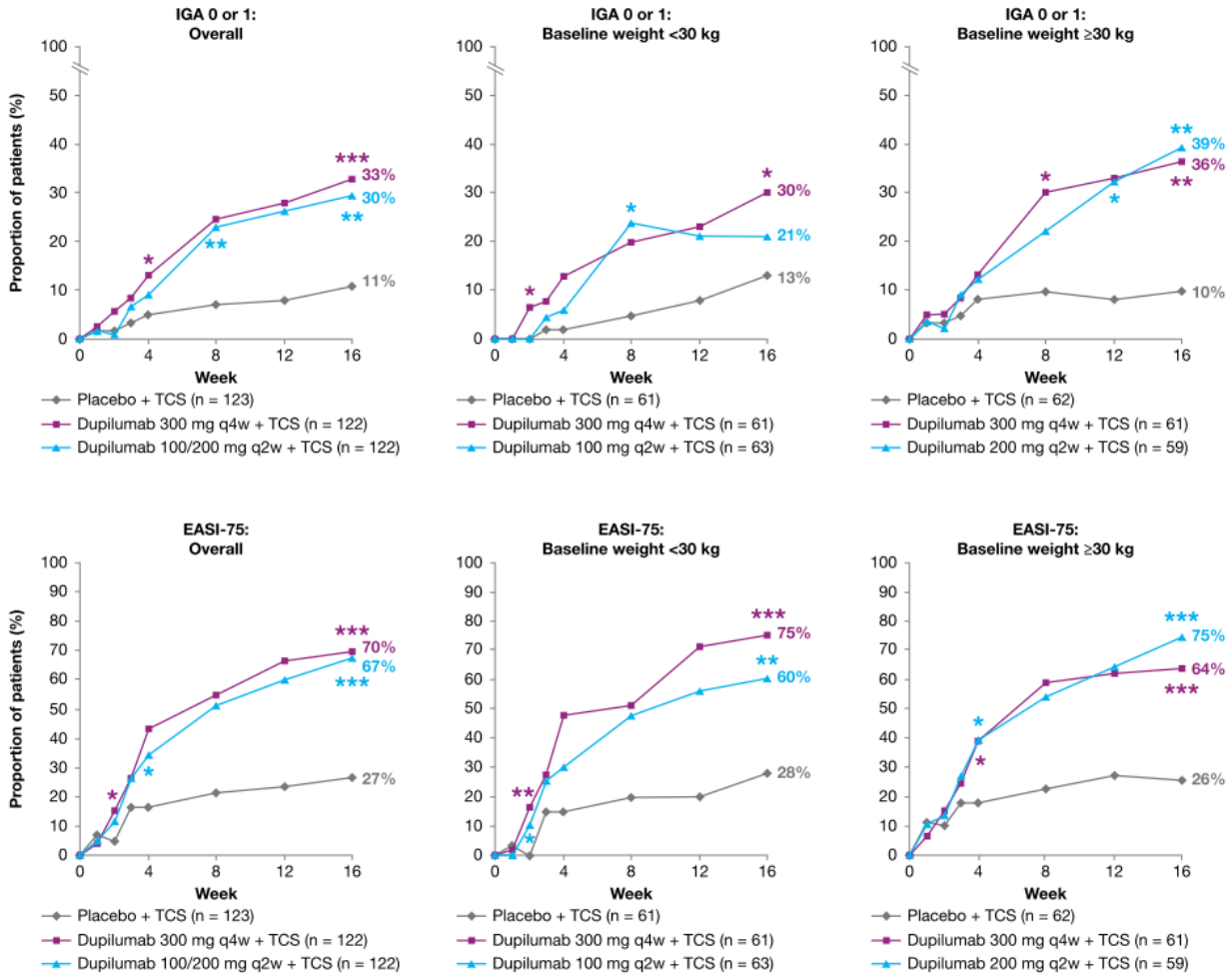
Figure 2.11 Proportion of Adolescents (12 to 17 years) with Moderate-to-Severe Atopic Dermatitis Achieving Co-Primary Endpoints in Study R668-AD-1526



EASE-75 = Patients achieving 75%or more improvement from baseline in Eczema Area and Severity Index; IGA = Investigator's Global Assessment (IGA); a = p-value of < .001 vs placebo

Figure adopted from [70].

Figure 2.12 Proportion of Children (6 to 11 years) with Severe Atopic Dermatitis Achieving Co-Primary Endpoints in Study R668-AD-1652



* = p-value < 0.05; ** = p-value < 0.001; and *** = p-value <0.0001

Figure adopted from [29].

Figure 2.13 Illustration of Hysteresis Loop in Effect vs. Concentration Plots

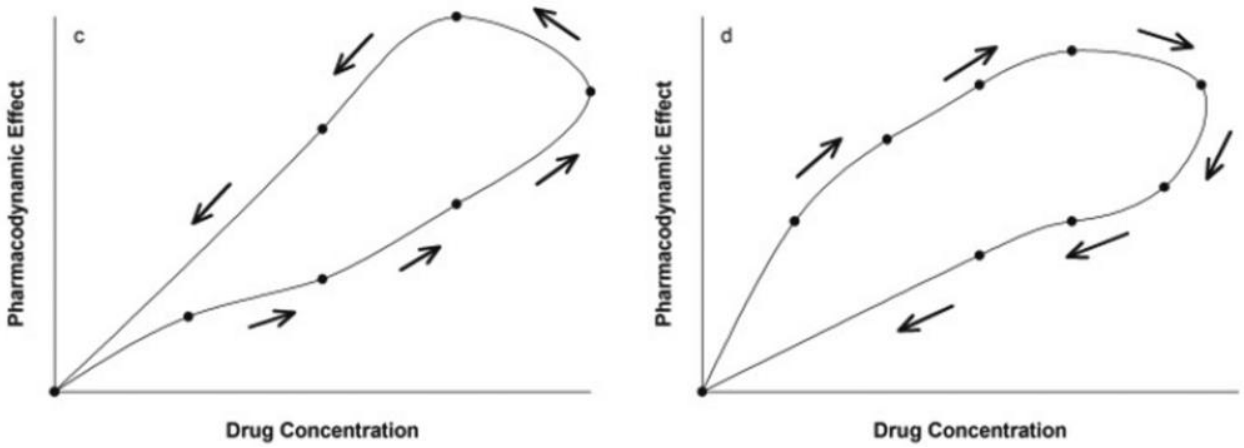


Figure adopted from [72].

Figure 2.14 Four Basic Indirect Response Models

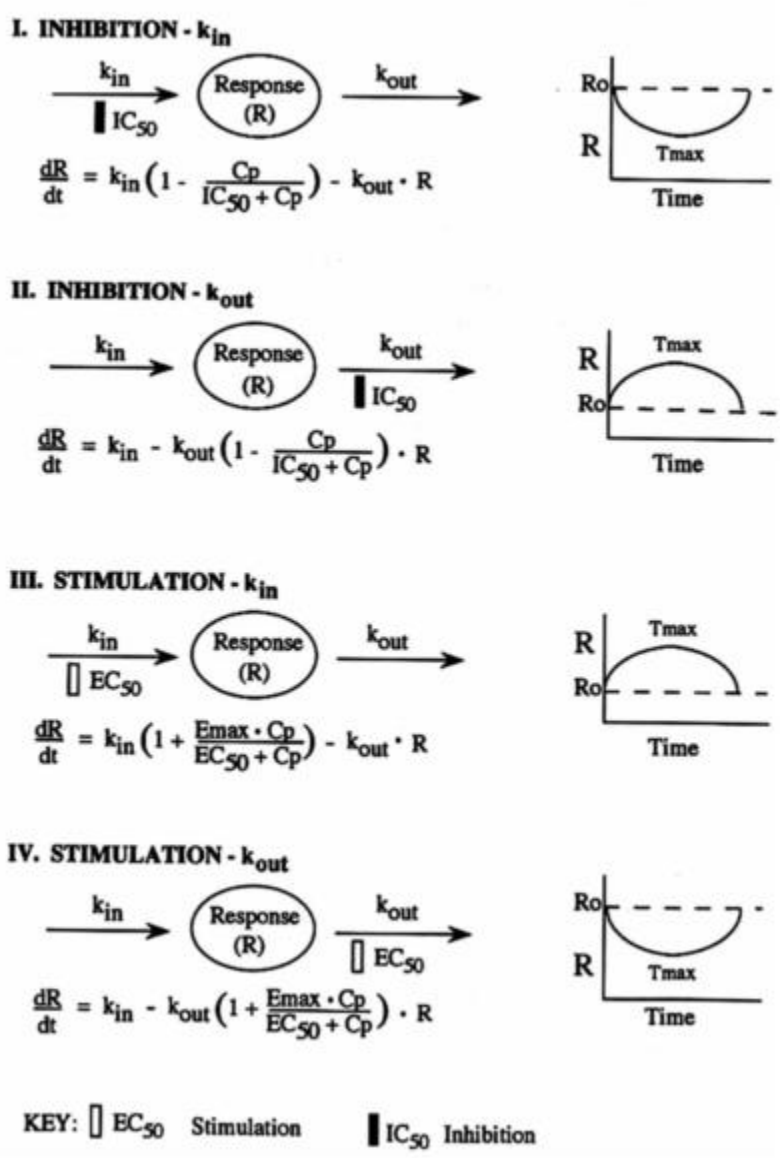


Figure adopted from [83].

References

[1] Bellanti, J.A. and R.A. Settipane, *The Atopic Disorders and Atopy ... "Strange Diseases" Now Better Defined!* Allergy Asthma Proc, 2017. **38**(4): p. 241-242.

[2] Cohen, S., M. Dworetzky, and O.L. Frick, *Coca and Cooke on the Classification of Hypersensitiveness.* J Allergy Clin Immunol, 2003. **111**(1): p. 205-10.

[3] Moreno, M.A., *Atopic Diseases in Children.* JAMA Pediatrics, 2016. **170**(1): p. 96-96.

[4] Brunello, L., *Atopic Dermatitis.* Nature Reviews Disease Primers, 2018. **4**(1): p. 2.

[5] Laughter, M.R., et al., *The Global Burden of Atopic Dermatitis: Lessons from the Global Burden of Disease Study 1990–2017**. British Journal of Dermatology, 2021. **184**(2): p. 304-309.

[6] Bannister, M.J. and S. Freeman, *Adult-Onset Atopic Dermatitis.* Australasian Journal of Dermatology, 2000. **41**(4): p. 225-228.

[7] Brunner, P.M. and E. Guttman-Yassky, *Racial Differences in Atopic Dermatitis.* Annals of Allergy, Asthma & Immunology, 2019. **122**(5): p. 449-455.

[8] Ständer, S., *Atopic Dermatitis.* New England Journal of Medicine, 2021. **384**(12): p. 1136-1143.

[9] Barnes, K.C., *An Update on the Genetics of Atopic Dermatitis: Scratching the Surface in 2009.* J Allergy Clin Immunol, 2010. **125**(1): p. 16-29 e1-11; quiz 30-1.

[10] Osawa, R., M. Akiyama, and H. Shimizu, *Filaggrin Gene Defects and the Risk of Developing Allergic Disorders.* Allergol Int, 2011. **60**(1): p. 1-9.

[11] Armengot-Carbo, M., Á. Hernández-Martín, and A. Torrelo, *The Role of Filaggrin in the Skin Barrier and Disease Development.* Actas Dermo-Sifiliográficas (English Edition), 2015. **106**(2): p. 86-95.

[12] Weidinger, S., et al., *Atopic Dermatitis.* Nature Reviews Disease Primers, 2018. **4**(1): p. 1.

[13] Byrd, A.L., Y. Belkaid, and J.A. Segre, *The Human Skin Microbiome.* Nature Reviews Microbiology, 2018. **16**(3): p. 143-155.

[14] Nowicka, D. and E. Grywalska, *The Role of Immune Defects and Colonization of Staphylococcus Aureus in the Pathogenesis of Atopic Dermatitis.* Anal Cell Pathol (Amst), 2018. **2018**: p. 1956403.

[15] Geoghegan, J.A., A.D. Irvine, and T.J. Foster, *Staphylococcus Aureus and Atopic Dermatitis: A Complex and Evolving Relationship.* Trends Microbiol, 2018. **26**(6): p. 484-497.

[16] Kalum Clayton, A.F.V., James Davies, Sofia Sirvent, Marta E. Polak, *Lengerhans Cells - Programmed by the Epidermis.* Frontiers in Immunology, 2017. **8**: p. 1676 - 1676.

[17] Guttman-Yassky, E., K.E. Nograles, and J.G. Krueger, *Contrasting Pathogenesis of Atopic Dermatitis and Psoriasis—Part Ii: Immune Cell Subsets and Therapeutic Concepts.* Journal of Allergy and Clinical Immunology, 2011. **127**(6): p. 1420-1432.

[18] Bieber, T., *Atopic Dermatitis.* New England Journal of Medicine, 2008. **358**(14): p. 1483-1494.

[19] Langan, S.M., A.D. Irvine, and S. Weidinger, *Atopic Dermatitis.* The Lancet, 2020. **396**(10247): p. 345-360.

[20] Zhu, J., *T Helper 2 (Th2) Cell Differentiation, Type 2 Innate Lymphoid Cell (Ilc2) Development and Regulation of Interleukin-4 (Il-4) and Il-13 Production.* Cytokine, 2015. **75**(1): p. 14-24.

[21] Kataoka, Y., *Thymus and Activation-Regulated Chemokine as a Clinical Biomarker in Atopic Dermatitis.* The Journal of Dermatology, 2014. **41**(3): p. 221-229.
[22] Werfel, T., et al., *Cellular and Molecular Immunologic Mechanisms in Patients with Atopic Dermatitis.* Journal of Allergy and Clinical Immunology, 2016. **138**(2): p. 336-349.
[23] Kapur, S., W. Watson, and S. Carr, *Atopic Dermatitis.* Allergy, Asthma & Clinical Immunology, 2018. **14**(2): p. 52.
[24] Bieber, T., *Atopic Dermatitis.* Ann Dermatol, 2010. **22**(2): p. 125-37.
[25] Yew, Y.W., J.P. Thyssen, and J.I. Silverberg, *A Systematic Review and Meta-Analysis of the Regional and Age-Related Differences in Atopic Dermatitis Clinical Characteristics.* Journal of the American Academy of Dermatology, 2019. **80**(2): p. 390-401.
[26] Hanifin J.M., T.M., Omoto M., Cherill R., Tofte S.J., Graeber M., EASI Evaluator Group, *The Eczema Area and Severity Index (Easi): Assessment of Reliability in Atopic Dermatitis.* Experimental Dermatology, 2001. **10**(1): p. 11-18.
[27] Hanifin, J.M., et al., *The Eczema Area and Severity Index-a Practical Guide.* Dermatitis, 2022. **33**(3): p. 187-192.
[28] Schmitt, J., S. Langan, and H.C. Williams, *What Are the Best Outcome Measurements For atopic Eczema? A Systematic Review.* Journal of Allergy and Clinical Immunology, 2007. **120**(6): p. 1389-1398.
[29] Paller, A.S., et al., *Efficacy and Safety of Dupilumab with Concomitant Topical Corticosteroids in Children 6 to 11 years Old with Severe Atopic Dermatitis: A Randomized, Double-Blinded, Placebo-Controlled Phase 3 Trial.* Journal of the American Academy of Dermatology, 2020. **83**(5): p. 1282-1293.
[30] Council, E., *Validated Investigator Global Assessment Scale for Atopic Dermatitis Viga-Ad™*, Validated-Investigator-Global-Assessment-Scale_vIGA-AD_2017.pdf, Editor. 2017: www.eczemacouncil.org.
[31] Simpson, E., et al., *The Validated Investigator Global Assessment for Atopic Dermatitis (Viga-Ad): The Development and Reliability Testing of a Novel Clinical Outcome Measurement Instrument for the Severity of Atopic Dermatitis.* Journal of the American Academy of Dermatology, 2020. **83**(3): p. 839-846.
[32] Futamura, M., et al., *A Systematic Review of Investigator Global Assessment (Iga) in Atopic Dermatitis (Ad) Trials: Many options, No Standards.* Journal of the American Academy of Dermatology, 2016. **74**(2): p. 288-294.
[33] Abędź, N. and R. Pawliczak, *Efficacy and Safety of Topical Calcineurin Inhibitors for the Treatment of Atopic Dermatitis: Meta-Analysis of Randomized Clinical Trials.* Postepy Dermatol Alergol, 2019. **36**(6): p. 752-759.
[34] Yang, H., et al., *Application of Topical Phosphodiesterase 4 Inhibitors in Mild to Moderate Atopic Dermatitis: A Systematic Review and Meta-Analysis.* JAMA Dermatology, 2019. **155**(5): p. 585-593.
[35] Nemoto, O., et al., *Effect of Topical Phosphodiesterase 4 Inhibitor E6005 on Japanese Children with Atopic Dermatitis: Results from a Randomized, Vehicle-Controlled Exploratory Trial.* The Journal of Dermatology, 2016. **43**(8): p. 881-887.
[36] McDowell, L. and B. Olin, *Crisaborole: A Novel Nonsteroidal Topical Treatment for Atopic Dermatitis.* J Pharm Technol, 2019. **35**(4): p. 172-178.
[37] Weiss, A., et al., *Topical Niclosamide (Atx201) Reduces Staphylococcus Aureus Colonization and Increases Shannon Diversity of the Skin Microbiome in Atopic*

Dermatitis Patients in a Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial. Clin Transl Med, 2022. **12**(5): p. e790.
[38] Bieber, T., *Novel Therapies Based on the Pathophysiology of Atopic Dermatitis.* JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 2019. **17**(11): p. 1150-1162.
[39] Alves de Medeiros, A.K., et al., *Jak3 as an Emerging Target for Topical Treatment of Inflammatory Skin Diseases.* PLoS ONE, 2016. **11**: p. e0164080.
[40] *Opzelura (Ruxolitinib) Cream. Highlights of Prescribing Information*, FDA, Editor. 2021.
[41] Lee, S.S., A.W. Tan, and Y.C. Giam, *Cyclosporin in the Treatment of Severe Atopic Dermatitis: A Retrospective Study.* Ann Acad Med Singap, 2004. **33**(3): p. 311-3.
[42] Wollenberg, A., et al., *Tralokinumab for Moderate-to-Severe Atopic Dermatitis: Results from Two 52-Week, Randomized, Double-Blind, Multicentre, Placebo-Controlled Phase Iii Trials (Ecztra 1 and Ecztra 2).* Br J Dermatol, 2021. **184**(3): p. 437-449.
[43] Guttman-Yassky, E., et al., *Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults with Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial.* JAMA Dermatology, 2020. **156**(4): p. 411-420.
[44] Kabashima, K., et al., *Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus.* New England Journal of Medicine, 2020. **383**(2): p. 141-150.
[45] Andrews, L., et al., *A Snapshot of Biologic Drug Development: Challenges and Opportunities.* Hum Exp Toxicol, 2015. **34**(12): p. 1279-85.
[46] Makurvet, F.D., *Biologics Vs. Small Molecules: Drug Costs and Patient Access.* Medicine in Drug Discovery, 2021. **9**: p. 100075.
[47] *1 - Introduction to Biologics and Monoclonal Antibodies*, in *Therapeutic Antibody Engineering*, W.R. Strohl and L.M. Strohl, Editors. 2012, Woodhead Publishing. p. 1-595.
[48] Johnston, S.L., *Biologic Therapies: What and When?* J Clin Pathol, 2007. **60**(1): p. 8-17.
[49] Justiz Vaillant A.A., J.Z., Ramphul K., *Immunoglobulin*. 2022, StatPearls: Treasure Island, FL.
[50] Daniella D'Ippolito, M.P., *Dupilumab (Dupixent): An Interleukin-4 Receptor Antagonist for Atopic Dermatitis.* P&T, 2018. **43**(9): p. 532-535.
[51] Ryman, J.T. and B. Meibohm, *Pharmacokinetics of Monoclonal Antibodies.* CPT Pharmacometrics Syst Pharmacol, 2017. **6**(9): p. 576-588.
[52] Bridle, H. and M. Desmulliez, *Chapter Seven - Biosensors for the Detection of Waterborne Pathogens*, in *Waterborne Pathogens*, H. Bridle, Editor. 2014, Academic Press: Amsterdam. p. 189-229.
[53] *Immunoglobulin Igg Class*. Immunoglobulins; Available from: https://www.thermofisher.com/us/en/home/life-science/antibodies/antibodies-learning-center/antibodies-resource-library/antibody-methods/immunoglobulin-igg-class.html.
[54] *Dupixent (Dupilumab). Highlights of Prescribing Information.*, FDA, Editor. 2021: USA.
[55] Tameez Ud Din, A., et al., *Dupilumab for Atopic Dermatitis: The Silver Bullet We Have Been Searching For?* Cureus, 2020. **12**(4): p. e7565.
[56] D'Ippolito, D. and M. Pisano, *Dupilumab (Dupixent): An Interleukin-4 Receptor Antagonist for Atopic Dermatitis.* P T, 2018. **43**(9): p. 532-535.
[57] *Summary of Risk Management Plan for Dupixent (Dupilumab)*, EMA, Editor. 2022.
[58] Gooderham, M.J., et al., *Dupilumab: A Review of Its Use in the Treatment of Atopic Dermatitis.* Journal of the American Academy of Dermatology, 2018. **78**(3, Supplement 1): p. S28-S36.

[59] Li, Z., et al., *Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Dupilumab in Healthy Adult Subjects.* Clinical Pharmacology in Drug Development, 2020. **9**(6): p. 742-755.
[60] *Dupixent Product Information*, E.M.A. (EMA), Editor.
[61] Kovalenko, P., et al., *Exploratory Population Pk Analysis of Dupilumab, a Fully Human Monoclonal Antibody against Il-4rα, in Atopic Dermatitis Patients and Normal Volunteers.* CPT Pharmacometrics Syst Pharmacol, 2016. **5**(11): p. 617-624.
[62] Ovacik, M. and K. Lin, *Tutorial on Monoclonal Antibody Pharmacokinetics and Its Considerations in Early Development.* Clin Transl Sci, 2018. **11**(6): p. 540-552.
[63] *Dupixent Public Assessment Report*, EMA, Editor. 2017.
[64] Strober, B., et al., *Treatment Outcomes Associated with Dupilumab Use in Patients with Atopic Dermatitis: 1-Year Results from the Relieve-Ad Study.* JAMA Dermatology, 2022. **158**(2): p. 142-150.
[65] Bauer, R.J., *Nonmem Tutorial Part I: Description of Commands and Options, with Simple Examples of Population Analysis.* CPT Pharmacometrics Syst Pharmacol, 2019. **8**(8): p. 525-37.
[66] Beal S., S.L.B., Boeckmann A., Bauer R.J., *Nonmem User's Guides (1989-2016)*. 2016, Icon Development Solutions: Ellicott City, MD, USA.
[67] Savic, R.M. and M.O. Karlsson, *Importance of Shrinkage in Empirical Bayes Estimates for Diagnostics: Problems and Solutions.* The AAPS Journal, 2009. **11**(3): p. 558-569.
[68] Thaçi, D., et al., *Efficacy and Safety of Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis Inadequately Controlled by Topical Treatments: A Randomised, Placebo-Controlled, Dose-Ranging Phase 2b Trial.* Lancet, 2016. **387**(10013): p. 40-52.
[69] Thaçi, D., et al., *Efficacy and Safety of Dupilumab Monotherapy in Adults with Moderate-to-Severe Atopic Dermatitis: A Pooled Analysis of Two Phase 3 Randomized Trials (Liberty Ad Solo 1 and Liberty Ad Solo 2).* Journal of Dermatological Science, 2019. **94**(2): p. 266-275.
[70] Simpson, E.L., et al., *Efficacy and Safety of Dupilumab in Adolescents with Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial.* JAMA Dermatology, 2020. **156**(1): p. 44-56.
[71] Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab Versus Placebo in Atopic Dermatitis.* New England Journal of Medicine, 2016. **375**(24): p. 2335-2348.
[72] Louizos, C., et al., *Understanding the Hysteresis Loop Conundrum in Pharmacokinetic/Pharmacodynamic Relationships.* Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques, 2014. **17**(1): p. 34-91.
[73] Sharma, A. and W.J. Jusko, *Characteristics of Indirect Pharmacodynamic Models and Applications to Clinical Drug Responses.* Br J Clin Pharmacol, 1998. **45**(3): p. 229-39.
[74] Hutmacher, M.M., S. Krishnaswami, and K.G. Kowalski, *Exposure-Response Modeling Using Latent Variables for the Efficacy of a Jak3 Inhibitor Administered to Rheumatoid Arthritis Patients.* Journal of Pharmacokinetics and Pharmacodynamics, 2007. **35**(2): p. 139.
[75] Hu, C., *Exposure-Response Modeling of Clinical End Points Using Latent Variable Indirect Response Models.* CPT Pharmacometrics Syst Pharmacol, 2014. **3**(6): p. e117.

[76] Byon, W., et al., *Establishing Best Practices and Guidance in Population Modeling: An Experience with an Internal Population Pharmacokinetic Analysis Guidance.* CPT Pharmacometrics Syst Pharmacol, 2013. **2**(7): p. e51.
[77] Montgomery D.C., P.E.A., Vining G.G., *Introduction to Linear Regression Analysis*. Vol. 821. 2012, Hoboken: John Wiley & Sons.
[78] Bergstrand, M., et al., *Prediction-Corrected Visual Predictive Checks for Diagnosing Nonlinear Mixed-Effects Models.* The AAPS Journal, 2011. **13**(2): p. 143-151.
[79] Ngo, H.X. and S. Garneau-Tsodikova, *What Are the Drugs of the Future?* Medchemcomm, 2018. **9**(5): p. 757-758.
[80] Dermatology, C.o.E.B. *Easi User Guide*. Harmonising Outcome Measures for Eczema (HOME) 2016; Available from: http://www.homeforeczema.org/research/easi-for-clinical-signs.aspx.
[81] Regeneron Pharmaceuticals, S. *Pre-Filled Pen Injection*. Dupixent (dupilumab) Injection 2022; Image]. Available from: https://www.dupixent.com/support-savings/prefilled-pen.
[82] Kychygina, A., et al., *Dupilumab-Associated Adverse Events During Treatment of Allergic Diseases.* Clinical Reviews in Allergy & Immunology, 2022. **62**(3): p. 519-533.
[83] Dayneka, N.L., V. Garg, and W.J. Jusko, *Comparison of Four Basic Models of Indirect Pharmacodynamic Responses.* J Pharmacokinet Biopharm, 1993. **21**(4): p. 457-78.

Chapter 3 – Integrated Exposure-Response of Dupilumab in Pediatric, Adolescent, and Adult Patients with Atopic Dermatitis using Categorical and Continuous Endpoints: A Population Analysis

3.1 Abstract

Atopic dermatitis (AD) is a chronic skin disease affecting all ages. Dupilumab has shown efficacy in reducing signs and symptoms of AD in adults, adolescents and children. The objective of this work was to develop a population exposure-response (E-R) model, using pooled data from six clinical trials (N=2,968 patients), to predict efficacy of dupilumab across age groups after adjusting for confounding factors.

A sequential PK/PD approach was applied where the empirical Bayes predictions of the individual PK parameters from previously developed PK models were incorporated when fitting the E-R model, along with actual dosing histories. Separate population E-R analyses were conducted for continuous Eczema Area and Severity Index (EASI) and categorical Investigator's Global Assessment (IGA) endpoints. For each endpoint, placebo response was modeled before accounting for drug effect. Indirect response models were developed to link measures of efficacy and functional dupilumab concentrations. For the categorical efficacy measure, a latent variable approach was used. Covariates assessed included body weight, age, race, baseline eosinophil count, and baseline thymus and activation-regulated chemokine, as well as extrinsic factors of topical corticosteroid-co-administration and prior exposure to systemic immunotherapies.

The final semi-mechanistic indirect response model adequately described the observed data. Drug concentrations achieving half the maximum effect (IC50) were estimated as 20.3 and 27.1 mg/L for the EASI and IGA analyses, respectively. In both E-R models, age was not a statistically significant covariate on drug effect parameters. These models can allow evaluation of potential differences in E-R across age groups as well as simulation of clinical scenarios not yet studied for dupilumab.

3.2 Study highlights

3.2.1 What is the current knowledge on the topic?

Dupilumab reduced signs and symptoms of AD in adults and adolescents with moderate-to-severe disease, and in children with severe AD. Weight-tiered dose regimens supported by population pharmacokinetic modeling and discrete empirical exposure-response analyses are available. However, no integrated exposure-response (E-R) analysis across age groups accounting for confounding factors such as differing placebo responses, baseline disease, and concomitant therapy has been performed.

3.2.2 What question did this study address?

This study aimed to quantify the relationship between two efficacy measures, continuous Eczema Area and Severity Index (EASI) and categorical Investigator's Global Assessment (IGA), and dupilumab concentrations in an integrated analysis across pediatric, adolescent, and adult patients with AD.

3.2.3 What does this study add to our knowledge?

Semi-mechanistic E-R models were developed that characterized relationships between EASI and IGA response with dupilumab concentrations.

3.2.4 How might this change drug discovery, development, and/or therapeutics?

These model analyses will allow direct comparison of E-R relationships between pediatric, adolescent, and adult patients with AD, and allow the simulation of prospective studies under differing clinical scenarios.

3.3 Introduction

Atopic dermatitis (AD) is a chronic skin disease characterized by inflammation and pruritis. According to the Global Burden of Disease (GBD) study from 2017, AD has the highest burden of all skin diseases [1]. Moreover, AD is a heterogeneous disease in both time of onset and duration, with some patients presenting with symptoms early in life, while others develop symptoms late into adulthood (late-onset). Some patients experience symptoms for their entire lives, while others outgrow the disease in adolescence or early adulthood [1].

Diagnostic criteria for atopic dermatitis is based on a list of core features described by the American Academy of Dermatology (Table 3.1), which includes the presentation of chronic eczema and family history of IgE reactivity [2]. Severity of AD is determined via subjective assessments such as the continuous Eczema Area and Severity Index (EASI) and the categorical Investigator's Global Assessment (IGA), which are used as co-primary endpoints of clinical trials for atopic dermatitis treatment in the European Union (EU) [3-7]. In addition, several biomarkers are correlated with disease severity in children and adults, such as thymus and activation-regulated chemokine (TARC), a member of the TH2 chemokine family, and blood eosinophil levels [8, 9]. In general, all patients with AD have strong T-helper (TH) 2 activation; however, some ethnic differences exist as Asian patients had stronger TH17/TH22 activation than African American and European American patients [10].

Dupilumab (Dupixent®, Regeneron Pharmaceuticals), a fully human VelocImmune®-derived monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13 [11-13]. Dupilumab has been shown to be effective in treating moderate-to-severe AD in adult and pediatric populations, as well as several

other Type 2 inflammatory disorders, including asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP) [3-7, 14-17].

The goal of this analysis was to fit semi-mechanistic models to the dupilumab concentration and clinical endpoint data in order to predict specific response outcomes across three age groups (i.e., pediatric, adolescent, and adult patients with AD). The analysis also addressed key parameters of interest such as the maximum inhibitory drug effect (Imax) and the steady-state concentration that achieves 50% of the maximum effect (IC_{50}) for dupilumab in patients with AD. Population exposure-response (E-R) models were developed for two efficacy endpoints, EASI and IGA, using data from patients with AD who were administered placebo or subcutaneous (SC) injections of dupilumab in clinical trials.

3.4 Methods

3.4.1 Study Participants

Data from one Phase 2b and five Phase 3 clinical studies were pooled to support the population E-R analyses, including one study in children with severe AD (R668-AD-1652), one study in adolescents with moderate or severe AD (R668-AD-1526), and four studies in adults with moderate or severe AD (R668-AD-1021, R668-AD-1416,6 R668-AD-1334, R668-AD-1224) [3, 5-7]. Across all studies and age groups, dupilumab was administered subcutaneously, with a single loading dose administered on Day 1 equivalent to twice the maintenance dose, either alone or with concomitant topical corticosteroids (TCS). Individual study designs and clinical trial identifiers are listed in Table 3.2. Study protocols were approved by medical ethics committees and institutional review boards of the participating centers, and all patients or their caregivers provided written informed consent before enrollment.

3.4.2 Bioanalytical Assay

Serum samples for quantitation of functional dupilumab were analyzed using a validated enzyme-linked immunosorbent assay (ELISA). Dupilumab was used as the assay standard and human IL-4 receptor alpha (IL-4Rα) served as the capture reagent. Concentrations of dupilumab with either one or two available binding sites were measured (functional drug). The assay did not detect dupilumab when both sIL-4Rα (soluble form) binding sites were occupied, or when at least one site was bound to mIL-4Rα (membrane bound form). The lower limit of quantitation (LLOQ) of functional dupilumab is 0.078 mg/L in undiluted human serum [18].

3.4.3 Eczema Area and Severity Index (EASI)

EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. The EASI score calculation is based on the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score (based on the % body surface area [BSA] affected) where 0 = 0% BSA, 1 = 1 to 9% BSA, 2 = 10 to 29% BSA, 3 = 30 to 49% BSA, 4 = 50 to 69% BSA, 5 = 70 to 89% BSA, 6 = 90 to 100% BSA [19].

For each major section of the body (head, upper extremities, trunk, and lower extremities), EASI score = (E+I+X+L) x Area Score. The total EASI score is the weighted total of the section EASI using the weights 10% = head, 20% = upper extremities, 30% = trunk, 40% = lower extremities. The minimum possible EASI score is 0 and the maximum possible EASI score is 72, with a higher score indicating increased extent and severity of atopic dermatitis. The formula is provided as:

$$EASI = \sum_{i \in B} (E_i + I_i + X_i + L_i) \cdot A_i w_i$$

The sum is taken over the set of body regions (B = [head and neck, upper extremities, trunk, lower extremities]) with corresponding set of weights of W = (w_h, w_u, w_t, w_l) = (0.1, 0.2, 0.3, 0.4) for ages ≥ 8 years and W = (w_h, w_u, w_t, w_l) = (0.2, 0.2, 0.3, 0.3) for ages <8 years.

3.4.4 Investigator's Global Assessment (IGA)

IGA score is a five-point scale (ranging from 0 to 4) to assess atopic dermatitis disease severity, where higher scores indicate greater severity. IGA uses clinical characteristics, such as

erythema, lichenification and oozing, to assess disease severity. Descriptions of each point for the IGA scale are shown in Table 3.3 [20].

3.4.5 Modeling software

Nonlinear mixed effects modeling methodology was implemented in this analysis using NONMEM® (version 7.3) software (ICON Development Solutions, Ellicott City, MD) [21]. Pre- and post-processing of data from each modeling step and graphical analysis of the data was performed using R software (version 3.6.1) [22].

The first-order conditional estimation method with interaction was used in the EASI analysis, and the Laplacian conditional estimation method was used in the IGA analysis. NONMEM model code and a sample of the NONMEM dataset for final models are provided in Appendix A and Appendix B – IGA Final Model.

3.4.6 Population Exposure-Response Model Development

A sequential modeling approach was applied using previously developed population pharmacokinetic (popPK) analyses performed separately for dupilumab administered in adult, adolescent (≥12 to <18 years), and pediatric (≥6 to <12 years) patients for input to the E-R models [23]. The popPK models consisted of two-compartment disposition with parallel linear and nonlinear (Michaelis-Menten) elimination and first-order absorption following SC dosing. Post-dose samples below the LLOQ were excluded. The final parameter estimates for each model are provided in Table 3.4.

Individual predicted PK parameters were incorporated when fitting the E-R model, along with actual dosing histories of each patient and efficacy observations. The functional form of the EASI response model was specified as:

$$EASI = f_{baseline} + f_{non-drug}(t) + f_{drug}\big(E(t)\big) + \varepsilon$$

where $f_{baseline}$ is the baseline component, $f_{non\text{-}drug}$ is the non-drug (placebo) time component, f_{drug} is the drug (exposure) component, $E(t)$ represents drug exposure as a function of time (t), and ε is the residual error assumed to be normally distributed with mean 0 and variance equal to σ^2 (i.e., $\varepsilon \sim N(0, \sigma^2)$).

Based on an understanding of the mechanism of action of dupilumab, an indirect response model was developed to link efficacy endpoints and functional dupilumab concentrations. Indirect response models have been well characterized in the literature and used when there is a temporal delay between peak drug concentrations and maximum drug response [24]. One such model can be represented by inhibition of k_{in} (Type I indirect-response model):

$$\frac{dR}{dt} = k_{in} \cdot \left(1 - \frac{Imax \cdot C(t)}{IC_{50} + C(t)}\right) - k_{out} \cdot R$$

where R denotes the response variable with initial condition $R_0 = k_{in}/k_{out}$ = BASE, k_{in} is the rate constant for indirect response production, k_{out} is the rate constant for indirect response elimination, $Imax$ is the maximum inhibitory drug effect, IC_{50} is the concentration at which 50% of the maximum effect is achieved and $C(t)$ is the drug concentration at time t.

Given the ordered categorical nature of IGA scores, an extension of the indirect response model was applied by incorporating a latent variable component. The latent variable is an unobservable variable that can be mapped to ordered categorical data [25]. The following form was used to represent the model, posited on the probit scale:

$$probit\ Pr(IGA \leq m) = f_{baseline}(m) + f_{non-drug}(t) + f_{drug}\big(E(t)\big)$$

$$\frac{dR}{dt} = k_{out} \cdot \left[1 - \frac{C(t)}{IC_{50} + C(t)}\right] - k_{out} \cdot (R + 1), \qquad k_{out} = \frac{\ln(2)}{THFD}$$

where the terms $f_{baseline}$, $f_{non\text{-}drug}$, and f_{drug}, represent the baseline, nondrug (or placebo), and drug functions, respectively, t represents time, and $E(t)$ represents drug exposure as a function of time.

The model was defined using the probit scale, where $probit = \Phi^{-1}$, $\Phi(\cdot)$ is the cumulative normal distribution function, and *m* represents the observed IGA score.

The baseline $f_{baseline}(m)$ component is defined recursively as:

$$f_{baseline}(m) = Q_m;\ \ Q_m = \begin{cases} BASE & m = 3 \\ Q_m = Q_{m+1} - exp(\beta_{m+1}) & 0 \le m \le 2 \end{cases}$$

where BASE is the baseline function for an IGA value of 3 and β_{m+1}, $m \in \{0,1,2\}$, are parameters that adjust the thresholds for the corresponding observed IGA values.

For both endpoints, inter-individual variability was modeled using a log-normal distribution and the residual error was described using an additive error model. Covariates were selected based on clinical relevance and mechanistic plausibility and tested simultaneously to form a full model followed by a stepwise backward elimination procedure. Covariates evaluated as part of the full covariate model included extrinsic factors (TCS co-administration and prior exposure of systemic immunotherapies), baseline demographic parameters (body weight, age and race) and baseline disease severity markers (eosinophil count, thymus and activation-regulated chemokine [TARC], and baseline IGA score). The backward elimination procedure was associated with a significance level of α=0.001. At each step, the covariate-parameter relationship which had the lowest change in the objective function value (OFV) and did not meet the inclusion criteria was eliminated, and the stepwise backward elimination procedure was repeated until all covariate-parameters met the inclusion criteria or were eliminated.

3.4.7 Population Exposure-Response Model Evaluation

Models were assessed using Akaike's Information Criterion (AIC), goodness-of-fit plots, precision of parameter estimates, and stability of the model. To avoid ill-conditioning, inspection of the covariance matrix of estimates at every stage of model development was performed in order to verify that extreme pairwise correlations ($\rho > 0.95$) of the parameters were not encountered. The

condition number was also assessed to ensure values less than 1000, above which would indicate a severely ill-conditioned model [26].

The predictive performance of the E-R models was evaluated using visual predictive checks (VPCs) [27]. Parameter estimates were fixed to the final values from the model and used to simulate 500 datasets which replicated the designs, patient populations, dose regimens, sample sizes, and covariate distributions of the pooled analysis dataset.

3.5 Results

The analysis included a total of 2,968 patients with AD (2,366 adults, 243 adolescents [age ≥12 to <18 years] and 359 pediatric subjects [age ≥6 to <12 years] with 29,413 EASI observations (24,921 samples in adults, 1,705 in adolescents [age ≥12 to <18 years] and 2,787 in pediatric subjects [age ≥6 to <12 years]) and 29,420 IGA observations (24,926 samples in adults, 1,706 in adolescents [age ≥12 to <18 years] and 2,788 in pediatric subjects [age ≥6 to <12 years]) shown in Table 3.5.

In the pooled dataset, more than half of the patients were male (58.1%) and the vast majority were given dupilumab without TCS co-administration (64.4%). Most patients were White (67.2%), whereas 8.1% of subjects were Black, 21.1% of subjects were Asian, 0.1% of patients were Native American, 0.2% were Pacific Islanders, 2.5% of patients were other race, and 0.9% were of unknown race. Most patients (68.2%) had no prior exposure to systemic immunotherapies. Patients had a median age of 31 years (range 6-88 years) and a median weight of 70 kg (range 15.3 – 175.4 kg). Overall, there was a wide range of baseline disease severity biomarkers such as TARC serum levels and eosinophil counts, with a median and range of 2034 pg/mL (15.7 – 130,262 pg/mL) and 0.48 $x10^9$/L (0 – 7.6$x10^9$/L), respectively. The median baseline EASI score was 30.8 (range 10.7 – 72), and more than half of the patients had severe AD characterized by a baseline IGA score of 4 (54.2%). However, 99.6% of pediatric subjects [age ≥6 to <12 years] had severe AD. Additional covariate summaries are shown in Table 3.6 and Table 3.7.

3.5.1 Exposure-Response Model

EASI was modeled as a continuous variable by transforming the bounded outcome score (range 0–72). The transformation of the EASI score was evaluated, and the model was postulated on the transformed scale: $(EASI + 1)^{0.4}$. Meanwhile, IGA was modeled using a latent variable

approach, in which the unobserved drug effect was mapped to the probability of response falling in each of the ordered categories (range 0–4).

The relationship of the efficacy endpoints (EASI or IGA) with dupilumab concentration and time was best described by an indirect response model, as shown in Figure 3.1 where dupilumab inhibits the production of response with rate constant k_{in} according to an Imax function. The model is considered semi-mechanistic, as it follows from the inhibitory action of dupilumab on IL-4 and IL-13 signaling, and consequent reduction in the inflammatory response, although these effects cannot themselves be measured. The indirect response model provides the framework to assess the effect of dupilumab on the measurable responses of EASI and IGA, which are postulated to represent inhibitory effects on factors governing the inflammation response in type 2 inflammatory disorders. Reduction in score, for both EASI and IGA, represents an improvement in AD symptoms.

Estimated parameters for both models are reported in Table 3.8. Inspection of standard diagnostic plots suggested good agreement between observed and predicted response for the pooled population and for those populations stratified by age classification (pediatric, adolescent, and adult patients). Dupilumab is efficacious in yielding a reduction in both EASI scores and IGA scores. The concentration achieving half the maximum effect (IC_{50}) were estimated as 20.3 and 27.1 mg/L for the EASI and IGA analyses, respectively. Both efficacy endpoints found similar statistically significant covariates on the drug effect parameter; specifically baseline body weight, baseline eosinophil count, and Asian race. Furthermore, age was not a significant covariate on drug-effect parameters.

Visual predictive checks (VPCs) were performed to assess the predictive performance of the dupilumab final models for EASI and IGA score. The VPC results are stratified by age group

(pediatric, adolescent, and adult patients) and treatment regimen, as shown in Figure 3.2. Both models described the data successfully, as observed responses were largely contained within the 90% confidence interval (CI).

The half-life of placebo effect onset was approximately 4 weeks for EASI and 1 week for IGA. The indirect response models predicted a delay in the effect of dupilumab for both EASI and IGA endpoints. Based on half-life estimates of drug onset (2.0 weeks for EASI and 2.8 weeks for IGA), the full effect of dupilumab would be reached after approximately 2 months for EASI and 3 months for IGA (~ 4-5 half-lives).

3.5.2 Model Applications

The impact of pharmacodynamic (PD) covariate effects on predicted placebo corrected EASI score and the proportion of patients achieving IGA scores of 0 or 1 (IGA 0/1 responders) in the final model were visually assessed using a forest plot. Comparator patients were simulated for each covariate condition differing from the reference subject only in the covariate value being tested. Note that the predicted differences reflect only PD effects, as the dupilumab exposure was held constant for all simulated patients. Results are illustrated in Figure 3.3.

Baseline body weight demonstrated a larger effect on placebo corrected EASI score for pediatric patients 6 to 12 years old (baseline body weight 21 to 41 kg), with greater improvement in EASI score compared to reference adult patients. Placebo corrected EASI score showed a larger effect (more negative score) with higher TARC (25422 pg/mL) and a smaller effect (less negative score) with lower TARC (344 pg/mL), relative to the TARC median value. Asian patients were predicted to have less improvement in placebo corrected EASI score than White patients.

No covariates were found to be clinically relevant for the placebo-corrected proportion of IGA 0/1 responders when compared to reference adult patients. This suggests that the stringent outcome of IGA 0/1 at Week 16 is not as sensitive as placebo corrected EASI scores.

3.6 Discussion

Dupilumab has demonstrated efficacy in the treatment of AD over a wide range of patient ages (6 years of age to adulthood). Due to variations in the design of clinical trials, it is difficult to directly compare the E-R of dupilumab across age groups. To address this dilemma, we conducted an integrated population E-R analysis using a data set comprised of 2,968 AD patients across ages ranging from 6 to 88 years.

Semi-mechanistic exposure-response models were developed to characterize continuous (EASI) and categorical (IGA) measures of AD severity with dupilumab treatment. The placebo model for each endpoint was an empirical maximum inhibitory time effect model, indicating some improvement in response measures with time for patients receiving sham SC injections. The half-life of placebo effect onset was approximately 4 weeks for EASI and 1 week for IGA. The indirect response models predicted a delay in the effect of dupilumab for both EASI and IGA endpoints. Based on half-life estimates of drug onset (2.0 weeks for EASI and 2.8 weeks for IGA), the full effect of dupilumab would be reached after approximately 2 months for EASI and 3 months for IGA (~ 4-5 half-lives). Dupilumab IC_{50} (95% CI) values were estimated as 20.3 (16.1, 25.5) mg/L for EASI and 27.1 (21.3, 34.4) mg/L for IGA (on the latent scale), which are approximately 2- to 2.5-fold below expected dupilumab mean steady-state trough concentrations for all FDA-approved dose regimens for AD [28]. The differences in the IC_{50} values suggest that EASI is a more sensitive assessment than IGA, as would be expected when comparing a 72-point continuous scale (EASI) with a 5-point categorical scale (IGA).

Several patient factors were assessed as potential sources of variability in efficacy response, including intrinsic factors of body weight, age, race, baseline eosinophil count, and baseline TARC, as well as extrinsic factors of TCS co-administration and prior exposure to

systemic immunotherapies. Both efficacy endpoints found similar statistically significant covariates on the drug effect parameter; specifically, baseline body weight, baseline eosinophil count and Asian race. In simulations evaluating PD covariates in isolation, no covariates were clinically significant when comparing the placebo corrected proportion of IGA 0/1 responders to adult reference subjects. Whilst simulating EASI scores, patients with body weight ≤ 40 kg demonstrated a larger dupilumab effect relative to reference patients with body weight of 70 kg. Higher baseline TARC, a type 2 chemokine correlated with higher baseline disease severity, predicted a larger EASI change from baseline than the reference. Asian patients were predicted to have lower dupilumab response possibly due to greater T_H17/T_H22 cell activation compared to African/European Americans, which is not targeted by dupilumab. These simulations do not account for expected differences in dupilumab PK, which can be found in Chapter 4.

The depth of observed data available across age groups provided a platform to perform integrated analyses to directly compare the E-R relationships between pediatric, adolescent, and adult populations, and to simulate clinical scenarios not yet studied.

Assumptions were necessary for clinical trial simulations as the scenarios were not studied, namely the impact of covariates in pediatric populations – i.e., TCS co-administration and baseline disease severity. Data from pediatric patients with moderate AD could be used to validate the assumptions made. Furthermore, data from pediatric patients <6 years of age were not available at the time of the analysis and future applications of this model should include these data.

In summary, modeling and simulation provided an integrated assessment of the exposure-response for dupilumab under equivalent clinical scenarios not yet studied pediatric, adolescent, and adult patients with AD. Further comparisons of response across age groups are provided in *Chapter 4*. Given the success of comparing dupilumab under similar E-R conditions in the three

age groups studied, it may be possible to justify full extrapolation (i.e., PK bridging) of dupilumab dosing in pediatric patients with other type 2 inflammatory disorders.

Tables and Figures

Table 3.1 Diagnostic criteria for atopic dermatitis according to the American Academy of Dermatology

Essential features	• Pruritus
	• Eczema (acute, subacute, chronic)
	  o Typical morphology and age-specific patterns*
	  o Chronic or relapsing history
	• *Patterns include:
	  o Facial, neck, and extensor involvement in infants and children
	  o Current or previous flexural lesions in any age group
	  o Sparing of the groin and axillary regions

Important features	• Early age of onset
	• Atopy
	  o Personal and/or family history
	  o Immunoglobulin E reactivity
	• Xerosis

Associated features (non-specific for atopic dermatitis)	• Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response) • Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis • Ocular/periorbital changes • Other regional findings (e.g., perioral changes/periauricular lesions) • Perifollicular accentuation/lichenification/prurigo lesions

Table adopted from [3].

Table 3.2 Summary of Studies Included in the Population Modeling Analysis

Study ID (Phase) [Age Group]	**AD Severity (IGA score)**	**Dosage/Drug Regimen[a]**	**No. Patients (Completed TRT/Planned)[b]**	**IGA and EASI Score Timepoints (Study Week)**
R668-AD-1652, NCT03345914 (Phase 3) [Children 6 – 11]	Severe (IGA=4)	Day 1 loading dose: 2x maintenance dose • Dupilumab SC Q2W + TCS: ○ 100 mg for patients <30 kg ○ 200 mg for patients ≥30 kg • Dupilumab 300 mg SC Q4W + TCS • Placebo SC Q2W + TCS[d]	N = 367 Placebo: 114/123 Dupilumab: 237/244	Screening, Baseline, Week 1, 2, 3, 4, 8, 12, EOT (Week 16), Follow-Up Period (Week 20, 24), EOS (Week 28), Unscheduled Visit, Early Termination[e]
R668-AD-1526, NCT03054428 (Phase 3) [Adolescents 12-17]	Moderate (IGA=3) Severe (IGA=4)	Day 1 loading dose: 2x maintenance dose • Dupilumab SC Q2W: ○ 200 mg for patients <60 kg ○ 300 mg for patients ≥60 kg • Dupilumab 300 mg SC Q4W • Placebo SC Q2W	N = 251 Placebo: 76/85 Dupilumab: 155/166	Screening, Baseline, Week 1, 2, 3, 4, 8, 12, EOT (Week 16), Follow-Up Period (Week 20, 24), EOS (Week 28), Unscheduled Visit, Early Termination
R668-AD-1021, NCT01859988 (Phase 2b) [Adults 18-75]	Moderate (IGA=3) Severe (IGA=4)	Day 1 loading dose: 2x maintenance dose (4x for 100 mg SC Q4W only) • Dupilumab ○ 100 mg SC Q4W ○ 300 mg SC Q4W ○ 200 mg SC Q2W ○ 300 mg SC Q2W ○ 300 mg SC QW • Placebo SC QW	N = 380 Placebo: 53/61 Dupilumab: 294/319	Screening, Baseline, Week 1, 2, 3, 4, 6, 8, 10, 12, 14, 15, EOT (Week 16), 18, 20, 22, 24, 26, 28, 30, EOS (Week 32), Unscheduled Visit, Early Termination

R668-AD-1416, NCT02277769[c] (Phase 3) [Adults 18-75]	Moderate (IGA=3) Severe (IGA=4)	Day 1 loading dose: 2x maintenance dose • Dupilumab 300 mg SC QW • Dupilumab 300 mg SC Q2W • Placebo SC QW	N = 708 Placebo: 190/236 Dupilumab: 441/472	Screening, Baseline, Week 1, 2, 4, 6, 8, 12, EOT (Week 16), Follow-Up Period (Week 20, 24), EOS (Week 28), Unscheduled Visit, Early Termination[e]
R668-AD-1334, NCT02277743[c] (Phase 3) [Adults 18-75]	Moderate (IGA=3) Severe (IGA=4)	Day 1 loading dose: 2x maintenance dose • Dupilumab 300 mg SC QW • Dupilumab 300 mg SC Q2W • Placebo SC QW	N = 671 Placebo: 184/224 Dupilumab: 405/447	Screening, Baseline, Week 1, 2, 4, 6, 8, 12, EOT (Week 16), Follow-Up Period (Week 20, 24), EOS (Week 28), Unscheduled Visit, Early Termination
R668-AD-1224, NCT02260986 (Phase 3) [Adults 18-75]	Moderate (IGA=3) Severe (IGA=4)	Day 1 loading dose: 2x maintenance dose • Dupilumab 300 mg SC QW + TCS • Dupilumab 300 mg SC Q2W + TCS • Placebo SC QW + TCS	N = 740 Dupilumab: 400/425 Placebo: 282/315	Screening, Baseline, Week 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, EOT (Week 52), Follow-Up Period (Week 56, 60), EOS (Week 64), Unscheduled Visit, Early Termination

[a] Dupilumab dosages are doubled for loading dose administered on Day 1. For consistency, the placebo amount administered on day 1 was also doubled to match the dupilumab loading doses.

[b] The study completion frequencies include only subjects that have completed week 16 of treatment (excludes patients in ongoing studies).

[c] Studies R668-AD-1416 and R668-AD-1334 are replicate phase 3 clinical trials in adults with moderate-to-severe AD (– TCS)

[d] Patients (<30 kg) randomly assigned (1:1 ratio) to Q2W SC PBO injections matching the 100 mg dupilumab or Q4W SC PBO injections matching the 300 mg dupilumab. Patients (≥30 kg) randomly assigned (1:1 ratio) to Q2W SC PBO injections matching the 200 mg dupilumab or Q4W SC PBO injections matching the 300 mg dupilumab. The placebo amount is doubled to match the loading dose on day 1.

[e] IGA and EASI assessment score timepoints are reported from the Study Protocol (not the CSR).

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; EASI75, ≥75% improvement from baseline in EASI; EOS, end of study; EOT, end of treatment; IGA, Investigator's Global Assessment; N, number of patients; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; TCS, topical corticosteroid;

Derived from Study Protocols [3-7].

Table 3.3 Investigator Global Assessment Description

IGA Score	**Description**
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost Clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Table adopted from [20].

Table 3.4 Final Population Pharmacokinetic Parameter Estimates

Parameter Name	**Children ≥6 to <12 years**	**Adolescents ≥12 to <18 years**	**Adults ≥18 years**
PK Parameter			
V_2 (L)	2.18 (0.0872)	2.47 (0.0501)	2.74 (0.021)
Ke (1/day)	0.0446 (0.00152)	0.0520 (0.00188)	0.0477 (0.00078)
V_m (mg/L/day)	1.64 (fixed)	1.43 (0.0379)	1.07 (fixed)
K_{23} (1/day)	0.211 (fixed)	0.211 (fixed)	0.211 (fixed)
K_{32} (1/day)	0.310 (fixed)	0.310 (fixed)	0.310 (fixed)
Ka (1/day)	0.641 (fixed)	0.306 (fixed)	0.306 (fixed)
MTT (day)	0.105 (fixed)	0.105 (fixed)	0.105 (fixed)
K_m (mg/L)	0.01 (fixed)	0.01 (fixed)	0.01 (fixed)
F (unitless)	0.642 (fixed)	0.642 (fixed)	0.642 (fixed)
Covariates			
V_2 ~ Weight	0.849 (0.0345)	0.755 (0.0517)	0.817 (0.031)
V_2 ~ Albumin	-0.525 (0.149)	---	-0.653 (0.072)
Ke ~ BMI	---	0.357 (0.116)	0.368 (0.053)
Ke ~ ADA	---	0.193 (0.05666)	0.164 (0.029)
Ke ~ EASI	0.169 (0.0471)	0.356 (0.0523)	0.143 (0.021)
Ke ~Race (White)	---	---	-0.123 (0.018)
Omega Matrix			
$\sigma(\ln(V_2))$	0.291 (0.0204)	0.140 (0.0145)	0.206 (0.0068)
$\sigma(\ln(K_e))$	0.417 (0.0282)	0.304 (0.0242)	0.293 (0.010)
Corr$(\ln(K_e), \ln(V_2))$	-0.883 (0.0212)	-0.529 (0.0902)	-0.450 (0.035)
Residual SD			
σ_{prop} (CV%)	13.1 (0.402)	9.94 (0.602)	12.5 (0.18)
σ_{add} (mg/L)	0.03 (fixed)	2.36 (0.24)	6.06 (0.23)

Parameter Name	Children ≥6 to <12 years	Adolescents ≥12 to <18 years	Adults ≥18 years
Derived Parameters			
CL (L/day)	0.0972	0.128	0.131
Q (L/day)	0.460	0.521	0.578
V_3 (L)	1.48	1.68	1.86

ADA, anti-drug antibody; BMI, body mass index; EASI, Eczema Area and Severity Index.

Table 3.5 Summary of patients and PD endpoint observations

Age Group	Number of patients	Number (%) of observations	
		EASI	IGA
Adults	2366 (79.7%)	24921 (84.7%)	24926 (84.7%)
Adolescents (12 to <18 years)	243 (8.2%)	1705 (5.8%)	1706 (5.8%)
Children (6 to <12 years)	359 (12.1%)	2787 (9.5%)	2788 (9.5%)
Total	2968 (100%)	29413 (100%)	29420 (100%)

EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment.

Table 3.6 Summary of baseline disease status and treatment variables for the patients included in the population E-R analysis, by age group and treatment

Covariate	Adults	Adolescents	Children	Total
Patients (n)	2366	243	359	2968
Age (years)				
Minimum	18	12	6	6
Mean (SD)	37.7 (13.7)	14.4 (1.7)	8.5 (1.7)	32.2 (16.4)
Median	36	14	9	30.5
Maximum	88	17	11	88
Body Weight (kg)				
Minimum	38.9	31.0	15.3	15.3
Mean (SD)	76.1 (18.5)	65.0 (21.8)	31.5 (10.4)	69.8 (23.2)
Median	73.6	58.9	29.8	69.6
Maximum	175.4	173.6	79.1	175.4
Body Mass Index (kg/m^2)				
Minimum	15.7	15.3	12.5	12.5
Mean (SD)	26.1 (5.7)	24.3 (6.6)	17.8 (3.6)	25.0 (6.2)
Median	25.0	22.5	16.9	24.1
Maximum	58.1	66.8	35.2	66.8
Missing, n (%)	2 (0.1%)	0 (0%)	0 (0%)	2 (0.07%)
Body Surface Area (m^2)				
Minimum	1.27	1.07	0.67	0.67
Mean (SD)	1.89 (0.26)	1.70 (0.31)	1.06 (0.21)	1.77 (0.37)
Median	1.87	1.64	1.04	1.80
Maximum	2.93	2.79	1.81	2.93
Missing, n (%)	2 (0.1%)	0 (0%)	0 (0%)	2 (0.07%)
Sex				
Male, n (%)	1403 (59.3%)	143 (58.8%)	179 (49.9%)	1725 (58.1%)

Female, n (%)	963 (40.7%)	100 (41.2%)	180 (50.1%)	1243 (41.9%)
Race				
White, n (%)	1592 (67.3%)	154 (63.4%)	248 (69.1%)	1994 (67.2%)
Black, n (%)	150 (6.3%)	29 (11.9%)	60 (16.7%)	239 (8.1%)
Asian, n (%)	561 (23.7%)	36 (14.8%)	28 (7.8%)	625 (21.1%)
Native Hawaiian or other Pacific Islander, n (%)	3 (0.1%)	3 (1.2%)	1 (0.3%)	7 (0.2%)
American Indian or Alaska Native, n (%)	2 (0.1%)	1 (0.4%)	1 (0.3%)	4 (0.1%)
Other, n (%)	41 (1.7%)	15 (6.2%)	17 (4.7%)	73 (2.5%)
Not Reported, n (%)	17 (0.7%)	5 (2.1%)	4 (1.1%)	26 (0.9%)
Japanese Ethnicity				
No, n (%)	2099 (88.7%)	243 (100%)	359 (100%)	2701 (91.0%)
Yes, n (%)	267 (11.3%)	0 (0%)	0 (0%)	267 (9.0%)
Prior Exposure of Systemic Immunotherapies				
No, n (%)	1726 (73.0%)	134 (55.1%)	171 (47.6%)	2023 (68.2%)
Yes, n (%)	40 (27.0%)	109 (44.9%)	188 (52.4%)	945 (31.8%)
TCS Co-administration				
No, n (%)	1667 (70.5%)	243 (100%)	0 (0%)	1910 (64.4%)
Yes, n (%)	699 (29.5%)	0 (0%)	359 (100%)	1058 (35.6%)
Baseline IGA Score				
Moderate AD (IGA = 3)	1245 (52.6%)	112 (46.1%)	1 (0.3%)	1358 (45.8%)
Severe AD (IGA = 4)	1121 (47.4%)	131 (53.9%)	358 (99.7%)	1610 (54.2%)
Baseline EASI Score				
Minimum	10.7	16.2	17.7	10.7
Mean (SD)	32.6 (13.4)	35.5 (14.1)	37.9 (11.7)	33.5 (13.4)
Median	29.6	32.8	36.2	30.8

Maximum	72.0	70.8	72.0	72.0
Baseline TARC (pg/mL)				
Minimum	58.4	183	15.7	15.7
Mean (SD)	6625 (13576)	5960 (9414)	3511 (6967)	6203 (12706)
Median	2255	2260	1620	2034
Maximum	130262	61900	97100	130262
Missing, n (%)	8 (0.3%)	4 (1.6%)	11 (3.1%)	23 (0.8%)
Baseline EOS ($x10^9$/L)				
Minimum	0	0.3	0	0
Mean (SD)	0.58 (0.55)	0.83 (0.65)	0.83 (0.62)	0.63 (0.57)
Median	0.40	0.64	0.70	0.48
Maximum	7.6	4.0	4.3	7.6
Missing, n (%)	5 (0.2%)	0 (0%)	4 (1.1%)	9 (0.3%)

EASI, Eczema Area and Severity Index; EOS, eosinophil count; IGA, Investigator's Global Assessment; N, number of patients; SD, standard deviation; TARC, thymus and activation-regulated chemokine; TCS, topical corticosteroid.

Table 3.7 Summary of baseline disease status and treatment variables for the patients included in the population E-R analysis, by age group and treatment

Covariate	**Adults**			
	Placebo	**Placebo +TCS**	**Dupilumab**	**Dupilumab +TCS**
Patients (n)	498	303	1169	396
Baseline EASI Score				
Minimum	15.2	16.0	10.7	16.0
Mean (SD)	33.9 (14.4)	32.6 (13.0)	32.2 (13.3)	32.3 (12.8)
Median	31.0	30.0	29.2	29.3
Maximum	72.0	70.8	72.0	69.6
Baseline IGA Score, n (%)				
Moderate AD (IGA = 3)	254 (51.0%)	164 (54.1%)	612 (52.4%)	215 (54.3%)
Severe AD (IGA = 4)	244 (49.0%)	139 (45.9%)	557 (47.6%)	181 (45.7%)
Baseline TARC (pg/mL)				
Minimum	75	154	91	58.4
Mean (SD)	6359 (11913)	7145 (13082)	6312 (12995)	7489 (17126)
Median	2149.5	2752.9	1999.5	2554.5
Maximum	130262	128000	128000	128000
Missing, n (%)	2 (0.4%)	2 (0.7%)	3 (0.3%)	1 (0.3%)
Baseline EOS ($x10^9$/L)				
Minimum	0	0.05	0	0
Mean (SD)	0.61 (0.61)	0.55 (0.45)	0.58 (0.53)	0.53 (0.57)
Median	0.40	0.42	0.40	0.40
Maximum	7.6	3.0	4.4	6.8
Missing, n (%)	2 (0.4%)	1 (0.3%)	2 (0.2%)	0 (0%)

Covariate	Adolescents		Children	
	Placebo	**Dupilumab**	**Placebo +TCS**	**Dupilumab +TCS**
Patients (n)	83	160	120	239
Baseline EASI Score				
Minimum	16.6	16.2	17.7	21.0
Mean (SD)	35.32 (13.7)	35.7 (14.4)	39.0 (11.9)	37.4 (11.5)
Median	31.6	33.4	38.4	35.4
Maximum	70.8	70.8	72.0	69.6
Baseline IGA Score, n (%)				
Moderate AD (IGA = 3)	39 (47.0%)	73 (45.6%)	0 (0%)	1 (0.4%)
Severe AD (IGA = 4)	44 (53.0%)	87 (54.4%)	120 (100%)	238 (99.6%)
Baseline TARC (pg/mL)				
Minimum	183	183	15.7	15.7
Mean (SD)	6079 (10657)	5897 (8731)	4027 (6434)	3257 (7215)
Median	2045	2630	1660	1570
Maximum	61900	60100	33800	97100
Missing, n (%)	1 (1.2%)	3 (1.9%)	5 (4.2%)	6 (2.5%)
Baseline EOS ($x10^9$/L)				
Minimum	0.03	0.08	0.1	0
Mean (SD)	0.85 (0.68)	0.82 (063)	0.85 (0.66)	0.82 (0.60)
Median	0.63	0.64	0.70	0.70
Maximum	3.1	4.0	4.1	4.3
Missing, n (%)	0 (0%)	0 (0%)	2 (1.7%)	2 (0.8%)

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; EOS, eosinophil count; IGA, Investigator's Global Assessment; n, number of patients; SD, standard deviation; TAR, thymus and activation-regulated chemokine; TCS, topical corticosteroid

Table 3.8 Parameter estimates of the dupilumab exposure-response final models for IGA score and EASI

Parameter[a]	IGA Model		EASI Model	
	Estimate (% RSE)	95% CI	Estimate (% RSE)	95% CI
Fixed Effects				
BASE (EASI score units)	--	--	30.4 (0.4)	(29.8, 31.0)
Baseline for IGA≤3	-3.35 (3.6)	(-3.59, -3.12)	--	--
Baseline adjustment for IGA≤2	2.64	(2.59, 2.69)	--	--
Baseline adjustment for IGA≤1	1.60	(1.56, 1.63)	--	--
Baseline adjustment for IGA≤0	1.75	(1.70, 1.79)	--	--
Maximum placebo effect (Pmax)	4.83 (2.5)	(4.60, 5.06)	-1.24 (2.6)	(-1.30, -1.17)
ET_{50} (days)	6.37 (3.0)	(5.72, 7.09)	29.2	(27.5, 31.0)
Drug effect (IGA: DSLP, EASI: Imax)	-2.20 (3.1)	(-2.33, -2.07)	0.266 (2.7)	(0.252, 0.280)
IC_{50} (mg/L)	27.1	(21.3, 34.4)	20.3	(16.1, 25.5)
Half-life for drug effect onset (day)	19.7	(18.2, 21.4)	--	--
Covariate Effects				
Moderate IGA baseline additive shift	4.39 (3.0)	(4.14, 4.65)	--	--
TCS on BASE	--	--	-0.0218 (27.9)	(-0.0338, -0.00987)
Prior immunotherapy on BASE	--	--	0.0233 (27.5)	(0.0107, 0.0358)
Age on BASE	--	--	-0.0372 (13.4)	(-0.0470, -0.0274)
Log baseline eosinophil count on BASE	--	--	0.0173 (15.6)	(0.0120, 0.0225)
Log baseline TARC on BASE	--	--	0.0508 (4.4)	(0.0464, 0.0552)
Age on PMAX	0.0550 (21.3)	(0.0320, 0.0780)	--	--
TCS on PMAX	0.229 (8.1)	(0.193, 0.266)	0.232 (16.9)	(0.156, 0.309)
Prior Immunotherapy on PMAX	-0.102 (13.1)	(-0.128, -0.0756)	-0.166 (18.2)	(-0.225, -0.107)
Moderate disease severity on PMAX	-0.727 (1.7)	(-0.751, -0.703)	--	--
Baseline body weight on Drug Effect	-0.174 (26.1)	(-0.263, -0.0852)	-0.185 (23.3)	(-0.270, -0.101)
Asian race on Drug Effect	-0.222 (14.2)	(-0.284, -0.160)	-0.374 (8.3)	(-0.434, -0.313)
Log baseline EOS on Drug Effect	-0.0776 (19.3)	(-0.107, -0.0482)	-0.0570 (29.3)	(-0.0897, -0.0242)
Log baseline TARC on Drug Effect	-0.0938 (13.4)	(-0.118, -0.0692)	--	--
Residual Variability - Additive	--	--	0.422 (0.5)	(0.418, 0.426)
IIV				
IGA Base Additive (ω^2)	1.49 (3.4)	(1.39, 1.59)		
EASI BASE-Exponential (ω^2)	--	--	0.0177 (3.4)	(0.0165, 0.0189)
EASI PMAX-Additive (ω^2)	--	--	0.788 (3.7)	(0.730, 0.846)
OFV	51593.055		-9277.145	
CN	200		20.4	

CI, confidence interval, CN, condition number DSLP, drug effect slope; EASI, Eczema Area and Severity Index; EOS, eosinophil count; ET_{50}, time at which 50% of maximum placebo effect is achieved; IC_{50}, concentration at which 50% of the maximum effect is achieved; IGA, Investigator's Global Assessment; IIV, interindividual variability; Imax, Maximum drug effect; OFV, objective function value; PMAX, maximum placebo effect; RSE, relative standard error (%); TARC, thymus and activation-regulated chemokine; TCS, topical corticosteroid;.
Note: Eta shrinkage 8.62% (IGA BASE); 11.8% (EASI BASE); 14.3% (EASI PMAX)

EASI Model Equations:

$$(EASI + 1)^{\lambda} = BASE + \frac{P_{max} * Time}{ET_{50} + Time} + IDR, \qquad \lambda = 0.4$$

$$\frac{dR}{dt} = k_{in} \cdot \left[1 - \frac{E_{max} \cdot C}{EC_{50} + C}\right] - k_{out} \cdot R, \qquad k_{in} = k_{out} * BASE$$

where IDR = Indirect response function; *Pmax* = maximum placebo effect; ET_{50} is the time at which 50% of maximum placebo effect; R = Response; k_{in} = Rate constant for indirect response production; k_{out} = Rate constant for indirect response elimination; C = Dupilumab concentration.

IGA Model equations:

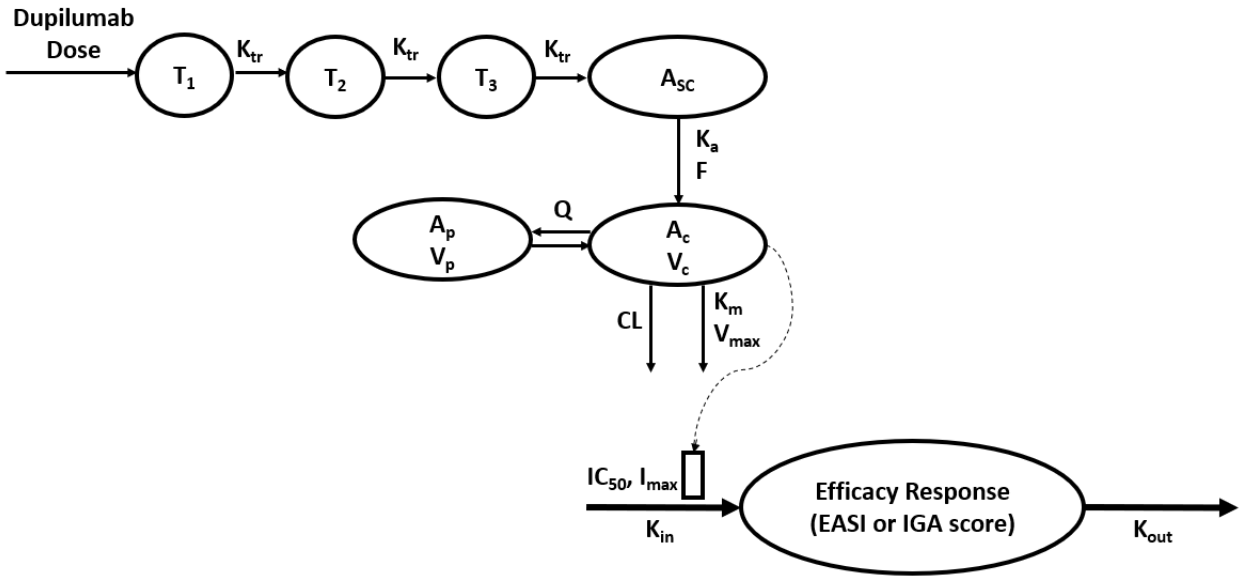
$$probit\ Pr(IGA \leq m) = \mathrm{Q_m} + \frac{P_{max} * Time}{ET_{50} + Time} + DSLP * R$$

$$Q_m = \begin{cases} BASE & m = 3 \\ Q_m = Q_{m+1} - exp(\beta_{m+1}) & 0 \leq m \leq 2 \end{cases}$$

$$\frac{dR}{dt} = k_{out} \cdot \left[1 - \frac{C}{EC_{50} + C}\right] - k_{out} \cdot (R + 1), \qquad k_{out} = \frac{\ln(2)}{THFD}$$

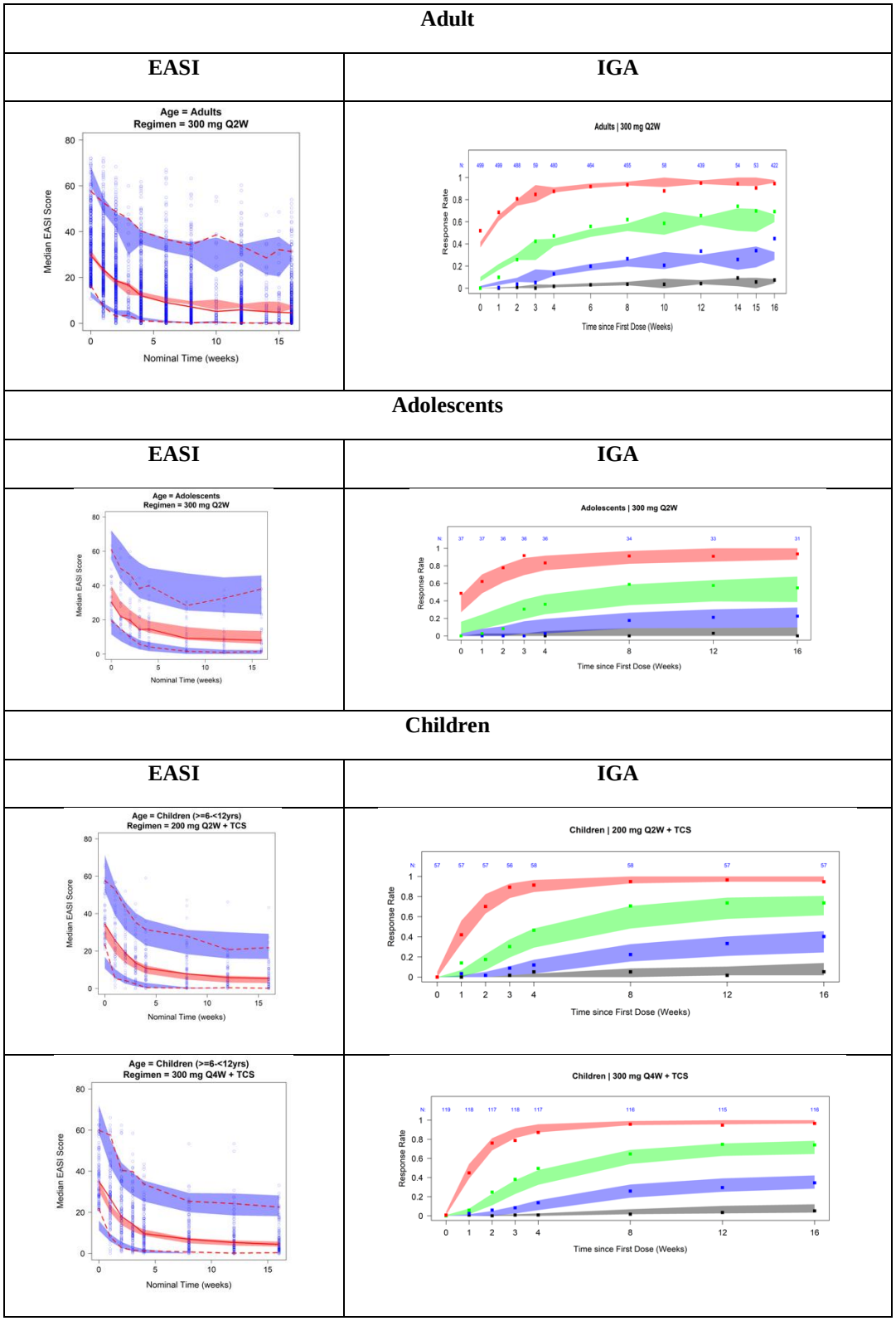
where BASE is the baseline function for an IGA value of 3 and β_{m+1}, $m \in \{0,1,2\}$, are parameters that adjust the thresholds for the corresponding observed IGA values; *Pmax* = maximum placebo effect; ET_{50} is the time at which 50% of maximum placebo effect; k_{out} = Rate constant for indirect response elimination; C = Dupilumab concentration; THFD = Half-life for drug effect onset (day).

Figure 3.1 E-R Model Diagram



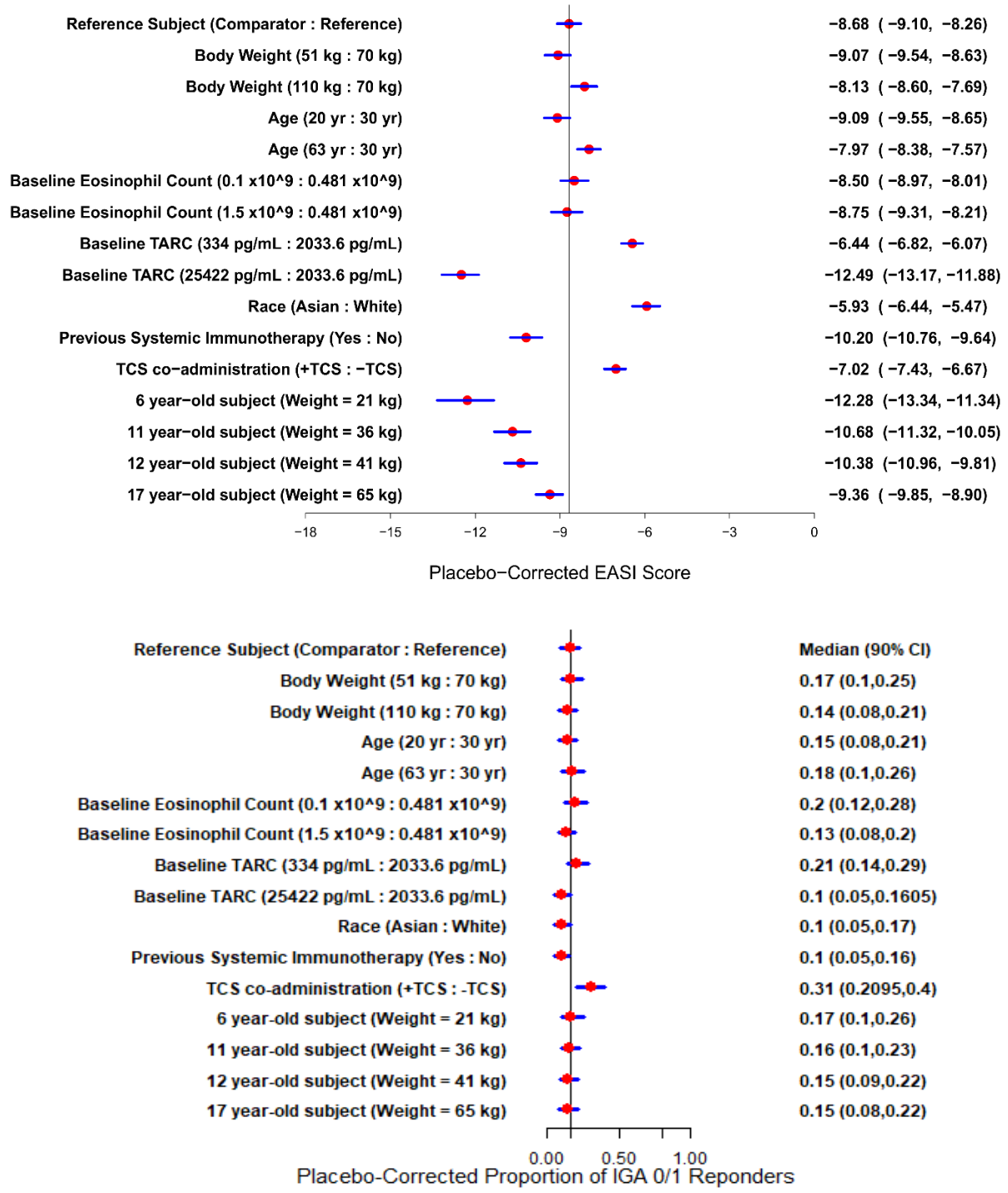
A_c, amount in central compartment; A_{sc}, amount in subcutaneous depot compartment; A_p, amount in peripheral compartment; CL, linear clearance; IC_{50}, concentration at which 50% of the maximum effect is achieved; EASI, Eczema Area and Severity Index; F, bioavailability; IGA, Investigator's Global Assessment; Imax, maximum drug effect; K_a, absorption rate constant; k_{in}, rate constant for indirect response production; K_m, the concentration at which the rate of elimination is half of the maximum value; k_{out}, rate constant for indirect response elimination; k_{tr}, rate constant for transit compartment; Q, inter-compartmental clearance; T_i, transit compartment *i*; Vmax, the maximum rate of elimination via the nonlinear pathway; V_c, volume of distribution in central compartment; V_p, volume of distribution in peripheral compartment.

Figure 3.2 Visual Predictive Check (VPC) for E-R Model



EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroid.

Figure 3.3 Covariate Effects on Placebo-Corrected EASI scores and Placebo-Corrected Proportions of IGA0/1 Responders



EASI, Eczema Area and Severity Index; IGA 0/1, proportions of patients achieving an Investigator's Global Assessment score of 0 or 1; Q2W, every 2 weeks; TARC, thymus and activation-regulated chemokine; TCS, topical corticosteroid

References

[1] Laughter, M.R., et al., *The Global Burden of Atopic Dermatitis: Lessons from the Global Burden of Disease Study 1990–2017**. British Journal of Dermatology, 2021. **184**(2): p. 304-309.

[2] Eichenfield, L.F., et al., *Guidelines of Care for the Management Of atopic dermatitis: Section 1. Diagnosis and Assessment of Atopic Dermatitis.* Journal of the American Academy of Dermatology, 2014. **70**(2): p. 338-351.

[3] Blauvelt, A., et al., *Long-Term Management of Moderate-to-Severe Atopic Dermatitis with Dupilumab and Concomitant Topical Corticosteroids (Liberty Ad Chronos): A 1-Year, Randomised, Double-Blinded, Placebo-Controlled, Phase 3 Trial.* The Lancet, 2017. **389**(10086): p. 2287-2303.

[4] Paller, A.S., et al., *Efficacy and Safety of Dupilumab with Concomitant Topical Corticosteroids in Children 6 to 11 years Old with Severe Atopic Dermatitis: A Randomized, Double-Blinded, Placebo-Controlled Phase 3 Trial.* Journal of the American Academy of Dermatology, 2020. **83**(5): p. 1282-1293.

[5] Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab Versus Placebo in Atopic Dermatitis.* New England Journal of Medicine, 2016. **375**(24): p. 2335-2348.

[6] Simpson, E.L., et al., *Efficacy and Safety of Dupilumab in Adolescents with Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial.* JAMA Dermatology, 2020. **156**(1): p. 44-56.

[7] Thaçi, D., et al., *Efficacy and Safety of Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis Inadequately Controlled by Topical Treatments: A Randomised, Placebo-Controlled, Dose-Ranging Phase 2b Trial.* Lancet, 2016. **387**(10013): p. 40-52.

[8] Ha E.K., K.J.H., Lee S.W., Jee H.M., Shin Y.H., Baek H.S., Han M.Y., *Atopic Dermatitis: Correlation of Severity with Allergic Sensitization and Eosinophilia.* Allergy and Asthma Proceedings, 2020. **41**(6): p. 428-435.

[9] Kataoka, Y., *Thymus and Activation-Regulated Chemokine as a Clinical Biomarker in Atopic Dermatitis.* The Journal of Dermatology, 2014. **41**(3): p. 221-229.

[10] Brunner, P.M. and E. Guttman-Yassky, *Racial Differences in Atopic Dermatitis.* Annals of Allergy, Asthma & Immunology, 2019. **122**(5): p. 449-455.

[11] Le Floc'h, A., et al., *Dual Blockade of Il-4 and Il-13 with Dupilumab, an Il-4rα Antibody, Is Required to Broadly Inhibit Type 2 Inflammation.* Allergy, 2020. **75**(5): p. 1188-1204.

[12] Macdonald, L.E., et al., *Precise and in Situ Genetic Humanization of 6 Mb of Mouse Immunoglobulin Genes.* Proceedings of the National Academy of Sciences of the United States of America, 2014. **111**(14): p. 5147-5152.

[13] Murphy, A.J., et al., *Mice with Megabase Humanization of Their Immunoglobulin Genes Generate Antibodies as Efficiently as Normal Mice.* Proc Natl Acad Sci U S A, 2014. **111**(14): p. 5153-8.

[14] Bacharier, L.B., et al., *Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma.* New England Journal of Medicine, 2021. **385**(24): p. 2230-2240.

[15] Bachert, C., et al., *Efficacy and Safety of Dupilumab in Patients with Severe Chronic Rhinosinusitis with Nasal Polyps (Liberty Np Sinus-24 and Liberty Np Sinus-52): Results from Two Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials.* The Lancet, 2019. **394**(10209): p. 1638-1650.

[16] Castro, M., et al., *Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma.* New England Journal of Medicine, 2018. **378**(26): p. 2486-2496.
[17] Rabe, K.F., et al., *Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma.* New England Journal of Medicine, 2018. **378**(26): p. 2475-2485.
[18] Davis, J.D., et al., *Evaluation of Potential Disease-Mediated Drug–Drug Interaction in Patients with Moderate-to-Severe Atopic Dermatitis Receiving Dupilumab.* Clinical Pharmacology & Therapeutics, 2018. **104**(6): p. 1146-1154.
[19] Hanifin J.M., T.M., Omoto M., Cherill R., Tofte S.J., Graeber M., EASI Evaluator Group, *The Eczema Area and Severity Index (Easi): Assessment of Reliability in Atopic Dermatitis.* Experimental Dermatology, 2001. **10**(1): p. 11-18.
[20] Council, E., *Validated Investigator Global Assessment Scale for Atopic Dermatitis Viga-Ad™*, Validated-Investigator-Global-Assessment-Scale_vIGA-AD_2017.pdf, Editor. 2017: www.eczemacouncil.org.
[21] Beal S., S.L.B., Boeckmann A., Bauer R.J., *Nonmem User's Guides (1989-2016)*. 2016, Icon Development Solutions: Ellicott City, MD, USA.
[22] Team, R.C., *R: A Language and Environment for Statistical Computing*. 2013, R Foundation for Statistical Computing: Vienna, Austria.
[23] Kovalenko, P., et al., *Exploratory Population Pk Analysis of Dupilumab, a Fully Human Monoclonal Antibody against Il-4rα, in Atopic Dermatitis Patients and Normal Volunteers.* CPT Pharmacometrics Syst Pharmacol, 2016. **5**(11): p. 617-624.
[24] Sharma, A. and W.J. Jusko, *Characteristics of Indirect Pharmacodynamic Models and Applications to Clinical Drug Responses.* Br J Clin Pharmacol, 1998. **45**(3): p. 229-39.
[25] Hutmacher, M.M., S. Krishnaswami, and K.G. Kowalski, *Exposure-Response Modeling Using Latent Variables for the Efficacy of a Jak3 Inhibitor Administered to Rheumatoid Arthritis Patients.* Journal of Pharmacokinetics and Pharmacodynamics, 2007. **35**(2): p. 139.
[26] Montgomery D.C., P.E.A., Vining G.G., *Introduction to Linear Regression Analysis*. Vol. 821. 2012, Hoboken: John Wiley & Sons.
[27] Bergstrand, M., et al., *Prediction-Corrected Visual Predictive Checks for Diagnosing Nonlinear Mixed-Effects Models.* The AAPS Journal, 2011. **13**(2): p. 143-151.
[28] *Dupixent (Dupilumab). Highlights of Prescribing Information.*, FDA, Editor. 2021: USA.

Chapter 4 – Integrated Exposure-Response of Dupilumab in Atopic Dermatitis Patients: Clinical Insights and Impact on Drug Development

4.1 Abstract

Integrated exposure-response (E-R) models were developed to characterize continuous (EASI) and categorical (IGA) measures in adults, adolescents, and children (6 to 11 years) with atopic dermatitis. Model parameters and covariates for both efficacy endpoints were compared. Clinical scenarios were simulated to directly compare E-R relationships across age. Adults and adolescents showed similar dupilumab E-R relationships, while children demonstrated a comparatively greater E-R, an effect more pronounced in children with severe baseline disease.

4.2 Introduction

An integrated exposure-response (E-R) analysis of dupilumab in adult (aged ≥18 years), adolescent (aged 12 to 17 years), and pediatric (aged 6 to 11 years) patients (N=2,968) with atopic dermatitis (AD) was conducted using non-linear mixed effects methodology (*Chapter 3*). This analysis compared the E-R of dupilumab in these three age groups using the Eczema Area and Severity Index Score (EASI) continuous scale that measures the extent and severity of AD, and the Investigator Global Assessment (IGA) categorical scale that measures the severity of AD [1].

4.3 Comparing Dupilumab E-R using Continuous and Categorical Efficacy Scales

To our knowledge, this is the first E-R analysis to compare continuous versus categorical disease measures using an integrated database spanning adults, adolescents, and children with AD using data from Phase 2 and Phase 3 studies [2-6].

The E-R analysis on EASI and IGA identified common covariates in both placebo and drug response. As expected, topical corticosteroid (TCS) co-administration and exposure to prior immunotherapies predicted a higher placebo response in patients with AD as measured by both the EASI and IGA scales. For dupilumab treatment, lower responses were generally seen in patients with low baseline eosinophil counts, which correlates with less severe Type 2 disease. This is consistent with the pharmacology of dupilumab that downregulates the key cytokines of Type 2 disease, IL-4 and IL-13, by binding to the IL-4 alpha receptor on T cells [5]. Higher body weight and Asian race also correlated with slightly lower dupilumab response. The statistically significant covariates identified in the IGA and EASI E-R analyses are unlikely to be of clinical relevance as no single covariate was found to necessitate dose modification in pediatric, adolescent, and adult patients with AD. On the other hand, some differences between both scales were observed in the covariate analysis. For example, some patients had higher baseline levels of serum thymus and activation-regulated chemokine (TARC), which is a type 2 chemokine that attracts inflammatory cells to tissues and correlates with higher baseline AD disease severity. TARC was a significant covariate on the drug effect parameter for the IGA model. Consequently, a higher baseline level of TARC was found to predict a greater response to dupilumab when using IGA. This prediction did not occur with EASI; TARC was a significant covariate on the baseline parameter for the EASI model but was not a significant covariate on the drug effect parameter. The IGA scale measures the disease severity of AD, whereas the EASI scale measures both the

extent and severity of AD symptoms. The responder rate of IGA was not significantly impacted by any single covariate, whereas TARC was the largest change in EASI response because the increase in baseline EASI score allowed for a larger change in baseline. The inherent differences in the IGA and EASI scales may explain why only the IGA scale was able to predict dupilumab response with higher baseline TARC levels. Overall, both models found biomarkers of AD disease severity, which were impacted during dupilumab treatment.

Another interesting observation was the comparison of estimates of dupilumab drug concentration in serum producing 50% inhibition of maximal effect (IC50), a measure of drug sensitivity, between the IGA and EASI E-R analyses. Consistent with the expectation that a continuous scale would be more sensitive to changes in E-R than a categorical scale, the IC50 estimate for EASI (20.3 mg/L) was lower compared with IGA (27.1 mg/L). Despite the slight difference, the estimates for both scales are consistent with the range of mean target concentrations of dupilumab associated with the maximal drug effect in pediatric, adolescent, and adult patients with AD (70–100 mg/L). When the sigmoidicity constant (γ) equals 1 in the Emax function (as in the case of the E-R analysis for IGA and EASI scales - *Chapter 3*), 4-fold increase of the IC50 is approximately equivalent to the IC90 on the exposure-response curve.

4.4 Comparing Dupilumab E-R across Adults, Adolescents, and Children

The integrated analysis allowed comparison of dupilumab E-R across age groups, namely adults, adolescents, and children 6 to <12 years of age with AD. The similarity of E-R of dupilumab across age groups bears clinical relevance as it has implications on the posology of dupilumab in pediatric patients compared with adults [7].

Empirical E-R analyses previously performed in pediatric patients with AD were deficient compared to the current E-R analysis in that: 1) the analyses were not integrated across adults and pediatric age groups; 2) the analysis did not employ a non-linear mixed effects methodology, which accounted for covariates of E-R and allowed a non-confounded, direct comparison of dupilumab E-R across age groups [7].

The advantages of the integrated analysis are especially important given the differing study designs between Phase 3 studies of adults, adolescents, and children 6–11 years of age [2-6]. For example, while the current analysis (*Chapter 3*) employed adult phase 3 studies of dupilumab administered as monotherapy or in combination with TCS, the adolescent Phase 3 study administered dupilumab as monotherapy whereas the study in children 6-11 years of age administered dupilumab in combination with TCS [2-5]. Other differences include the differing placebo responses between these three age groups and the differing baseline disease severity, namely that the adult and adolescent studies included patients with moderate-to-severe AD, whereas the study in children included only patients with severe AD at baseline. The integrated E-R analysis (*Chapter 3*) allowed simulation of clinical scenarios where factors including concomitant TCS therapy and baseline disease severity were kept constant and where differing placebo responses were corrected for when comparing dupilumab E-R across age groups.

Clinical trial simulations that predicted placebo-corrected efficacy response measures over time after co-administration of approved dose regimens of dupilumab and TCS therapy in severe AD patients across the three age groups is shown in Figure 4.1. The top panel shows continuous EASI as percent change from baseline, whereas the lower 3 panels show three categorical measures of response: probability of achieving 75% reduction from baseline in EASI (EASI-75), 90% reduction from baseline in EASI (EASI-90) and achieving an IGA score of 1 (near clear skin) or 0 (completely clear skin) [IGA (0,1)]. While percent change from baseline in EASI is a more sensitive endpoint than the categorical endpoints, it is difficult to determine what constitutes a clinically significant response. EASI-75 represents a clinically significant EASI response that has become standard for some dermatologists [8]. EASI-90 represents a higher bar of clinical improvement, but is generally equivalent to IGA (0,1) – the gold standard of clinical response in patients with AD. The figure shows that the mean efficacy responses are generally similar for adults and adolescents, but greater for children. However, even for weight-tiered dosing regimens, dupilumab exposure was not entirely uniform across age groups. Adolescents had slightly lower concentrations of dupilumab, and children had slightly higher drug concentrations when compared to adults [7]. As such, it was imperative to simulate scenarios where the efficacy could be visualized while maintaining the dupilumab concentration as a constant, to properly investigate any intrinsic E-R differences between age groups.

In parallel to the scenario presented in Figure 4.1, model-predicted E-R profiles holding Week 16 trough concentrations constant between age groups are presented in Figure 4.2, while other clinical scenarios (varying baseline disease and concomitant TCS therapy) are presented in Figure 4.3, Figure 4.4, and Figure 4.5. As shown in Figure 4.2, even when correcting for differences in dupilumab exposure between age groups, the initial observation still holds: adults

and adolescents showed similar dupilumab E-R, while children 6 to <12 years of age had a higher E-R. While concomitant TCS administration did not appear to affect this finding, the E-R difference between children and adults/adolescents is not as pronounced in patients with moderate baseline disease as for patients with severe baseline disease (Figure 4.2, Figure 4.3, Figure 4.4, and Figure 4.5). Nonetheless, the general observation that dupilumab E-R is higher in children when potential confounding factors are accounted for supports the hypothesis that younger patients may have a higher skew to type 2 inflammation compared to adults. A study by Czarnowicki *et al* found similar results, where flow cytometry of peripheral blood of patients with moderate-to-severe AD showed similar expression of Th2 (T helper type 2) cytokines but a lower expression of Th1 cytokines in children compared with adults in the skin homing CD4 and CD8 T cell subsets [9]. The resulting Th2/Th1 imbalance in children suggests that reduced counter-regulation of Th1 cells in children may contribute to excess Th2 activation.

4.5 Supporting Dupilumab Posology and Dose Selection in Pediatrics

The database of the current analysis provided dose-ranging information to allow full characterization of E-R in adults, adolescents, and children with AD. Results of the integrated analysis (*Chapter 3*) corroborate the selection of weight-tiered regimens in adolescents and children [2-6]. Although alternative regimens studied in the Phase 3 studies of adolescents and children demonstrated efficacy, the approved weight-tiered regimens are supported by this E-R analysis. Plots of drug effect measured by both EASI and IGA over time (Figure 4.1) in pediatric patients who received the approved weight-tiered regimens show maximal effect at Week 16. Moreover, consistent with the empirical E-R analyses, the E-R plots generated by the current integrated analysis (Figure 4.2, Figure 4.3, Figure 4.4, and Figure 4.5) show a plateauing of effect at steady state trough concentrations achieved by the weight-tiered regimens (70–100 mg/L) in adolescents and children.

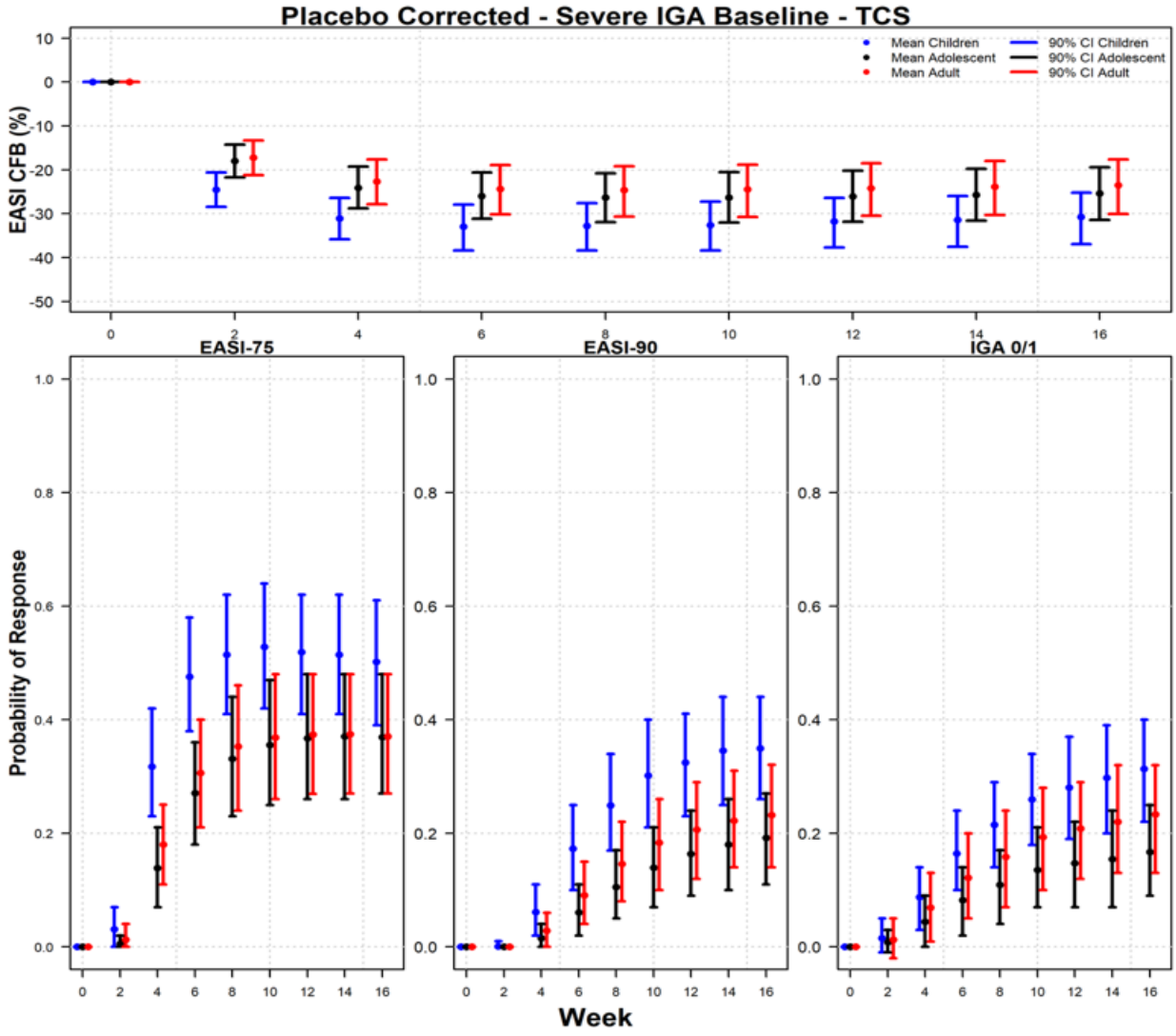
4.6 Impact on Drug Development and Future Directions

The integrated PK/PD model will allow simulation of clinical scenarios of interest not studied prospectively in clinical trials. For example, the impact of administering a loading dose in children on early onset of effect can be evaluated by simulating E-R with and without a loading dose. More importantly, the efficacy of dupilumab is being investigated in pediatric patients with other type 2 inflammatory diseases including, but not limited to, eosinophilic esophagitis, chronic spontaneous urticaria, and asthma. Because the current analysis demonstrated similar (or better) E-R in pediatric patients compared with adults in AD, we may justify full extrapolation (pharmacokinetic bridging) to pediatric patients in scenarios in which conducting prospective, randomized, controlled trials may not be feasible. This is consistent with FDA guidance that details the criteria for full extrapolation of data in pediatric patients receiving biologics [10].

A limitation of the current integrated analysis is the lack of data from younger children <6 years of age, due to the unavailability of these data at the time of database assembly. Future directions will include an extension of the E-R analysis to include data from children <6 years of age.

Tables and Figures

Figure 4.1 Model-Predicted Longitudinal Efficacy Response Profiles for Dupilumab with TCS in Patients with Severe Disease by Age Group, Corrected for Placebo Response



CI, confidence interval; EASI-75/90, ≥75%/90% improvement from baseline in Eczema Area and Severity Index scores; IGA, Investigator's Global Assessment; TCS, topical corticosteroids.

Note: Mean (90% CI) represent summary statistics for 500 simulations in each unique combination of categories (age group, disease severity and TCS co-administration).
Dupilumab dosing regimen in adult AD patients:

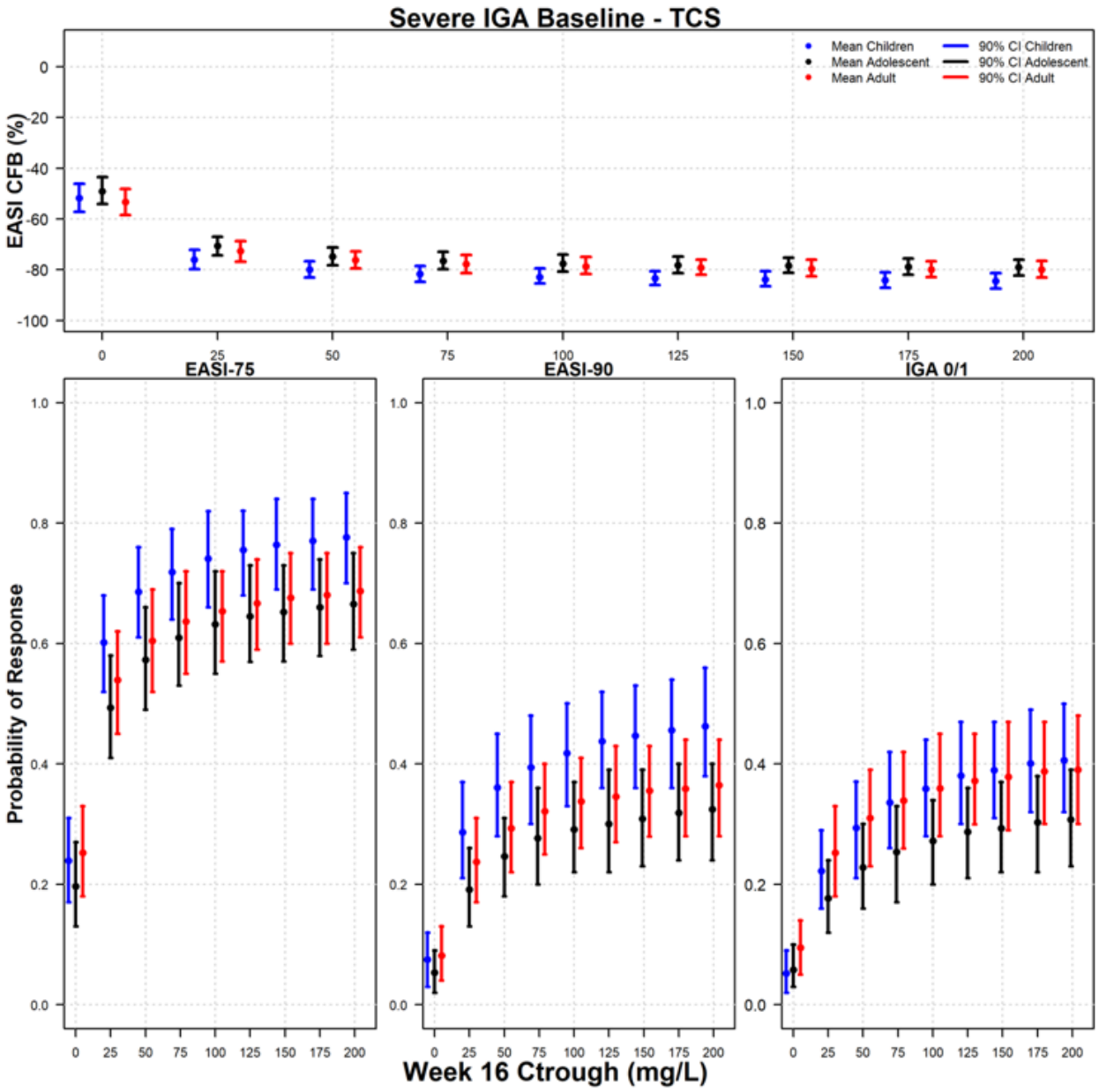
- 600 mg loading dose followed by 300 mg Q2W

Dupilumab dosing regimen in pediatric AD patients (adolescents and children):

- 15 kg to < 30 kg: 600 mg loading dose followed by 300 mg Q4W
- 30 kg to < 60 kg: 400 mg loading dose followed by 200 mg Q2W

≥ 60 kg: 600 mg loading dose followed by 300 mg Q2W (same as adult dose regimen)

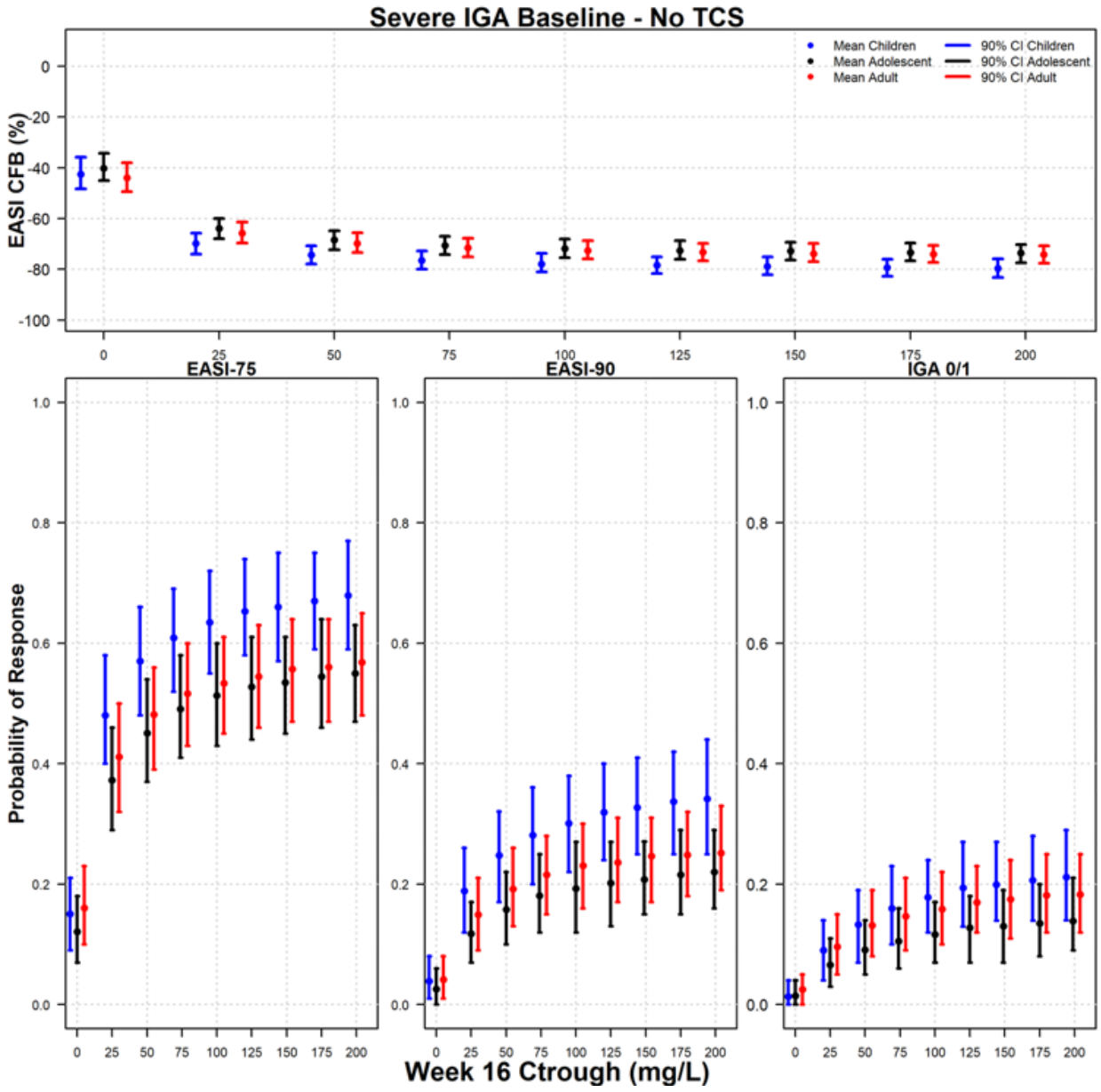
Figure 4.2 Model-Predicted Exposure-Response Profiles at Week 16 for Dupilumab with TCS in Patients with Severe Disease by Age Group



CI, confidence interval; Ctrough, dupilumab concentration at the end of a dosing interval; EASI-75/90, ≥75%/90% improvement from baseline in Eczema Area and Severity Index scores; IGA, Investigator's Global Assessment; TCS, topical corticosteroids.

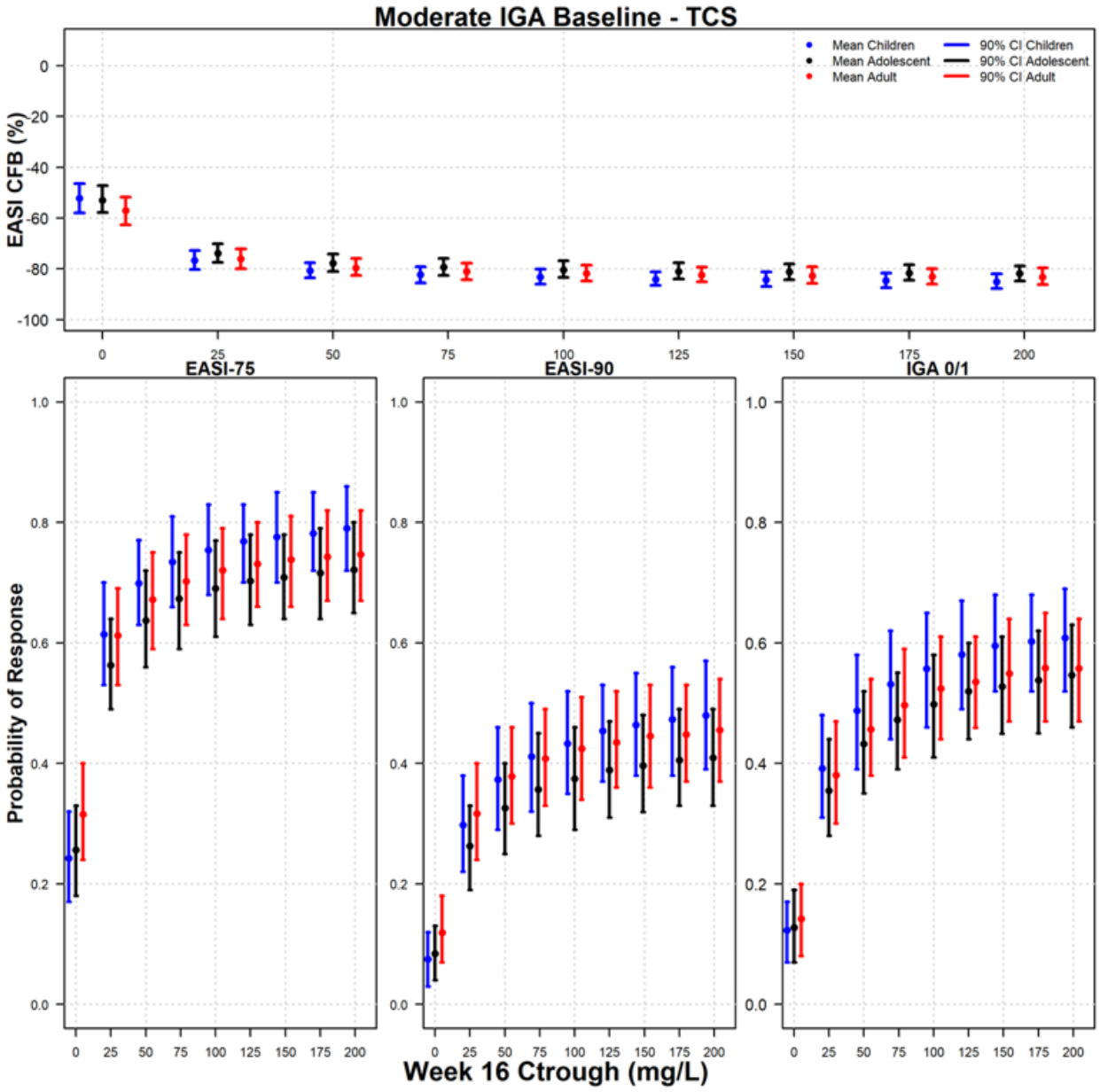
Note: Mean (90% CI) represent summary statistics for 500 simulations in each unique combination of categories (age group, disease severity and TCS co-administration)

Figure 4.3 Model-Predicted Exposure-Response Profiles at Week 16 for Dupilumab without TCS in Patients with Severe Disease by Age Group



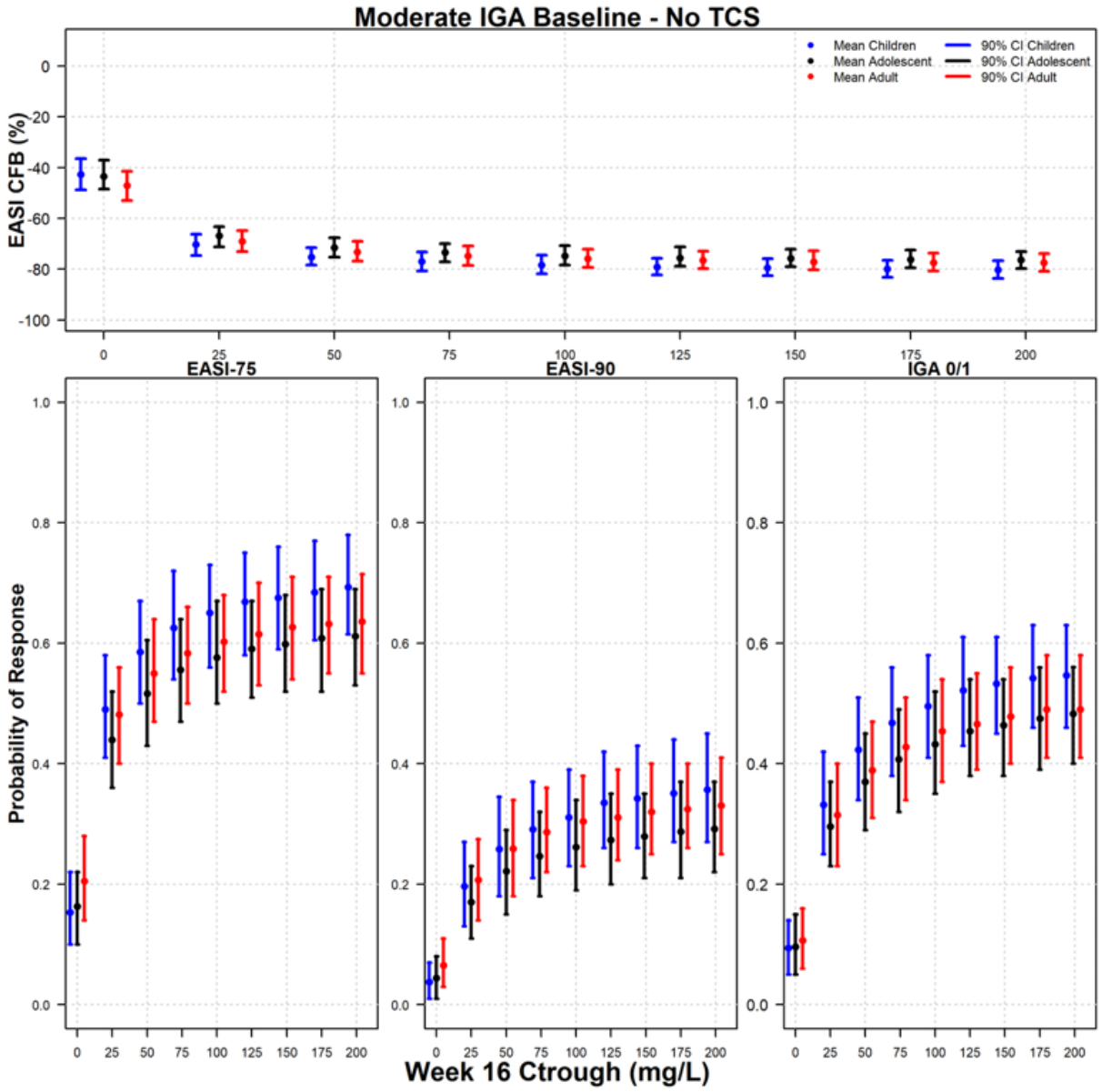
CI, confidence interval; EASI-50/75/90, ≥50%/75%/90% improvement from baseline in Eczema Area and Severity Index scores; IGA, Investigator's Global Assessment; TCS, topical corticosteroids.

Figure 4.4 Model-Predicted Exposure-Response Profiles at Week 16 for Dupilumab with TCS in Patients with Moderate Disease by Age Group



CI, confidence interval; EASI-50/75/90, ≥50%/75%/90% improvement from baseline in Eczema Area and Severity Index scores; IGA, Investigator's Global Assessment; TCS, topical corticosteroids.

Figure 4.5 Model-Predicted Exposure-Response Profiles at Week 16 for Dupilumab without TCS in Patients with Moderate Disease by Age Group



CI, confidence interval; EASI-50/75/90, ≥50%/75%/90% improvement from baseline in Eczema Area and Severity Index scores; IGA, Investigator's Global Assessment; TCS, topical corticosteroids.

References

[1] Leshem, Y.A., et al., *What the Eczema Area and Severity Index Score Tells Us About the Severity of Atopic Dermatitis: An Interpretability Study.* British Journal of Dermatology, 2015. **172**(5): p. 1353-1357.

[2] Blauvelt, A., et al., *Long-Term Management of Moderate-to-Severe Atopic Dermatitis with Dupilumab and Concomitant Topical Corticosteroids (Liberty Ad Chronos): A 1-Year, Randomised, Double-Blinded, Placebo-Controlled, Phase 3 Trial.* The Lancet, 2017. **389**(10086): p. 2287-2303.

[3] Paller, A.S., et al., *Efficacy and Safety of Dupilumab with Concomitant Topical Corticosteroids in Children 6 to 11 years Old with Severe Atopic Dermatitis: A Randomized, Double-Blinded, Placebo-Controlled Phase 3 Trial.* Journal of the American Academy of Dermatology, 2020. **83**(5): p. 1282-1293.

[4] Simpson, E.L., et al., *Two Phase 3 Trials of Dupilumab Versus Placebo in Atopic Dermatitis.* New England Journal of Medicine, 2016. **375**(24): p. 2335-2348.

[5] Simpson, E.L., et al., *Efficacy and Safety of Dupilumab in Adolescents with Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial.* JAMA Dermatology, 2020. **156**(1): p. 44-56.

[6] Thaçi, D., et al., *Efficacy and Safety of Dupilumab in Adults with Moderate-to-Severe Atopic Dermatitis Inadequately Controlled by Topical Treatments: A Randomised, Placebo-Controlled, Dose-Ranging Phase 2b Trial.* Lancet, 2016. **387**(10013): p. 40-52.

[7] Kamal, M.A., et al., *The Posology of Dupilumab in Pediatric Patients with Atopic Dermatitis.* Clinical Pharmacology & Therapeutics, 2021. **110**(5): p. 1318-1328.

[8] Silverberg, J.I., et al., *Dupilumab Provides Important Clinical Benefits to Patients with Atopic Dermatitis Who Do Not Achieve Clear or Almost Clear Skin According to the Investigator's Global Assessment: A Pooled Analysis of Data from Two Phase Iii Trials.* British Journal of Dermatology, 2019. **181**(1): p. 80-87.

[9] Czarnowicki, T., et al., *Early Pediatric Atopic Dermatitis Shows Only a Cutaneous Lymphocyte Antigen (Cla)+ Th2/Th1 Cell Imbalance, Whereas Adults Acquire Cla+ Th22/Tc22 Cell Subsets.* Journal of Allergy and Clinical Immunology, 2015. **136**(4): p. 941-951.e3.

[10] *Fda Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.*, FDA, Editor. 2014.

Chapter 5 – Future Applications

Atopic dermatitis and other type 2 inflammatory diseases may present symptoms early in life and have a specific unmet need that could be addressed with the treatment of dupilumab, a fully human monoclonal antibody that is an interleukin-4 (IL-4) receptor alpha antagonist that blocks IL-4 and IL-13 signaling.

When developing a pediatric development program for a new drug application or biological license application, multiple clinical pharmacology considerations are needed. The FDA recommendations include a thorough understanding of exposure-response in pediatric patients compared to adult patients and describes three possible options for pediatric development programs. The first scenario, in which the pediatric indication is different from the approved adult indication, generally requires a full pediatric development program (i.e., Phase 2 and Phase 3 clinical trials). The second scenario, in which the same indications are observed in pediatric and adult patients, but exposure-response is not directly extrapolatable, requires a confirmatory study and can utilize a partial extrapolation method. The final scenario, in which the indications in pediatric and adult patients, and course of the disease and exposure-response are sufficiently similar across age group, allows for a full extrapolation method.

For the development of dupilumab, a staggered clinical pediatric development program (i.e., clinical trials in adults, followed by adolescents, followed by pediatric patients) was performed within the atopic dermatitis program, as the exposure-response had not been formally characterized across age groups. However, this dissertation has formally analyzed the exposure-

response relationship of dupilumab, and the two efficacy endpoints IGA and EASI, and concluded a sufficiently similar exposure-response relationship across adult, adolescent, and pediatric patients. This is the first time, to the author's knowledge, that an integrated exposure-response analysis was applied over such a wide age range in patients with atopic dermatitis. The predictive models that have been developed in this dissertation provide conclusive evidence that may justify full extrapolation (i.e., pharmacokinetic bridging) to pediatric patients for other type 2 inflammatory diseases in scenarios in which conducting prospective, randomized, controlled trials may not be feasible.

The full extrapolation method would not only provide a financial benefit to the pharmaceutical industry by removing costs of clinical trials and minimizing the time to market in pediatrics, but more importantly would also provide direct ethical benefits to the pediatric populations. With the findings from this dissertation, young children would not need to be unnecessarily enrolled in clinical trials, as the exposure-response relationship of dupilumab in type 2 inflammatory diseases has already been characterized. Both the EMA and FDA explicitly discuss in regulatory documents that young children should not participate in clinical trials unless there are specific objectives that further scientific understanding.

The integrated exposure-response model developed for this dissertation provides a tool to accurately predict clinical trial scenarios not yet studied. As discussed in *Chapter 4*, clinical trial simulations were conducted to compare efficacy across age groups. However, this model may also be used to explore the impact of alternative dosing regimens on efficacy (e.g., loading dose versus no loading dose). To gain further confidence in the model, data in children < 6 years of age, not available at the time of the analysis, could be used as an external validation dataset.

Although this exercise was particular to atopic dermatitis and dupilumab, the framework to model both continuous and categorical endpoints have been described and could be applied to other drugs of clinical significance.

Appendices

Appendix A – EASI Final Model

NONMEM Control File from Chapter 3

```
$PROBLEM EASI ER MODEL
$INPUT  C STDY UID=ID TIME EASI EASITRANS=DV IGABL EVID MDV AMT
          V3I QI CLI MULTI MTTI KTRI KEI K23I K32I KAI VMI KMI V2I
          BIOI WGTBL BMI ALB RACEW RACEA HML DTYPE TCS
          AGE SEXF JPNF TARCBL EOSBL IMMUNO RACEN

$DATA EASI_Data.csv
    IGNORE=@

$SUBROUTINES  ADVAN13 TRANS1 TOL=6

$MODEL COMP=(INJ,DEFDOSE)
     COMP=(BLOOD)
     COMP=(AUC)
     COMP=(KLETKI)
     COMP=(RT1) COMP=(RT2) COMP=(RT2)
     COMP=(PD,DEFOBS)

$PK
 V2    = V2I
 KE    = KEI
 VM    = VMI
 KA    = KAI
 MTT   = MTTI
 BIO   = BIOI
 K23   = K23I
 K32   = K32I
 KM    = KMI
 KTR   = KTRI
 F1    = BIOI
 S2    = V2I
 Q     = QI
 V3    = V3I
 CL    = CLI
 MULT  = MULTI
```

```
;;;;;;;;;;;;;;;;;;;;;;;; COVARIATES ;;;;;;;;;;;;;;;;;;;;;;;;
        ASIAN = 0
        IF(RACEN.EQ.3) ASIAN =1             ; Race = Asian

        BLACK = 0
        IF(RACEN.EQ.2) BLACK =1   ; Race = Black

        OTHER = 0
        IF(RACEN.EQ.4) OTHER =1   ; Race = American Indian/Alaska Native
        IF(RACEN.EQ.5) OTHER =1   ; Race = Native Hawaiian or Pacific
        IF(RACEN.EQ.6) OTHER =1   ; Race = Other

        IMM = 0
        IF(IMMUNO.EQ.1) IMM=1               ; Previous systemic immunotherapy

        COAD = 0
        IF(TCS.EQ.1) COAD = 1               ; TCS co-administration

        AGEREF = 30
        AGE2 = 30                           ; Impute Missing to Median
        IF(AGE.GT.0)AGE2=AGE                ; Age in years

        WTREF = 70
        WT = 70
        IF(WGTBL.GT.0) WT=WGTBL                   ; Weight in kg

        EOSREF = 0.48+0.001
        EOS = 0.48+0.001                          ; Impute Missing to Median
        IF(EOSBL.GE.0) EOS=EOSBL+0.001  ; Baseline Eosinophil Count

        TARCREF = 2033.6
        TARC = 2033.6                       ; Impute Missing to Median
        IF(TARCBL.GT.0)TARC=TARCBL    ; Baseline TARC Count
```

```
;;;;;;;;;;;;;;;;;;;;;;; COVARIATE EFFECTS ;;;;;;;;;;;;;;;;;;;;;;;

;PD PARAMETERS
  TBASE = THETA(1)
  BASE = TBASE*(1+COAD*THETA(10))                ; TCS co-administration on BASE
  BASE = BASE*(1+IMM*THETA(11))                  ; Prior Immunotherapy (IMM) on BASE
  BASE = BASE*((AGE2/AGEREF)**THETA(12))         ; Age (AGE) on BASE
  BASE = BASE*((WT/WTREF)**THETA(13))                    ; Weight (WT) on BASE
  BASE = BASE*(1+(THETA(14)*LOG(EOS/EOSREF)))   ; Baseline Eos on BASE
  BASE = BASE*(1+(THETA(15)*LOG(TARC/TARCREF)))    ; Baseline TARC on BASE
  BASE = BASE*EXP(ETA(1))

;PLACEBO (PLC) EFFECT
  TPMAX = THETA(2)
  PMAX = TPMAX*(1+COAD*THETA(9))                         ; TCS co-administration on PMAX
  PMAX = PMAX*(1+IMM*THETA(16))                  ; Prior Immunotherapy (IMM) on PMAX
  PMAX = PMAX*((AGE2/AGEREF)**THETA(17))    ; Age (AGE) on PMAX
  PMAX = PMAX*((WT/WTREF)**THETA(18))                    ; Weight (WT) on PMAX
  PMAX = PMAX*(1+ASIAN*THETA(19))*(1+BLACK*THETA(20))*(1+OTHER*THETA(21))
         ; RACE on PMAX
  PMAX = PMAX + ETA(2)
  ET50 = EXP(THETA(3))

;DRUG EFFECT
  TEMAX = THETA(4)
  EMAX = TEMAX*(1+IMM*THETA(22))                 ; Prior Immunotherapy (IMM) on EMAX
  EMAX = EMAX*((AGE2/AGEREF)**THETA(23))    ; Age (AGE) on EMAX
  EMAX = EMAX*((WT/WTREF)**THETA(24))                    ; Weight (WT) on EMAX
  EMAX = EMAX*(1+(THETA(25)*LOG(EOS/EOSREF)))       ; Baseline Eos  on EMAX
  EMAX = EMAX*(1+(THETA(26)*LOG(TARC/TARCREF)))           ; Baseline TARC on EMAX
  EMAX = EMAX*(1+ASIAN*THETA(27))*(1+BLACK*THETA(28))*(1+OTHER*THETA(29))
         ; RACE on EMAX
  EMAX = EMAX + ETA(3)

;EC50
  EC50 = EXP(THETA(5))

;KOUT
  KOUT = THETA(6)

;INTIAL CONDITIONS
  A_0(8) = BASE

$DES
  CPX  =  A(2)/S2
  KIN  =  KOUT*BASE
  EFF  =  1-((EMAX*CPX)/(EC50+CPX))
  IND=1                                                          ; All records SC
  DADT(1)= -KTR*A(1)*IND
  DADT(2)= -A(2)*KE-K23*A(2)+K32*A(4)+KA*A(7)*IND-A(2)*VM/(KM+A(2)/V2)
  DADT(3)= A(2)/V2
```

```
  DADT(4)= K23*A(2)-K32*A(4)
  DADT(5) = -KTR*A(5) +KTR*A(1)
  DADT(6) = -KTR*A(6) +KTR*A(5)
  DADT(7) = -KA *A(7) +KTR*A(6)
  DADT(8) =  KIN*EFF - KOUT*(A(8))

$ERROR (OBSERVATION ONLY)
 CP   = A(2)/S2
 IDR  = A(8)

;PLACEBO (PLC) EFFECT --> PMAX Model Structure:
  PLC = PMAX*TIME/(TIME+ET50)
;DRUG EFFECT --> IDR MODEL
  DRG = IDR
  IPRED  = DRG+ PLC ;IDR at TIME=0 is BASE
  W = SQRT(THETA(7)**2*IPRED**2+THETA(8)**2)
  Y=IPRED+EPS(1)*W
  IWRES=(DV-IPRED)/W

$THETA
   4                    ;1   BASE
  -1.5                  ;2   PMAX
   3.1                  ;3   LOG ET50
   0.4                  ;4   EMAX
   2.5                  ;5   LOG EC50
   0.5                  ;6   KOUT
   0 FIX                ;7   W - PROP
  (0, 0.3)              ;8   W - ADDITIVE
  (-1, 0.5)             ;9   TCS on PMAX
  (-1, -0.05)           ;10  TCS on BASE
  (-1, 0.01)            ;11  IMM on BASE
  (-0.05)         ;12  AGE on BASE
(0 FIX)                 ;13  WT on BASE
  (0.01)          ;14  EOSBL on BASE
  (0.1)                 ;15  TARCBL on BASE
  (-1, -0.1)            ;16  IMM on PMAX
(0 FIX)                 ;17  AGE on PMAX
(0 FIX)                 ;18  WT on PMAX
(0 FIX)                 ;19  ASIAN on PMAX
(0 FIX)                 ;20  BLACK on PMAX
(0 FIX)                 ;21  OTHER on PMAX
(0 FIX)                 ;22  IMM on EMAX
  (0 FIX)               ;23  AGE on EMAX
  (-0.1)                ;24  WT on EMAX
  (-0.1)                ;25  EOSBL on EMAX
  (0 FIX)               ;26  TARCBL on EMAX
  (-1, -0.7)            ;27  ASIAN on EMAX
(0 FIX)                 ;28  BLACK on EMAX
(0 FIX)                 ;29  OTHER RACE on EMAX
$OMEGA
   0.05                 ;1   IIV on BASE
```

```
  0.1                     ;2   IIV on PMAX
  0 FIX           ;3   IIV on EMAX
$SIGMA
   1 FIXED
$EST MAXEVAL=8000 PRINT=5 METHOD=1 INTER NOABORT NSIG=2
$COV COMPRESS MATRIX=R PRINT=E
```

Appendix B – IGA Final Model

NONMEM Control File from Chapter 3

```
$PROBLEM DUPILUMAB IGA MODEL

$INPUT  C STDY UID=ID TIME IGA=DV NMWK IGABL EVID MDV AMT NDOSE V3I QI CLI
        MULTI MTTI KTRI KEI K23I K32I KAI VMI KMI V2I BIOI ALB EASI TCS
        RACEN AGE SEXF WGTBL EOSBL TARCBL IMMUNO

$DATA    IGA_Data.csv
      IGNORE=@

$SUBROUTINES  ADVAN13 TRANS1 TOL=6

;Time in Days
;DV = Observed IGA Score
;Drug Effect: IDR model - exposure inhibited production of latent variable

$MODEL
        COMP=(INJ)
        COMP=(BLOOD)
        COMP=(AUC)
        COMP=(KLETKI)
        COMP=(RT1) COMP=(RT2) COMP=(RT2)
        COMP = (PD,DEFOBS)

$PK
V2    = V2I
 KE    = KEI
 VM    = VMI
 KA    = KAI
 MTT   = MTTI
 BIO   = BIOI
 K23   = K23I
 K32   = K32I
 KM    = KMI
 KTR   = KTRI
 F1    = BIOI
 S2    = V2I
 Q     = QI
 V3    = V3I
 CL    = CLI
 MULT  = MULTI
```

```
;;;;;;;;;;;;;;;;;; COVARIATES ;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;

MOD = 0
IF(IGABL.EQ.3) MOD=1          ; Moderate Disease Severity

ASIAN = 0
IF(RACEN.EQ.3) ASIAN =1     ; Race = Asian

BLACK = 0
IF(RACEN.EQ.2) BLACK =1   ; Race = Black

OTHER = 0
IF(RACEN.EQ.4) OTHER =1   ; Race = American Indian/Alaska Native
IF(RACEN.EQ.5) OTHER =1   ; Race = Native Hawaiian or Pacific
IF(RACEN.EQ.6) OTHER =1   ; Race = Other

IMM = 0
IF(IMMUNO.EQ.1) IMM=1      ; Previous systemic immunotherapy

COAD = 0
IF(TCS.EQ.1) COAD = 1          ; TCS co-administration

AGEREF = 30
AGE2 = 30                  ; Impute Missing to Median
IF(AGE.NE.-99)AGE2=AGE    ; Age in years

WTREF = 70
WT = 70
IF(WGTBL.NE.-99) WT=WGTBL        ; Weight in kg

;;;; Log - Transform for EOS and TARC Baseline
;;; Add 0.001 to Eosinophil because there are true 0 values in the observed data.
EOSREF = 0.48+0.001                        ; Reference Med Eosinophil Count
EOS = 0.48+0.001                                 ; Impute Missing to Median
IF(EOSBL.GE.0) EOS=EOSBL+0.001  ; Baseline Eosinophil Count

TARCREF = 2033.6
TARC = 2033.6                        ; Impute Missing to Median
IF(TARCBL.GT.0)TARC=TARCBL     ; Baseline TARC Count


;PD parameters
 MU_1 = THETA(1)
 BASE = MU_1 + ETA(1)         ; baseline for IGA<=3
 BASE2= EXP(THETA(2))   ; adjust baseline for DV<=2
 BASE1= EXP(THETA(3))   ; adjust baseline for DV<=1
 BASE0= EXP(THETA(4))   ; adjust baseline for DV<=0
```

```
;Placebo Parameters
 PMAX = THETA(5)
 ET50 = EXP(THETA(6))

;Drug Effect Parameters
 DSLP = THETA(7)
 EC50 = EXP(THETA(8))
 THFD = EXP(THETA(9))
 KOUT = LOG(2)/THFD

;Covariates on BASE

;Baseline Disease Severity on BASE
BASE = BASE + MOD*THETA(10)

;Covariates on PMAX
PMAX = PMAX*((WT/WTREF)**THETA(11))*((AGE2/AGEREF)**THETA(12))
PMAX = PMAX*(1+ASIAN*THETA(13))*(1+BLACK*THETA(14))*(1+OTHER*THETA(15))
PMAX = PMAX*(1+COAD*THETA(16))*(1+IMM*THETA(17))*(1+MOD*THETA(18))

;Covariates on DSLP
DSLP= DSLP*((WT/WTREF)**THETA(19))*((AGE2/AGEREF)**THETA(20))
DSLP= DSLP*(1+ASIAN*THETA(21))*(1+BLACK*THETA(22))*(1+OTHER*THETA(23))
DSLP= DSLP*(1+IMM*THETA(24))*(1+MOD*THETA(25))
DSLP= DSLP*(1+THETA(26)*LOG(EOS/EOSREF))*(1+THETA(27)*LOG(TARC/TARCREF))

$DES
  CPX  =  A(2)/S2
  EFF  =  1-CPX/(EC50+CPX)
  IND=1                              ;All records SC
  DADT(1)= -KTR*A(1)*IND
  DADT(2)= -A(2)*KE-K23*A(2)+K32*A(4)+KA*A(7)*IND-A(2)*VM/(KM+A(2)/V2)
  DADT(3)= A(2)/V2
  DADT(4)= K23*A(2)-K32*A(4)
  DADT(5) = -KTR*A(5) +KTR*A(1)
  DADT(6) = -KTR*A(6) +KTR*A(5)
  DADT(7) = -KA *A(7) +KTR*A(6)
  DADT(8) =  KOUT*EFF - KOUT*(A(8)+1)       ;IDR(inhibit production)

$ERROR (OBSERVATION ONLY)
 CP   = A(2)/S2
 LVR  = A(8)

;Placebo Model
 PLACEBO  = PMAX*TIME/(TIME+ET50)

;Drug Effect Model (inhibit production)
DRG  = DSLP*LVR
```

```
A3   = BASE + PLACEBO + DRG
A2   = BASE - BASE2 + PLACEBO + DRG
A1   = BASE - BASE2 - BASE1 + PLACEBO + DRG
A0   = BASE - BASE2 - BASE1 - BASE0 + PLACEBO + DRG

P3   = PHI(A3)                    ; Probability of Category<=3
P2   = PHI(A2)                    ; Probability of Category<=2
P1   = PHI(A1)                    ; Probability of Category<=1
P0   = PHI(A0)                    ; Probability of Category<=0

PR4  = 1- P3                      ; Probability of = 4
PR3  = P3 - P2                    ; Probability of = 3
PR2  = P2 - P1                    ; Probability of = 2
PR1  = P1 - P0                    ; Probability of = 1
PR0  = P0                         ; Probability of = 0

IF (DV.EQ.0) Y = PR0
IF (DV.EQ.1) Y = PR1
IF (DV.EQ.2) Y = PR2
IF (DV.EQ.3) Y = PR3
IF (DV.EQ.4) Y = PR4

$THETA
-3                  ; 1 Base
1                   ; 2 Base2 LOG
 0.5                ; 3 Base1 LOG
 0.5                ; 4 Base0 LOG
 5                  ; 5 Pmax
 2                  ; 6 ET50 Placebo LOG
 -1                 ; 7 Drug Effect Slope
 3                  ; 8 Drug EC50 LOG
 2                  ; 9 Drug Delay Half-Life LOG
4                   ; 10 Moderate_BL Additive Shift
(0 FIX)             ; 11 Weight_PMAX Power Model
0.08                ; 12 Age_PMAX Power Model
(0 FIX)             ; 13 Asian_PMAX Prop
(0 FIX)             ; 14 Black_PMAX Prop Shift
(0 FIX)             ; 15 Other_PMAX Prop Shift
(-1,0.1)            ; 16 TCS_PMAX Prop Shift
(-1,-0.2)           ; 17 IMMUNO_PMAX Prop Shift
(-1,-0.5)           ; 18 Moderate_PMAX Prop Shift
-0.3                ; 19 Weight_DSLP Power Model
(0 FIX)             ; 20 Age_DSLP Power
(-1,-0.3)           ; 21 Asian_DSLP Prop Shift
(0 FIX)             ; 22 Black_DSLP Prop Shift
(0 FIX)             ; 23 Other_DSLP Prop Shift
(0 FIX)             ; 24 IMMUNO_DSLP Prop Shift
(0 FIX)             ; 25 Moderate_DSLP Prop Shift
-0.2                ; 26 EOS_DSLP Log-Linear
-0.2                ; 27 TARC_DSLP Log-Linear
```

```
$OMEGA
 0.5                    ; 1 IIV on Baseline ADD

$EST   MAXEVAL=9999 PRINT=5 METHOD=COND LAPLACIAN LIKELIHOOD NUMERICAL
NOABORT MSF=model.msf NSIG=2

$COV   PRINT=E MATRIX=R COMPRESS
```