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Regulatory Note

Model-Informed Drug Development Approach Supporting Approval of Adalimumab (HUMIRA) in Adolescent Patients with Hidradenitis Suppurativa: a Regulatory Perspective

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Abstract. On October 16, 2018, FDA expanded the adalimumab dosing regimen to adolescent hidradenitis suppurativa (HS) patients 12 years and older, weighing at least 30 kg without new clinical data. This approval was mainly supported by the model-informed drug development approach. Population pharmacokinetic simulations suggest body weight-tiered dosing regimens in adolescent patients will achieve similar exposure to adult patients across all weight range. Adalimumab has a well-established, 16-year long-term safety profile in various diseases in adult and pediatric populations. Current data of adalimumab in the pediatric population demonstrate no exposure-response relationship for adverse events. The effectiveness in adolescent patients was extrapolated from two adequate and well-controlled phase 3 studies in adult patients, assuming similar positive exposure-efficacy relationships in adults and adolescents. This article provides the insight of the application of MIDD on the adalimumab approval in adolescent HS patients and its implication on drug development and regulatory decision especially for pediatrics or rare diseases.

KEY WORDS: adalimumab; hidradenitis suppurativa; model-informed drug development; pediatric drug development; regulatory perspective.

INTRODUCTION

HUMIRA® (adalimumab) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNFα) (1). Since initial US licensure in 2002, adalimumab has become licensed for the following indications in adults: rheumatoid arthritis (RA); psoriatic arthritis (PsA); ankylosing spondylitis (AS); Crohn's disease (CD); plaque psoriasis (PsO); juvenile idiopathic arthritis (JIA); ulcerative colitis (UC); hidradenitis suppurativa (HS); uveitis (2). In the pediatric population, adalimumab is approved for CD patients 6 years and older, and for JIA and uveitis patients 2 years and older. Adalimumab has not been approved by FDA to treat pediatric PsO patients, but was approved by the European Medicines Agency (EMA) to treat pediatric patients with severe chronic PsO (3).

HS is a serious, chronic, recurrent, inflammatory skin disease characterized by multifocal nodules, abscesses, and fistulas, predominantly affecting the axillary, inguinal, mammary, anogenital, and intertriginous regions (4). Disease onset is typically after puberty. HS prevalence in the US adult population is approximately 0.1% and the prevalence among pediatric patients is 0.002%, 0.027%, and 0.114% for those younger than 9 years old, between 10 and 14 years, and between 15 and 17 years, respectively (5). On September 9, 2015, FDA approved adalimumab for the treatment of moderate-to-severe HS in adults, with the recommended dosing regimen of 160 mg initially on day 1, and 80 mg on day 15, followed by maintenance dosing of 40 mg every week (EW) starting from day 29 (2).

On October 16, 2018, FDA expanded the adalimumab dosing regimen to adolescent HS patients 12 years and older, weighing at least 30 kg[2], without additional data from clinical PK or efficacy trials in adolescent HS patients. The recommended dosing regimen in adolescent HS patients is body weight-tiered dosing with a cut-off weight of 60 kg (Table I). Model-informed drug development (MIDD) approach played a pivotal *role* in informing the dose selection and regulatory evaluation in this approval. MIDD refers to the application of quantitative models in facilitating drug development and informing decision-making. It has been increasingly used in drug development and regulatory evaluation (6,7). This article provides the regulatory perspective for the approval of the adalimumab in adolescent HS patients and discusses the implication of MIDD approach on drug

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development and regulatory decision especially for pediatrics or rare diseases.

METHODS

Assessment of Predicted Adalimumab Exposure in Adolescent HS Patients

The pharmacokinetics (PK) of adalimumab in pediatric HS patients has not been characterized in a clinical trial. The exposure of adalimumab in the adolescent HS population was predicted using a population PK (popPK) model established by AbbVie. In brief, the PK of adalimumab was described by a linear one-compartment model with first order absorption and elimination and combined proportional and additive residual error model. The popPK model incorporated the following covariate effects on adalimumab clearance: baseline body weight; baseline C-reactive protein (CRP); anti-drug antibody (ADA) status; serum creatinine concentration; disease type. Also, the popPK model incorporated covariate effects of baseline body weight, disease type and age on volume of distribution. PK data include 521 pediatric patients and 3095 adult patients from 17 clinical studies with several diseases, including RA, CD, PsO, UC, uveitis, and HS. The dosing regimens evaluated ranged from 10 mg every other week (EOW) to 40 mg every week (EW). Most patients in the analysis dataset ($N = 2{,}063$) were treated with 40 mg EOW. Clinical experience and adalimumab exposure are available in patients treated with a loading dose of 80 mg or 160 mg. Simulations based on final popPK modeling were performed to explore various dosing regimens in adolescent HS patients 12 years and older. The exposure metrics (time-averaged concentration, C_{avgss}; trough concentration, $C_{troughss}$; peak concentration at steady state, C_{maxss}) predicted at the proposed dosing regimen in adolescent HS patients were compared to those observed in adult HS patients. C_{avgss} is calculated as the AUC_{ss} divided by the dosing interval.

Safety Extrapolation of Adalimumab in Adolescent HS Patients

No trial safety data are available for adalimumab use in adolescent HS patients. Adalimumab has been studied in several clinical trials in different pediatric populations including pediatric PsO, CD, and JIA. Safety assessment in adolescent HS patients was bridged by evaluating the adalimumab exposure-safety relationship in pediatric patients with JIA ($N = 181$), CD ($N = 179$), and PsO ($N = 72$). The evaluated safety endpoints collected any adverse event (AE) and infectious AE. The predicted adalimumab exposure in adolescent HS patients was compared to observed adalimumab exposure in pediatric patients with PsO, CD, or JIA.

Efficacy Extrapolation of Adalimumab in Adolescent HS Patients

No clinical trial efficacy data are available for adalimumab use in adolescent HS patients. The effectiveness of adalimumab for adolescent HS patients was extrapolated from two adequate and well-controlled phase 3 studies in adult HS patients (8). Extrapolation was based upon two assumptions: (1) similar HS disease progression and response to adalimumab and (2) similar exposure-efficacy relationship in adults and adolescents. The exposure-efficacy relationship in adult HS patients was evaluated in 297 patients receiving adalimumab 40 mg EW dosing regimen and 296 patients receiving placebo. The efficacy endpoint was Hidradenitis Suppurativa Clinical Response (HiSCR) (9) and the evaluated exposure metric was adalimumab concentration at week 12. A summary of data included for population pharmacokinetics (popPK) analysis, efficacy and safety extrapolation is provided in Table II.

RESULTS

Assessment of Predicted Adalimumab Exposures in Adolescent HS Patients with Different Regimens

The popPK model has been qualified to reasonably describe the adalimumab concentrations in adult and pediatric patients with different diseases. Weight and ADA status were demonstrated to have a clinically relevant impact on adalimumab exposure. Adalimumab clearance increases nearly proportionally with weight with a coefficient estimated to be 0.92, and increases almost four-fold in the presence of ADA. HS patients appeared to have higher clearance than patients with RA or CD.

The predicted trough adalimumab concentrations at week 13 with different dosing regimens stratified by weight cut-off are shown in Fig. 1. The simulation results demonstrate that (1) Following the dosing regimen recommended by EMA in adolescent HS patients (80 mg at week 0, followed by 40 mg EOW starting at week 1), the adalimumab exposure in adolescent HS patients with low body weight is similar to that in adult HS patients. However, for adolescent patients with high body weight (greater than 60 kg), the exposure is approximately 50% lower than that in adult HS patients. (2) Following the approved dosing regimen in adult HS patients (160 mg at week 0, 80 mg at week 2, 40 mg EW), the adalimumab exposure in adolescent HS patients with high body weight is similar to that in adult HS patients; however, adolescent HS patients with low body weight would have much higher exposure than that in adult HS patients. Predicted C_{avg} and C_{max} at different dosing regimens in adolescent HS patients demonstrated similar trends. The PK simulation results in general support body weight-tiered dosing regimens in adolescent HS patients.

Safety Extrapolation of Adalimumab in Adolescent HS Patients

Adalimumab has a well-established, 16-year long-term safety profile based on clinical trial and post-marketing data in various diseases in adult and pediatric populations. The most frequently reported serious adverse events were serious infections and new malignancies (2). In the clinical development program for adults with HS, the safety profile for subjects with HS treated with adalimumab weekly was consistent with the known safety profile in other indications for adalimumab. Similarly, the safety profile across approved pediatric indications is similar or consistent with the expected rates due to underlying disease and has not revealed any new

Table I. Recommended Weight-Tiered Dosing Regimens for Adolescent HS Patients

Body weight of adolescent HS patients (12 years and older)	Recommended dosing regimens
30 kg (66 lbs) to < 60 kg (132 lbs)	• 80 mg initially on day 1 • 40 mg on day 8 and subsequent doses: 40 mg *every other week*
≥ 60 kg (132 lbs)	• 160 mg initially on day 1; and • 80 mg on day 15 • 40 mg on day 29 and subsequent doses: 40 mg *every week*

safety signals compared with adults (2). Current available data of adalimumab use in the pediatric CD, JIA, and PsO populations demonstrate no exposure-response (E-R) relationship for adverse events (AE) (Fig. 2). Overall, there is no apparent relationship between adalimumab concentrations and adverse events in pediatric patients treated with adalimumab.

Efficacy Extrapolation of Adalimumab in Adolescent HS Patients

Among 593 adult patients pooled in the analysis, adalimumab exposure and week 12 HiSCR appear to be positively associated: the response rate was higher in patients with higher trough serum adalimumab concentrations (Fig. 3). The final logistic regression model identified adalimumab concentration at week 12 and baseline CRP level as significant covariates on the HiSCR (Fig. 3). The positive exposure-efficacy relationship suggests that a suboptimal dose would likely compromise the effectiveness of adalimumab for the treatment of HS in adolescent patients, thus an appropriate dosing regimen to ensure similar adalimumab exposure across adolescent HS patients with different ages or weights is important.

DISCUSSION

Pediatric extrapolation can be used to maximize the efficiency of pediatric product development while maintaining important regulatory standards for approval (10). According to the Pediatric Research Equity Act (PREA) (section 505B(a) (2)(B) of the FD&C Act) (11,12), effectiveness in pediatric patients may be extrapolated from adequate and well-controlled studies in adults if the course of disease and the response to therapy are sufficiently similar between the pediatric and adult population. HS occurs after puberty generally. Key clinical features (i.e., inflammatory nodules and abscesses) (13) appear to be similar between adolescent and adult HS populations, and it is reasonable to assert that the course of HS and response to adalimumab treatment will be comparable for adolescents and adults. Therefore, the effectiveness of adalimumab to treat HS in the adolescent population was extrapolated from efficacy data in adult HS patients. The efficacy results in adult phase 3 trials have demonstrated an E-R relationship for HiSCR at week 12 in which higher serum adalimumab concentrations were associated with greater HiSCR scores. The favorable HiSCR in the 40-mg EW group compared to the 40-mg EOW group in

Table II. Summary of Data Used for PopPK Analysis, Efficacy, and Safety Extrapolation Assessment

PopPK			Efficacy			Safety		
Disease	Dosing regimen	*N*	Disease	Dosing regimen	*N*	Disease	Dosing regimen	*N*
Ped PsO	0.4 mg/kg EOW	34	Adult HS	40 mg EW	297	Ped CD	10 mg EOW	29
Ped PsO	0.8 mg/kg EOW	35	Adult HS	Placebo	296	Ped CD	20 mg EOW	89
Ped PsO	Placebo to 0.8 mg/kg EOW	30				Ped CD	40 mg EOW	60
JIA	24 mg/m^2 up to 40 mg max EOW	231				JIA	24 mg/m^2 up to 40 mg max EOW	181
Ped CD	10 mg EOW	31				Ped PsO	0.4 mg/kg EOW	36
Ped CD	20 mg EOW	93				Ped PsO	0.8 mg/kg EOW	36
Ped CD	40 mg EOW	67						
Adult HS	40 mg EOW	52						
Adult HS	40 mg EW	265						
Adult HS	40 mg EW to EOW	101						
Adult HS	Placebo to 40 mg EOW	45						
Adult HS	Placebo to 40 mg EW	144						
Adult PsO	40 mg EOW	864						
Adult PsO	40 mg EW	50						
Adult RA	40 mg EOW	573						
Adult RA	Placebo to 40 mg EOW	49						
Adult CD	40 mg EOW	89						
Adult CD	40 mg EW	197						
Adult UC	40 mg EOW	257						
Adult UC	Placebo to 40 mg EOW	140						
Adult UV	40 mg EOW	250						

EW, every week; *EOW*, every other week; *RA*, rheumatoid arthritis; *CD*, Crohn's disease; *PsO*, plaque psoriasis; *JIA*, juvenile idiopathic arthritis; *UC*, ulcerative colitis; *HS*, hidradenitis suppurativa

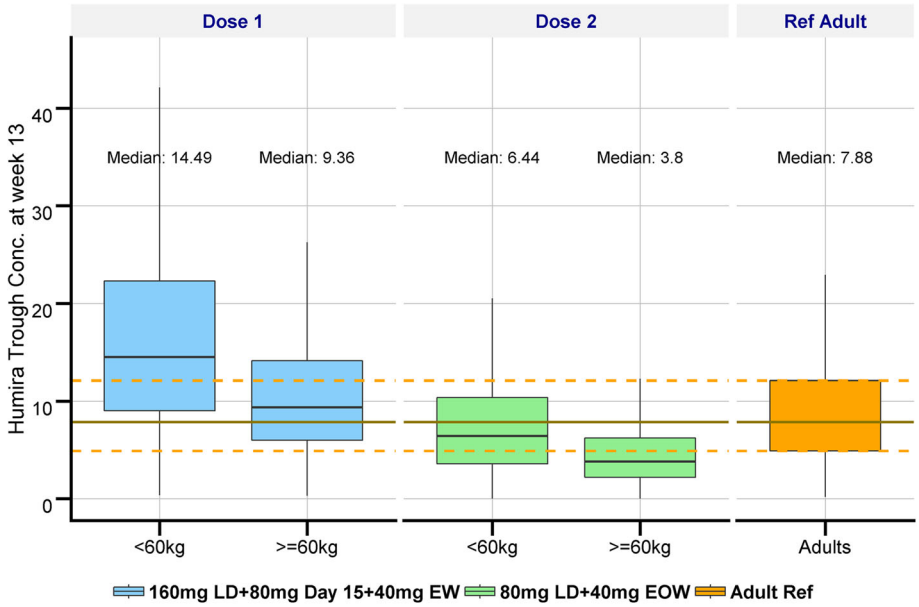

Fig. 1. Boxplots of predicted adult and adolescent trough concentrations at week 13 by weight achieved by two evaluated dosing regimens. Note: Ctrough adalimumab trough concentration at week 13; dose 1, 160 mg loading dose + 80 mg at day 15 + 40 mg every week (approved dose in adult patients); dose 2, 80 mg loading dose +40 mg every other week; fifty replicates of simulations were conducted in virtual adolescent patients stratified by weight (40 patients per 10 kg increment, 280 patients total). Body weight, age, and serum creatinine concentration in these virtual patients were sampled with replacement from 351 adolescent patients with pediatric RA, PsO, or CD with the age range of 12–17 years (assuming the demography for the above baseline covariates is comparable in adolescents across indications). The CRP and ADA were simulated based on the distribution parameters of log normally distributed CRP and binomially distributed ADA status from the adult HS population

these two trials support the positive E-R relationship for efficacy (8,14). Assuming similar exposure-efficacy relationships in adults and adolescents, a significant exposure-efficacy relationship is expected in adolescent HS patients.

Extrapolation of data from adult to pediatric populations under PREA generally refers only to efficacy. Usually, the drug safety in pediatric populations is studied directly as pediatric patients may be susceptible to drug toxicities based on organ system immaturity. In some circumstances, leveraging of safety data from the reference of other pediatric population to the indicated pediatric population may be used (15). Adalimumab has a well-established, 16-year long-term safety profile in various diseases in adult and pediatric populations. The available safety data of adalimumab in pediatric populations support a lack of an exposure-safety relationship in CD, JIA, and PsO indications. No increased safety risks were observed with EW dosing compared to EOW dosing in pediatric CD patients (16). The adult HS clinical trials demonstrated that overall safety was comparable for adalimumab 40 mg EW and 40 mg EOW dosing regimens (14,17). PK simulation also suggests with the recommended dosing regimens the highest adalimumab exposure is achieved in adolescent HS patients with body weight from 60 to 70 kg. The predicted adalimumab concentration in this subgroup is still within the range of the observed adalimumab concentrations in pediatric CD patients with body weight from 40 to 50 kg. In addition, the organ system development in the adolescent population is closer to the adult population than to children before puberty.

The PK of adalimumab in adolescent HS patients has not been characterized in a clinical trial. However, given that extensive PK data are available in adult HS patients and pediatric patients with different diseases, the exposure of adalimumab in adolescent HS patients achieved by different dosing regimens could be predicted reliably based on the simulation results from a robust popPK model. As drug clearance and weight increases are nearly proportional, adalimumab exposure is lower in patients with high body weight at the same administered dose. In Europe, one dosing regimen (80 mg at week 0, followed by 40 mg EOW starting at week 1) was approved for all adolescent patients regardless of body weight (3). However, FDA simulation results suggest that adalimumab exposure is approximately 50% lower for high body weight adolescent HS patients than exposure in adults. Adolescent HS patients tend to have higher body weight than healthy adolescents. In an observational registry whose primary objective is to evaluate the natural history of disease and risk of progression of HS, the median weight in 65 adolescent patients is 75 kg, which is higher than the median weight of 60 kg in a healthy 16-year-old adolescent (18). When considering the positive exposure-efficacy relationship, an adolescent HS dosing regimen not based on body weight could result in lower adalimumab exposure in > 50% of patients, thereby compromising the effectiveness of adalimumab. Due to significant effect of weight on PK and positive exposure-efficacy relationship, the review team determined that body weight-tiered adolescent HS dosing regimens are necessary to achieve similar adalimumab exposure to adult HS patients across all weight range.

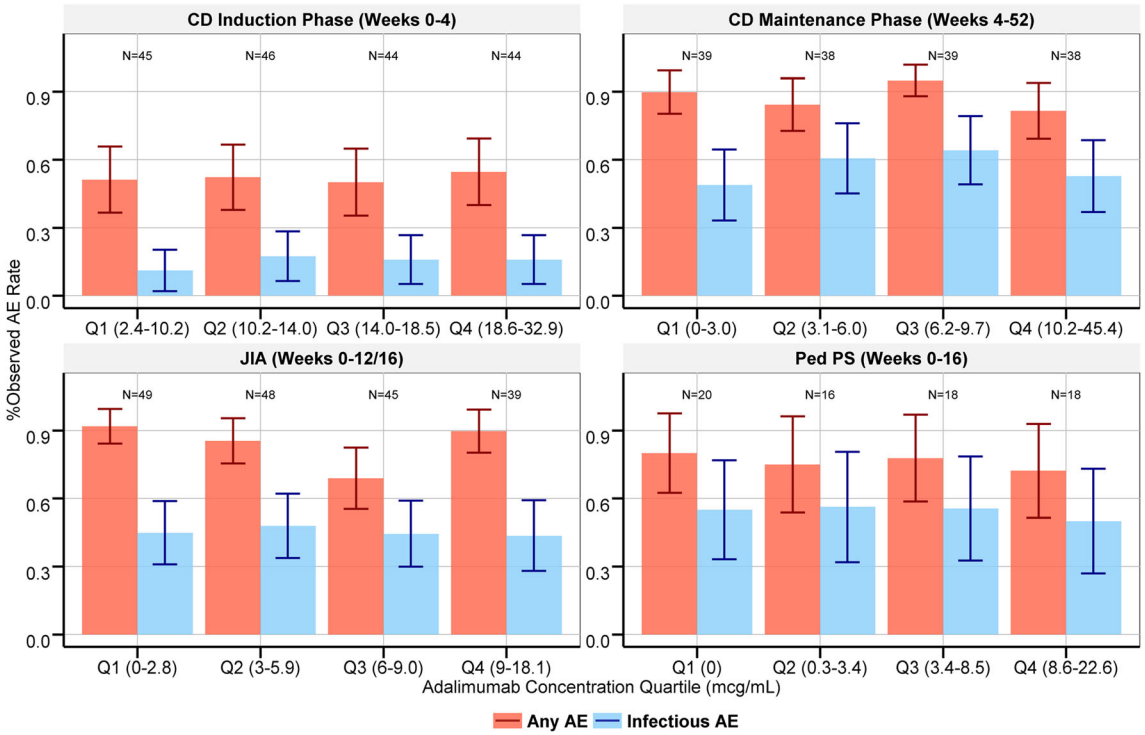

Fig. 2. The E-R relationships for any AE and infectious AE in pediatric patients with CD in both induction phase or maintenance phase of Study M06-806, in pediatric patients with JIA in studies DE038 and M10-444 and in pediatric patients with PsO in Study M04-717. Note: CD, Crohn's disease; PsO, plaque psoriasis; JIA, juvenile idiopathic arthritis. The error bar indicates the 95% CI for the %observed AE rate

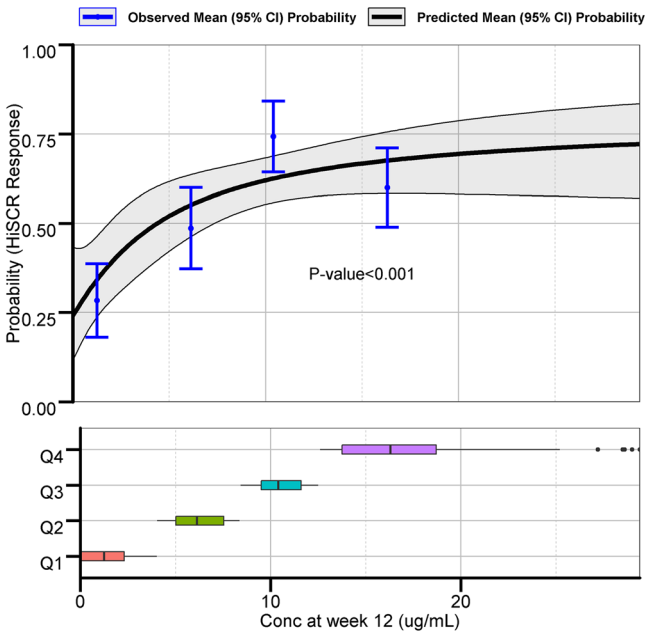

Fig. 3. The E-R relationship for HiSCR in phase 3 studies in adult HS patients. Note: The observed week 12 HiSCR response rates (blue points and error bars) were 28.4%, 48.6%, 74.3%, and 60% across the four quartiles of increasing trough serum adalimumab concentrations compared to a 28% response rate in the placebo group (not included in the analysis and not shown in this figure). Predicted probability of HiSCR as a function of adalimumab concentration at week 12 (black line) was based on final logistic regression model

According to the European public assessment report (EPAR), a dose escalation from 40 mg EOW to 40 mg EW or 80 mg EOW may be considered for adolescent HS patients with an inadequate response (3). FDA does not recommend the dose escalation option with the current weight-tiered dosing regimen for the following reasons. For adolescent HS patients with body weight less than 60 kg, the dose escalation to 40 mg EW will achieve adalimumab concentrations much higher than that in adults. Because the E-R for efficacy appears to plateau at the exposure level achieved with recommended dosing regimen in adult HS patients (Fig. 3), a higher exposure is unlikely to improve efficacy. Additionally, the highest maintenance dose currently approved in other pediatric indications is 40 mg EOW; clinical safety data are insufficient to support the proposed dose escalation and consequent higher exposure in adolescent HS patients of low body weight. Although Dubinsky *et al.* suggested weekly adalimumab dosing could be clinically beneficial for pediatric CD patients who experienced nonresponse or flare on EOW dosing based on results from CD trial, escalation to the 40 mg weekly regimen only occurred in 17 pediatric patients who weigh less than 60 kg (16). Furthermore, formation of ADA is expected to have a negative impact on efficacy due to a four-fold increase in drug clearance and positive E-R for efficacy. The rate of ADA reported in each study is highly dependent on the assay (2). Using the new titer-based assay, ADA titers were measurable in 61% of HS patients treated with adalimumab (2). One can reasonably assume that a relatively high percentage of adolescent HS patients with an inadequate clinical response to adalimumab 40 mg EOW could have developed ADA. The effectiveness of dose

escalation in HS patients who have developed ADA has not been studied; therefore, whether dose escalation can improve efficacy in those with inadequate response to EOW dosing is unknown.

Pediatric drug development is filled with unique difficulties and challenges. On average, it takes 9 years from the time of a product's approval for use in adults until the incorporation of pediatric information in the label. MIDD is an innovative and efficient tool which can help avoid unnecessary pediatric studies and enroll the smallest number of pediatric patients possible to generate appropriate data. In the current case, modeling and simulation predicted the recommended dosage in adolescent HS patients can provide generally similar exposure and the benefit/risk profile to adult HS patients. The consistent, well-characterized exposure-safety relationship across several pediatric indications provided supportive evidence that no additional safety concern should be expected in adolescent HS patients. These MIDD analyses provided regulatory basis for the approval of adalimumab in the adolescent HS population without efficacy and safety data in the target population. As the value of MIDD being increasingly recognized by the stakeholders, MIDD is expected to supplement or replace the experimental clinical trial in more cases in the future, especially in pediatric drug development or rare disease with unmet medical need.

CONCLUSION

FDA recommends weight-tiered dosing regimen of adalimumab in adolescent HS patients. The predicted adalimumab exposure in adolescent patients, efficacy extrapolation from 2 phase 3 trials in adult HS patients, and the lack of exposure-safety relationship across several pediatric indications provided the regulatory basis for the approval of adalimumab in adolescent HS patients without the need for new experimental clinical efficacy and safety data.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest All listed authors are employees of the Food and Drug Administration of the United States. The authors indicated no potential conflicts of interest.

Disclaimer The views expressed in this article are those of the authors and do not necessarily reflect the official views of the FDA.

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