BLA Multi-Disciplinary Review and Evaluation

<table>
<tr><td>Application Type</td><td>BLA</td></tr>
<tr><td>Application Number</td><td>125521/S-020</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date</td><td>27 Sep 2019</td></tr>
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<tr><td>Division/Office</td><td>DDD/OII</td></tr>
<tr><td>Review Completion Date</td><td>23 Mar 2020</td></tr>
<tr><td>Established/Proper Name</td><td>Ixekizumab</td></tr>
<tr><td>Trade Name</td><td>TALTZ</td></tr>
<tr><td>Pharmacologic Class</td><td>Humanized interleukin-17A antagonist</td></tr>
<tr><td>Code Name</td><td>N/A</td></tr>
<tr><td>Applicant</td><td>Eli Lilly and Company</td></tr>
<tr><td>Dosage Form</td><td>Injection, for subcutaneous use</td></tr>
<tr><td>Applicant Proposed Dosing Regimen</td><td>
<table>
<tr><th>Pediatric Patient's Weight</th><th>Starting Dose (Week 0)</th><th>Dose every 4 weeks (Q4W) Thereafter</th></tr>
<tr><td>Greater than 50 kg</td><td>160 mg (two 80 mg injections)</td><td>80 mg</td></tr>
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<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>New Patient Population - pediatric subjects 6 to <18 years of age with moderate-to-severe psoriasis</td></tr>
<tr><td>Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication</td><td>200965009 [Plaque psoriasis (disorder)]</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s) (if applicable)</td><td>TALTZ® is indicated for the treatment of adults and pediatric patients 6 years of age and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.</td></tr>
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DDS=Deputy Director for Safety
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
PLT=Patient Labeling Team
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

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Clinical Team Leader	David Kettl, MD	OII/DDD	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13.2, 13.3	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
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	Signature: See DARRTS signature page			

Glossary

ADA	anti-drug antibodies
AE	adverse event
BLA	biologics license application
BSA	body surface area
CSR	clinical study report
FDA	Food and Drug Administration
IBD	inflammatory bowel disease
ITT	intent-to-treat
LOCF	last observation carried forward
NAb	neutralizing antibodies
NRI	non-responder imputation
NRS	numeric rating scale
OC	observed cases
PASI	Psoriasis Area and Severity Index
PI	prescribing information
PK	pharmacokinetics
popPK	population PK
PP	per-protocol
Q4W	every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
sPGA	Static Physician's Global Assessment
TE-ADA	treatment-emergent anti-drug antibodies
TEAE	treatment-emergent adverse event
WCS	worst-case scenario

1 Executive Summary

1.1. Product Introduction

TALTZ (ixekizumab) is an immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds with high affinity (less than 3 pM) and specificity to interleukin (IL)--17A, a cytokine. TALTZ was approved on March 22, 2016 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The approved dosing regimen for TALTZ is 160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80-mg injection at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every 4 weeks (Q4W). TALTZ comes in a subcutaneous (SC) injection that includes an 80 mg/mL solution in a single-dose prefilled syringe, and 80 mg/mL solution in a single dose autoinjector. Since the approval for plaque psoriasis, TALTZ has been approved for treatment of adults with active psoriatic arthritis (December 1, 2017) and treatment of adults with ankylosing spondylitis (August 23, 2019).

At the time of the initial approval, the Agency waived pediatric study requirements for ages 0 to less than 6 years of age due to studies being impossible or highly impracticable. The Applicant received a deferment for pediatric studies ages 6 to less than 18 years old. The Applicant agreed to conduct a pediatric study as a post-marketing requirement.

3049-1	Conduct a dose-ranging Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 to less than 18 years of age with moderate to severe psoriasis (with a duration of exposure to ixekizumab of at least one year). Final Protocol Submission: 03/2017 Study Completion: 09/2021 Final Report Submission: 03/2022

This supplement to the Biologic License Application (sBLA) for TALTZ (ixekizumab) is for the treatment of pediatric patients with moderate-to-severe plaque psoriasis. The completed postmarketing requirement study I1F-MC-RHCD is included in this supplement along with updates to the labeling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Eli Lilly and Co. has submitted one pediatric study, I1F-MC-RHCD (RHCD), "A Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate Safety and Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis," to conduct 3049-1 in the approval letter dated March 22, 2016. This study (RHCD) showed that TALTZ provided statistically significant improvements relative to placebo

on the primary and all major secondary endpoints in patients aged 6 to less than 18 years with moderate-to-severe plaque psoriasis.

In addition, the safety data collected up to 1 year of study drug exposure support a safety profile that is consistent with the adult data in the U.S. Prescribing Information (PI). Although inflammatory bowel disease (IBD) is an identified adverse drug reaction and present in the Warning and Precautions section of the current labeling, the increased pediatric reporting in this study does not rise to the need for a Boxed Warning. The identified increase in the frequency of Crohn's disease can be included in labeling so that physician can discuss the risk/benefits of TALTZ in their pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations affecting approximately 2 percent to 3 percent of the U.S. population. Pediatric plaque psoriasis affects approximately 1 percent of children and adolescents globally (Napolitano et al. 2016). An estimated 35 percent to 50 percent of adults with plaque psoriasis develop their disease before the age of 20 years old (Jager et al. 2009). Pediatric plaque psoriasis can be a burdensome disease because it can present on the face and scalp, as well as other highly visible areas during a sensitive time of life. Accordingly, pediatric plaque psoriasis can have a profound long-term impact on the psychological health of affected children by interfering with self-esteem, family and social relationships, and school activities. In addition, plaque psoriasis has been associated with comorbidities such as obesity, hypertension, hyperlipidemia, diabetes mellitus, inflammatory bowel disease, anxiety, depression, and rheumatoid arthritis. Moderate to severe psoriasis is a serious and at times disabling condition that has a substantial impact on patients' lives (Paller et al. 2019). There are multiple drugs approved for psoriasis that have an acceptable risk-benefit profile and achieve moderate to high efficacy for the treatment of moderate to severe disease. All of the approved products have significant risks and there is room for both more efficacious and potentially safer products for these patients.

TALTZ every 4 weeks (Q4W) treatment was efficacious across all weight groups (more than 50 kg; 25 kg to 50 kg or less; and less than 25 kg) in study I1F-MC-RHCD (RHCD). Of the small number of patients within the low baseline weight category (less than 25 kg; placebo: n = 1, TALTZ Q4W: n = 2), both TALTZ Q4W patients did achieve clinically meaningful response as measured by the Psoriasis Area and Severity Index (PASI). Furthermore, a simulation with the pediatric pharmacokinetics (PK) model developed using data across all weight groups indicates that patients less than 25 kg have trough concentrations in the range of 2.51 µg/mL (1.01 to 5.11 µg/mL); there is substantial overlap with trough concentrations predicted in the 25 kg to 50 kg and greater than 50 kg weight groups (2.96 µg/mL [1.11 to 6.10 µg/mL] and 3.48 µg/mL [1.04 to 7.27 µg/mL], respectively). These concentrations are predicted to be associated with high levels of response using the static Physician Global Assessment (sPGA) and PASI week 12 static time point PK/PD models.

Safety data collected after up to 1 year of study drug exposure (RHCD) support a safety profile that is consistent with the adult data in the U.S. Prescribing Information (PI). Although inflammatory bowel disease (IBD) is an identified adverse drug reaction and present in the Warning and Precautions section of the current labeling, the increased pediatric reporting in this study does not rise to the need for a Boxed Warning. The identified increase in the frequency of Crohn's disease can be included in labeling so that physician can discuss the risk/benefits of TALTZ in their pediatric patients.

The addition of TALTZ to pediatric moderate-to-severe plaque psoriasis provides for another systemic treatment to the armamentarium for the dermatologist.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Pediatric plaque psoriasis affects approximately 1 percent of children and adolescents globally. An estimated 35 percent to 50 percent of adults with plaque psoriasis develop their disease before the age of 20 years old. Pediatric plaque psoriasis can be a burdensome disease because it can present on the face and scalp, as well as other highly visible areas during a sensitive time of life. Accordingly, pediatric plaque psoriasis can have a profound long-term impact on the psychological health of affected children by interfering with self-esteem, family and social relationships, and school activities. In addition, plaque psoriasis has been associated with comorbidities such as obesity, hypertension, hyperlipidemia, diabetes mellitus, inflammatory bowel disease, anxiety, depression, and rheumatoid arthritis.	Moderate to severe psoriasis is a serious and at times disabling condition that can have a substantial impact on patients' lives. Safe and effective treatment has the potential to greatly improve the quality of life for a patient with moderate to severe psoriasis.
Current Treatment Options	• Currently approved drugs for the treatment of moderate to severe psoriasis in children include the antimetabolite methotrexate (MTX), tumor necrosis factor inhibitors such as etanercept (approved for kids down to 4 years of age), T-cell inhibitor cyclosporine (CSA), and off label use of the retinoid Soriatane (acitretin). Phototherapy, either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy (narrow or broadband) is also a standard of care treatment for moderate to severe psoriasis in children. • Significant safety concerns for the moderately and highly efficacious approved products include immunosuppression with the associated risk for serious and in some cases opportunistic or unusual infections, cytopenias, hepatotoxicity and hypersensitivity events.	There are drugs approved for the treatment of children with plaque psoriasis. All approved products have risk associated with use. There is room in the marketplace for additional efficacious and potentially safer products for pediatric psoriasis.
Benefit	The RHCD study showed statistically significant and clinically meaningful improvements in efficacy observed for the TALTZ Q4W treatment group compared to placebo across the co-primary and all gated secondary objectives.	The evidence submitted by the Applicant supports approval of labeling to include the treatment of moderate-to-severe plaque psoriasis down to 6 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The risk of TALTZ is consistent with the known safety profiles in other systemic agents used for psoriasis. This includes risks of immunosuppression with serious and in some cases opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease and hypersensitivity events. Inflammatory bowel disease (IBD) has been identified as an increase risk in this pediatric study. IBD is present in the Warning and Precautions section of the current labeling, the increased pediatric reporting in this study does not rise to the need for a Boxed Warning. The identified increase in the frequency of Crohn's disease can be properly included in labeling so that physicians may access the risk/benefits of TALTZ in their pediatric patients.	The identified increase in the frequency of Crohn's disease can be properly labeled so that physicians may consider the risk/benefits of TALTZ in their pediatric patients.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

SDN: 951, 1015, 1049, 1109

2 Therapeutic Context

2.1. Analysis of Condition

Plaque psoriasis is a chronic inflammatory disease affecting primarily the skin and joints, that is characterized by circumscribed erythematous scaly plaques on the skin and substantial impairment of quality of life. Overall prevalence of psoriasis in the U.S. is approximately 2 percent, and prevalence in childhood and adolescence is reported to be between 0.3 percent and 2 percent. An estimated 20 percent of patients have moderate to severe disease, affecting greater than 5 percent or 10 percent of the body surface area (BSA) or involving body areas such as the hands and feet. One-third of patients have concomitant arthritis. Co-morbidities include depression/suicide, autoimmune disease, cardiovascular disease, metabolic syndrome. The negative impact of psoriasis on quality of life has been found to be comparable or in excess of that with cancer, arthritis, hypertension, heart disease and diabetes, and childhood onset of disease correlates with impaired social development, social withdrawal, sleep problems and substance abuse.

2.2. Analysis of Current Treatment Options

The Guidelines of Care For the Management of Psoriasis and Psoriatic Arthritis, published by the American Academy of Dermatology in six parts from 2008 to 2011, recommend, as a general approach for patients with psoriasis without concomitant psoriatic arthritis, treatment with topical products or targeted phototherapy for limited disease, and phototherapy or systemic therapy with drugs or biologic products for extensive disease (greater than 5 percent BSA involvement). The current therapeutic armamentarium approved or cleared for treatment of adults with moderate to severe disease includes topical therapies (corticosteroids, tazarotene, corticosteroid and vitamin D analog combination products), phototherapy and photochemotherapy (methoxsalen), systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and systemic biologic products (adalimumab, etanercept, infliximab, ixekizumab, and secukinumab). However, for children with moderate-to-severe psoriasis, approved systemic biologic therapy only consists of ustekinumab, for use in adolescents down to 12 years of age, or etanercept, approved in 2016 for the treatment of moderate-to-severe plaque psoriasis down to 4 years of age.

Other approved options are UVB phototherapy, memetasone furoate (a mid-potency topical steroid), tazarotene gel (for patients 12 years and older) and calcipotriene/betamethasone diproprionate ointment (for patients 12 years and older). For children with BSA involvement of 10 percent or more, topical treatments and phototherapy may be impractical due to time and expense, or ineffective. The need for additional systemic biologic therapies is compelling in pediatric patients with extensive or refractory disease.

Table 1: Summary of Systemic Treatments for Moderate-to-Severe Psoriasis

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Antimetabolite/Immunosuppressant						
Methotrexate	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy	1972	Psoriasis: Starting Dose Schedules 1. Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved. 2. Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses. 30 mg/week should not be exceeded ordinarily	No efficacy information for psoriasis in the label. AAD guidelines 6 - 3 trials quoted (Heydendael et al. 2003) MTX vs CSA (no placebo arm), PASI 75 at 16 weeks 60% - MTX vs 71% CSA (no statistically significant difference) (Flytstrom et al. 2008) MTX vs CSA (no placebo arm), mean PASI change from baseline 58%-MTX vs 72%-CSA (Saurat et al. 2011) DB,PC MTX vs adalimumab vs placebo PASI 75 at 16 weeks MTX-36% vs adalimumab- 80% vs placebo-19%	Boxed Warning (BW) - potentially fatal toxic reactions including hepatotoxicity, bone marrow suppression, aplastic anemia, gastrointestinal toxicity, pulmonary toxicity and opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies “should not be used in pregnant women with psoriasis”	Major AE derm dosing: ↑ LFT’s stomatitis, diarrhea, nausea and vomiting, lymphoproliferative disorders Pregnancy: X

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Tumor Necrosis Factor Inhibitors						
Infliximab (Remicade)	Chronic Severe (extensive or Disabling) plaque psoriasis candidates for phototherapy or systemic therapy	200	5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	From the label: 3 R,DB,PC trials PASI 75 at week 10 1-Infliximab (Inflix) (5mg/kg)- 80% vs 3% placebo 2- Inflix (5mg/kg)- 75% vs 2% placebo 3- Inflix (5mg/kg)- 88% vs Inflix (3mg/kg) 72% vs 6% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), Hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hep B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivety events, malignancy	Pregnancy: B
Adalimumab (Humira)	Moderate to Severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	2008	80 mg initial dose, followed by 40 mg every other week starting one week after initial dose	From the label: 2 Randomized, DB, PC trial PASI75 at week 16 1- Adalimumab 71% vs 7% Placebo 2- Adalimumab 78% vs 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), Warnings: Hypersensitivity reactions, Hepatitis B reactivation, demyelinating disease, cytopenia, heart failure, Lupus-like syndrome	Pregnancy: B
Etanercept (Enbrel)	Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy **ONLY systemic biologic approved for children down to 4 years of age**	2004	50 mg twice weekly for 3 months, followed by 50 mg once weekly	From the label: 2 Randomized, DB, PC5 trials PASI75 at 3 months 1- Etanercept - 47% vs 4% placebo 2-Etan-46% vs 3% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, pancytopenia, malignancy, Hepatitis B reactivation	Pregnancy: B

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-12 and 23 Antagonist						
Ustekinumab (Stelara)	Moderate to Severe psoriasis, Candidates for phototherapy or systemic therapy	2009	For patients weighing <100 kg :45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks For patients weighing >100 kg: 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks	From the label: 2 Randomized, DB, PC trials PASI 75 at week 12 1)-ustekinumab (90mg)-66% vs ustekinumab (45mg)-67% vs 3% placebo 2)-ustekinumab (90mg)-76% vs ustekinumab (45mg)-67% vs 4% placebo	Warnings and Precautions (W&Ps): Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB.	Pregnancy: B
IL - 17A Antagonist						
Secukinumab (Cosentyx)	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	2015	300 mg by Subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg Q4W. For some patients, a dose of 150 mg may be acceptable	From the label: 4 Randomized, DB, PC trials PASI75 at week 12 1-secukinumab (sec) (300mg)-82% vs sec (150mg) 71% vs 4% placebo 2-sec (300mg)-76% vs sec (150mg)-67% vs 5% placebo 3-sec (300mg)-75% vs sec (150mg)-69% vs 0% placebo 4-sec (300mg)-87% vs sec (150mg)-70% vs 3% placebo	W&Ps: Infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment evaluation for TB.	Pregnancy: B

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
T-Cell Inhibitor / Immunosuppressant						
Cyclosporine	Severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	1997	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day.	From the label: PASI 75 - 51% at 8 weeks, 79% at 16 weeks	BW-Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUVA, UVB, coal tar or radiation Rx- ↑ risk of skin malignancies	Pregnancy: C
Retinoid						
Acitretin (Soriatane)	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments	1996	Starting dose: 25 to 50 mg per day, Maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	BW-pregnancy must be prevented during Tx and for 3 years following due to teratogenicity, no ethanol ingestion by females of childbearing potential (FOCBP) due to metabolism to etretinate and ↑ ½ life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs@FDA for details. Patients cannot donate blood for 3 years post Tx. See label for data on pregnancies in partners of male patients on acitretin	W&P: hepatotoxicity, skeletal abnormalities, lipids↑, Cardiovascular risk ↑, Ophthalmologic effects, Pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression	Pregnancy: X

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Phosphodiesterase 4 (PDE4) Inhibitor						
Apremilast (Otezla)	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	2014	To reduce risk of gastro-intestinal symptoms, titrate to recommended dose of 30 mg twice daily	From the label: 2R, DB, PC trials PASI 75 at 16 weeks 1- apremilast 33% vs placebo 5% 2-apremilast 28.8% vs placebo 5.8%	W&P: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, car bamazepine, phenytoin)	Diarrhea, nausea, URI, headache Pregnancy: C
Immunoglobulin G subclass 4 (IgG4) Monoclonal Antibody						
Ixekizumab (TALTZ)	Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy	2016	Week 0: two 80 mg injections; 80 mg weeks 2, 4, 6, 8, 10, 12; then 80 mg Q4W	From the label: 3 PC and AC trials PASI75 at 12 weeks	W&P: infections, tuberculosis, hypersensitivity, inflammatory bowel disease	Nausea, URO, tinea infections Pregnancy: No available data
Phototherapy						
PUVA-8-MOP (methoxsalen + UVA) therapy	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy	NA	20 -70 mg (based on weight) taken 2-4 hours before exposure to UVA light	No efficacy information for psoriasis in the label. AAD Guidelines: 2 systematic reviews: 70-100% of patients achieved skin clearing	BW: Should only be used by MDs who have special competence in psoriasis management, serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) to eyes and skin for 24 hours after ingestion Pregnancy: C
Combination Vitamin D analogue and corticosteroid						
Betamethasone dipropionate and Calcipotriene(Enstilar)	Plaque psoriasis	2015	Apply once daily for up to 4 weeks	Randomized, DB, PC trial For ages 12 and older	W&P: hypercalcemia, hypercalciuria, HPA axis suppression	Pregnancy: C

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Topical Corticosteroid						
Clobetasol propionate cream (Temovate E)	Moderate to severe plaque psoriasis	1994	Apply thin layer twice daily, up to 2 consecutive weeks, up to 50g/wk	Controlled trial for ages 16 years and older	W&P: HPA axis suppression (as low as 2 g/day), Cushing's syndrome, hyperglycemia, glycosuria. Local-folliculitis, acneiform eruptions, striae, hypertrichosis, hy popigmentation, ACD, miliaria, secondary infection	Pregnancy: C
Mometasone furoate cream (Elocon®)	Corticosteroid –responsive dermatoses	1987	Apply a thin film up to twice daily, up to 3 weeks	Two DB, PC trials age 12 -81 years; in atopic and psoriasis. Open label pediatric trial ages 2 to 12 years	W & P: HPA axis suppression, skin atrophy	Pregnancy: C
Other Treatments						
Ultraviolet Light	Approved as devices	Multiple years	Per clinician's judgment	Approved for all ages	Risk of burns, pigmentation; skin cancer with increased dosing	Presumed safe in pregnancy
Laser Therapy						
Excimer UVB laser (308nm UVB)	Mild, moderate, severe psoriasis, less than 10% BSA	2003	Initial dose by skin type and plaque thickness, then increase/ decrease with clinical response. Treat 2 to 3 times a week until clear.	Approved in adults	W & P: Erythema, hyperpigmentatio n, blistering possible at higher doses.	Not studied in pregnant women. Presumed to be safe
Pulse dye laser system 595 nm	Chronic localized psoriasis	2004	Treat every 3 weeks	Approved in adults	W & P: Bruising, scarring	Not studied in pregnant women. Presumed to be safe

Source: Table adapted from ENBREL (etanercept) BLA 103795/Clinical Review S-5552 Table 1, Dr. Roselyn Epps.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

TALTZ was approved on March 22, 2016, for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Since the approval for plaque psoriasis, TALTZ has also been approved for treatment of adults with active psoriatic arthritis (December 1, 2017) and treatment of adults with ankylosing spondylitis (August 23, 2019).

3.2. Summary of Presubmission/Submission Regulatory Activity

The final protocol for study I1F-MC-RHCD (RHCD) was submitted to the Agency on January 16, 2017. Two protocol amendments have also been submitted to the Agency. The Applicant requested a Type C meeting with the Agency on December 7, 2018, to confirm the submission strategy for the supplement to support a potential indication of TALTZ in pediatric patients aged 6 years to less than 18 years with moderate-to-severe plaque psoriasis who are eligible for systemic or phototherapy. The Applicant planned the submission of the supplement prior to study completion of RHCD.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

No inspections were requested for the study RHCD.

4.2. Product Quality

Overall, the in-use compatibility data support the conclusion that 20 mg/0.25 mL, 40 mg/0.50 mL doses of ixekizumab Drug Product (DP) used for administration to pediatric patients are compatible with the administration materials that come in contact with the DP and the DP remains stable for up to (b) (4) hours at (b) (4)°C. Also, the exposure of various strength dosage forms of ixekizumab DP to ambient laboratory temperature and ambient light conditions had no impact on the compatibility and stability of the DP. Therefore, storage of ixekizumab DP for up to 4 hours at room temperature and ambient light following puncture of the sterile vial until administration of the drug product poses very little risk to DP quality, safety or efficacy. See the Product Quality review in the Center for Drug Evaluation and Research informatics platform for additional details.

5 Clinical Pharmacology

5.1. Executive Summary

TALTZ (ixekizumab) is a humanized immunoglobulin G subclass 4 (IgG4) monoclonal antibody that selectively inhibits interleukin-17A, a key proinflammatory cytokine in the pathophysiology of plaque psoriasis. TALTZ was approved in 2016 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The approved dose in adults is 160 mg by SC injection at week 0, followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12, then 80 mg Q4W.

The current efficacy supplement was submitted to fulfill a post-marketing requirement and to seek an extended indication in pediatric patients 6 years of age and older with moderate-to-severe plaque psoriasis. The Applicant conducted study I1F-MC-RHCD, which was a double-blind, randomized, placebo-controlled study to evaluate safety, tolerability, and efficacy of ixekizumab in subjects from 6 to less than 18 years of age with moderate-to-severe plaque psoriasis. The Applicant also conducted a population pharmacokinetic/pharmacodynamic analysis to evaluate the relationships between ixekizumab exposure and efficacy/safety, and the potential development of anti-ixekizumab antibodies and their impact on efficacy and PK.

The Applicant proposed a weight-based dosage regimen in pediatric patients based on the following weight categories:

Table 2: Proposed Dosage Regimen in Pediatric Patients From 6 to Less Than 18 Years of Age

Pediatric Patient's Weight	Starting Dose (Week 0)	Dose Every 4 weeks (Q4W) Thereafter
Greater than 50 kg	160 mg (two 80 mg injections)	80 mg
25 to 50 kg	80 mg	40 mg
Less than 25 kg	40 mg	20 mg

Source: Table 2.2.1., Module 2.2.

5.1.1. Recommendations

The clinical pharmacology data from study I1F-MC-RHCD are determined to be adequate to support fulfilment of the post-marketing requirement and approval of this efficacy supplement from a clinical pharmacology perspective.

5.1.2. Post-Marketing Requirements and Commitments

None.

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics

Following administration of ixekizumab based on the proposed dosage regimen (Table 2), the ixekizumab serum trough concentrations were generally similar among different body weight groups* and were similar to those observed in adult subjects. The geometric mean (%CV) of ixekizumab concentrations in 25-kg to 50-kg group and greater than 50-kg group at weeks 4, 8, and 12 ranged from 2.75 (224 percent) mcg/mL to 4.32 (61 percent) mcg/mL.

** The generalized summary here does not include the lowest weight group (less than 25-kg) because strong inference could not be made based on observed data due to limited number of subjects. There were only two subjects in the lowest weight group, and one of the subjects was overdosed at week 4 and the other subject had a very low trough concentration associated with a treatment-emergent anti-drug antibodies (TE-ADAs). Hence no definitive conclusions could be made based on observed data. Approval in this weight range is based on modeling and simulation, which suggested that proposed dosing regimen will achieve similar exposure in patients less than 25 kg compared to patients with higher body weight. This approach is considered reasonable as finding pediatric subjects with moderate to severe psoriasis in the low weight range (i.e., below 25 kg) is challenging.*

Immunogenicity

From 326 samples collected from week 0 to week 12, 10.7 percent (35 samples in 20 subjects) of samples were TE-ADA positive. Among the TE-ADA positive samples, 48.6 percent were classified as low titer (less than 1:160), 31.4 percent as moderate titer (1:160 or greater to less than 1:1280), and 20 percent as high titer (greater than 1:1280). Furthermore, 20 percent of TE-ADA samples (seven samples) were tested positive for neutralizing antibodies (NAb). The incidence of TE-ADA in this pediatric study was similar to that observed in adult subjects with plaque psoriasis (9 percent by week 12 in adults versus 11 percent week 12 in pediatric subjects). Although there was no apparent correlation between antibody positive subjects and reduced efficacy in study I1F-MC-RHCD, due to the small sample size of pediatric subjects definitive conclusions could not be made.

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosage regimen in pediatric patients 6 years to less than 18 years of age is weight-based as follows:

Pediatric Patient's Weight	Starting Dose (Week 0)	Dose every 4 weeks (Q4W) Thereafter
Greater than 50 kg	160 mg (two 80 mg injections)	80 mg
25 to 50 kg	80 mg	40 mg
Less than 25 kg	40 mg	20 mg

Therapeutic Individualization

Therapeutic individualization based on intrinsic factors has not been evaluated in the current efficacy and is not recommended.

Outstanding Issues

None.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

Study I1F-MC-RHCD

This study was a multicenter, double-blind, randomized, placebo-controlled study examining the safety, tolerability and PK of ixekizumab versus placebo in pediatric subjects from 6 to less than 18 years of age with moderate to severe plaque psoriasis. The pertinent inclusion criteria included subjects with Psoriasis Area and Severity Index (PASI) score 12 or greater, static Physician Global Assessment (sPGA) score 3 or greater, and BSA involvement 10 percent or greater at screening and baseline. The submitted data is from three treatment periods:

1) A double-blind treatment induction period, from week 0 to week 12, evaluating the efficacy and safety of ixekizumab compared with placebo.
2) An open-label maintenance period, occurring after week 12 to week 60, inclusive, assessing the long-term efficacy and safety of ixekizumab.
3) An open-label extension period, occurring after week 60 to week 108, inclusive, assessing long-term efficacy and safety of ixekizumab.

The post-treatment follow-up period for up to 24 weeks after the open-label extension period is ongoing. The submitted Clinical Study Report is based on database lock of June 28, 2019, at which all subjects have completed or had an early termination visit from the double-blind treatment period.

A total of 171 subjects were randomized at week 0 (115 subjects to ixekizumab and 56 subjects to placebo). In the ixekizumab treatment arm, 113 subjects completed the 12-week double-blind treatment period. The summary of subject demographics can be found in Table 3.

Table 3: Summary of Subject Demographics

	Placebo (n=56)	Ixekizumab (n=115)	Total (n=171)
Age (years)			
N of subjects	56	115	171
Mean (SD)	13.1 (2.79)	13.7 (3.14)	13.5 (3.04)
Range	6-17	6-17	6-17
Median	13.5	15.0	14.0
Gender, n (%)			
N of subjects	56	115	171
Male	20 (35.7)	52 (45.2)	72 (42.1)
Female	36 (64.3)	63 (54.8)	99 (57.9)
Race, n (%)			
N of subjects	53	114	167
American Indian or Alaska Native	0	2 (1.8)	2 (1.2)
Asian	2 (3.8)	4 (3.5)	6 (3.6)
Black or African American	3 (5.7)	3 (2.6)	6 (3.6)
White	45 (84.9)	95 (83.3)	140 (83.8)
Multiple	3 (5.7)	10 (8.8)	13 (7.8)
Ethnicity, n (%)			
N of subjects	56	115	171
Hispanic or Latino	11 (19.6)	30 (26.1)	41 (24.0)
Not Hispanic or Latino	42 (75.0)	82 (71.3)	124 (72.5)
Not Applicable	3 (5.4)	3 (2.6)	6 (3.5)
Weight category, n (%)			
N of subjects	56	115	171
<25 kg	1 (1.8)	2 (1.7)	3 (1.8)
≥25 and ≤50 kg	14 (25)	29 (25.2)	43 (25.1)
>50 kg	41 (73.2)	84 (73.0)	125 (73.1)
BMI, (kg/m^2)			
N of subjects	56	115	171
Mean (SD)	23.53 (5.57)	24.12 (6.77)	23.93 (6.39)
Range	15.0-41.2	14.6-49.6	14.6-49.6
Median	21.65	22.89	22.74

Source: Adapted from Table RHCD.14.6, CSR

Pharmacokinetics

The submitted PK data include a total of 562 post-dose ixekizumab concentrations from 184 subjects, up to and including week 108. Among those samples, 330 (59.1 percent) samples were taken at time points up to week 12 and majority of samples were trough samples. There were four (0.712 percent) samples that had concentrations below the lower limit of quantification (6.30 ng/mL).

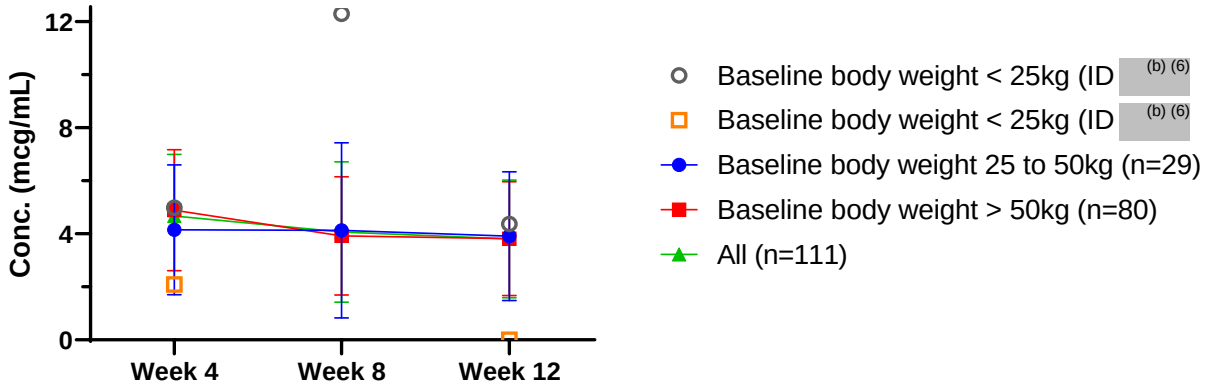
The geometric mean ixekizumab serum trough concentrations during the 12-week double-blind treatment period is shown in Table 4. The arithmetic mean (SD) serum trough concentrations during the same period is presented in Figure 1.

Table 4: Arithmetic Mean (SD) of Ixekizumab Trough Concentrations (mcg/mL) by Baseline Weight Category During Week 0 to Week 12

Treatment Group	Double-Blind Treatment Period		
	Week 4	Week 8[c]	Week 12
<25-kg Group (n=2)	2.09, 4.99[a]	12.3[a,b]	0.009[d], 4.37[a]
25- to 50-kg Group (n=29)	4.15 (2.45)	4.13 (3.30)	3.91 (2.42)
>50-kg Group (n=80)	4.89 (2.28)	3.92 (2.23)	3.82 (2.15)
Overall - All subjects (n=111)	4.67 (2.33)	4.07 (2.65)	3.81 (2.22)

[a] Due to small sample size (n=2; Subjects (b) (6) and (b) (6) individual data are shown
[b] Subject (b) (6) received 80 mg instead of 20 mg at week 4. No TEAEs were reported from this patient during the Double-Blind Treatment Period
[c] Subject (b) (6) did not have sample collected at week 8
[d] This sample was associated with a TE-ADA-positive sample with a high titer that was also detected as NAb positive
Source: Reviewer's analysis

Figure 1: Arithmetic Mean (SD) of Ixekizumab Trough Concentrations (mcg/mL) by Baseline Weight Category During Week 0 to Week 12



Source: Reviewer's plot

Reviewer's Comment: Although there is very limited data in the lowest weight group (less than 25 kg), the concentrations of ixekizumab appear to be similar among different body weight groups. The trough concentrations at predicted steady state (weeks 8 and 12) in pediatric subjects are similar to those observed in adult subjects. The mean (SD) steady-state trough concentration in adults was 3.5 (2.5) mcg/mL per the approved label.

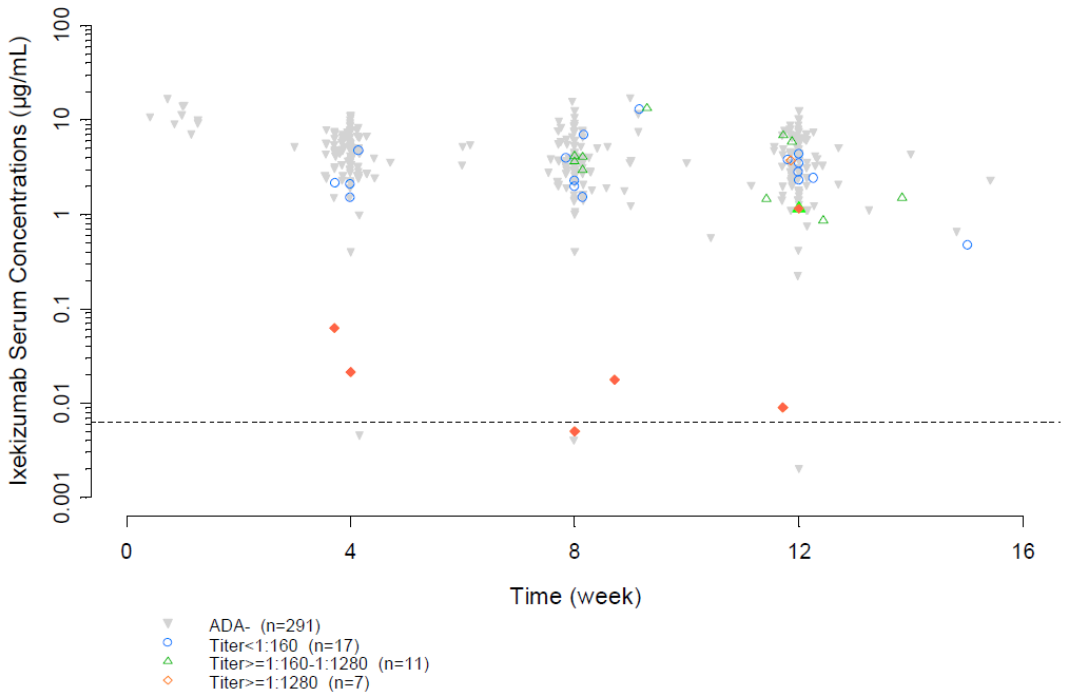
Immunogenicity

Among the 171 subjects randomized at week 0, eight subjects (six in the ixekizumab group and two in the placebo group) had ADAs present at baseline with no neutralizing activity. Among the 115 subjects in the ixekizumab group, 21 subjects (18.3 percent) were TE-ADA positive through week 12, of which 10 subjects were classified as low titer, seven as moderate titer, and four as high titer. Five subjects (two with moderate titer and three with high titer) were NAb positive.

1) Impact of immunogenicity on PK

Among all immunogenicity samples in the ixekizumab treatment group from weeks 0 to 12, 89.3 percent (291 out of 326) samples were ADA negative, whereas 10.7 percent of samples were identified as TE-ADA. The observed ixekizumab concentrations by ADA status and sample ADA titers are shown in Figure 2. The majority of TE-ADA-positive samples were associated with ixekizumab concentrations similar to those associated with ADA-negative samples, except those that were NAb positive and with high titer. Among the seven NAb-positive samples that were classified as high titer, six samples were associated with concentrations that were at the low end or below the range of concentrations associated with ADA-negative samples.

Figure 2: Observed Ixekizumab Concentrations Per ADA Status for Patients in the Ixekizumab Treatment Group



Abbreviations: ADA = anti-drug antibodies
NAb-positive samples are represented by the solid symbols
The dotted horizontal line represents the lower limit of the assay (0.0063 mcg/mL). Samples that were below the lower limit were set to a randomly assigned nominal value lower than the lower limit of the assay for the purpose of plotting the data
Samples collected at weeks 1 and 9 were non-troughs, but all other samples were trough samples
Source: Figure RHCD.11.7, CSR

2) Impact of immunogenicity on efficacy

No apparent relationship between the TE-ADA-positive subjects and efficacy was found in this study. The proportion of subjects responding to the treatment, evaluated by the two-co-primary endpoints of the study (PASI 74 and sPGA at week 12), was similar without a statistically significant difference (*p* greater than 0.05) between the TE-ADA-positive subjects and TE-ADA-negative subjects (Table 5).

Among the 21 subjects who were TE-ADA positive, four subjects were classified as high titer. All four subjects achieved PASI 75, but only one (25 percent) subject met sPGA (0,1) at week 12.

There were five subjects who were NAb positive (two subjects with moderate titer and three subjects with high titer). All five subjects achieved PASI 75, but only three subjects (60 percent) met sPGA (0,1) at week 12.

Table 5: Proportion of Efficacy Responders Per Treatment-Emergent Anti-Drug Antibody Status

	PASI 75 responder at Week 12	sPGA responder at Week 12
TE-ADA positive at Week 12 (21subjects)	90.5% (n=19)	71.4% (n=15)
TE-ADA negative at Week 12 (94 subjects)	88.3% (n=83)	83.0% (n=78)
***p*-value**	0.776	0.229

Abbreviations: TE-ADA = treatment-emergent anti-drug antibodies; PASI = Psoriasis Area and Severity Index; sPGA = Static Physician's Global Assessment
Source: Adapted from Tables RHCD.14.35 and RHCD.14.36, CSR

Reviewer's Comment: There was no apparent relationship between the TE-ADA status and efficacy in this study. While all subjects who were classified as high titer for TE-ADA positive and those who were NAb positive achieved PASI 75 at week 12, the response rate for the other co-primary endpoint, sPGA(0,1) was lower in these subject populations. In addition, higher antibody titers were associated with lower efficacy response in adult subjects with plaque psoriasis. Although this was not clearly evident in pediatric subjects, due to low number of subjects, this reviewer opines that a definitive conclusion regarding the lack of impact of TE-ADA on efficacy in pediatric patients should not be made.

5.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The efficacy of ixekizumab for the treatment of pediatric patients with moderate-to-severe plaque psoriasis was supported by efficacy data from study I1F-MC-RHCD. See Section 7.1 for evaluation of efficacy.

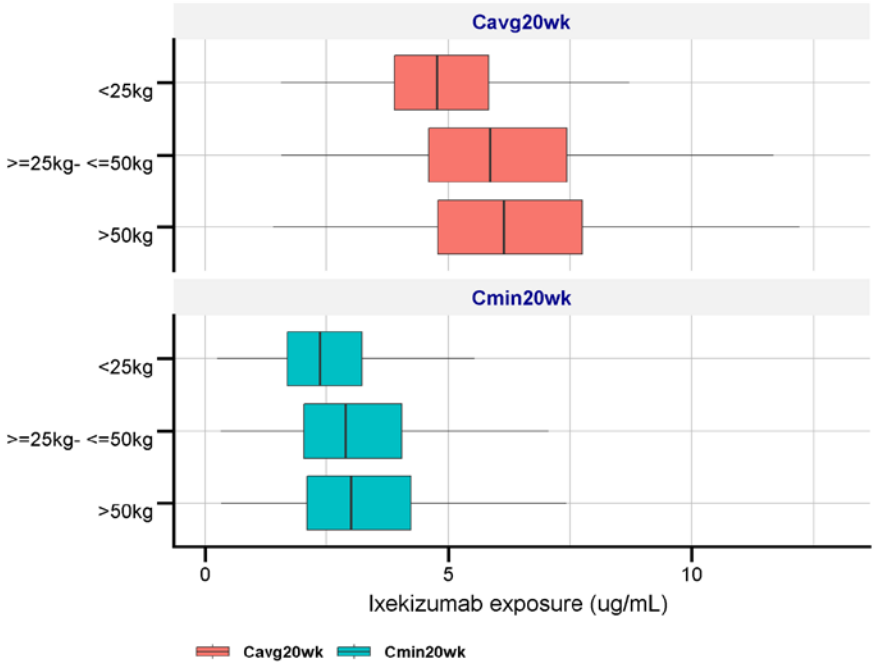
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed weight-based dosing regimen is appropriate for pediatric patients from 6 years to less than 18 years of age and is supported by the exposure-response analysis. The analysis indicated that pediatric subjects in different weight groups are expected to achieve similar response rate for both PASI75 and sPGA when dosed with the proposed dosing regimen (Section 13.4.3).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The proposed dosing regimen is based on weight, as weight was identified as an important covariate factor on clearance and volume of distribution in the adult population PK model. The population-pharmacokinetic analysis suggested that the proposed dosing regimen will result in similar exposure of ixekizumab in different weight groups (Figure 3). The model predictions were in general agreement with the observed data supporting body-weight based dosing in pediatric patients.

Figure 3: Simulated Exposure of Ixekizumab in Different Weight Groups When Dosed With the Proposed Dosing Regimen



Source: Pharmacometric reviewer's analysis

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Drug interactions were not studied in this efficacy supplement.

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

This supplemental Biologics License Application (sBLA) for TALTZ (ixekizumab) is for the treatment of pediatric patients down to 6 years of age with moderate-to-severe plaque psoriasis. The adult indication for patients with moderate-to-severe plaque psoriasis was initially approved for TALTZ (BLA 125521) on March 22, 2016.

A single clinical study was conducted for the pediatric requirement:

Table 6: Study I1F-MC-RHCD

Study Identifier; Location; Report Type	Objectives	Design; Control Type	Treatment and Regimen: Dose/Route/Frequency	Number of Patients	Diagnosis or Inclusion Criteria	Treatment Duration
Population PK/PD Study Report						
I1F-MC-RHCD Population PK/PD Section 5.3.3.5; Population PK and PK/PD	The PK/PD analysis plan was to address the following secondary objectives in pediatric patients with moderate-to-severe plaque Ps: • to measure ixekizumab exposure, • to characterise the PK of ixekizumab, and • to assess the relationship between exposure and efficacy, exposure and safety, and exposure and immunogenicity.	PK determined using a population approach evaluating sparsely sampled ixekizumab concentrations. Exposure-efficacy relationship evaluated using a population approach, using static time point and time course PK/PD models. Exposure-safety relationship evaluated using a graphical approach.	All study drugs were given SC. Double-Blind Treatment Period (Period 2): Placebo Ixekizumab: Weight-based dosing as follows: >50 kg: 160 mg (administered as two 80-mg SC injections) at Week 0 followed by 80-mg Q4W SC injections. 25-50 kg: 80 mg SC injection at Week 0 followed by 40-mg Q4W SC injections. <25 kg: 40 mg SC injection at Week 0 followed by 20-mg Q4W SC injections. Maintenance and Extension Periods (Period 3 and Period 4): open-label ixekizumab dosed by weight (as described above). If a patient changes weight category during the maintenance and/or the extension periods, the dose was adjusted accordingly.	The population PK analysis includes 558 measurable ixekizumab serum concentration samples from 184 patients. The population exposure-response analyses include data from 152 patients (PASI and sPGA Week 12 static time point PK/PD models) and 171 patients (PASI time course PK/PD model). The exposure-safety analyses include data from 152 patients.	Diagnosis of moderate-to-severe plaque-type psoriasis for at least 6 months prior to baseline (Week 0; Visit 2), as determined by the investigator PASI ≥12, sPGA ≥3, and BSA involvement ≥10% at screening (Visit 1) and baseline (Week 0; Visit 2) Were candidates for phototherapy or systemic treatment or considered by the investigator as not adequately controlled by topical therapies.	Population PK analyses and descriptive PK summaries: from Week 0 up to and including Week 108 (time of the last PK sample at the time of the database lock). Exposure-efficacy and exposure-safety analyses: from Week 0 up to and including Week 12.

Source: Applicant submission; Final Study Report I1F-MC-RHCD

6.2. Review Strategy

Evaluation of the single clinical trial in pediatrics (RHCD) was completed for efficacy at the 12-week treatment period (double-blind). In addition, the safety evaluations for the combined treatment period (12-week to 60-week open-label) collected safety data for up to 1-year. In total, 171 unique patients were randomized to the two treatment groups as the ITT population: 115 to the TALTZ Q4W group, and 56 to placebo group. A total of 166 (97.1 percent) of patients completed the double-blind treatment period (113 TALTZ Q4W and 53 placebo).

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Studies Used to Support Efficacy

7.1.1. Study Design and Endpoints

The Applicant is conducting a randomized, multicenter, double-blind, placebo-controlled, phase 3 study (I1F-MC-RHCD; RHCD hereafter) to evaluate efficacy and safety of TALTZ SC injections in subjects from 6 years to less than 18 years of age with moderate to severe plaque psoriasis. The study contained an active-controlled reference arm (etanercept; Enbrel) per the protocol addendum submitted on August 30, 2019 [Protocol Addendum I1F-MC-RHCD (2)]. The Applicant noted that the addendum was conducted in order to address requirements in the European Union (EU) for pediatric psoriasis. According to the protocol addendum, etanercept is an open-label, "reference" control arm for countries where etanercept is approved for treatment of severe pediatric plaque psoriasis (emerging markets and EU countries). Therefore, this review will not discuss results for etanercept.

Study RHCD is ongoing at the time of this review. It is noted that the database lock for the submitted RHCD Clinical Study Report occurred on June 28, 2019 and contains data after all subjects completed the week 12 visit or discontinued study drug early and a minimum of 100 subjects were treated with TALTZ for at least 1 year.

For enrollment in study RHCD, subjects should have met the following key inclusion criteria:

- Male or female from 6 years to less than 18 years of age
- Diagnosis of plaque-type psoriasis for at least 6 months prior to baseline
- Static Physician's Global Assessment (sPGA) equal to or greater than 3 (moderate); see Appendix 13.3 for the sPGA scale
- Psoriasis Area and Severity Index (PASI) score equal to or greater than 12; see Appendix 13.3 for the PASI scale
- BSA of involvement equal to or greater than 10 percent at screening and baseline

The study consists of the following five periods:

- Period 1: Screening period
- Period 2: 12-week double-blind treatment period, which the Applicant called induction period (week 0 to week 12)
- Period 3: 48-week open-label maintenance period (week 12 to week 60)
- Period 4: Extension period or double-blind, randomized, withdrawal period (week 60 to week 108)
- Period 5: Post-treatment follow-up period

According to the main protocol, approximately 165 subjects were planned to be randomized in a 2:1 ratio to receive TALTZ SC Q4W (N=110) or placebo SC Q4W (N=55). Later, the protocol addendum was submitted on August 30, 2020, to include the active-controlled reference arm of etanercept. The protocol addendum specified randomizing subjects from etanercept-approved countries who meet all enrollment criteria in a 2:2:1 ratio to TALTZ, etanercept, or placebo until approximately 75 subjects are randomized to TALTZ (30 subjects), etanercept (30 subjects), and placebo (15 subjects). Randomization was stratified by region (United

States/Canada, European countries, and the rest of the world) and by etanercept approval status. In particular, subjects who had moderate psoriasis irrespective of country and subjects who had severe psoriasis (PASI equal to or greater than 20 or sPGA equal to or greater than 4) in Canada/U.S. region were randomized in a 2:1 ratio to TALTZ or placebo (block size 3), while subjects who had severe psoriasis in the European Union or the rest of the world were randomized in a 2:2:1 ratio to TALTZ, etanercept or placebo (block size 5).

Subjects randomized to TALTZ received a regimen based on their weight as shown below:

- Subjects less than 25 kg will receive a starting dose of 40 mg, then 20 mg (Q4W) thereafter (TALTZ 20mg Q4W)
- Subjects 25 kg to-50 kg will receive a starting dose of 80 mg, then 40 mg Q4W thereafter (TALTZ 40mg Q4W)
- Subjects more than 50 kg will receive a starting dose of 160 mg, then 80 mg Q4W thereafter (TALTZ 80mg Q4W)

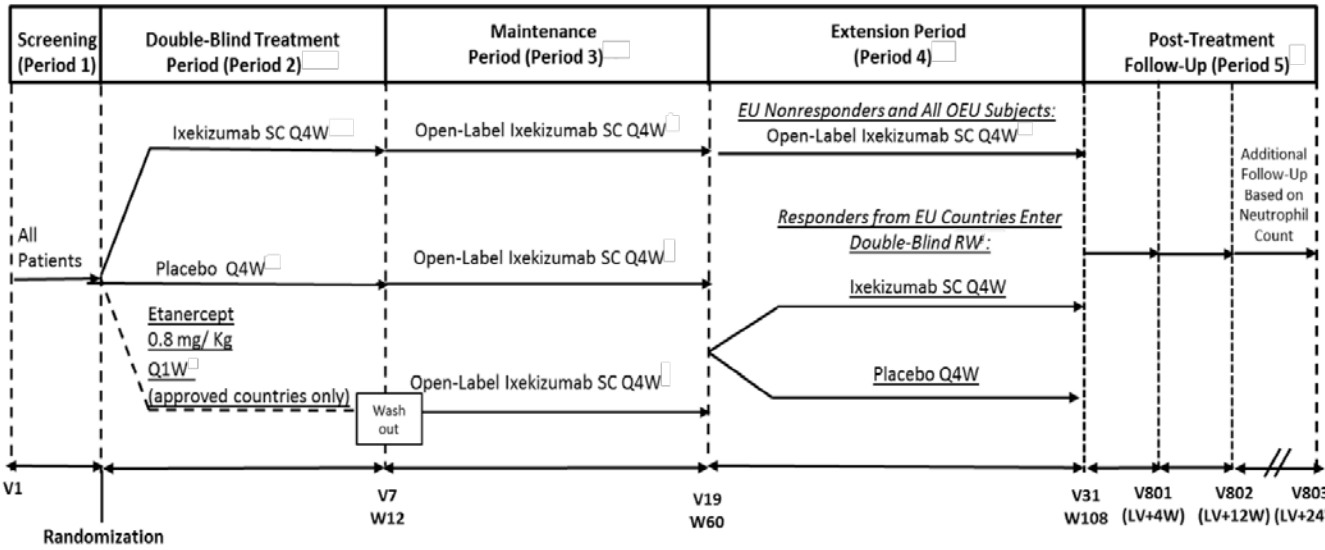
Subjects randomized to etanercept were administered etanercept 0.8 mg/kg, not exceeding 50 mg per dose, every week from week 0 through week 11.

Figure 4 presents the study design schematic for study RHCD. During the double-blind treatment period (period 2), subjects had study visits at baseline and weeks 1, 4, 6, 8 and 12.

Subjects randomized to TALTZ during period 2 are planned to maintain their dose during the maintenance period (period 3). Subjects randomized to placebo during period 2 are planned to receive TALTZ at doses of 20, 40, or 80 mg based on their weight during the maintenance period (period 3). If a subject changed weight category during the study, after completing the period 2, the dose would be adjusted accordingly. Subjects randomized to etanercept during period 2 are also planned to receive TALTZ based on weight following completion of an 8-week washout period (week 12 through week 20).

During the extension period (period 4), all non-EU subjects (responders and non-responders) and EU non-responders are planned to continue open-label treatment with TALTZ at the dose received during the previous period (period 3). EU responders (sPGA 0 or 1 at week 60) are planned to be re-randomized at week 60 in a 1:1 ratio to TALTZ or placebo in period 4. Subjects re-randomized to TALTZ are planned to receive a dose based on weight at the time of re-randomization. For the EU responders, the protocol addendum specified that upon disease relapse (sPGA greater than or equal to 2), subjects are planned to receive TALTZ dose based on weight.

Figure 4: Design for Study RHCD



Abbreviations: EU = European Union; LV = date of last visit; OEU = outside the European Union; Ps = plaque psoriasis; Q1W = every week; Q4W = every 4 weeks; RW = randomized withdrawal; SC = subcutaneous; V = visit; W = weeks
Source: RHCD Clinical Study Report Addendum

The protocol specified the following co-primary efficacy endpoints:

1. Proportion of subjects achieving equal to or greater than 75 percent improvement in PASI (PASI 75) from baseline to week 12
2. Proportion of subjects achieving sPGA score of 0 (clear) or 1 (minimal) with at least a two-grade improvement from baseline to week 12

The protocol specified the following "gated secondary" endpoints:

1. Proportion of subjects achieving PASI 90 at week 12
2. Proportion of subjects achieving sPGA of 0 at week 12
3. Proportion of subjects achieving PASI 100 at week 12
4. Improvement equal to or greater than 4 for subjects who had a baseline Itch Numerical Rating Scale (NRS) score equal to or greater than 4 at week 12; refer to Appendix 13.3 for the Itch NRS
5. Proportion of subjects achieving PASI 75 at week 2
6. Proportion of subjects achieving sPGA 0 or 1 at week 2

It should be noted that week 2 time point for the gated secondary endpoints No. 5 and No. 6 was updated to week 4 in the Statistical Analysis Plan (SAP), as shown below. The Applicant noted that this change occurred in the SAP Version 2, which was approved on March 18, 2019, prior to database lock and unblinding of treatment assignments for the primary timepoint. The study does not include a week 2 visit.

5. Proportion of subjects achieving PASI 75 at week 4
6. Proportion of subjects achieving sPGA 0 or 1 at week 4

The protocol specified many "other" secondary and "tertiary/exploratory" efficacy endpoints; however, such endpoints were not included in the multiplicity testing strategy. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

7.1.2. Statistical Methodologies

The Applicant submitted three versions of the SAP under the BLA. The Applicant noted that SAP version 1 was approved on June 6, 2017, SAP version 2 was approved on March 18, 2019, and SAP version 3 was approved on June 26, 2019. The database lock occurred on June 28, 2019. Revisions in version 2 included among others updating the time point of week 2 to week 4 for two gated secondary endpoints. Revisions in version 3 included updating important protocol violations (to incorporate post-hoc change after the primary database lock).

The primary efficacy analysis population specified in the protocol was the intent-to-treat (ITT) population, defined as all randomized subjects who dispensed drug medication. The protocol also specified supportive analyses for the co-primary endpoints using the per-protocol (PP) set, defined as all randomized subjects who do not have significant protocol violations. The SAP listed the major violations (not presented here) for excluding subjects from the PP set.

The protocol-specified analysis method for the co-primary efficacy endpoints (sPGA 0/1; PASI 75) was the Fisher's Exact Test (2-sided; $\alpha = 0.05$). The same method is specified for all binary endpoints. The protocol/SAP also specified secondary analyses for the co-primary endpoints using a logistic regression analysis with treatment group, region, baseline sPGA score, and baseline weight category (less than 25 kg, 25 kg to 50 kg or less, greater than 50 kg) as factors.

The protocol/SAP specified a sequential gatekeeping approach to control the Type I error rate for testing multiple primary and secondary efficacy endpoints. The co-primary endpoint No. 1 (i.e., PASI 75) was to be tested first, and if successful, the co-primary endpoint No. 2 (i.e., sPGA 0/1) was to be tested. If the co-primary endpoint No. 2 was successful, the secondary endpoints were to be tested in the order listed in Section 7.1.1.

The protocol-specified primary imputation method for the handling of missing binary data was non-responder imputation (NRI). For the co-primary endpoints (both binary), the protocol/SAP did not specify sensitivity analyses for the handling of missing data.

Three planned interim analyses and database locks were conducted. A staggered approach to enrollment by weight group was used so that a minimum of 15 subjects older than 12 years and more than 50 kg were enrolled and safety evaluated for the initial 12 weeks of dosing before opening enrollment in the middle weight group (25 kg to 50 kg). The first interim analysis was conducted when approximately 15 subjects were enrolled in the 25 kg to 50 kg weight group and completed up to week 12. An analysis of all available PK data was conducted to confirm that exposures were within the range expected. The SAP specified that only the data monitoring committee was authorized to evaluate unblinded interim efficacy and safety analyses, and "study sites would receive information about interim results only if they needed to know for the safety of their subjects." The data monitoring committee recommendation was to continue as planned per protocol, all weight groups were open for enrollment of the remaining subjects needed to complete the study.

The second interim database lock, unblinding, and data analysis were performed at the time the last subject completed period 2 (week 12) or early termination visit (cutoff date of March 22, 2019). The Applicant stated that because the study was ongoing at the time of this database lock, the analysis is referred to as an interim analysis. However, as this analysis includes the final analysis for period 2 of the study, there is no alpha

adjustment due to this interim analysis, and the data monitoring committee was not needed for this interim analysis.

A third interim database lock (cutoff date of June 28, 2019) and data analysis was performed after a minimum of 100 subjects were treated with TALTZ for at least 1 year to meet the U.S. submission timeline. Data and analysis from this database lock form the basis of the RHCD Clinical Study Report for this BLA.

7.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Study RHCD enrolled and randomized a total of 171 subjects (115 subjects in TALTZ and 56 subjects in placebo). Table 7 presents the disposition of subjects. The discontinuation rates were generally similar across the two treatment arms.

Table 7: Subject Disposition for Double-Blind Period (Period 2) in Study RHCD (ITT)

	TALTZ N=115	Placebo N=56
Completed	113 (98%)	53 (95%)
Discontinued	2 (2%)	3 (5%)
Reasons of Discontinuation		
Adverse Event	0 (0%)	1 (2%)
Physician Decision	1 (1%)	0 (0%)
Protocol Deviation	0 (0%)	1 (2%)
Withdrawal by Subject	1 (1%)	1 (2%)

Abbreviations: ITT = intent-to-treat
Source: Reviewer's Analysis (same as Applicant's Analysis); ITT population is defined as all randomized subjects

The demographics for study RHCD are presented in Table 8. The demographics were generally balanced across the treatment arms. Approximately 75 percent of the subjects were older than 12 years old, and approximately 58 percent of the subjects were females. Approximately 82 percent of the subjects were white. Only three subjects weighed less than 25 kg.

Table 8: Demographics in Study RHCD (ITT)

	TALTZ N=115	Placebo N=56
Age		
Mean (SD)	13.7 (3.14)	13.1 (2.79)
Median	15	13.5
Range	6 – 17	6 – 17
<12 years, n (%)	27 (23%)	16 (29%)
≥12 years, n (%)	88 (77%)	40 (71%)
Sex		
Male	52 (45%)	20 (36%)
Female	63 (55%)	36 (64%)
Race		
White	95 (83%)	45 (85%)
Black or African American	3 (3%)	3 (6%)
American Indian or Alaska Native	2 (2%)	0 (0%)
Asian	4 (3%)	2 (4%)
Multiple	10 (9%)	3 (6%)
Geographical Region		
US/Canada	53 (46%)	26 (46%)
EU*	44 (38%)	22 (39%)
Rest of the World**	18 (16%)	8 (14%)
Weight (Kg)		
Mean (SD)	63.8 (24.94)	60.3 (20.33)
Median	62.8	56.85
Range	21.5 – 135.5	21.5 – 111.2
< 25 kg	2 (2%)	1 (2%)
≥ 25 to ≤ 50 kg	29 (25%)	14 (25%)
> 50 kg	84 (73%)	41 (73%)

Abbreviations: ITT = intent-to-treat
Note: Three subjects in the placebo arm (Subjects (b) (6)) and one subject in the active arm (Subject (b) (6)) did not have values for race
*EU: Czech Republic, France, Germany, Hungary, Netherlands, Poland, Spain
**Rest of the world: Argentina, Mexico, Russia
Source: Reviewer's Analysis (same as Applicant's Analysis); ITT population is defined as all randomized subjects

Table 9 presents the baseline disease characteristics for study RHCD. The baseline disease characteristics were generally balanced across the treatment arms. Only a small proportion of subjects had sPGA score of very severe at baseline.

Table 9: Baseline Disease Characteristics in Study RHCD (ITT)

Characteristic	TALTZ N=115	Placebo N=56
sPGA		
Moderate (3)	57 (50%)	31 (55%)
Severe (4)	51 (44%)	21 (38%)
Very Severe (5)	7 (6%)	4 (7%)
PASI		
Mean (SD)	19.7 (7.51)	19.7 (8.01)
Median	18.0	16.85
Range	12.0 – 49.2	12.0 – 47.8
Percent BSA		
Mean (SD)	24.1 (6.77)	23.5 (5.57)
Median	22.9	21.6
Range	14.6 – 49.6	15.0 – 41.2

Abbreviations: sPGA = Static Physician's Global Assessment; PASI = Psoriasis Area and Severity Index; ITT = intent-to-treat; BSA = body surface area
Source: Statistical Reviewer's Analysis; ITT population is defined as all randomized subjects

7.1.4. Results for the Co-Primary Efficacy Endpoints

Table 10 presents the proportion of subjects with missing data for the co-primary endpoints by treatment arm at each study visit. Overall, the proportion of subjects with missing data was low, ranging from 0 percent to 6 percent. Missing data were generally balanced across the treatment arms.

Table 10: Missing Data for the Co-Primary Efficacy Endpoints by Week 12 in Study RHCD, ITT Population

Week	TALTZ N=115	Placebo N=56
Week 1	0 (0%)	0 (0%)
Week 4	0 (0%)	0 (0%)
Week 6	2 (2%)	2 (2%)
Week 8	2 (2%)	2 (2%)
Week 12	2 (2%)	3 (5%)

Abbreviations: ITT = intent-to-treat
Source: Statistical Reviewer's Analysis; ITT population is defined as all randomized subjects

Table 11 presents the results for the co-primary efficacy endpoints at week 12 using the pre-specified primary imputation method of NRI. TALTZ was statistically superior to vehicle for both co-primary efficacy endpoints (p-values less than 0.0001). The results for the PP population (not presented here) were similar to those for the ITT population.

Table 11: Results for the Co-Primary Efficacy Endpoints at Week 12 in Study RHCD (ITT; NRI*)

Endpoint	TALTZ N=115	Placebo N=56
sPGA of 0 or 1	93 (81%)	6 (11%)
Treatment Effect		70%
P-value[(1)]		<0.0001
PASI 75	102 (89%)	14 (25%)
Treatment Effect		64%
P-value[(1)]		<0.0001

Abbreviations: sPGA = Static Physician's Global Assessment; PASI = Psoriasis Area and Severity Index; ITT = intent-to-treat; NRI = non-responder imputation
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
(1) P-Value obtained using the Fisher's exact test
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

As noted in Section 7.1.2, the protocol/SAP did not specify sensitivity analyses for the handling the missing data for the co-primary endpoints. The statistical reviewer explored sensitivity analyses for the handling of missing data using the following methods: Placebo Multiple Imputation (pMI), last observation carried forward (LOCF), observed cases (OC), and worst-case scenario (WCS; i.e., missing data for TALTZ is imputed as non-responders and missing data for placebo is imputed as responders). The pMI approach assumes that the statistical behavior of drug- and placebo-treated subjects after discontinuing study product becomes that of the placebo-treated subjects. For this approach, missing data for both subjects on active and placebo were imputed based on only the placebo arm data using the Markov Chain Monte Carlo method and generating 100 imputed datasets. The results for the statistical reviewer's analysis are presented in Table 12. In all cases (including the extreme case of WCS), TALTZ was still statistically superior (p-values less than 0.0001) to placebo for both co-primary efficacy endpoints.

Table 12: Results for the Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data in Study RHCD (ITT*)

Endpoint	TALTZ N=115	Placebo N=56	Treatment Effect
sPGA of 0 or 1			
pMI	82%	11%	71%
LOCF	82%	11%	71%
OC**	82%	11%	71%
WCS	81%	16%	65%
PASI 75			
pMI	89%	26%	63%
LOCF	89%	25%	64%
OC**	90%	26%	64%
WCS	88%	30%	53%

Abbreviations: sPGA = Static Physician's Global Assessment; PASI = Psoriasis Area and Severity Index; ITT = intent-to-treat; pMI = placebo multiple imputation; LOCF = last observation carried forward; OC = observed cases; WCS = worst-case scenario
*ITT population is defined as all randomized subjects
** A total of 113 subjects in TALTZ and 53 subjects in placebo had OC at week 12
Source: Statistical Reviewer's Analysis

7.1.5. Results for the Secondary Efficacy Endpoints

Table 13 presents the results for the gated secondary efficacy endpoints in the ITT population. TALTZ was statistically superior (p-values less than 0.001) to placebo for all presented secondary endpoints. The results for the PP set (not presented here) were similar to those for the ITT population.

Table 13: Results for Secondary Efficacy Endpoints in Study RHCD (ITT; NRI*)

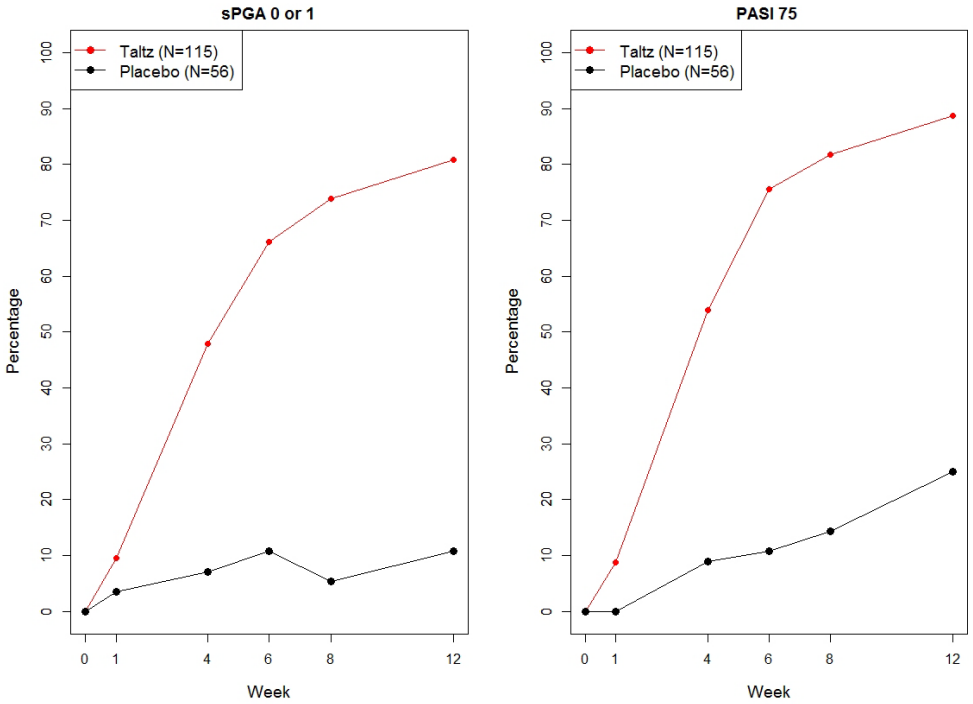
	TALTZ N=115	Placebo N=56	Treatment Effect	P-Value[(1)]
Week 12				
PASI 90	90 (78%)	3 (5%)	73%	<0.001
sPGA of 0	60 (52%)	1 (2%)	50%	<0.001
PASI 100	57 (50%)	1 (2%)	48%	<0.001
≥ 4-point reduction in Itch NRS**	59 (71%)	8 (20%)	51%	<0.001
Week 4				
PASI 75	62 (54%)	5 (9%)	45%	<0.001
sPGA 0 or 1	55 (48%)	4 (7%)	41%	<0.001

Abbreviations: sPGA = Static Physician's Global Assessment; PASI = Psoriasis Area and Severity Index; ITT = intent-to-treat; NRI = non-responder imputation
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
** Among subjects with baseline itch NRS score ≥ 4 (83 subjects in TALTZ and 40 subjects in placebo)
(1) P-Value obtained using the Fisher's exact test
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

7.1.6. Efficacy Over Time

For the double-blind treatment period, subjects were evaluated for sPGA and PASI at weeks 1, 2, 4, 8, and 12. Figure 5 presents the results of the co-primary efficacy endpoints during the double-blind treatment period for study RHCD.

Figure 5: Co-Primary Efficacy Results for the Double-Bling Treatment Period in Study RHCD (ITT; NRI*)



Abbreviations: ITT = intent-to-treat; NRI = non-responder imputation
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis)

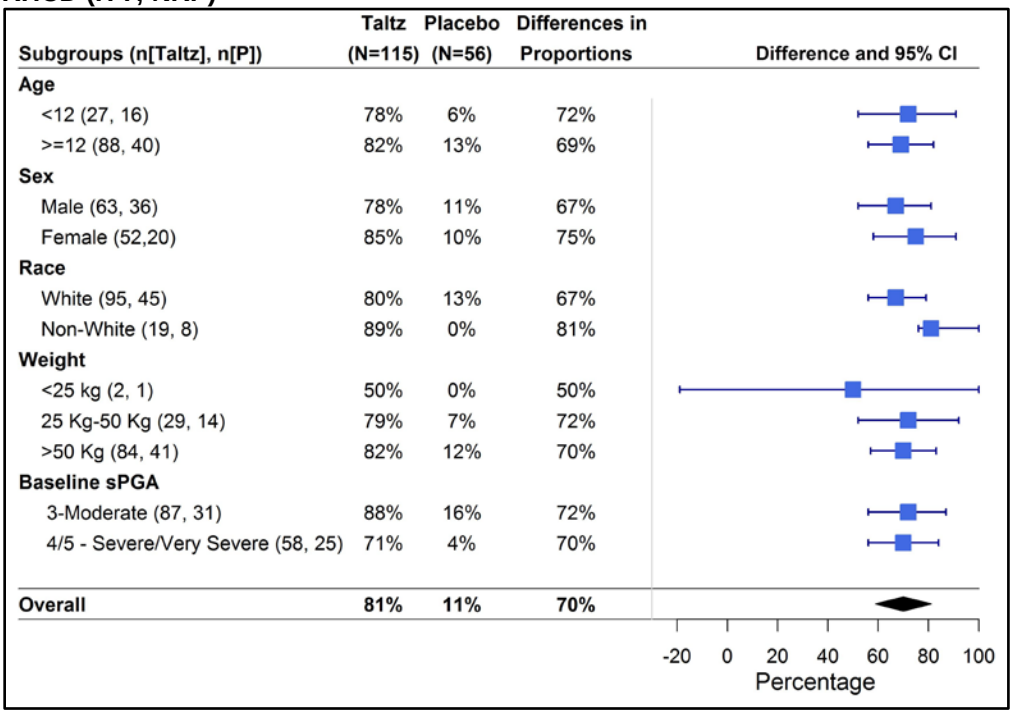
7.1.7. Findings in Special/Subgroup Populations

7.1.7.1. Sex, Race, Age, and Baseline Disease Severity

Figure 6 and Figure 7 present the results for the co-primary efficacy endpoints (i.e., sPGA score of 0 or 1 at week 12 and PASI 75 at week 12) by sex, race (white versus non-white), age (younger than 12 versus 12 or older), baseline weight (less than 25 kg, 25 kg to 50 kg, greater than 50 kg) and baseline sPGA score for study RHCD. The forest plots in these figures contain 95 percent confidence intervals for the difference in proportions of success between the active and placebo arms for the ITT population using the NRI method for handling the missing data.

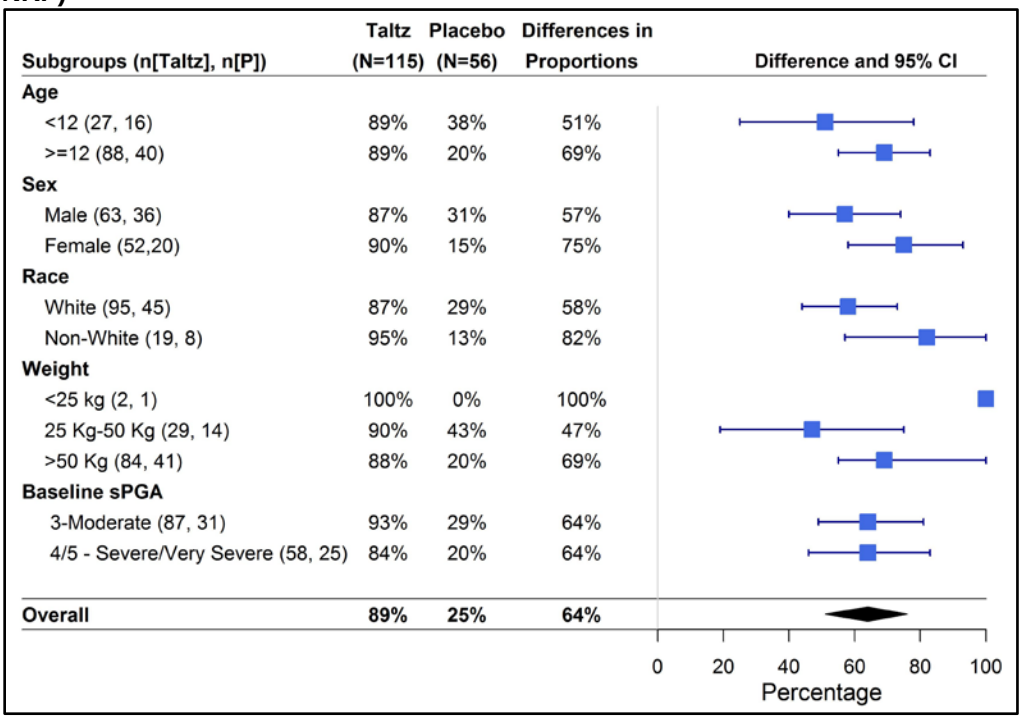
For success on sPGA, treatment effects were generally consistent across subgroups with some variability from the smaller subgroups (i.e., non-white subjects and subjects who weigh less than 25 kg). For PASI 75, there is more variability in efficacy across the subgroups; however, all subgroup showed a positive treatment effect.

Figure 6: sPGA Score of 0 or 1 at Week 12 by Age, Sex, Race, Baseline Weight and Baseline sPGA Score for Trial RHCD (ITT; NRI*)



Abbreviations: ITT = intent-to-treat; CI = confidence interval; sPGA = Static Physician's Global Assessment; NRI = non-responder imputation
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
n[TALTZ] = subgroup sample size for active arm, n[P] = subgroup sample size for placebo arm
Source: Statistical Reviewer's Analysis

Figure 7: PASI 75 at Week 12 by Age, Sex, Race, Baseline Weight and Baseline sPGA Score for Trial RHCD (ITT; NRI*)



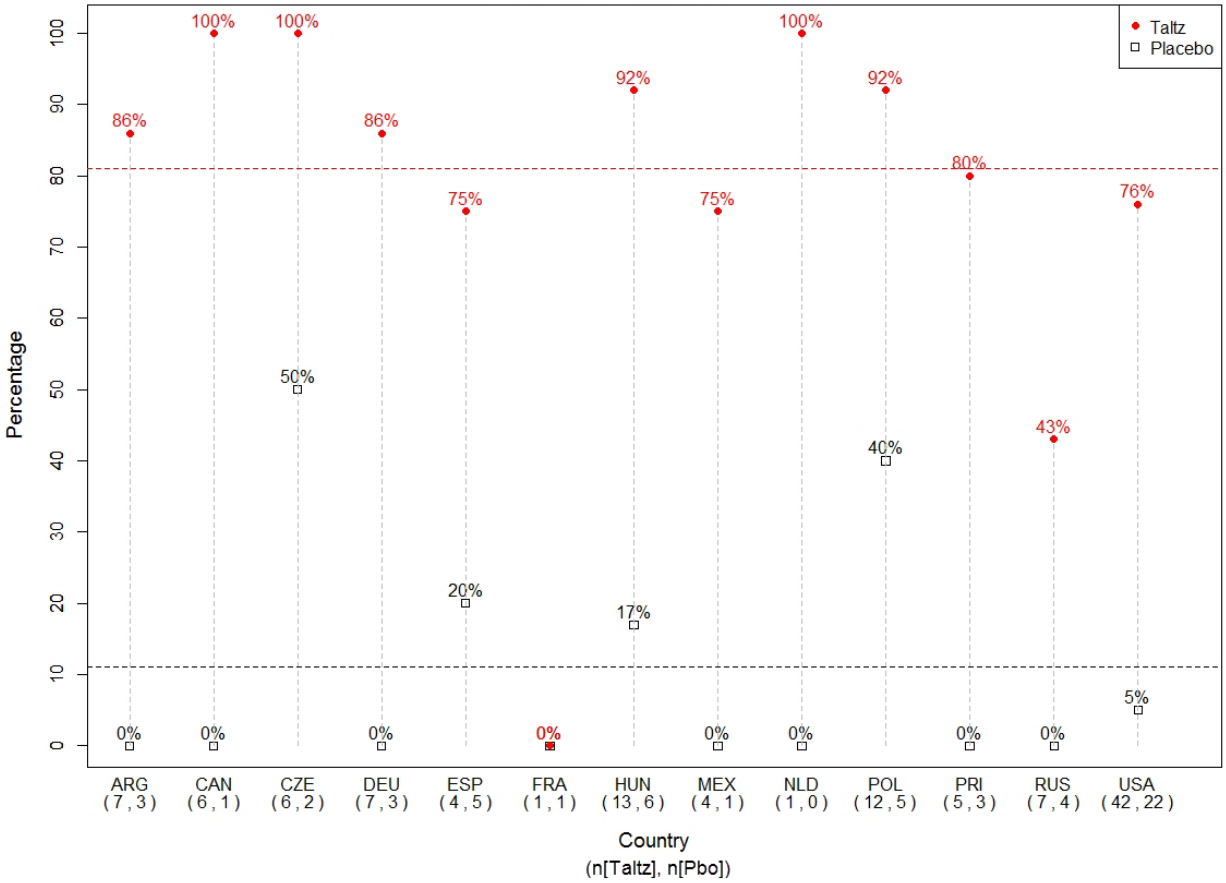
Abbreviations: ITT = intent-to-treat; CI = confidence interval; sPGA = Static Physician's Global Assessment; PASI = Psoriasis Area and Severity Index; NRI = non-responder imputation
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
n[TALTZ] = subgroup sample size for active arm, n[P] = subgroup sample size for placebo arm
Source: Statistical Reviewer's Analysis

7.1.7.2. Geographic Location (Country)

Study RHCD was conducted in 13 countries (Argentina, Canada, Czech Republic, France, Germany, Hungary, Mexico, Netherlands, Poland, Russia, Spain, Puerto Rico, United States). Figure 8 and Figure 9 present the results for the co-primary efficacy endpoints at week 12 by country for study RHCD for the ITT population using the NRI method for handling the missing data.

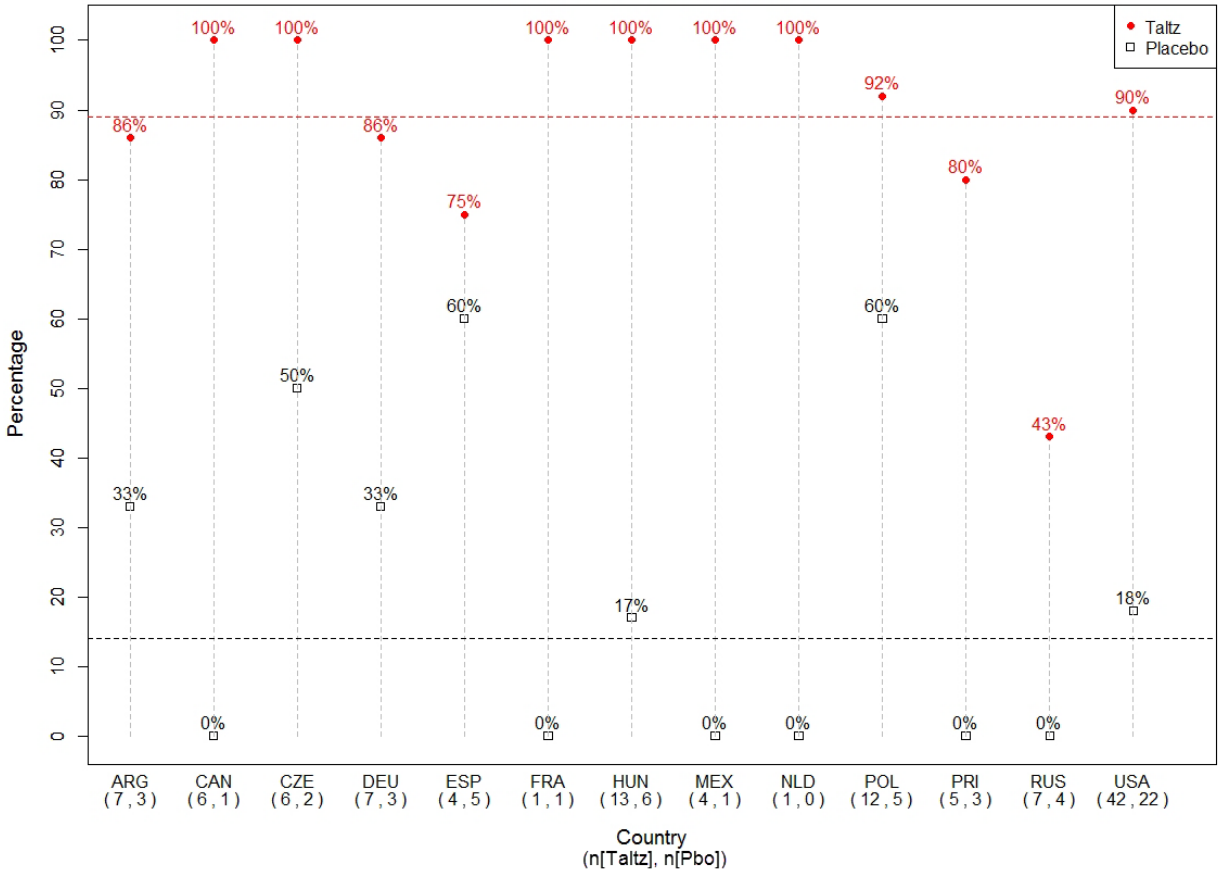
For both endpoints, there was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes in several of the countries.

Figure 8: Results of sPGA Score of 0 or 1 at Week 12 by Country for Study RHCD – (ITT; NRI*)



Abbreviations: ITT = intent-to-treat; sPGA = Static Physician's Global Assessment; NRI = non-responder imputation
Country code: ARG = Argentina; CAN = Canada; CZE = Czech Republic; DEU = Germany; ESP = Spain; FRA = France; HUN = Hungary; MEX = Mexico; NLD = Netherlands; POL = Poland; PRI = Puerto Rico; RUS = Russia; USA = United Stated of America
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
Note: The dotted horizontal line denotes the overall for each treatment arm. The numbers on the plot denote the sample size of each treatment arm within each country
Source: Statistical Reviewer's Analysis

Figure 9: Results of PASI 75 at Week 12 by Country for Trial RHCD – (ITT; NRI*)



Abbreviations: ITT = intent-to-treat; PASI = Psoriasis Area and Severity Index; NRI = non-responder imputation
Country code: ARG = Argentina; CAN = Canada; CZE = Czech Republic; DEU = Germany; ESP = Spain; FRA = France; HUN = Hungary; MEX = Mexico; NLD = Netherlands; POL = Poland; PRI = Puerto Rico; RUS = Russia; USA = United Stated of America
*ITT population is defined as all randomized subjects. Missing data imputed using NRI
Note: The dotted horizontal line denotes the overall for each treatment arm. The numbers on the plot denote the sample size of each treatment arm within each country.
Source: Statistical Reviewer's Analysis

7.1.8. Comparison with Results for Plaque psoriasis in Adult Subjects

Table 14 presents the results for the co-primary efficacy endpoints at week 12 for the three pivotal phase 3 studies used to approve TALTZ for the treatment of plaque psoriasis in adult subjects (studies RHAZ, RHBA and RHBC), as well as study RHCD for pediatric subjects. The results are presented for the ITT population using the NRI method for handling the missing data. It should be noted that although the studies in adults evaluated two dose regiments of TALTZ (80 mg Q2W and Q4W), the Agency only approved TALTZ 80 mg Q2W. Only the results of the approved dose regimen are included in Table 14 for the studies in adult subjects. The reader is reminded that for pediatric subjects, study RHCD evaluated the dose regimen of 20 mg, 40 mg or 80 mg Q4W depending on the weight.

The TALTZ response rates for both co-primary efficacy endpoints were similar between adult and pediatric subjects. The placebo sPGA response rate was slightly higher for pediatric subjects compared to adult subjects. The placebo PASI 75 response rate was also higher in pediatric subjects compared to adult subjects (25 percent versus 3 percent to 7 percent). The statistical reviewer notes that the sample size in study RHCD (pediatric subjects) was much smaller compared to the studies in adult subjects.

Table 14: Results for the Co-Primary Efficacy Endpoints at Week 12 in Studies RHAZ, RHBA, RHBC and RHCD (ITT; NRI*)

	TALTZ**	Placebo	Treatment Effect
Study RHAZ [(1)]	N=433	N=431	
sPGA of 0 or 1	354 (82%)	14 (3%)	79%
PASI 75	386 (89%)	17 (4%)	85%
Study RHBA [(1)]	N=351	N=168	
sPGA of 0 or 1	292 (83%)	4 (2%)	81%
PASI 75	315 (90%)	4 (2%)	88%
Study RHBC [(1)]	N=385	N=193	
sPGA of 0 or 1	310 (81%)	13 (7%)	74%
PASI 75	336 (87%)	14 (7%)	80%
Study RHCD [(2)]	N=115	N=56	
sPGA of 0 or 1	93 (81%)	6 (11%)	70%
PASI 75	102 (89%)	14 (25%)	64%

Abbreviations: ITT = intent-to-treat; PASI = Psoriasis Area and Severity Index; NRI = non-responder imputation; sPGA = Static Physician's Global Assessment; PASI = Psoriasis Area and Severity Index
* ITT population is defined as all randomized subjects. Missing data imputed using NRI
** For studies RHAZ, RHBA and RHBC, the approved TALTZ dose regimen was 80 mg Q4W; for study RHCD, the TALTZ dose regimen is 20 mg, 40 mg or 80 mg Q4W depending on the weight
Study enrolled adult subjects
Study enrolled pediatric subjects 6 to <18 years of age
Source: Label for BLA 125521 and Statistical Reviewer's Analysis

7.2. Review of Safety

7.2.1. Safety Review Approach

The review of safety will focus on the single submitted pediatric study and a comparison of the adverse events profile to the adult population in the clinical trials of original approval.

7.2.2. Review of the Safety Database

Overall Exposure

A total of 115 subjects were initially randomized to TALTZ Q4W, representing 26.9 patient-years of exposure to TALTZ, and 56 subjects were initially randomized to placebo, representing 12.9 patient-years of exposure to placebo. The mean patient-days of exposure were similar between the TALTZ Q4W group (85.5 days) and the placebo group (84.1 days).

In the combined treatment period, 196 subjects were treated with at least one dose of TALTZ Q4W, representing 206.8 years of patient-years of exposure, which includes 114 subjects who were treated with TALTZ for at least 1 year. The mean patient-days exposure was 385.3 days.

Adequacy of the Safety Database:

The safety database is adequate for this pediatric supplement.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Summary Categorization of Adverse Events

Safety data collected on the adverse events are as follows:

Treatment-Emergent Adverse Events (TEAEs): Treatment-emergent AEs were reported by 80.6 percent of all TALTZ-treated subjects. Most TEAEs were mild (41.3 percent) or moderate (35.2 percent) in severity. Severe TEAEs were reported by 4.1 percent of all TALTZ-treated subjects. The percentage of TALTZ-treated subjects with TEAEs judged by the investigator to be related to study treatment was 38.3 percent.

AESIs: The most frequently reported categories of AESIs were Infections (62.8 percent) and Injection Site Reactions (19.9 percent).

Deaths: No deaths were reported during the double-blind or combined treatment period.

Serious Adverse Events (SAEs): SAEs were reported by 13 TALTZ-treated subjects (6.6 percent).

Discontinuations: Discontinuation of study drug due to an adverse event (AE) occurred in three TALTZ-treated subjects (1.5 percent).

Routine Clinical Tests

The study protocol collected clinical laboratory tests and will be discussed in the specific AE sections of this review.

7.2.4. Safety Results

In the double-blind treatment period, the TEAE (treatment emergent adverse events):

- 64 subjects (55.7 percent), TALTZ Q4W
- 25 subjects (44.6 percent), placebo

Majority of TEAEs were mild, and none were severe. The following standards of care were most commonly reported in the TALTZ-treated group):

- Infections and infestations: TALTZ Q4W (32.2 percent) had a higher percentage of subjects reporting events compared with placebo (25.0 percent).
- General disorders and administration site conditions: TALTZ Q4W (16.5 percent) had a higher percentage of subjects reporting events compared with placebo (3.6 percent).
- Gastrointestinal disorders: TALTZ Q4W (13.9 percent) had a higher percentage of subjects reporting events compared with placebo (5.4 percent).
- Respiratory, thoracic and mediastinal disorders: TALTZ Q4W (12.2 percent) had a higher percentage of subjects reporting events compared with placebo (5.4 percent).
- Nervous system disorders: TALTZ Q4W (12.2 percent) had a higher percentage of subjects reporting events compared with placebo (1.8 percent).
- Skin and subcutaneous disorders: TALTZ Q4W (11.3 percent) had a higher percentage of subjects reporting events compared with placebo (7.1 percent).

In the combined treatment periods, 158 TALTZ-treated subjects (80.6 percent) reported at least one TEAE. The majority of TEAEs were mild. The most commonly reported Preferred Terms were (greater than 5 percent):

- Nasopharyngitis (17.3 percent)
- Injection site reaction (16.3 percent)
- Upper respiratory tract infection (15.3 percent)
- Headache (12.8 percent)
- Nausea (8.2 percent)
- Diarrhea (7.7 percent)
- Pharyngitis (7.7 percent)
- Vomiting (7.7 percent)
- Conjunctivitis (6.6 percent)
- Impetigo (6.6 percent)
- Tonsillitis (5.6 percent)
- Arthralgia (5.6 percent)
- Pyrexia (5.1 percent), and
- Oropharyngeal pain (5.1 percent)

Reviewer's Comment: The AE profile reported for this pediatric study is comparable to the adult study in the original approval. Clinically, no significant common AE were identified as "new."

Deaths

There were no deaths in this clinical study.

Serious Adverse Events

During the double-blind treatment period, one subject (0.9 percent) reported an SAE. This subject was in the TALTZ Q4W treatment group (RHCD (b) (6)) and reported an SAE of accidental overdose of moderate severity. The subject was hospitalized and treated as an accidental overdose (not on investigational drug). The subject recovered.

In the combined treatment period, 13 TALTZ-treated subjects (6.6 percent) reported at least one SAE. The significant events:

- Crohn's disease: n=2 (1.0 percent) will be discuss in Significant Adverse Events section.
- Dehydration: n=2 (1.0 percent)
  - Subject (**RHCD-** (b) (6)) reported an SAE of dehydration of moderate severity and was hospitalized. In the opinion of the investigator, the SAE was not related to study treatment, and the patient recovered and was discharged in 7 days. Study treatment was not discontinued.
  - Subject (**RHCD** (b) (6)) reported an SAE of dehydration of moderate severity related to food poisoning and was hospitalized for corrective treatment. In the opinion of the investigator, the SAE was not related to study treatment, and the patient recovered and was discharged in 4 days. Study treatment was not discontinued.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no discontinuations in the TALTZ group during the double-blind treatment period. One subject in the placebo group discontinued due to guttate psoriasis of moderate severity.

In the combined period, discontinuations will be discussed in the next section.

Significant Adverse Events

<u>Inflammatory Bowel Disease (Crohn's)</u>:

Double-Blind Period (2)

- Subject (**RHCD-** (b) (6)) A 9-year-old female; TALTZ 40 mg Q4W; 25-kg to 50-kg weight group) reported AEs of gastrointestinal inflammation (moderate) and Abdominal pain (mild) on study day 1, the same day as starting the Double-Blind Treatment Period. On study day 43, the patient reported an AE of diarrhea (moderate). Study drug was temporarily interrupted due to the AEs of diarrhea and gastrointestinal inflammation. The subject was seen by a gastroenterologist. Study drug was permanently discontinued on study day 64 due to physician decision (suspected inflammatory bowel disease). No treatment details were reported for the AEs. The AEs of abdominal pain and diarrhea were reported as resolved on study day 138. The patient permanently discontinued from the Post-Treatment Follow-Up Period of the study on study day 356 due to the AE of gastrointestinal inflammation, which was not resolved. The investigator considered the AEs of gastrointestinal inflammation, abdominal pain, and diarrhea as related to study drug. The case was adjudicated as probable Crohn's disease.

Combined Treatment Period (3)

One TALTZ-treated subject reported inflammatory bowel disease, two reported Crohn's disease, and one reported probable Crohn's disease, which was the same subject in the double-blind period.

- Subject (**RHCD** (b) (6)) reported 2 SAEs of Crohn's disease, both severe. Nine-year-old female; TALTZ 40 mg Q4W; 25-kg to 50-kg weight group; reported four events of Crohn's disease on study day 151 (severe; study drug interrupted, patient recovered), study day 172 (SAE, study drug interrupted, severe; patient recovered), study day 177 (moderate; study drug withdrawn, patient recovered) of the maintenance period, and study day 404 (study day 118 of post-treatment period; [SAE, severe; patient recovered]). The events were related by the investigator to the study treatment. The case was adjudicated as probable Crohn's disease.
- Subject (**RHCD-** (b) (6) reported an SAE of Crohn's disease that was moderate in severity. Thirteen-year-old female; TALTZ 40 mg Q4W; 25-kg to 50-kg weight group; reported two events of Crohn's disease. The first event, on study day 248 of the maintenance period (moderate severity), was an SAE. The subject was hospitalized for abdominal pain, diagnosed with Crohn's disease, received corrective treatment, and was discharged from the hospital on study day 255. The AE of Crohn's disease was not resolved at the time of discharge. The second event was reported on study day 255 of the maintenance period and was moderate in severity. At the time of the database lock, the AE of Crohn's disease was ongoing, and the patient had not recovered. Both events were related by the investigator to study treatment. The patient permanently discontinued from study treatment on study day 344 (from date

of randomization due to the AE of Crohn's disease. The case was adjudicated as probable Crohn's disease.

- Subject (**RHCD-** (b) (6)) 15-year-old male; TALTZ 80 mg Q4W; greater than 50-kg weight group; reported an SAE of inflammatory bowel disease (severe) on study day 281 of the maintenance period. This SAE was not related to study drug per the investigator, and no change was made in the dose of study drug. The subject was hospitalized, received corrective treatment, and recovered on study day 288. Subsequently, the subject withdrew from study drug and the study per request of his primary care physician. This case was adjudicated as probable Crohn's disease.

Cytopenias

One report of neutropenia during the double-blind period in the TALTZ treatment group. Three reports of mild neutropenia and leukopenia were reported during the combined treatment period. All were mild in nature and subjects recovered without infections.

Hepatic Events

Mild increase in hepatic enzymes were reported in three subjects during the combined treatment period. No changes in hepatic-related events were reported in the double-blind period.

Infections

During the double-blind treatment period, a higher percentage of infection-related TEAEs was reported in the TALTZ Q4W group than in the placebo group (32.2 percent versus 25.0 percent). Nasopharyngitis, upper respiratory tract infection, and conjunctivitis were the most frequently reported (more than 2 percent) infections, with nasopharyngitis and conjunctivitis occurring more frequently in the TALTZ Q4W group than in the placebo group. The majority of the infections were mild or moderate in severity. There were no severe or serious infection-related AEs. No patients discontinued study drug due to an infection-related AE. There were no opportunistic infections or candida infections.

During the Combined Treatment Periods, 62.8 percent of TALTZ-treated subjects reported at least one infection-related TEAE. Nasopharyngitis, upper respiratory tract infection, pharyngitis, conjunctivitis, impetigo, and tonsillitis were the most frequently reported (greater than 5 percent) infections. The majority of the infections were mild to moderate in severity, with one TALTZ-treated subject (0.5 percent) reporting a severe infection (pharyngitis). Two TALTZ-treated subjects (1.0 percent) reported serious infections (one subject reported otitis media acute and one subject reported tonsillitis). No subjects discontinued study drug due to an infection-related AE. One TALTZ-treated subject (0.5 percent) reported a TEAE of varicella zoster virus infection, which was considered by the investigator to be an opportunistic infection. One TALTZ-treated subject (0.5 percent) reported a TEAE of fungal infection, which was a mild oral candida infection of 5 days duration.

Allergic Reactions/Hypersensitivity

During the double-blind treatment period, allergic reaction/hypersensitivity TEAEs were more frequent for TALTZ Q4W group than the placebo group. None were anaphylactic in nature.

- Six subjects (5.2 percent) in the TALTZ Q4W group; two subjects (1.7 percent) reported urticaria, and each of the following AEs were reported in one subject (0.9 percent): bronchospasm, atopic dermatitis, eczema, and maculo-papular rash.
- One subject (1.8 percent) in the placebo group reported pustular rash.

No subjects discontinued due to allergic reaction/hypersensitivity AEs.

During the combined treatment period, allergic reaction/hypersensitivity were not anaphylactic in nature; TEAEs were reported by 15 (7.7 percent) of TALTZ-treated subjects (four atopic dermatitis, three urticaria, and one subject with bronchospasm, dermatitis, drug eruption, eczema, eye edema, injection related reaction, rash, and skin reaction). Most TEAEs were mild to moderate. No subject discontinued study treatment due to an allergic reaction/hypersensitivity.

Depression and Suicidal Ideation and Behavior (SIB)

A single subject (0.9 percent) reported TEAE of depression in the TALTZ Q4W group during the double-blind treatment period. The TEAE was mild and nonserious and did not lead to investigational drug discontinuation. The shifts in Children's Depression Rating Scale-Revised (CDRS-R) total score from baseline to postbaseline showed improvement in baseline depression rating scores.

During the combined treatment periods, six (3.1 percent) of TALTZ-treated subjects reported at least one depression-related TEAE. None of the subjects had a previous history of depression or positive response to C-SSRS postbaseline.

Reviewer's Comment:

- *There's no indication that depression or Suicidal Ideation and Behavior (SIB) was found due to TALTZ treatment. Depression-related TEAEs were uncommon during the double-blind and combined treatment period. No differences were found in the baseline Children's Depression Rating Scale- Revised (CDRS-R) total score to post-baseline.*
- *There is clear inflammatory bowel disease AE risk associated with treatment of TALTZ. This AE is known from the adult studies and is labeled in the PI. This reviewer intends to strengthen the warning for pediatric development of Crohn's and IBD in the labeling.*

Laboratory Findings

See hepatic events and cytopenias for clinically significant laboratory discussions. Overall, the differences between treatment groups were not clinically meaningful.

Vital Signs

No clinically significant changes in vital signs.

Immunogenicity

During the double-blind period, of the 171 evaluable subjects, eight (4.7 percent) had ADAs present at baseline (all were classified as low titer) with no neutralizing activity:

- Six subjects (5.2 percent) in the TALTZ Q4W group and
- Two subjects (3.6 percent) in the placebo group.

Among the 115 evaluable subjects in the TALTZ Q4W group, 21 (18.3 percent) were TE-ADA positive postbaseline through week 12, of which 10 were classified as low titer, seven were classified as moderate titer, and four were classified as high titer. Five subjects (4.3 percent) were NAb positive (two with moderate titer and three with high titer). In addition, 15 subjects (13.0 percent) were NAb inconclusive, meaning that no NAbs were detected at any time during the study period in these subjects but each subject had at least one sample with a TALTZ concentration above the limit of drug tolerance of the NAb assay.

During the combined treatment period, of the 183 immunogenicity evaluable subjects, 50 (27.3 percent) were TE-ADA positive, of which 28 were classified as low titer, 20 were classified as moderate titer, and two were classified as high titer. Five subjects (2.7 percent) were NAb positive. In addition, 42 subjects (23.0 percent) were NAb inconclusive, meaning that no NAbs were detected at any time during the study period in these subjects but each subject had at least one sample with a TALTZ concentration above the limit of drug tolerance of the NAb assay. See Clinical Pharmacology Section for discussion.

7.2.5. Analysis of Submission-Specific Safety Issues

The safety profile of TALTZ for pediatric subjects from 6 years to less than 18 years of age with moderate-to-severe plaque psoriasis was consistent with the reported safety profile of the adult studies for plaque psoriasis. Crohn's disease was seen at a higher frequency in pediatric patients with psoriasis. The higher frequency, compared to placebo, was noted in both the double-blind periods and the combined period. The 120-day safety update noted no new Crohn's disease events. The incidence rate of 1.9 in the all TALTZ safety population was higher than the background rate in the juvenile psoriasis population (IR=0.097) (Paller et al. 2019). This safety issue is known and in this Reviewer's opinion does not rise to the level of Black Box Warning for the PI. The labeling will reflect the seriousness of the safety issue and allow physicians to discuss TALTZ treatment with their pediatric patients without restricting the use of this product in clinical practice.

7.2.6. Safety Analyses by Demographic Subgroups

No significant treatment-by-subgroup differences were observed.

7.2.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Periodic Safety Update Report (PSUR) for March 2019 showed no new safety issues and no significant changes to the Core Data Sheet. TALTZ is currently marketed in 61 countries for adults with moderate-to-severe plaque psoriasis and active psoriatic arthritis. Cumulatively, nearly 10,000 subjects have been exposed to TALTZ in the clinical development program.

7.2.8. Integrated Assessment of Safety

Safety data collected up to 1 year of study drug exposure (RHCD) support a safety profile that is consistent with the adult data in the PI. The risk of TALTZ is consistent with the known safety profiles in other systemic agents used for psoriasis. This includes risks of immunosuppression with serious and in some cases

opportunistic or unusual infections, reactivation of latent tuberculosis, cytopenias, inflammatory bowel disease and hypersensitivity events. IBD has been identified as an increase risk in this pediatric study. IBD is present in the Warning and Precautions section of the current labeling, the increased pediatric reporting in this study does not rise to the need for a Black Box Warning. The identified increase in the frequency of Crohn's disease can be properly included in labeling so that physician can discuss the risk/benefits of TALTZ in their pediatric patients.

7.3.Summary and Conclusions

7.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were large and consistent across endpoints. The amount of missing data was relatively small (approximately 2 percent) at week 12 (i.e., the primary efficacy timepoint). For the handling of missing data, the protocol/SAP did not specify sensitivity analyses. The statistical reviewer conducted sensitivity analyses using the following methods: Placebo Multiple Imputation (pMI), last observation carried forward (LOCF), observed cases (OC), and worst-case scenario (WCS; i.e., missing data for TALTZ is imputed as non-responders and missing data for placebo is imputed as responders). In all sensitivity analyses, TALTZ remained statistically superior to placebo (p-values less than 0.001) for both co-primary efficacy endpoints.

There were no substantial differences in efficacy among subgroups, with some variability in the smaller subgroups (i.e., non-white subjects and subjects who weigh less than 25 kg). For PASI 75, there is more variability in efficacy across the subgroups compared to sPGA; however, all subgroup showed a positive treatment effect. For both endpoints, there was some variability in treatment effect across countries; however, this may be due to the relatively small sample sizes in several of the countries.

The statistical reviewer compared the results for the co-primary efficacy endpoints at week 12 between the three pivotal phase 3 studies used to approve TALTZ for the treatment of plaque psoriasis in adults (studies RHAZ, RHBA and RHBC) and study RHCD for pediatric subjects. Response rates for TALTZ in both co-primary efficacy endpoints were similar across adult and pediatric subjects. The placebo sPGA response rate was slightly higher for pediatric subjects compared to adult subjects. The placebo PASI 75 response rate was also higher in pediatric subjects compared to adult subjects (25 percent versus 3 percent to 7 percent).

7.3.2. Conclusions and Recommendations

This reviewer recommends an approval for NDA 125521/Supplement-20. The labeling will be updated to describe TALTZ treatment for patients 6 years and older with moderate-to-severe plaque psoriasis who are candidates for systemic or phototherapy.

8 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not convened for this supplement. No novel or complex regulatory issues were identified that required an open forum discussion for this supplement.

9 Pediatrics

A Pediatric Review Committee meeting was held on February 20, 2020, to discuss the submitted supplemental clinical trial results. The committee agreed with the Division that the study RHCD provided adequate pediatric data to be included in labeling and that the Applicant has fulfilled the postmarketing requirement as stated in the approval letter for TALTZ.

19 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

11 Risk Evaluation and Mitigation Strategies

None

12 Postmarketing Requirements and Commitment

The Applicant is released from its postmarketing requirement as fulfilled.

13 Appendices

13.1. References

Flytstrom, I, B Stenberg, A Svensson, and IM Bergbrant, 2008, Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial, Br J Dermatol, 158(1):116-121.

Heydendael, VM, PI Spuls, BC Opmeer, CA de Borgie, JB Reitsma, WF Goldschmidt, PM Bossuyt, JD Bos, and MA de Rie, 2003, Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis, N Engl J Med, 349(7):658-665.

ME, DJ, VdK PC, DJ EM, and S MM, 2009, Epidemiology and prescribed treatments in childhood psoriasis: a survey among medical professionals, J Dermatolog Treat, 20(5):254-258.

Napolitano, M, M Megna, A Balato, F Ayala, S Lembo, A Villani, and N Balato, 2016, Systemic Treatment of Pediatric Psoriasis: A Review, Dermatol Ther (Heidelb), 6(2):125-142.

Paller, AS, J Schenfeld, NA Accortt, and G Kricorian, 2019, A retrospective cohort study to evaluate the development of comorbidities, including psychiatric comorbidities, among a pediatric psoriasis population, Pediatr Dermatol, 36(3):290-297.

Saurat, JH, RG Langley, K Reich, K Unnebrink, EH Sasso, and W Kampman, 2011, Relationship between methotrexate dosing and clinical response in patients with moderate to severe psoriasis: subanalysis of the CHAMPION study, Br J Dermatol, 165(2):399-406.

13.2. Financial Disclosure

[Insert text here]

Covered Clinical Study (Name and/or Number): I1F-MC-RHCD

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 66		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: Honorarium and speaking fee Proprietary interest in the product tested held by investigator:unknown Significant equity interest held by investigator in Study: unknown Sponsor of covered study: 11		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Clinical/Biostatistics

Static Physician's Global Assessment (sPGA)

Numerical Score	Description	Criteria
0	Clear	Plaque elevation = 0 (no elevation over normal skin), scaling = 0 (no scale), erythema = 0 (residual post-inflammatory hyperpigmentation or hypopigmentation may be present)
1	Minimal	Plaque elevation = +/- (possible but difficult to ascertain whether there is a slight elevation above normal skin), scaling = +/- (surface dryness with some white coloration), erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped), scaling = fine (fine scale partially or mostly covering lesions), erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges), scaling = coarser (coarse scale covering most of all of the lesions), erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard sharp edges), scaling = coarse (coarse, non-tenacious scale predominates

		covering most or all of the lesions), erythema = severe (very bright red coloration)
5	Very Severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges), scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface), erythema = very severe (extreme red coloration; dusky to deep red coloration)

Source: Applicant's BLA submission; Module 5.3.5.1 (Case Report Forms)

Psoriasis Area and Severity Index

PASI combines assessments of the extent of body-surface involvement in four anatomical regions (head and neck, trunk, arms, and legs) and the severity of scaling (S), redness (R), and plaque induration/infiltration (thickness, T) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease. Severity is rated for each index (R, S, T) on a 0 to 4 scale: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe.

The body is divided into four anatomical regions comprising the head (h), upper limb (u), trunk (t), and lower limb (l). In each of these areas, the fraction of total BSA affected is graded on a 0 to 6 scale (0 for no involvement up to 6 for 90 percent to 100 percent involvement):

0 = 0 percent (clear)
1 = more than 0 percent to less than 10 percent
2 = 10 percent to less than 30 percent
3 = 30 percent to less than 50 percent
4 = 50 percent to less than 70 percent
5 = 70 percent to less than 90 percent
6 = 90 percent to 100 percent

The PASI score is calculated by multiplying the sum of the individual-severity scores for each area by the weighted area of involvement score for that respective area, and then summing the four resulting quantities as follows:
PASI = 0.1 (Rh + Th + Sh) Ah + 0.2 (Ru + Tu + Su) Au + 0.3 (Rt + Tt + St) At + 0.4 (Rl + Tl + Sl) Al

Itch Numeric Rating Scale

The Itch NRS is a single-item, patient-reported outcome measure designed to capture information on the overall severity of a patient's itching due to their psoriatic skin condition by having the patient circle the integer that best describes the worst level of itching in the past 24 hours on an 11-point NRS anchored at 0 representing "no itching" and 10 representing "worst itch imaginable."

13.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

13.4.1. Summary of Bioanalytical Method

The serum samples obtained from study I1F-MC-RHCD were analyzed using a validated enzyme linked immune-sorbent assay (ELISA) to quantify ixekizumab concentrations.

The bioanalytical method used was acceptable, and all samples were analyzed within 781 days of collection, which is within the established long-term stability window.

Table 15: Summary of ELISA Method Validation and Performance

Validation Report	**184959; Determination of LY2439821 in Human Serum by ELISA**
Method type	Quantitative ELISA
Matrix	Human serum
Analyte	LY2439821 (ixekizumab)
Capture molecule	LSN2815254
Blocking Buffer	Blocker™ Casein in PBS
Minimum Required Dilution	5-fold
Secondary Antibody	Mouse anti-human IgG4 horseradish peroxidase
Substrate	o-phenylenediamine
Detection	Plate reader wavelengths of 490 nm; 650 nm reference
LLOQ	6.30 ng/mL
ULOQ	400 ng/mL
Calibration range	3.20 ng/mL to 800 ng/mL Samples above the limit of quantification (400 ng/mL) were diluted and reanalyzed to yield results within the validation range. Validated dilution limit was 20,000-fold.
Inter-assay accuracy	-1.00 to 1.60%
Intra-assay accuracy (%relative error)	1.15 to 8.93%
Inter-assay precision (%CV)	4.07 to 12.0%
Intra-assay precision (%CV)	1.48 to 2.78%
Stability	Long-term stability storage period is 1095 days in human serum at approximately -70°C. Benchtop stability is 25 hours at ambient temperature. 6 cycle freeze/thaw stability has been validated.

Abbreviations: LLOQ = lower limit of quantification; ULOQ = upper limit of quantification
Source:Summarized from Module 5.3.5.1. Bionalytical Report

13.4.2. Population Pharmacokinetic Analyses

The goal of population PK (popPK) analysis was to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) of ixekizumab in patients.

The population PK model included 184 pediatric patients in study I1F-MC-RHCD (RHCD). The baseline population characteristics across weight categories in the popPK model evaluation dataset is provided in Table 16.

The popPK analysis was conducted by the Applicant and evaluated by the reviewer. The PK of ixekizumab administered SC was best characterized by a two-compartment model with first-order absorption and linear elimination. The residual error model was described by a proportional error model. Covariate modeling are evaluated on relevant PK parameters using stepwise covariate modeling implemented in PsN 4.2. The criterion for forward inclusion and backward deletion is a p-value no greater than 0.001 (Δ10.828 objective function value for inclusion/exclusion of 1 parameter).

Parameter estimates of final covariate model were provided in Table 17. The final model included effects of weight and ADA titer on CL/F as well as an effect of weight on volume of distribution. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 10). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of ixekizumab in pediatric patients (Figure 11). Bootstrap analyses demonstrated consistency in parameter estimates and indicated the robustness of the model.

Weight has a statistically significant and clinically relevant effect on ixekizumab clearance. The popPK model indicated that the weight category-based dosing regimens used in study I1F-MC-RHCD (RHCD) were able to achieve similar targeted concentrations in pediatric patients across proposed weight range. The observed concentration-time profile of ixekizumab by weight categories is shown in Figure 12. The PK profile appears similar between patients with weight higher than 50 kg and patients with weight between 25 kg and 50 kg. The observed PK profile in four patients weighing less than 25 kg were within the range of observed PK profile in other weight groups. Simulation based on final model was conducted by the reviewer to compare the exposure with proposed dosing regimen in patients across different weight categories (Figure 13). It suggests proposed dosing regimen will achieve similar exposure (about 20 percent lower) in patients less than 25 kg compared to patients with higher body weight.

In pediatric psoriasis patients treated with ixekizumab at the recommended dosing regimen up to 12 weeks, 21 patients (18 percent) developed anti-drug antibodies, five patients (4 percent) had confirmed neutralizing antibodies. Immunogenicity was found to have an impact on CL in the form of titer, where higher titers are associated with faster clearance. Patients with high titers (equal to or greater than 1:1280) were estimated to have approximately 20.9 percent to 22.9 percent higher clearance compared to ADA-negative patients. Other covariates including site of injection, age, sex, race, baseline sPGA or PASI score and geographic region were not found to be statistically significant in the analysis.

Table 16: Baseline Characteristics for Patients in Study RHCD Included in the Pharmacokinetic Analysis by Baseline Weight Categories

Baseline Covariate	<25 kg (N=4)	25-50 kg (N=45)	>50 kg (N=135)	Overall (N=184)
Age (years)[a]	7 (6-9)	10 (6-17)	15 (9-17)	14 (6-17)
Body weight (kg)[a]	21.7 (21.5-22.6)	40 (25.0-50)	65.2 (50.1-136)	58.6 (21.5-136)
BMI (kg/m^2)[a]	14.9 (14.3-15.7)	19.1 (13.5-23.4)	24.6 (17.5-49.8)	22.7 (13.5-49.8)
Sex – female (%)	75.0	60.0	54.8	56.5
Baseline PASI[a]	18.3 (13.6-33.1)	18.4 (12.0-47.8)	18.0 (12.0-49.2)	18.1 (12.0-49.2)
Baseline sPGA[a]	4 (4-4)	4 (3-5)	4 (3-5)	4 (3-5)
Race (%): White/ Black or African American/Asian/American Indian or Alaska Native/Other/Missing	75/0/0/25 /0/0	75.6/2.22/6.67/2.22 /8.89/4.44	83.7/3.70/2.22/0.741 /7.41/2.22	81.5/3.26/3.26/1.63 /7.61/2.72
Site of SC injection (%): Abdomen/Arm/Thigh	24.3/70.3/5.41	27.9/55.4/16.7	28.9/57.2/13.8	28.6/57.0/14.4
Geographic Region (%) (US, Europe, Rest of World [ROW])	25/25/50	35.6/40.0/24.4	38.5/42.2/19.3	37.5/41.3/21.2

Abbreviations: BMI = body mass index; N = total number of patients included in the pharmacokinetic analysis; PASI = Psoriasis Area and Severity Index; SC = subcutaneous; sPGA = static Physician's Global Assessment
[a] Median (range)
Source: Table 8.1 in Applicant's popPK report, page 51

Table 17: Parameter Estimates of the Final popPK Model

Parameter Description	Population Estimate (95% CI, %SEE)[a]	Inter-Individual Variability (95% CI, %SEE)[a,b]
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.00801 (0.00446 – 0.0201, 29.3)	---
Clearance		
Parameter for CL (L/hr)	0.0120 (0.0107 – 0.0131, 3.94)	28.4% (23.7% - 33.2%, 14.5)
Titer effect on CL[c]	0.0292 (0.0130 – 0.0499, 32.3)	---
Parameter for Q (L/hr)	0.0119 (0.00249 – 0.0208, 27.6)	---
Weight effect on CL and Q[c,d]	0.989 (0.827 – 1.17, 8.43)	---
Volume of Distribution		
Parameter for V_2 (L)	2.72 (1.16 – 5.36, 31.8)	---
Parameter for V_3 (L)	2.11 (0.638 – 2.93, 17.6)	---
Weight effect on V_2 and V_3[e]	0.998 (0.753 – 1.27, 11.8)	
Bioavailability		
Parameter for F1	0.72 (FIXED)[f]	---
Residual Error (proportional)	27.7% (23.2% - 31.9%, 7.62)	

Abbreviations: ADA = antidrug antibody; CI = confidence interval; CL = clearance; F1 = bioavailability; IV = intravenous; Ka = absorption rate constant; LOG_e = natural logarithm; Ps = plaque psoriasis; PsA = psoriatic arthritis; Q = inter-compartmental clearance; SEE = standard error of the estimate; V_2 = volume of distribution of the central compartment; V_3 = volume of distribution of the peripheral compartment.

Note: The final population model is the same as the base population model.

[a] The CI was estimated using bootstrap.

[b] Inter-individual variability (IIV) was calculated using the following equation for log-normal distributions of the random effects for CL: $\%IIV = 100 \times \sqrt{(e^{OMEGA_N} - 1)}$, where $OMEGA_N$ is the variance of the CL parameter.

[c] The table provides the population estimate. To obtain individual clearance estimates, use the following equation: $CL_{individual} = CL*(bodyweight/58.6)^{0.989}*(1+0.0292*LOG_e[ADA\ titer])$.

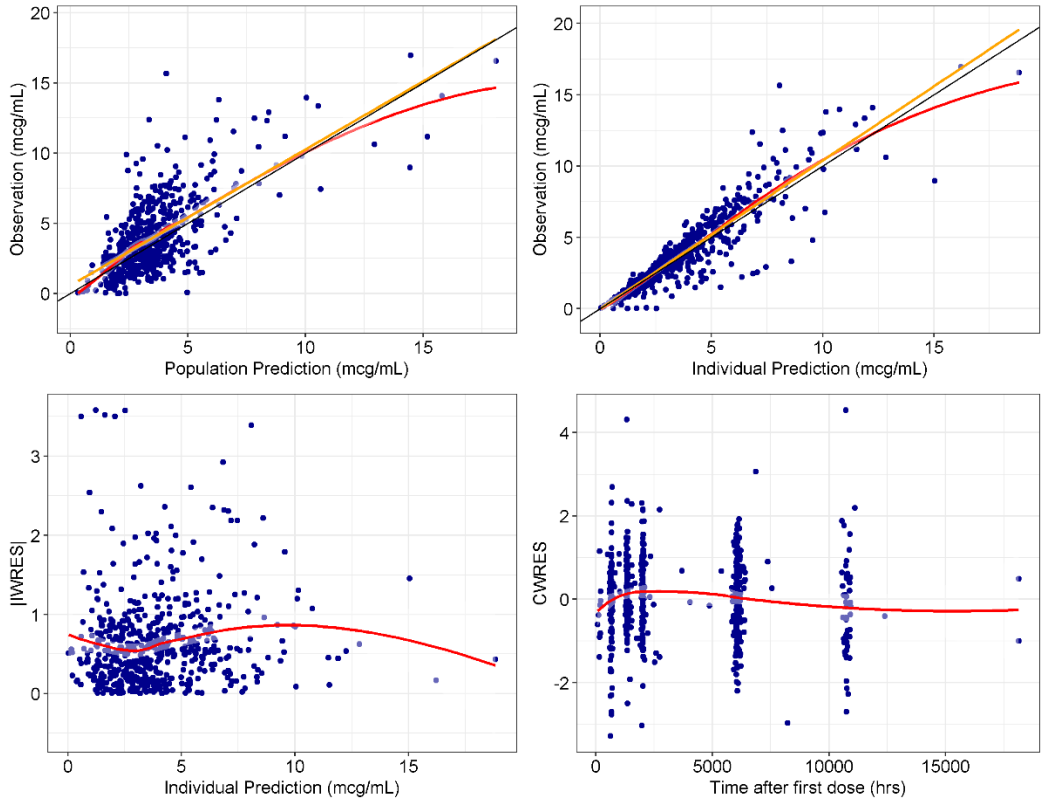
[d] $Q_{individual} = Q*(bodyweight/58.6)^{0.989}$

[e] $V_{2,individual} = V_2*(bodyweight/58.6)^{0.998}$, $V_{3,individual} = V_3*(bodyweight/58.6)^{0.998}$

[f] Bioavailability was fixed to the mean value across the Ps and PsA Phase 3 trials from the existing Ps/PsA model (F = 0.72) as the same formulation was utilized in all studies and no IV data are included in the RHCD analysis.

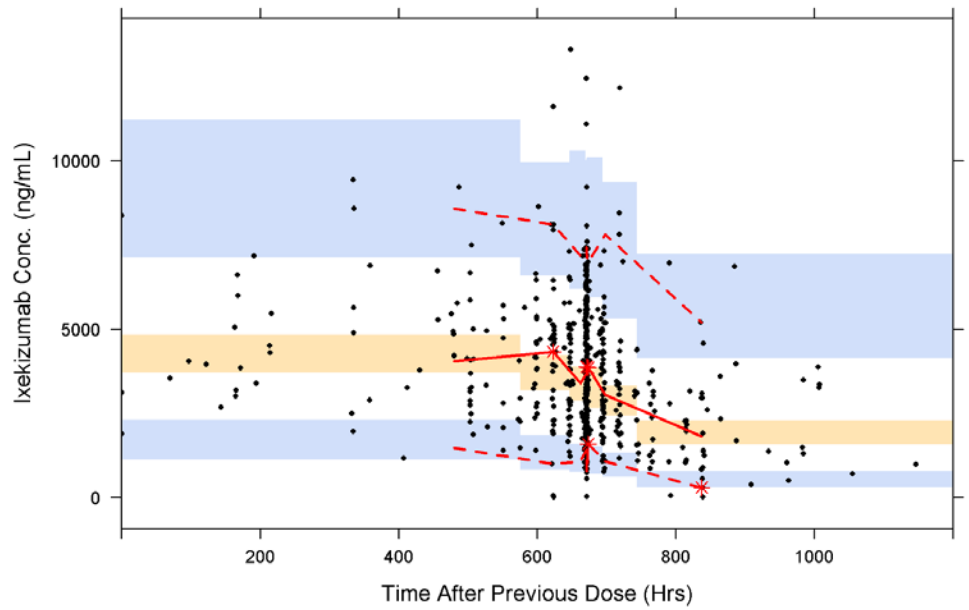
Source: Table 8.4 in Applicant's popPK report, page 64

Figure 10: Goodness of Fit Plots of the Final Model



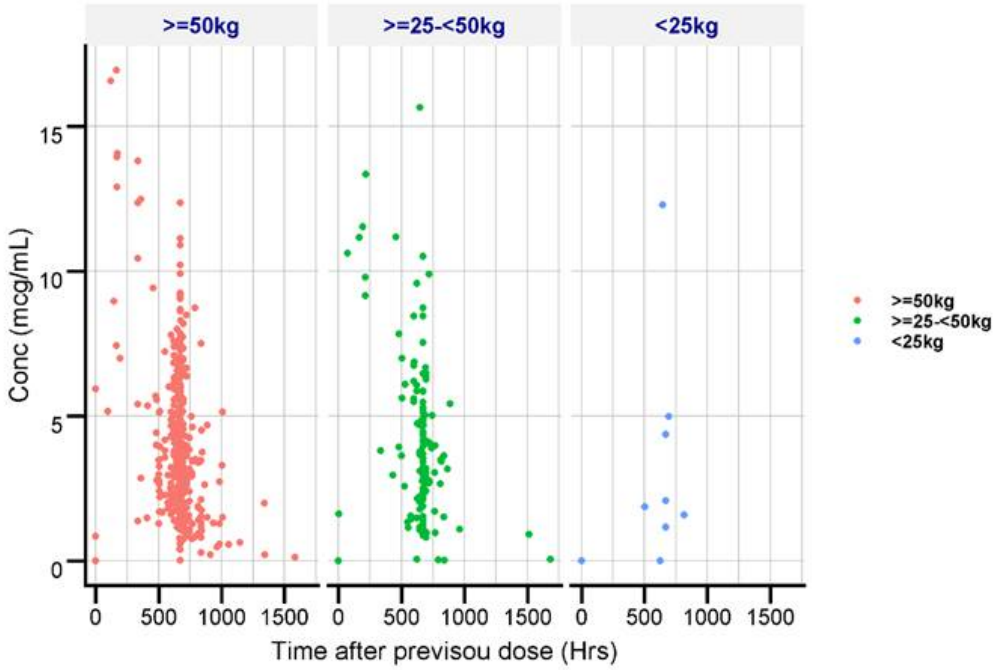
Source: Reviewer's Analysis based on "rhcd_iad3_pk_nm.csv"

Figure 11: Visual Predictive Checks of Ixekizumab Concentration-Time Data



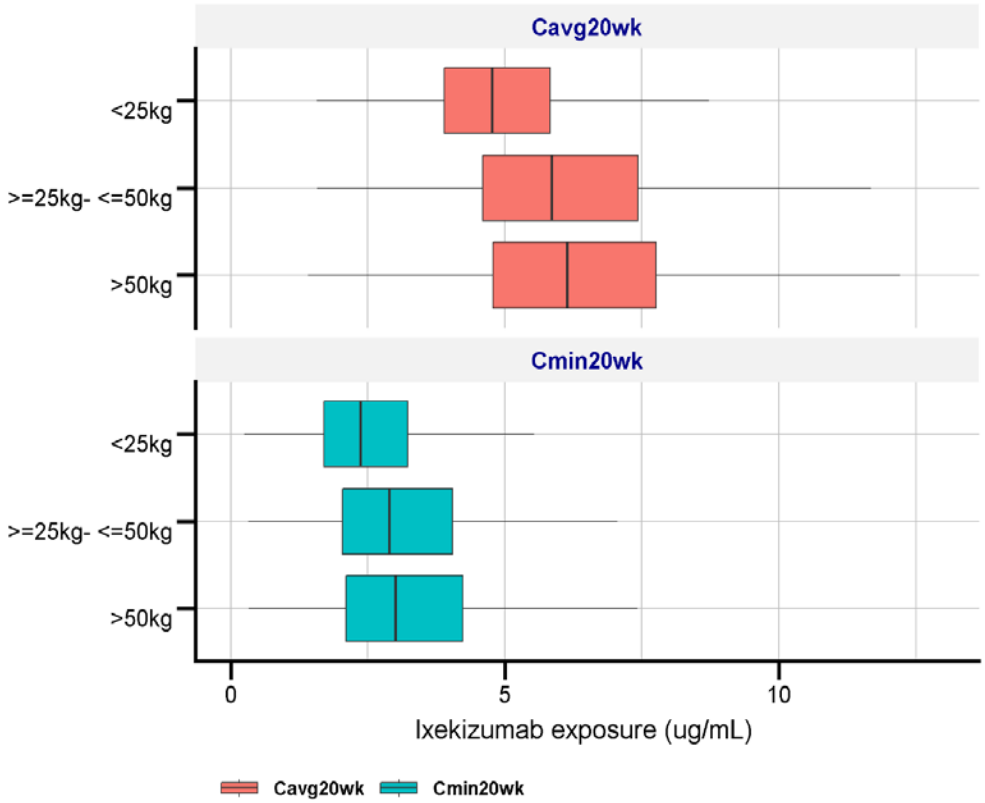
Source: Reviewer's Analysis based on "rhcd_iad3_pk_nm.csv"

Figure 12: Observed Concentration-Time Profile of Ixekizumab in Different Weight Groups



Source: Reviewer's Analysis based on "rhcd_iad3_pk_nm.csv"

Figure 13: Prediction of Ixekizumab Exposure Achieved by the Proposed Dosing Regimen Across Different Weight Groups



Source: Reviewer's Analysis based on "rhcd_iad3_pk_nm.csv"

13.4.3. Exposure-Response Analyses

1) Methods and Data

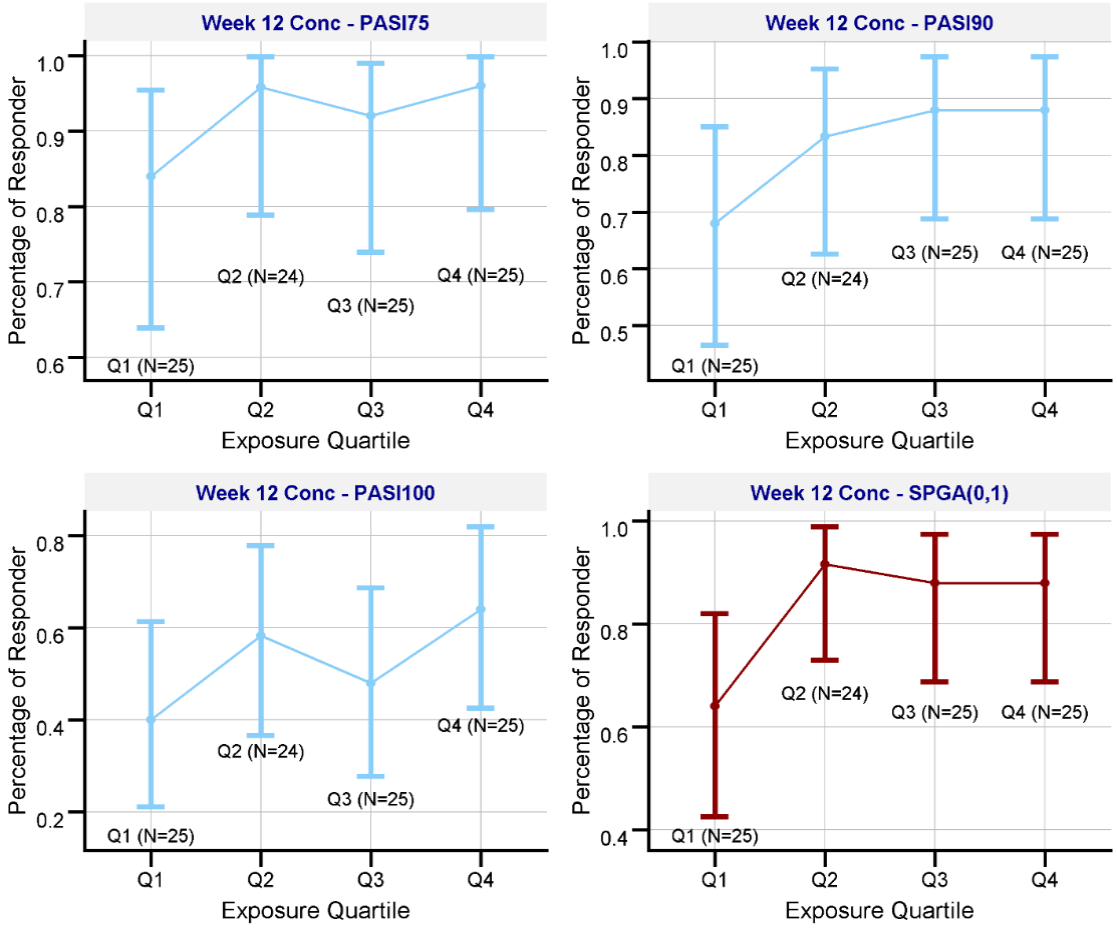
Exposure-response analyses for efficacy and safety were conducted by the Applicant to explore the relationship between exposure of ixekizumab and efficacy and safety in patients who received ixekizumab. The analyses were conducted in 99 patients in the treatment group from study RHCD who have evaluable response and ixekizumab exposure data. The evaluated efficacy endpoints were sPGA and PASI responses at week 12. The safety endpoint was incidence of all treatment emergent adverse events from week 0 to week 12. The primary exposure metric for both exposure-efficacy and exposure-safety assessment was observed ixekizumab concentration at week 12. Graphical quartile analyses were used to investigate the exposure-efficacy and exposure-AE relationships. Efficacy endpoints were also compared across different weight-based dose groups.

2) Exposure-Efficacy Relationships

Overall, there appears to be a positive trend of exposure-response relationship for PASI and sPGA with shallow slope. While PASI and sPGA responses are numerically lower in the Q1 quartile compared to Q2 to Q4 quartiles, high response was achieved in all exposure quartiles (Figure 14). The baseline covariates across all exposure quartiles in the analyses generally appeared to be balanced, except a higher incidence of the moderate/high titer ADA in Q1 (Table 18). No baseline covariate was found to be significant in the logistic regression analysis. Although the analysis was based on only 99 pediatric patients, the trend of ER relationship is consistent with what was observed in adult patients with psoriasis (Reference ID: 3841002).

The response rate also appears to be similar across different dose groups (Figure 15). Only two patients had body weight less than 25 kg at baseline and received 20mg Q4W dose in the efficacy trial. Although both are responders for PASI75, the comparison is limited as the number is small.

Figure 14: Relationship Between Ixekizumab Exposure and sPGA and PASI in Pediatric Psoriasis Patients



Source: Reviewer's Analysis based on rhcd_iad3_wk12_pasi_nm.xpt

Figure 15: sPGA and PASI Responses Across Weight Groups in Pediatric Psoriasis Patients

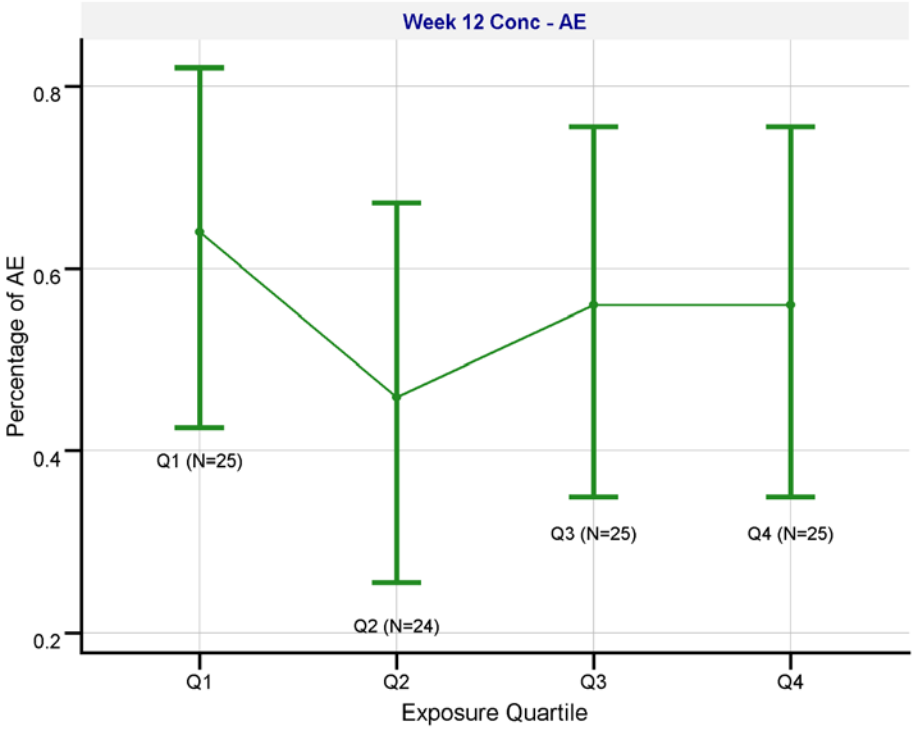
Dose	Efficacy	Week	Responder	Total N	Percent
Ixekizumab 20 mg Q4W	PASI75	Week 4	1	2	0.5
Ixekizumab 40 mg Q4W	PASI75	Week 4	18	29	0.62
Ixekizumab 80 mg Q4W	PASI75	Week 4	43	84	0.51
Ixekizumab 20 mg Q4W	PASI75	Week 12	2	2	1
Ixekizumab 40 mg Q4W	PASI75	Week 12	26	28	0.93
Ixekizumab 80 mg Q4W	PASI75	Week 12	74	83	0.89
Ixekizumab 20 mg Q4W	sPGA clear(0)	Week 12	1	2	0.5
Ixekizumab 40 mg Q4W	sPGA clear(0)	Week 12	16	28	0.57
Ixekizumab 80 mg Q4W	sPGA clear(0)	Week 12	43	83	0.52

Source: Reviewer's Analysis based on rhcd_iad3_wk12_pasi_nm.xpt

3) Exposure-safety Relationships

The probability of All TEAE from week 0 to week 12 by quartiles of week 12 concentration is shown in Figure 16. No meaningful E-R relationship was observed for TEAE from 99 patients in study RHCD. This ER relationship for TEAE is in general consistent with what was observed in adult patients (Reference ID: 3841002).

Figure 16: Incidence of All TEAE Across Weight Groups in Pediatric Psoriasis Patients



Source: Reviewer's Analysis based on rhcd_iad3_wk12_pasi_nm.xpt

Table 18: Baseline Covariates Across Exposure Quartiles in the Exposure-Efficacy and Exposure-Safety Analyses

Covariate	Value	Q1	Q2	Q3	Q4
Number of Subjects		25	24	25	25
Body Weight		58.3 (33.8)	66 (23.6)	63.6 (21.4)	52 (15.9)
Age		14 (3.4)	15.5 (2.1)	14 (2.9)	15 (3.6)
Baseline PASI Total Score		19.5 (9.5)	20 (7.4)	18.1 (5.3)	15 (5.6)
Baseline sPGA		4 (0.6)	4 (0.7)	3 (0.5)	3 (0.5)
ADA Titer	Negative	20 (80%)	19 (79.2%)	21 (84%)	23 (92%)
ADA Titer	Low	NA	5 (20.8%)	3 (12%)	NA
ADA Titer	Moderate	3 (12%)	NA	NA	2 (8%)
ADA Titer	High	2 (8%)	NA	1 (4%)	NA
Gender	F	14 (56%)	18 (75%)	8 (32%)	17 (68%)
Gender	M	11 (44%)	6 (25%)	17 (68%)	8 (32%)
Palmoplantar Psoriasis Involvement	No	19 (76%)	21 (87.5%)	23 (92%)	25 (100%)
Palmoplantar Psoriasis Involvement	Yes	6 (24%)	3 (12.5%)	2 (8%)	NA

Continuous variable: Median (SD)
Categorical variable: Frequency (Percentage)
Source: Reviewer's Analysis based on rhcd_iad3_wk12_pasi_nm.xpt

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