CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

DUPILUMAB (DUPIXENT)

(Sanofi Genzyme, a division of sanofi-aventis Canada Inc.)

Indication: Indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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Abbreviations

AAD	American Academy of Dermatologists
AD	atopic dermatitis
AE	adverse event
ANCOVA	analysis of covariance
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CDR	CADTH Common Drug Review
CI	confidence interval
CSA	cyclosporine-A
CSPA	Canadian Skin Patient Alliance
DB	double-blind
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI-75	Eczema Area and Severity Index score improvement from baseline ≥ 75%
EQ-5D	EuroQol 5-Dimensions
ESC	Eczema Society of Canada
EU	European Union
HADS	Hospital Anxiety and Depression Scale
ICC	intra-class correlation coefficient
IDMC	independent data monitoring committee
IGA	Investigator Global Assessment
IL	interleukin
ITC	indirect treatment comparison
ITT	intention-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
LOCF	last observation carried forward
LSMD	least squares mean difference
MAIC	matching-adjusted indirect comparison
MIC	minimally important chance

MID	minimal important difference
NRS	numeric rating scale
OLE	open-label extension
PGADS	Patient Global Assessment of Disease Status
POEM	Patient-Oriented Eczema Measure
RCT	randomized controlled trial
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
SD	standard deviation
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
Th2	T-helper type-2
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event
WOCF	worst observation carried forward

Drug	Dupilumab (Dupixent)
Indication	Indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Reimbursement request	For the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and/or who are refractory to or ineligible for systemic immunosuppressant therapies (i.e., due to contraindications, intolerance, or need for long-term treatment)
Dosage form(s) and route of administration)/strength(s)	Solution for subcutaneous injection: 300 mg single-use syringe (300 mg/2 mL) and 200 mg single-use syringe (200 mg/1.14 mL)
NOC date	September 25, 2019
Sponsor	Sanofi Genzyme, a division of sanofi-aventis Canada Inc.

Executive Summary

Introduction

Atopic dermatitis (AD) is a common hereditary form of eczema characterized by severely itchy skin (pruritus) that results in redness and swelling.[1] AD typically involves the popliteal (skin folds behind the knees) and the antecubital (in front of the elbows) areas, but can also affect the face, neck, and hands. AD is a chronic, relapsing, inflammatory skin condition that often negatively affects quality of life. The Canadian Dermatology Association reports that the lifetime prevalence of AD is up to 17% in the Canadian population, and there is evidence to suggest that the prevalence has increased over the past 30 years.[1-3]

AD results in impaired barrier function and reduced water-holding capacity of the skin; this causes dry skin that requires specific bathing, cleansing, and moisturizing treatments. While there is no cure for AD, several therapeutic options are available to patients to manage the condition. The majority of patients treat AD by using general skin-care methods, avoiding skin irritants, and applying topical anti-inflammatory therapy. The management of the disease is dependent on its severity and the individual's response to common therapies such as topical corticosteroid (TCS) and topical calcineurin (TCI) compounds. AD is commonly associated with secondary skin infections, and the use of anti-infectious agents is common. If common first-line therapies fail to improve AD, patients may use phototherapy, off-label systemic therapy, such as immunosuppressant therapy or therapy approved for other skin conditions (i.e., psoriasis).

Dupilumab is a fully human monoclonal antibody in solution administered via subcutaneous injection. Dupilumab inhibits interleukin (IL)-4 and IL-13 signalling by binding to the IL-4R-alpha subunit. Both IL-4 and IL-13 are important cytokines involved in the release of pro-inflammatory cytokines. CADTH previously reviewed dupilumab for treatment of adult patients with moderate-to-severe AD and a recommendation regarding reimbursement was issued.[1] The indication has been expanded to include patients 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The sponsor reimbursement request is largely consistent with the indication: for those whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and/or those refractory to or ineligible for systemic immunosuppressant therapies (i.e., due

to contraindications, intolerance, or need for long-term treatment). Dupilumab can be used with or without topical corticosteroids.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of dupilumab for the treatment of patients 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

- The Eczema Society of Canada and the Canadian Skin Patient Alliance provided input through an online survey, a written questionnaire, interviews, and statements provided by patients and caregivers.
- Patients described the debilitating effects of moderate-to-severe AD, including constant itching that interferes with all aspects of life, most notably sleep. In its more severe form, AD can result in open wounds that bleed and are prone to infection, and patients may become bed-ridden. Patients also noted the impact that AD may have on their mood, as a result of bullying, loss of self-esteem, stress, and anxiety.
- Symptoms such as pruritus, burning pain, rash, and open sores, as well as loss of sleep, anxiety, and depression, were identified as key outcomes by patients. Patients wanted to see an improvement in their quality of life and in their work and/or school productivity.

Clinician Input

The most common first-line therapies for AD are TCS and TCI drugs, with crisaborole, a phosphodiesterase type-4 inhibitor that is used much less commonly. Patients who proceed to phototherapy or systemic drugs will typically continue on topical therapy. TCS and TCI treatments are used concomitantly, with TCIs being safe to use on delicate areas of the body. Sedating antihistamines may be used for intractable nocturnal pruritus, although their use is declining due to concerns over cognitive impairment in children. Topical antibiotics are also used in cases of chronic impetiginization, and systemic antibiotics may be used in cases of more serious infection. In cases of inadequate response, patients may move onto phototherapy (if available), and if topical therapy and phototherapy still do not elicit an adequate response, then they move on to systemic therapies.

Issues specific to adolescents include concerns over adherence to therapies, impact of the disease on the adolescent psyche, and on the family. Although community dermatologists are often uncomfortable prescribing systemic immunosuppressants for children and adolescents, pediatric dermatologists are unlikely to have the same reluctance.

An ideal treatment would have a proven long-term safety record, completely reverse the barrier dysfunction and immunologic abnormalities that characterize AD, and be cost-effective. Such a treatment, which does not yet exist, would also maintain complete clearance of AD without ongoing therapy, eliminate pruritus, and produce resolution of all visible dermatitis.

Patients with suboptimal responses to topical therapies and disease-specific skin measures have to use systemic therapies. Some patients are ineligible for these therapies due to contraindications or toxicities that limit their use. Dupilumab may prove to be useful in

patients who have contraindications to, experience adverse effects from, or are unresponsive to immunosuppressives, yet require continuous long-term systemic therapy. All patients with AD who are prescribed dupilumab are likely to continue with emollients or a TCI or TCS. However, dupilumab is unlikely to be combined with systemic immunosuppressives. Dupilumab is likely to be an addition to the armamentarium in managing AD rather than shifting the treatment paradigm in a significant way.

Before initiating treatment with dupilumab, it would be appropriate to recommend trials of both methotrexate and cyclosporine. Both of these therapies are efficacious, dermatologists have experience with dosing, duration of therapy, and appropriate monitoring for toxicities, and many patients can be managed with intermittent immunosuppressives. The immunosuppressives have likely been underutilized, due in part to a paucity of research.

Any patient with moderate-to-severe AD could potentially benefit from dupilumab. It is unclear whether this drug can be effectively used in patients who have failed methotrexate. There may be a preference toward prescribing dupilumab to patients with concomitant asthma, if in the opinion of the pediatrician or respirologist they could benefit from dupilumab for their asthma. Patients least suitable would include those whose AD is well controlled with topical therapy, phototherapy, and/or conventional systemic therapy; patients with untreated potentially serious helminth infections; and possibly those with a history of severe conjunctivitis or keratitis. It is not currently possible to predict those most likely to respond to dupilumab.

Dermatologists would be the clinicians to diagnose AD; diagnosis can be complex because the differential diagnosis includes psoriasis, ichthyoses, allergic contact dermatitis, irritant contact dermatitis, and cutaneous T-cell lymphoma. Because loss of the barrier function of the skin predisposes patients to superimposed allergic contact dermatitis and dermatophytosis, patch tests and skin scrapings for potassium hydroxide and fungal culture may be beneficial in certain cases. Biopsies would normally be reserved for patients who are recalcitrant to all therapy in which cutaneous T-cell lymphoma is a consideration, or occasionally to distinguish AD from psoriasis. Dupilumab would never be considered for pre-symptomatic patients.

Outcomes used in clinical practice are aligned with those typically used in clinical trials. An Eczema Area and Severity Index (EASI) score would be a reasonable choice as it is the benchmark for clinical assessment for reimbursement and can be calculated and recorded at each patient visit. Physicians may also assess treatment impact on quality of life using the age-appropriate version of the Dermatology Life Quality Index (DLQI). Reduction in pruritus will also be noted but not formally scored in practice. Patients' impression of their overall improvement will also be recorded.

Achieving an EASI score improvement from baseline greater than or equal to 75% (EASI-75) with treatment would be clinically significant. Patients with severe disease recalcitrant to all previous therapies may find an EASI score reduction of between 50% and 75% to be clinically meaningful. Patients placed on dupilumab will be re-evaluated at 16 weeks, and those who are responders will likely be seen at six-month intervals. Those who have not reached response targets at 16 weeks will be re-evaluated at 24 weeks following initiation of the drug, and a decision on whether to stop or continue therapy made at the 24-week visit. Factors to consider when deciding whether to discontinue therapy would include failure to achieve a clinically meaningful response at 16 weeks, failure to maintain adequate response on long-term maintenance, severe injection reactions, adverse effects such as severe keratitis, ectropion or alopecia areata, helminth infections that do not respond to appropriate therapy, and a generalized hypersensitivity response, such as severe urticaria, erythema nodosum, anaphylaxis, or serum sickness.

A dermatologist would be required to prescribe dupilumab, which will likely be self-injected or injected by a parent and/or caregiver. It is unlikely to be administered in a hospital or physician's office.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Adolescents (12 to < 18 years old)

One pivotal sponsor-funded phase III, double-blind (DB), randomized controlled trial (RCT), Study 1526, featuring a population of 251 adolescents with moderate-to-severe AD was included in this review. Study 1526 was a 16-week comparison of two different dose regimens of dupilumab, administered every four weeks or every two weeks to matching placebo, with the strength of dose (200 mg or 300 mg) determined by weight (< 60 kg or ≥ 60 kg). The every two weeks regimen was the focus of this review as it is the one approved by Health Canada. Patients were those who had demonstrated a recent history of inadequate response to topical therapies or for whom topicals were not advised (due to intolerance, side effects, or safety risk). The co-primary outcomes were patients with an Investigator'Global Assessment (IGA) score of 0 or 1 and patients who had achieved an EASI score of ≥ 75% at week 16. Key secondary outcomes included percent change from baseline to week 16 in EASI, weekly average of daily peak pruritus numeric rating scale (NRS), and patients with an improvement of ≥ 3 or ≥ 4 in weekly average of daily peak pruritus NRS.

Adults

SOLO CONTINUE was a phase III, DB, placebo-controlled RCT that sought to determine which dosing regimens of dupilumab would be able to maintain the treatment response achieved in two initial 16-week studies, SOLO 1 and SOLO 2. Patients who had achieved an IGA score of 0 or 1 or an EASI score of ≥ 75% in these initial studies were randomized to either the same regimen they received in SOLO 1 or SOLO 2 (dupilumab every two weeks or weekly), every four weeks, every eight weeks, or matched placebo. Patients who had received placebo in the initial studies were eligible to enroll in SOLO CONTINUE to maintain blinding; however, they were not randomized and simply received placebo for the duration of the study and were not included in efficacy analyses. An interactive voice/web response system was used and randomization was stratified by the original dupilumab regimen received in the parent study, region (North America, Europe, Asia, Japan), and baseline IGA (0 versus 1 versus > 1). Patients began treatment following randomization on day 1 (week 16 of the initial study) and underwent a 36-week treatment period and a 12-week follow-up period.

Three phase III RCTs identified as pivotal trials by the sponsor (SOLO 1, SOLO 2, and LIBERTY AD CHRONOS) were included in the original review, as well as an additional RCT, LIBERTY AD CAFÉ, which was sponsored by the sponsor.

SOLO 1 and SOLO 2 were 16-week, randomized DB, placebo-controlled, parallel-group trials. Patients in the SOLO trials were recruited globally and randomized for treatment with dupilumab 600 mg on day 1, followed by 300 mg weekly subcutaneous injections for 16 weeks, dupilumab 600 mg on day 1, followed by 300 mg subcutaneous injections every other week for 16 weeks, or weekly matched subcutaneous injections of placebo. The Health Canada–recommended dose of 300 mg dupilumab once every other week is the focus of this review. SOLO 1 and SOLO 2 randomized 671 and 708 patients, respectively.

Following completion of the 16-week trial, patients were either followed up for an additional 12 weeks or transitioned to an open-label or maintenance study. LIBERTY AD CHRONOS was similar to the SOLO trials but was 52 weeks in duration and, regardless of treatment group, patients were concomitantly treated daily with a medium-potency TCS on areas of the skin with active lesions. In LIBERTY AD CHRONOS, 740 patients recruited from North America, Europe, and Asia were randomized. At the time of the Clinical Study Report publication, data from 623 patients were available. Patients enrolled in the trial were treated over the course of 52 weeks and either followed up for an additional 12 weeks or transitioned to an open-label extension study. LIBERTY AD CAFÉ was a 16-week trial similar to LIBERTY AD CHRONOS in which 325 patients were randomized to one of three groups with concomitant use of a TCS. In contrast to the other studies, patients in LIBERTY AD CAFÉ were recruited from Europe and required to have either a history of prior cyclosporine-A (CSA) exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or patients had to be CSA-naive and not eligible for CSA due to medical contraindications or other reasons.

Efficacy Results

Adolescents (12 to < 18 years)

Markers of disease severity assessed in Study 1526 included the IGA, EASI, and Scoring Atopic Dermatitis (SCORAD). With dupilumab, 24% of patients achieved an IGA score of 0 ("clear") or 1 at week 16 versus 2% in placebo. The difference between dupilumab and placebo (22.0%; 95% confidence interval [CI], 12.2 to 31.9; P < 0.0001) was statistically significant. A minimal important difference (MID) between groups could not be found in the literature. Sensitivity analyses were performed using all observed values, with missing values counted as nonresponders, and those results were consistent with those of the primary analysis. EASI-75 responses occurred in 42% of dupilumab and 8% of placebo patients, and the difference between dupilumab and placebo groups (33.2%; 95% CI, 21.1 to 45.4; P < 0.0001) was statistically significant. Results from a sensitivity analysis performed with all observed values (patients with missing values were counted as nonresponders) were consistent with that of the primary analysis (dupilumab every two weeks: 45% and placebo: 15%). Mean percent EASI scores were reduced from baseline to week 16 to a greater extent with dupilumab compared to placebo (a least squares mean difference [LSMD] versus placebo of −42.3%; 95% CI, −55.6 to −29.0; P < 0.0001) and this difference was statistically significant. Sensitivity analyses performed on the full analysis set regardless of treatment rescue and sensitivity analyses based on last observation carried forward and worst observation carried forward were all consistent with the primary analysis. The percentage of patients with an EASI score ≥ 50% at week 16 was 61% with dupilumab every two weeks and 13% with placebo. Compared to placebo, this was statistically significant (difference of 48.0%; 95% CI, 35.3 to 60.8; P < 0.0001). The proportion of patients with an EASI score ≥ 90% at week 16 was 23.2% with dupilumab and 2.4% with placebo, and these differences were considered statistically significant (difference of 20.8; 95% CI, 11.1 to 30.5; P < 0.0001). There was an improvement (reduction) in mean SCORAD scores from baseline to week 16 for dupilumab compared to placebo (an LSMD between dupilumab and placebo of −34.0; 95% CI, −43.4 to −24.6; P < 0.0001) and this difference was statistically and clinically significant, given the MID of 8.7 points.

Mean percent change in daily peak pruritus NRS was reduced from baseline to week 16 in the dupilumab group compared to placebo (an LSMD of −29.0%; 95% CI, −39.5 to –18.4; P < 0.0001) and this difference was statistically significant. Dupilumab elicited a statistically significant improvement at week 16 in patients achieving a reduction of at least 3 points from baseline in weekly average of daily peak pruritus (49% with dupilumab and 9% with placebo; difference of 39.4%; 95% CI, 26.9 to 51.8; P < 0.0001) and in patients achieving a reduction of at least 4 points from baseline (37% versus 5%; difference of 31.8%; 95% CI,

20.5 to 43.2; P < 0.0001). A reduction of 3 or 4 points is considered to be a response on this scale. There was an improvement (reduction) in weekly average of daily peak pruritus scores from baseline to week 16 for dupilumab versus placebo (an LSMD between dupilumab and placebo of −2.2; 95% CI, −2.9 to −1.4; P < 0.0001) and this difference was statistically significant. The percent change from baseline to week 4 in weekly average of daily peak pruritus NRS score was also assessed, and again there were improvements from baseline for dupilumab versus placebo (an LSMD between dupilumab and placebo of −22.2%; 95% CI, −30.6 to −13.9; P < 0.0001) and this difference was statistically significant. Patient-Oriented Eczema Measure (POEM) scores improved from baseline to week 16 with dupilumab versus placebo (an LSMD between dupilumab and placebo of −6.3; 95% CI, −8.6 to −4.0; P < 0.0001) and these differences were statistically significant and likely clinically significant, given the MID of 4.

With respect to health-related quality of life, there was a larger improvement (reduction) in mean Children's DLQI scores from baseline to week 16 with dupilumab compared to placebo (an LSMD between dupilumab and placebo of −3.4; 95% CI, −5.0 to −1.8; P < 0.0001) and these differences were statistically significant. There is no established MID for this instrument. Mood and anxiety were assessed using the Hospital Anxiety and Depression Score, and the mean improvement (reduction) in HADS total scores from baseline to week 16 was not statistically significant for dupilumab versus placebo (an LSMD between groups of −1.3; 95% CI, −3.30, 0.76; P = 0.2203). The change from baseline to week 16 in HADS anxiety scores was not statistically significant between dupilumab and placebo groups. Patients in each of the dupilumab groups missed an average of one day of school over 16 weeks versus two days in the placebo group. By the end of the 16 weeks, 24% of patients in the dupilumab group and 30% of patients in the placebo group had missed a day of school.

Adults

The severity of AD was assessed using the proportion of patients with 75% or greater improvement from baseline in the EASI, IGA, and SCORAD tools. An EASI score of greater than or equal to 75% at week 16 was the primary (or co-primary) efficacy end point across all studies. This proportion was consistently greater in the dupilumab group compared to the placebo group, with a range in difference of proportions across trials from 32.3% (95% CI, 24.75 to 39.94) to 45.7% (95% CI, 35.72 to 55.66). Each trial yielded statistically significant (P < 0.0001) findings. The proportion of patients with an IGA score of 0 or 1 and reduction from baseline of 2 or more points at week 16 was a second primary end point in SOLO 1, SOLO 2, and LIBERTY AD CHRONOS and a secondary end point in LIBERTY AD CAFÉ. This proportion was consistently greater in the dupilumab group compared to the placebo group, with a range in difference of proportions of 26.3% (95% CI, 14.95 to 37.65) to 27.7% (95% CI, 20.18 to 35.17). Each trial yielded statistically significant findings (P < 0.0001). While no relevant MID was found in the literature search for the IGA for patients with AD, the clinical expert consulted for this review indicated that the findings were clinically relevant. The percent change in SCORAD from baseline to week 16 was a secondary end point across all four trials. The least squares percent mean change from baseline was greater in the dupilumab group compared to the placebo group. Across trials the least squares mean change of SCORAD scores between dupilumab and placebo groups ranged from −27.7 (95% CI, −33.46 to −21.90) to −32.9 (95% CI, −39.70 to −26.06) and was statistically significant (P < 0.0001) across all trials at week 16. The LIBERTY AD CHRONOS trial included an additional end point at week 52; all efficacy results remained consistent and statistically significant (P < 0.0001). Sensitivity analyses showed minor numerical differences but statistical significance remained consistent. A subgroup analysis for moderate AD and severe AD revealed greater efficacy in the dupilumab groups compared to placebo for both the EASI-75 and IGA end points.

Symptoms of AD were assessed using the pruritus NRS and the POEM. The proportion of patients with an improvement (reduction) in weekly averages of peak daily pruritus NRS of 4 or more points from baseline to week 16 was one of the secondary end points in all of the studies. Compared to placebo, the proportion of patients in the dupilumab group was statistically greater (P < 0.0001) across all trials, with a range in difference between groups of 26.5% (95% CI, 19.13% to 33.87%) to 39.1% (95% CI, 28.53% to 49.65%). Similar findings were seen in the proportion of patients with an improvement (reduction) in weekly averages of peak daily pruritus NRS of 3 or more points from baseline to week 16. The LIBERTY AD CHRONOS trial included an additional end point at week 52 for the pruritus NRS end points, which resulted in consistent and statistically significant (P < 0.0001) findings. The percent change in POEM from baseline to week 16 was an additional secondary end point across all four trials. The LSMD from baseline was greater in the dupilumab group compared to the placebo group. Across trials the LSMD of POEM scores between dupilumab and placebo groups ranged from −6.5 (95% CI, −8.02 to −5.01) to −7.6 (95% CI, −9.29 to −5.97) and were statistically and clinically significant (P < 0.0001) (MID = 3.4)[8] across all trials. Although the pruritus NRS was statistically significant, no AD-specific validity or MID information was found in a literature search. However, the clinical expert stated that the findings were clinically relevant.

Health-related quality of life was assessed as a secondary end point across all trials via the change from baseline to week 16 in the DLQI and the EuroQol 5-Dimensions (EQ-5D) questionnaire. The least squares mean change from baseline was greater in the dupilumab compared to the placebo group. Across trials the difference in the least squares mean change from baseline in DLQI score between dupilumab and placebo groups ranged from −4.0 (95% CI, −5.16 to −2.80) to −5.7 (95% CI, −6.86 to −4.47) and were both statistically significant (P < 0.0001) and potentially clinically relevant based on an MID range of 2.2 to 6.9. The LIBERTY AD CHRONOS trial included an additional end point at week 52 for the DLQI end point, which resulted in consistent and statistically significant (P < 0.0001) findings. For the EQ-5D index utility score, the least squares mean change from baseline was numerically greater in the dupilumab group compared to the placebo group in the SOLO trials and LIBERTY AD CHRONOS. Across the three trials the difference in least squares mean change from baseline in EQ-5D 3-Levels index utility score between dupilumab and placebo groups ranged from 0.060 (95% CI, 0.02 to 0.10) to 0.167 (95% CI, 0.12 to 0.21). The LSMD was statistically significant (P < 0.0001) in SOLO 1 and SOLO 2, and, while no AD-specific MID existed, the results in the trials were clinically relevant based on a general MID for the EQ-5D, which ranged from 0.033 to 0.074. The change in EQ-5D VAS scores from baseline to week 16 was statistically significant (P < 0.0001) in SOLO 1, SOLO 2, and LIBERTY AD CHRONOS.

Harms Results

Adolescents (12 to < 18 years)

Adverse events (AEs) were reported in 72.0% of dupilumab and 69.4% of placebo patients. The most common AEs were upper respiratory tract infections, in 12.2% of dupilumab and 17.6% of placebo patients, AD in 18.3% of dupilumab and 24.7% of placebo patients, and headache in 11.0% of dupilumab and 10.6% of placebo patients. Few serious adverse events (SAEs) were reported in the 16-week study (none with dupilumab and 1.2% of patients treated with placebo). No dupilumab-treated patients discontinued the study drug due to an AE while the comparable number for placebo patients was 1.2%. Among notable harms, conjunctivitis occurred in 4.9% of dupilumab and 1.2% of placebo patients, injection-site pain or swelling occurred in 3.7% of dupilumab and 1.2% of placebo patients, injection-site erythema in 2.4% of dupilumab and 1.2% of placebo patients, and injection-site pruritus in 2.4% of patients in each group.

Adults

In SOLO CONTINUE, 3.6% of patients in the dupilumab group versus 1.2% in the placebo group had an SAE. No dupilumab patients and 3.7% of placebo patients permanently discontinued the study drug due to an AE. The most common notable harms were conjunctivitis (3.6% with dupilumab versus 2.4% placebo) and acute allergic reactions (1.8% dupilumab versus 1.2% placebo).

In the studies identified in the previous review, AEs were reported in 65.3% to 73.6% of patients in the dupilumab group and 65.3% to 71.8% in the placebo group. The most common AEs were infections and infestations that affected between 27.5% and 45.8% of patients in the dupilumab group, and 28.4% to 40.7% of patients in the placebo group. Across all studies, nasopharyngitis was the most common infection and/or infestation, affecting between 8.5% and 20.6% of patients in the dupilumab group, and 7.7% to 16.7% of patients in the placebo group. Patients enrolled in the LIBERTY AD CAFÉ trial were associated with the highest prevalence of infections, infestations, and nasopharyngitis. SAEs were reported in 1.7% to 4.7% of patients in the dupilumab group and 3.5% to 9.3% in the placebo group. The most common severe AE was related to an AD flare, worsening, or aggravation that required or prolonged hospitalization (reported as "dermatitis atopic") and affected 0.4% to 1.9% of patients in the dupilumab group and 1.4% to 5.6% of patients in the placebo group. Withdrawals due to AEs were reported in 0% to 1.7% of patients in the dupilumab group, and 0.9% to 4.7% of patients in the placebo group. In LIBERTY AD CHRONOS at week 52, the most common reasons for withdrawal were related to AD flares (58%).[9]

The most common AEs related to an AD flare worsening or aggravation that required prolonged hospitalization occurred in 7.5% to 14% of patients in the dupilumab group and 14.8% to 35% of patients in the placebo group for SOLO 1, SOLO 2, and LIBERTY AD CAFÉ.[10,11] In LIBERTY AD CHRONOS at week 52, AD flare–related AEs were reported by 46% of patients in the placebo group and 18% of patients in the dupilumab group.[9] Trials without the use of a TCS (SOLO 1 and SOLO 2) had the highest proportion of patients who experienced AD flare worsening or aggravation that required or prolonged hospitalization.

Rescue medication was used in 21.0% and 16.1% of patients in the dupilumab group, and in 51.8% and 52.1% of patients in the placebo group in the SOLO trials. In LIBERTY AD CHRONOS and LIBERTY AD CAFÉ, rescue medication was used in 10.9% and 3.7% of patients in the dupilumab group, and 34.6% and 14.8% of patients in the placebo group. Across all trials, the most common form of rescue medication was a potent (group III) TCS. In the SOLO trials, 8.5% and 13.1% of patients in the dupilumab group, and 29.1% and 34.2% of patients in the placebo group used a potent TCS. In LIBERTY AD CHRONOS and LIBERTY AD CAFÉ, a potent TCS was used in 8.2% and 2.8% of patients in the dupilumab group, and 28.3% and 10.2% of patients in the placebo group for each trial, respectively. Consistently across trials, general eye disorders affected more patients in the dupilumab group compared to the placebo group, at rates of 3.8% to 15.0% and 0.4% to 6.5%, respectively.

Table 1: Summary of Key Results from Pivotal and Protocol-Selected Studies

Aged 12 to < 18: Study 1526		
	Dupilumab every 2 weeks N = 82	Placebo N = 85
Disease severity		
Patients with IGA of 0 or 1 at week 16, n (%)	20 (24)	2 (2)
Difference vs placebo, % (95% CI)[a]	22.0 (12.20 to 31.87; P < 0.0001)	
Patients with EASI ≥ 75 at week 16, n (%)	34 (42)	7 (8)
Difference vs. placebo, % (95% CI)[a]	33.2 (21.07 to 45.39; P < 0.0001)	
Mean (SD) baseline EASI	35.26 (13.836)	35.53 (13.971)
LSM (SE) % change in EASI score, baseline to week 16 (sample observed/imputed)	−65.9 (3.99) (66/16)	−23.6 (5.49) (33/52)
LS mean difference (95% CI)[b]	−42.3 (−55.60 to −29.04; P < 0.0001)	
Symptom: pruritus		
Mean (SD) baseline	7.52 (1.52)	7.73 (1.62)
LSM (SE) % change from baseline to week 16 in weekly average of daily peak pruritus NRS (sample observed/imputed)	−47.9 (3.43) (66/16)	−19.0 (4.09) (31/54)
LSMD (95% CI)[b]	−29.0 (−39.54 to −18.38; P < 0.0001)	
Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 3 from baseline to week 16, n/N (%)	40/82 (48.8)	8/85 (9.4)
Difference vs. placebo, % (95% CI)[a]	39.4 (26.90 to 51.84; P < 0.0001)	
Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 4 from baseline to week 16, n (%)	30/82 (36.6)	4/84 (4.8)
Difference vs. placebo, % (95% CI)[a]	31.8 (20.45 to 43.20; P < 0.0001)	
Body surface area		
Mean (SD) baseline BSA	55.99 (21.40)	56.41 (24.13)
LSM (SE) change from baseline to week 16 in percent BSA affected by AD (sample observed/imputed)	−30.11 (2.337) (67/15)	−11.66 (2.720) (33/52)
LSMD (95% CI)[b]	−18.44 (−25.117 to −11.770; P < 0.0001)	
SCORAD		
Mean (SD) baseline SCORAD	70.60 (13.89)	70.44 (13.25)
LSM (SE) percent change from baseline to week 16 in SCORAD (sample observed/imputed)	−51.6 (3.23) (67/15)	−17.6 (3.76) (33/52)
LSMD (95% CI)[b]	−34.0 (−43.41 to −24.58; P < 0.0001)	
Health-related quality of life: CDLQI		
Mean (SD) baseline CDLQI	13.0 (6.2)	13.1 (6.7)
LSM (SE) change from baseline to week 16 in CDLQI (sample observed/imputed)	−8.5 (0.50) (66/16)	−5.1 (0.62) (33/ 52)
LSMD (95% CI)[b]	−3.4 (−5.01 to −1.80; P < 0.0001)	
POEM		
Mean (SD) baseline POEM	21.0 (5.0)	21.1 (5.4)
LSM (SE) change from baseline to week 16 in POEM (sample observed/imputed)	−10.1 (0.76) (67/15)	−3.8 (0.96) (33/52)
LSMD (95% CI)[b]	−6.3 (−8.63 to −4.01; P < 0.0001)	
Mood: HADS		
Mean (SD) baseline HADS total score	12.6 (8.0)	11.6 (7.8)
LSM (SE) change from baseline to week 16 in HADS total score (sample observed/imputed)	−3.8 (0.68) (67/15)	−2.5 (0.80) (33/52)

Aged 12 to < 18: Study 1526		
	Dupilumab every 2 weeks N = 82	Placebo N = 85
LSMD (95% CI)[b]	−1.3 (−3.30 to 0.76; P = 0.2203)	
PGADS		
Patients with no symptoms or mild symptoms (scale = 1 or 2) at week 16, n (%)	42 (51.2)	11 (12.9)
Difference vs. placebo, % (95% CI)	38.3 (25.32 to 51.24)	
Productivity: missed school		
Cumulative missed school days through week 16 for patients attending school full-time, mean (SD)	1.01 (3.323) N = 79	2.00 (8.598) N = 84
Patients with any day missed, n (%)	19 (24.1)	25 (29.8)
Harms		
Any TEAE leading to permanent discontinuation of study drug, n (%)	0	1 (1.2)
Patients with a serious adverse event, n (%)	0	1 (1.2)
Notable harms		
Conjunctivitis	4 (4.9)	1 (1.2)
Injection-site pain	3 (3.7)	1 (1.2)
Injection-site swelling	3 (3.7)	1 (1.2)

AD = atopic dermatitis; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; LSM = least squares mean; LSMD = least squares mean difference; NRS = numerical rating scale; PGADS = Patient Global Assessment of Disease Status; POEM = Patient-Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; SE = standard error; TEAE = treatment-emergent adverse event; vs. = versus.

[a] P values were derived by Cochran-Mantel-Haenszel tests stratified by baseline disease severity (IGA = 3 vs. IGA = 4) and baseline weight group (< 60 kg vs. ≥ 60 kg).

[b] The confidence interval with a P value is based on treatment difference (dupilumab group vs. placebo) of the LSM percent change using an analysis of covariance model with baseline measurement as the covariate and the treatment and randomization strata (baseline disease severity [IGA = 3 vs. IGA = 4], and baseline weight group [< 60 kg vs. ≥ 60 kg]) as fixed factors.

Table 2: Summary of Key Results from Pivotal and Protocol-Selected Studies (Adults)

	SOLO CONTINUE	
	Dupilumab q.2.w./q.w. N = 167	Placebo N = 85
EASI		
Mean (SD) % change in EASI from parent study baseline to current study baseline	−91.27 (9.344)	−91.17 (8.207)
Difference between current study baseline and week 36 in LSM % change in EASI from parent study baseline, % (SE)	0.06 (1.736)	21.67 (3.134)
LSMD vs. placebo (95% CI)[a]	−21.61 (−28.36 to −14.87; P < 0.0001)	
Patients with EASI ≥ 75 at week 36 for patients with EASI ≥ 75 at baseline, patients considered nonresponders after rescue, n (%)	116 (71.6)	24 (30.4)
Difference vs. placebo, % (95% CI)[b]	41.2 (28.93 to 53.52; P < 0.0001)	
IGA		
Patients whose IGA score was maintained within 1 point of baseline at week 36, patients considered nonresponders after rescue, n (%)	89 (70.6)	18 (28.6)
Difference vs. placebo, % (95% CI)[b]	42.1 (28.36 to 55.76; P < 0.0001)	
Patients whose IGA score increased to 3 or 4 at week 36; patients considered responder after rescue, n (%)	33 (26.2)	42 (66.7)
Difference vs. placebo, % (95% CI)[b]	−40.5 (−54.42 to −26.53; P < 0.0001)	
Symptom: pruritus		
Patients with peak weekly pruritus NRS increased by 3 or more points from baseline at week 35, excluding patients whose peak weekly NRS scores are more than 7 at baseline; patients considered a responder after rescue, n (%)	57 (33.9)	56 (70.0)
Difference vs. placebo, % (95% CI)[b]	−36.1 (−48.40 to −23.74; P < 0.0001)	
Mean (SD) % change in pruritus NRS; parent study baseline to current study baseline	−60.1 (26.82)	−59.6 (29.95)
Difference between current study baseline and week 35 in LSM % change in pruritus NRS from parent study, % (SE)	−0.1 (3.05)	35.6 (4.32)
Difference vs. placebo of LSM of the end point (95% CI)[b]	−35.8 (−45.4 to −26.1; P < 0.0001)	
SCORAD		
Difference between current study baseline and week 36 in % change in SCORAD from parent study baseline, multiple imputation method with data set to missing after rescue		
Mean (SD) baseline	−73.71 (15.931)	−73.12 (16.751)
LSM change (SE)	0.33 (2.092)	28.97 (3.683)
LSMD (95% CI)[a]	−28.64 (−36.56 to −20.72; P < 0.0001)	
Harms		
Patients with an SAE, n (%)	6 (3.6)	1 (1.2)
Any TEAE leading to discontinuation of study drug permanently	0	3 (3.7)
Notable harms		
Conjunctivitis	6 (3.6)	2 (2.4)
Acute allergic reactions	3 (1.8)	1 (1.2)

CI = confidence interval; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; LSM = least squares mean; LSMD = least squares mean difference; NRS = numerical rating scale; q.2.w. = every 2 weeks; q.w. = every week; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; SE = standard error; TEAE = treatment-emergent adverse event; vs. = versus.

[a] The confidence interval with P value is based on treatment difference (dupilumab group vs. placebo) of the LSM change using an analysis of covariance model with baseline measurement as the covariate and the treatment, region, baseline IGA strata (0, 1, > 1), and dupilumab regimen received in parent studies as fixed factors.

[b] For dupilumab vs. placebo, P values were derived by Cochran-Mantel-Haenszel tests stratified by baseline disease severity (IGA = 0 vs. 1), region, and dupilumab regimen received in parent studies.

Table 3: Summary of Key Results from Pivotal and Protocol-Selected Studies (Adults, Original Review)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
IGA score of 0 or 1 and reduction from baseline of ≥ 2 points										
N (%)	85 (37.9)	23 (10.3)	84 (36.1)	20 (8.5)	41 (38.7)	39 (12.4)	32 (36.0)	33 (12.5)	43 (40.2)	15 (13.9)
Difference, % (95% CI)[a,b]	27.7 (20.2 to 35.2) P < 0.0001		27.6 (20.5 to 34.7) P < 0.0001		26.3 (16.3 to 36.3) P < 0.0001		23.5 (12.7 to 34.2) P < 0.0001		26.3 (15.0 to 37.6) P < 0.0001	
EASI-75										
N (%)	115 (51.3)	33 (14.7)	103 (44.2)	28 (11.9)	73 (68.9)	73 (23.2)	58 (65.2)	57 (21.6)	67 (62.6)	32 (29.6)
Difference, % (95% CI)[a,b]	36.6 (28.6 to 44.6) P < 0.0001		32.3 (24.8 to 39.9) P < 0.0001		45.7 (35.7 to 55.7) P < 0.0001		43.6 (32.5 to 54.6) P < 0.0001		33.0 (20.4 to 45.6) P < 0.0001	
SCORAD										
Baseline mean (SD)	66.9 (13.9)	68.3 (13.9)	67.2 (13.4)	69.2 (14.8)	69.3 (15.2)	66.0 (13.5)	69.9 (15.1)	65.7(13.3)	68.6 (11.9)	67.0(12.2)
N observed/imputed	172/52	97/127	193/40	105/131	92/14	188/127	71/18	101/163	103/4	89/19
LSM change (SE)	−57.7 (2.1)	−29.0 (3.2)	−51.1 (2.0)	−19.7 (2.5)	−63.9 (2.5)	−36.2 (1.7)	−69.7 (3.1)	−47.3 (2.2)	−62.4 (2.5)	−29.5 (2.6)
LSMD (95% CI)[c]	−28.7 (−35.8 to −21.5) P < 0.0001		−31.4 (−37.4 to −25.4) P < 0.0001		−27.7 (−33.5 to −21.9) P < 0.0001		−22.4 (−29.4 to −15.3) P < 0.0001		−32.9 (−39.7 to −26.1) P < 0.0001	
Peak daily pruritus NRS score reduction of ≥ 4										
n/N (%)	87/213 (40.8)	26/212 (12.3)	81/225 (36.0)	21/221 (9.5)	60/102 (58.8)	59/299 (19.7)	44/86 (51.2)	32/249 (12.9)	43/94 (45.7)	13/91 (14.3)
Difference, % (95% CI)[a, b]	28.6 (20.6 to 36.5) P < 0.0001		26.5 (19.1 to 33.9) P < 0.0001		39.1 (28.5 to 49.6) P < 0.0001		38.3 (27.0 to 49.7) P < 0.0001		31.5 (19.1 to 43.8) P < 0.0001	
Peak daily pruritus NRS score reduction of ≥ 3										
n/N (%)	103/220 (46.8)	38/221 (17.2)	117/231 (50.6)	29/226 (12.8)	69/105 (65.7)	85/306 (27.8)	49/88 (55.7)	40/256 (15.6)	57/99 (57.6)	20/98 (20.4)
Difference, % (95% CI)[a,b]	29.6 (21.4 to 37.9) P < 0.0001		37.8 (30.0 to 45.6) P < 0.0001		37.9 (27.6 to 48.3) P < 0.0001		40.1 (28.8 to 51.4) P < 0.0001		37.2 (24.6 to 49.8) P < 0.0001	
POEM										
Baseline mean (SD)	19.8 (6.37)	20.3 (5.89)	20.8 (5.49)	21.0 (5.94)	20.3 (5.68)	20.0 (5.98)	20.6 (5.66)	20.1 (6.03)	19.3 (6.21)	19.1 (5.96)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
N observed/imputed	173/51	96/128	196/37	104/132	92/14	187/128	71/18	99/165	103/4	88/20
LSM change (SE)	−11.6 (0.5)	−5.1 (0.7)	−10.2 (0.5)	−3.3 (0.6)	−12.7 (0.6)	−5.3 (0.41)	−14.2 (0.78)	−7.0 (0.57)	−11.9 (0.60)	−4.3 (0.62)
LSMD (95% CI)[c]	−6.5 (−8.0 to −5.0) P < 0.0001		−7.0 (−8.4 to −5.6) P < 0.0001		−7.4 (−8.8 to −5.9) P < 0.0001		−7.2 (−9.0 to −5.4) P < 0.0001		−7.6 (−9.3 to −6.0) P < 0.0001	
EQ-5D index utility score										
Baseline mean (SD)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	NA	NA	0.7 (0.3)	0.7 (0.3)
N observed/imputed	173/51	96/128	197/36	105/131	92/14	188/127	NR	NR	103/4	89/19
LSM change (SE)[e]	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	NR	NR	−8.2 (79.2)	−90.0 (79.0)
P value[c,d]	< 0.0001		< 0.0001		0.0058		NR		0.4577	
LSMD (95% CI)[c,e]	0.1 08 (0.06 to 0.15)		0.17 (0.12 to 0.21)		0.06 (0.02 to 0.10)		NR		81.8 (−134.0 to 297.6)	
DLQI										
Baseline mean (SD)	13.9 (7.37)	14.8 (7.21)	15.4 (7.07)	15.4 (7.69)	14.5 (7.31)	14.7 (7.37)	15.0 (7.32)	15.2 (7.35)	14.5 (7.63)	13.2 (7.60)
N observed/imputed	173/51	97/127	197/36	105/131	92/14	187/128	71/18	101/163	103/4	89/19
LSM change (SE)	−9.3 (0.4)	−5.3 (0.5)	−9.3 (0.4)	−3.6 (0.5)	−10.0 (0.5)	−5.8 (0.3)	−11.4 (0.6)	−7.2 (0.4)	−9.5 (0.5)	-4.5 (0.5)
LSMD (95% CI)[c]	−4.0 (−5.2 to −2.8)		−5.7 (−6.9 to −4.5)		−4.2 (−5.3 to −3.0)		−4.2 (−5.5 to −2.9)		−5.0 (−6.3 to −3.7)	
P value[c]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
Withdrawals										
N (%)	16 (7.1)	40 (17.9)	13 (5.6)	46 (19.5)			9 (8.5)	52 (16.5)	0	5 (4.6)
SAEs										
N (%)	7 (3.1)	11 (5.0)	4 (1.7)	17 (7.3)			4 (3.6)	11 (3.5)	5 (4.7)	10 (9.3)
WDAEs										
N (%)	4 (1.7)	2 (0.9)	2 (0.8)	5 (2.1)			1 (0.9)	15 (4.8)	0	1 (0.9)
Notable harms, N (%)										

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Dermatitis atopic[f]	30 (13)	67 (30)	32 (14)	81 (35)	12 (10.9)	84 (26.7)	20 (18)	144 (46)	8 (7.5)	16 (14.8)
Rescue medication use										
N (%)	48 (21.0)	115 (51.8)	38 (16.1)	122 (52.1)			12 (10.9)	120 (38.1)	4 (3.7)	19 (17.6)

CI = confidence interval; DLQI = Dermatology Life Quality Index; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; EQ-5D = EuroQol 5-Dimensions; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; LSM = least squares mean; LSM = least squares mean difference; NA = not applicable; NR = not recorded; NRS = numerical rating scale; q.2.w. = every two weeks;

POEM = Patient-Oriented Eczema Measure; SAE = serious adverse event; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; SE = standard error; TCS = topical corticosteroid; WDAE = withdrawal due to adverse event.

[a] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.

[b] P values were derived by the Cochran-Mantel-Haenszel tests stratified by region and baseline disease severity (IGA = 3 versus IGA = 4).

[c] The confidence interval with P value is based on treatment difference (dupilumab group versus placebo) of the LSM change using an analysis of covariance model with baseline measurement as the covariate and the treatment, region and baseline IGA strata as fixed factors.

[d] The P value is not adjusted for multiplicity and is presented for descriptive purposes only.

[e] The percent LSM change/difference in LIBERTY AD CAFÉ.

[f] Reported as flare worsening or aggravation that required or prolonged hospitalization.

Source: Clinical Study Reports for SOLO 1,[4] SOLO 2,[5] LIBERTY AD CHRONOS,[6] and LIBERTY AD CAFÉ.[7]

Critical Appraisal

Generally, the studies were well designed with various measures in place to prevent biases. Internal validity was potentially compromised by missing data, with some of the secondary outcomes missing more than 50% of the data. In addition, several of the secondary outcomes did not have AD-specific MID values, limiting the ability to make quantitative conclusions regarding clinical significance. Because external validity of the studies was limited by the use of placebo controls, no information on the relative efficacy of dupilumab to active comparators could be obtained from the trials.

Indirect Comparisons

Description of Studies

A CADTH literature search identified three potentially relevant indirect treatment comparisons (ITCs)[2-4] that compared dupilumab to other agents used for the treatment of patients with moderate-to-severe AD.

Efficacy and Harms Results

The results of the three ITCs were not summarized because the findings were associated with significant uncertainty due to critical methodological limitations.

Critical Appraisal

The ITC by Ariens et al.[3] was not based on a systematic review. Only two studies were chosen in the ITC, which only compared dupilumab with cyclosporine. In the ITC by Alexander et al.,[4] no detailed methodological information about the systematic review was reported. There was insufficient information to adequately assess the methodological quality and the risk of bias. The ITC by NICE[2] (a matching-adjusted indirect comparison), was based on a systematic review. However, the body of evidence for the comparison was limited by small sample sizes and heterogeneity in terms of design of the included studies. Therefore, the validity of the findings reported in the three identified ITCs is highly uncertain.

Other Relevant Evidence

Description of Studies

Study 1434 is an ongoing (October 2015 to November 2023; data cut-off date for this review: April 21, 2018), global, multi-centre, non-randomized, phase III, open-label extension, single-group trial (N = 765) in adolescents (≥ 12 to < 18 years) with moderate-to-severe AD. Enrolled patients were adolescent patients who participated in one of the three previous parent clinical trials on dupilumab in children with AD: Study 1526 (phase III), Study 1412 (phase IIa), and Study 1607 (phase I). The primary outcome was the incidence and rate (events per patient-year) of treatment-emergent AEs. Results presented in this document were based on a pre-specified first-step analysis (data cut-off on April 21, 2018).

Study 1225 is an ongoing study (October 2013 to November 2022; data cut-off date for this review: April 11, 2016). Study 1225 is a multi-centre, non-randomized, open-label extension, single-group study (N = 2,678). Study 1225 evaluated long-term dupilumab treatment in adults with AD who had previously participated in one of the 12 parent phase I, II, or III dupilumab clinical trials. The 12 parent studies consisted of four of the reviewed phase III trials (SOLO 1 [Study 1334]; SOLO 2 [Study 1416], LIBERTY AD CHRONOS [Study 1224]; and SOLO CONTINUE [Study 1415]) and eight that were phase I or II trials. The primary outcome was incidence and rate (events per 100 patient-years) of AEs. The results reported in this summary were based on a pre-specified first-step analysis (cut-off date of April 11, 2016). Given limitations on design, heterogeneous populations, and analyses, only safety data were reported.

Harms Results

No new safety signals arose over the course of Study 1434 and Study 1225.

Critical Appraisal

In both Study 1434 and Study 1225, there was considerable heterogeneity among the parent studies in terms of study design, population, intervention (i.e., dosage regimens), comparators, outcomes, and study duration. Variation in terms of dupilumab dosage regimens were evident due to several protocol amendments during the extension phase. In addition, the lack of a control arm in both Study 1434 and Study 1225 limits interpretation of study outcomes.

Conclusions

Six DB RCTs in patients with moderate-to-severe AD — four in adults from the original review of dupilumab (SOLO 1 and 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ), one in adolescents (Study 1526), and one longer-term extension in adults (SOLO CONTINUE) — were included in this review. In both adults and adolescents, dupilumab improved various measures of disease severity (IGA, EASI), symptoms (pruritus), and health-related quality of life (DLQI or Children's DLQI) compared with placebo after 16

weeks (and 52 weeks with LIBERTY AD CHRONOS) of treatment. Where the minimum clinically important differences were known, these differences were clinically significant. Results from SOLO CONTINUE suggest durability of the effects after an initial 16-week treatment response; however, longer-term studies are needed. No direct comparisons of dupilumab to other systemic therapies for AD were found, and published ITCs were inconclusive due to poor methodological quality and limitations with the base data. There was no clear evidence of important harms occurring at greater risk with dupilumab than placebo, and longer-term safety extensions in both adolescents and adults revealed no new safety signals, with a mean follow-up of an additional 26 and 38 weeks, respectively.

Introduction

Disease Background

Atopic dermatitis (AD) is the most common type of eczema.[1] It is a chronic, relapsing, inflammatory skin condition characterized by severely itchy skin (pruritus) that results in red and swollen skin (rashes). AD lesions may appear as fluid-filled vesicles that ooze, crack, and crust. Pruritus of the skin can cause frequent scratching and may result in lichenification (thickening of the skin) and secondary skin infections. AD typically involves the popliteal (skin folds behind the knees) and the antecubital (skin folds in front of the elbows) areas. AD may also appear on the face, neck, and hands. Individuals with AD have skin with impaired barrier function and reduced water-holding capacity, resulting in dry skin that requires treatment with specific bathing, cleansing, and moisturizing practices.

As a hereditary form of eczema, AD generally presents in infancy, with most cases beginning before the age of 5.[1,12] The majority of these children will outgrow the condition by adolescence.[2,3] It is common for children with AD to develop asthma and/or hay fever. This process is referred to as the "atopic march" and AD is often the first step in the sequential development of these other atopic conditions.[13] The clinical manifestations of AD vary with age, with infants showing AD on the extensor surfaces of extremities, face, neck, scalp, and trunk. Children are typically affected on the flexural surfaces of extremities, neck, wrists, and ankles, while adolescents and adults are generally affected on the flexural surfaces of extremities and the hands and feet.[2]

The Canadian Dermatology Association reports that the lifetime prevalence of AD is up to 17% in the Canadian population, and evidence suggests that the prevalence has increased over the past 30 years.[1-3] Patients often experience worsening itching symptoms throughout the night and this may result in sleep loss, which may be associated with detrimental effects pertaining to school or work.[2] Individuals with AD may also suffer from the social stigma of having a highly visible condition. Overall, these patients describe a physically and mentally exhausting condition that can result in anxiety, depression, and a decrease in quality of life.

The goals of AD management are to prevent flares (episodes of worsening of symptoms typically requiring escalation of treatment), and effectively manage flares when they occur by preventing their progression.[3] While there is no cure for AD, several therapeutic options are available to patients to manage the condition. The majority of patients treat AD using general skin-care methods, avoidance of skin irritants, and topical anti-inflammatory therapy. If these common methods fail to improve AD, patients may use off-label systemic (i.e., immunosuppressant) therapy or other therapies such as phototherapy.

Standards of Therapy

General skin-care practices for patients with AD include irritant avoidance and managing dry skin. The symptoms of AD may be reduced or prevented by avoiding known skin irritants or triggers.[1,3] Some common irritants include temperature, humidity, dust, pets (animal dander), smoke, and grass. Using mild detergents to wash clothing with no bleach or fabric softener, and double-rinsing clothing, have been recommended for those with AD. Dry skin associated with AD can be countered through specific bathing, cleansing, and moisturizing practices. Baths using lukewarm water and emulsifying oil followed by the use of moisturizers is recommended. Limiting the use of soap and fragranced products may also help reduce symptoms.[1-3,14]

Topical Therapy

While a number of non-pharmacological topical therapies exist for treating the symptoms of AD, the most common therapy is the use of moisturizers to combat dry skin through hydration and the prevention of trans-epidermal water loss. Moisturizers are routinely used to provide some barrier protection for the skin from irritants or allergens and can soften skin, reduce itching, and minimize cracking, fissuring and lichenification.[3,14] Moisturizers are routinely used frequently throughout the day, preferably after bathing. Moisturizers can contain a combination of emollients, humectants, and occlusive agents. Emollients (e.g., glycol and glyceryl stearate and soy sterols) lubricate and soften the skin by smoothing out the surface of the skin, filling the spaces with droplets. Humectants (e.g., glycerol, lactic acid, and urea) attract water and increase the skin's water-holding capacity. Humectants sting open skin and are not useful in children with AD. Occlusive agents (e.g., petrolatum, dimethicone, and mineral oil) provide a layer of oil on the surface of the skin to slow trans-epidermal water loss and prevent water loss though evaporation, increasing the moisture content of the skin. The choice of moisturizer depends on the area of the body and the degree of dryness of the skin.[3,14]

The most common pharmaceutical topical therapies include the use of a topical corticosteroid (TCS) or calcineurin inhibitor (TCI). A TCS acts as anti-inflammatory therapy and is considered to be the first-line treatment for AD.[2] There are more than 30 different TCS types, which can take the form of lotions, creams, oily creams, ointments or gels and be combined with other agents, such as antibiotics.[15] Topical corticosteroids vary in potency. In Canada, hydrocortisone 1% (low potency) is the most commonly prescribed type of TCS for the face.[3] For the body, moderately potent triamcinolone or betamethasone valerate are the most commonly prescribed options. A TCS is applied directly to the area of affected skin prior to the use of emollients, and a response is typically seen within 10 to 14 days. Side effects associated with long-term use include striae (stretch marks), petechiae (small red/purple spots), telangiectasia (small, dilated blood vessels on the surface of the skin), skin thinning, atrophy and acne.[2] TCS products are also recommended for use in children, according to the American Academy of Dermatology (AAD), with cautions regarding dosing, as children have a larger surface-area-to-body-mass ratio and mixed results from various studies suggest that systemic absorption may have an impact on growth. TCIs are steroid-free, anti-inflammatory, immunosuppressant agents that can be used long-term. In Canada, the two available second-line agents are pimecrolimus and tacrolimus. Pimecrolimus 1% cream can be used for short-term and intermittent long-term therapy for mild-to-moderate AD and is effective in controlling pruritus.[3] Topical tacrolimus, an ointment that can be used for short-term and intermittent long-term therapy of moderate-to-severe AD, offers rapid and sustained AD symptom control.[3,15] The most common adverse event (AE) associated with TCIs is application site–specific burning and irritation.[2,3] A black box warning regarding lymphoma accompanies TCIs, but long-term (10-year) surveillance studies have found no increased risk of lymphoma over that of the general pediatric population.

Other topical therapies for AD include treatments with diluted bleach baths, which can help reduce the occurrence of secondary skin infections.[3,16]

Systemic Therapy

Systemic therapy for the treatment of AD typically involves the use of antimicrobials, antihistamines, or immunomodulators.[15-17] Systemic antibiotic treatment can be used to counter widespread secondary bacterial infection. Many patients encounter infection with *Staphylococcus aureus* and this may cause new inflammation and exacerbate AD symptoms. The choice of systemic antibiotic agent depends upon the skin culture and sensitivity profile. Sedating antihistamines have been used when patients are not achieving

adequate sleep due to itching.[1,15] Immunomodulatory agents including cyclosporine-A, azathioprine, methotrexate, and mycophenolate mofetil can be used in patients who are not responsive to other treatments.[13,15,16] However, these common off-label treatments are used at the lowest dose for the shortest duration possible due to side effects.[16,17] According to the AAD, cyclosporine is an effective treatment in pediatrics. The AAD acknowledges the evidence for use of methotrexate in pediatric cases of AD is limited. However, a recent 12-week study showed it was associated with slower onset than low-dose cyclosporine but increased time before relapse after discontinuation. Regarding azathioprine, the AAD noted there was evidence of efficacy in children, but recommended reserving its use for recalcitrant AD, or in cases where AD is having a significant psychosocial impact. The AAD noted that mycophenolate mofetil is a relatively safe systemic therapy in pediatric AD, although its long-term (> 24 months) efficacy and safety in pediatrics have not been studied. With respect to corticosteroids, there is a longstanding understanding that chronic use can affect growth in children. The AAD does not recommend corticosteroid use in children with AD unless given as part of a short-term transition to systemic immunomodulators.

Other Therapies

Phototherapy is another second-line therapy that is commonly used after failure of a TCS or TCI. This therapy includes several sessions and is guided by a number of factors, including patient skin type and skin cancer history.[16] According to the AAD guidelines, phototherapy is considered a safe and effective treatment for AD in children. No studies of the long-term consequences of phototherapy use in pediatric AD patients are available, although an increased risk of nonmelanoma skin cancer has been reported in children receiving psoralen and ultraviolet-A radiation for psoriasis.

Drug

Dupilumab, an interleukin (IL)-4 receptor alpha antagonist, is a human monoclonal antibody of the immunoglobin G4 subclass that binds to the IL-4R-alpha subunit and inhibits IL-4 and IL-13 signalling, both of which are believed to facilitate release of pro-inflammatory cytokines. Inhibition of these cytokines therefore has an anti-inflammatory effect. Dupilumab is indicated for the treatment of patients 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The sponsor's reimbursement request is largely consistent with the indication: for those whose disease is not adequately controlled with topical prescription therapies or those for whom therapies are not advisable and/or those refractory to or ineligible for systemic immunosuppressant therapies (i.e., due to contraindications, intolerance, or need for long-term treatment). Dupilumab is administered every other week by subcutaneous injection, at a dose of 300 mg in adults and adolescents ≥ 60 kg, and a dose of 200 mg in adolescents weighing < than 60 kg.

Dupilumab was previously reviewed in 2018 by a CADTH Common Drug Review (CDR) for adults with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. A recommendation of "do not reimburse" was issued by the CADTH Canadian Drug Expert Committee in June 2018. Reasons for the recommendation included a lack of trials comparing dupilumab to an active comparator, lack of long-term safety data, questions over generalizability of results to clinical settings, and a lack of efficacy and safety data in patients for whom topical prescription therapies are not advisable.

Table 4: Key Characteristics of Dupilumab and Other Systemic Therapies for AD

	Dupilumab	Azathioprine	Mycophenolate mofetil
Mechanism of action	Inhibits IL-4 and IL-13	• Immune suppressant • Antimetabolite – reduces proliferation of lymphocytes	• Immune suppressant • Inhibits purine synthesis, reduces lymphocyte proliferation • Reduces antibody formation by B lymphocytes
Indication[a]	Moderate-to-severe atopic dermatitis	• Rheumatoid arthritis • Prevention of transplant rejection (renal)	Prevention of transplant rejection (renal)
Route of administration	Subcutaneous	Oral	• Oral • Intravenous
Recommended dose			
Serious adverse effects or safety issues	• Conjunctivitis • Keratitis • Hypersensitivity • Helminth infections	• Carcinogenic • Leukopenia • Thrombocytopenia • Infection • Hepatoxicity	• Infection • Lymphoma
Other	No evidence of fetal harm; however, limited data	Can cause fetal harm	Fetal harm/pregnancy loss
	Cyclosporine	**Methotrexate**	
Mechanism of action	• Immune suppressive • Inhibits IL-2 and T-cell activation	Immune suppressive	
Indication[a]	• Prevention of transplant rejection • Psoriasis • Rheumatoid arthritis • Nephrotic syndrome	• Various neoplasia • Psoriasis • Rheumatoid arthritis	
Route of administration	Oral	• Oral • Subcutaneous	
Recommended dose	• Psoriasis: • Initial: 2.5 mg/kg/day in two divided doses • Not to exceed 5 mg/kg/day		
Serious adverse effects or safety issues	• Infection • Malignancy • Nephrotoxicity • Hypertension • Hepatotoxicity • Neurotoxicity	• Malignancy • Serious rash • Bone-marrow suppression • Vomiting, diarrhea • Hepatotoxicity	
Other	Reports of fetal harm	Causes fetal harm	

AD = atopic dermatitis; IL = interleukin.

[a] Health Canada–approved indication.

Source: Product monographs from the online e-CPS database.[5]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the patient groups and information gathered

Two patient groups, the Eczema Society of Canada (ESC) and the Canadian Skin Patient Alliance (CSPA), provided input for this review. The ESC also provided input for the original CADTH submission for dupilumab.

The ESC is a registered Canadian charity dedicated to improving the lives of Canadians living with eczema. With the help of physicians and contributors, the ESC delivers evidence-based, up-to-date disease and treatment information to Canadians living with eczema, their caregivers, and health care providers. ESC gathered information for this submission via written questionnaires and interviews, and by asking patients and caregivers to provide statements and testimonials about their experience with uncontrolled moderate-to-severe AD and with dupilumab and other systemic medications. In 2016, the ESC conducted online quality-of-life surveys with 1,035 respondents from across Canada, including both adults and caregivers of children living with AD. The data in this submission pertain to respondents who reported moderate or severe AD, and content specifically related to adolescents with AD is also included. In 2019, the ESC conducted an online survey of 299 respondents from across Canada pertaining specifically to systemic treatments for AD. Data in this submission pertain to both adult and pediatric populations as reported from the systemic treatments survey.

The CSPA is a national non-profit organization dedicated to advocating, educating, and supporting Canadians living with diseases, conditions, and traumas that affect skin, hair, and nails. CSPA's mission is to promote skin health and improve the quality of life of Canadians living with skin conditions, diseases, and traumas. The CSPA advocates for best treatment options for all such patients. The CSPA developed the Atopic Dermatitis Patient Experience Survey using SurveyMonkey, which was reviewed for clarity and comprehensiveness by a Canadian dermatologist and members of the public. The survey was disseminated between November 3 and 24, 2017, using social media strategies designed to target those in Canada living with AD and their caregivers. In total, 194 eligible responses were received from patients with AD and caregivers, with Canadians accounting for 92% (n = 120) of patients and 87% (n = 54) of caregivers. Responses from US and international patients were included because the experiences and needs of people with AD were considered to be similar regardless of where they live. Of the 132 patient respondents living with AD, 55% had moderate-to-severe AD, 78% were female and the average age was 42 years old, although respondents' ages ranged from 18 to 92 years. The remaining 62 responses were from caregivers, of whom 68% said they cared for someone living with moderate-to-severe AD. The CSPA also published a separate survey using SurveyMonkey that was circulated to their patient community using social media strategies from September 8 to November 18, 2019. CADTH shared three detailed submissions by Canadian individuals (one patient and two caregivers) with the CSPA that have been incorporated into this submission.

Disease Experience

The impact of AD varies considerably depending on severity. The symptoms of moderate-to-severe AD can be debilitating and life-altering for patients, as well as caregivers and family members. For patients with a more severe form of the disease, the itchiness can be intense and persist all day and night, interrupting all aspects of life, including work, school,

social relationships, and sleep. Living with the chronic itch and pain can reduce the quality of life and sleep. The ESC indicated that 79% of survey respondents suffered from interrupted sleep, with 29% reporting poor sleep more than 14 nights per month. Some respondents reported falling asleep during the day and experiencing daytime exhaustion, changes in mood, and impatience due to fatigue. Patients reported missing work and school. They also reported being bed-ridden during severe flare-ups, their skin covered in open wounds, sores, and rashes, and bleeding through their clothing. AD also affects mental health, with 64% of surveyed patients reporting feelings of anxiety and 44% reporting depression related to their AD. Patients reported poor self-esteem, increased stress, and even suicidal thoughts. The ESC submission indicated that a recent Canadian study revealed that patients with AD were 20% more likely to die from suicide compared with the general population.[6]

Itches are consistently rated as the most bothersome symptom of the disease by patients. Three out of four adolescents with moderate-to-severe AD reported their day-to-day life was negatively affected by their condition, and more than half missed school due to their AD. Adolescents reported bullying due to their condition. The top three quality-of-life challenges of the disease, as reported by adolescents, were: (1) avoidance of social activities, (2) an inability to participate in sports and physical activities, and (3) interrupted sleep. For adolescents suffering with AD, living with an uncontrolled chronic disease can compound stressors already associated with the teen years. The negative impact of AD on mood, sleep, social interactions, self-esteem, and school performance can be particularly difficult to manage for patients in this age group.

Following are some patient quotations:

- Having chronic moderate-to-severe AD is like having chicken pox 24 hours a day, seven days a week.
- Prior to being on Dupixent, I always had an urge to itch. This led to cuts on large portions of my body. I was always bleeding from somewhere. The thought of itching consumed my life; I was always thinking about the itching or the pain or the impact of living with AD… People would never understand how it feels to want to itch so much that you rip your skin open, over and over and over again... This has caused significant negative impacts to my quality of life…
- When our child went into high school, the bullying started. The name-calling, isolation, and nasty rumors about him being "contagious" all took an immense toll. It broke our hearts. It got so bad, we decided to keep him home …
- I often shy away from social encounters due to the embarrassment of my skin, constant shedding, and sores all over my body.
- Our son is now in his teen years and he has lived like a prisoner in his own body. He's never had healthy skin since he was an infant. We use the medicated creams exactly as our doctor tells us to, and while he may get initial relief, the disease inevitably flares up again, and we are back at square one. We have one of the best dermatologists in the country and we still cannot get this relentless disease under control.

The following quotations, provided by the ESC in the original review of dupilumab, offer additional insight into the day-to-day challenges to patients with severe AD:

- The worst part of eczema is itch and then sleep. I itch all day long and night long and can't sleep. I wake up in the night due to scratching. It's a terrible cycle of itching, scratching, and eczema flare-ups.

- Atopic dermatitis (eczema) is completely physically and emotionally draining. The itch is always there and is sometimes so intense that you just can't live with it anymore.
- My AD has been a never ending battle all my life. Sometimes I feel it is a losing battle.
- Every aspect of my life is limited due to my eczema. I itch all day, I'm always tired, I can't exercise, and I can't do many activities because of the way my skin feels and looks.
- My eczema impacts my mental health too — I experience depression and terrible anxiety because of the flare-ups. The flares are so unpredictable and I have anxiety about waking up in the morning with my face covered in eczema, or bleeding skin because I ripped it apart scratching in the night.

Experience With Treatment

Both patients and caregivers reported that currently available treatments have limited effectiveness. Caregivers often opt for non-prescription options, "possibly due to fear of using potentially harsh medications on their children." They may also be instructed by their health care providers to be cautious about using such treatments in younger patients. Typical management of AD includes frequent bathing and moisturizing, trigger avoidance, and topical medications. This is currently the mainstay of therapy. For some patients, despite their best efforts at trigger avoidance, flare prevention, and adherence to topical therapy, their AD is still not well managed and current therapies are inadequate. For this group of patients there is a significant gap in effective therapies. Among patients with moderate-to-severe AD who have tried topical treatments to manage their condition, 41% have tried four to nine different topical treatments, and 29% have tried 15 or more different topical treatments. There is a significant gap in care for patients who are not well managed on currently available therapies. For patients with recalcitrant AD that does not respond adequately to topical therapy, systemic therapy is the next step. Before dupilumab was approved, systemic therapy included phototherapy, oral corticosteroids, and off-label systemic immunosuppressants. While phototherapy may be helpful for some patients, a recent survey on systemic medications indicated phototherapy did not control the disease in most respondents. Oral corticosteroids may work well for some patients in the short term, but many patients reported extreme cases of rebound flares when coming off the drug. Off-label immunosuppressive medications are sometimes used to provide temporary relief to patients, as these medications cannot be used over the long term. These off-label therapies often come with serious side effects both in the short term (e.g., nausea) and long term (e.g., organ damage). The ESC's 2019 survey on systemic therapies revealed the percentages of patients surveyed who had to stop following treatments due to lack of efficacy, management difficulty, and/or side effects: cyclosporine: 100%; systemic corticosteroids: 91%; methotrexate: 76%; phototherapy: 73%; and dupilumab: 12%. These data highlight the unmet need for effective, long-term, and safe therapies for chronic AD.

Surveyed patients said the following:

- We tried any and all treatments suggested for our son; including the full gamut of topical steroids, Elidel and other nonsteroidal creams, oral steroids (several treatments lasting weeks at a time), light therapy and naturopathic and herbal remedies involving removing most foods from his diet. None of these had any lasting benefits, and in many cases the rebound effect made our son's eczema and suffering much worse. Alternative drugs to dupilumab had worse side-effects and could not be used long term.
- I've used topical medications my whole life and now sections of my skin are permanently damaged, and the worst part is that I still live with the eczema.

- I was trying every cream I was prescribed, and my skin got a little better and then would flare again. I've tried the diets, I've tried light therapy, and neither worked. I felt completely hopeless.
- I tried an [off-label] oral pill with mixed results, and it caused severe immunosuppression, such that I developed infections and was forced to take months off work. The infections were very severe, often with very high fevers and many sores all over my body.
- We found out that my teen was only allowed to be on prednisone for a short time. I almost wish we never tried it; yes, it was this magic pill that helped us for a few days, but we knew it was only a matter of time until the eczema was going to come back. It gave a snippet of what life without eczema was like, only to have it taken away.
- Methotrexate and other immune-suppressors are treatment options but have severe complications and require constant monitoring from a doctor. These options do not actually target the disease specifically and cannot control severe AD. Itching still remains and eczema can still be found on the entire body. This is not an adequate treatment option when compared to Dupixent.

Experience With Drug Under Review

Patients taking dupilumab reported significant improvements in their disease symptoms and quality of life. This finding was confirmed by the ESC's 2019 survey data. Patients reported improved sleep, returning to work, increased productivity and concentration at work and school, resumption of intimate and social relationships, and increased ability to exercise. Caregivers of adolescents reported their child's mood significantly improved after taking dupilumab. Of the systemic survey respondents who have taken dupilumab, 80% agreed it contributed to the optimal management of their AD. A total of 75% of respondents also agreed that the benefits outweighed potential side effects. The percentages of respondents who reported improvements in the following areas while using various systemic therapies were itching: dupilumab 93%, systemic corticosteroids 89%, methotrexate 82%, cyclosporine 79%, light therapy 61%, sleep: dupilumab 85%, cyclosporine 73%, light therapy 65%, methotrexate 61%, systemic corticosteroids 59%, productivity at school and/or work: dupilumab 77%, cyclosporine 63%, light therapy 45%, systemic corticosteroids 45%, methotrexate 33%. The ESC submission for the original review of dupilumab emphasized that "dupilumab is a life-altering medication and the first medication to dramatically reduce or eliminate flare-ups, and most significantly, reduce or eliminate itch, which is the hallmark of this disease."

In the CSPA's input, eight patients had used dupilumab to treat their moderate-to-severe AD. Five of the respondents to the CSPA dupilumab survey commented on their experiences using the drug to treat their AD, four of whom had a positive experience and one of whom "disliked it altogether" and experienced "terrible side effects." As noted above, one patient and two caregivers who provided patient input directly to CADTH consented to have their experiences with dupilumab shared as part of this submission. The patient indicated that there are no alternatives to dupilumab for severe AD patients.

Below are some patient testimonials:

- This drug is much easier to use than other therapies; one injection bi-weekly is easy to plan and getting a supply for the month is not difficult. Refrigeration is required. I have experienced dry eyes that I fully control with eye drops when I feel dryness. This drug seems to completely control severe AD for patients. No other drug has been able to do that (for me and many others).

- The cost of this drug is high so without coverage, severe AD patients are forced to use inadequate treatment options that can result in complications. Now that I am on Dupixent, I can live a normal life. Without Dupixent, I am forced to choose an inadequate treatment option due to the cost of the drug. Without Dupixent, I will suffer again.
- [Dupilumab] has been the most effective form of treatment for me. The itch is non-existent neck down and I'm not used to living like that.
- This treatment did the impossible — it took the itch away. I never knew it was possible and my quality of life has changed drastically because of it. I no longer rip my skin apart and my outbreaks are gone.
- This treatment opened my world. I was able to find success at work and in my personal life by way of intimate relationships; things I never thought to be possible for me due to my eczema.

Improved Outcomes

Patients are seeking a treatment that can reduce or eliminate the symptoms, such as itching, burning pain, rashes, open sores, sleep disturbance, anxiety, and depression, as well as improve their quality of life and work or school productivity.

Below are some patient quotations:

- The eczema on my eyelids is disfiguring and prevents me from wearing make-up or contact lenses. I am embarrassed to be seen during flare-ups which happen almost weekly.
- It makes me hesitate to join people at gatherings and outings because I'm embarrassed to be seen with nasty rashes and flakes.
- I'm black and have darker skin, and my topical treatments cause patches of discoloration which makes me self-conscious and, in some ways, bothers me more [than the rash].
- The bar is set so low as to what I would want from a treatment. I really want a treatment that actually works and eliminates my symptoms – stopping the inflammation inside me – instead of just masking the symptoms over and over again.

Overall, both ESC and CSPA patient input emphasized that AD patients, including adolescents, suffer from significant discomfort, pain, and diminished quality of life. There is an urgent need for new, safe, and effective treatments for moderate-to-severe AD. Dupilumab is a new treatment that has been shown to be effective in reducing signs and symptoms of AD, and most notably, improving or eliminating itch, the most bothersome symptom of AD. Patients believed that dupilumab has been reported to be a life-altering medication. Uncontrolled moderate-to-severe AD can be a devastating condition and there is a clinically significant unmet need for new therapies in this patient population. Equitable access to medications is critically important to patients with AD as well as to the ESC and CSPA, both of which want to ensure the true burden of this disease is understood and appreciated, and communicate the essential need for access to new therapies for AD. The CSPA believes patients deserve to be treated with respect and dignity by the health system, and calls for the embrace of new treatment options.

The CSPA indicated that this is a real issue for patients with AD, and that the need for new treatment options that address the underlying mechanisms of the disease is critical. For those living with moderate-to-severe AD, when their treatment stops being effective, this heightens the psychological harm of AD and contributes to a feeling of hopelessness as well as landing them back at square one in the effort to determine whether other treatment options (or combinations of them) will help offset the physical manifestations of the disease. Some patients said the following:

I can't describe the level of hopelessness you feel when there's something out there that could help you, but the system in place won't give you access.

If someone you loved was suffering with this disease, and there was a medication out there that could help them, but it costs too much, it is inhumane to not give them access.

I'm all for the government watching our money, but if you have chronic, recalcitrant eczema that doesn't respond to other treatments, you need to be able to try Dupixent. Yes, eczema is not technically a "deadly" disease, but I've learned there are a lot of teenagers that don't make it through. The government needs to understand that it's not just an itch, it's your whole mental health.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of AD.

Description of the Current Treatment Paradigm for the Disease

The most common first-line drug therapies for AD are TCSs and TCIs, with crisaborole, a phosphodiesterase type-4 inhibitor that is used much less commonly. Patients who proceed to phototherapy or systemic drugs will typically continue with topical therapy. TCS and TCI therapies are used concomitantly, with TCIs being safe to use on delicate areas such as eyelids, periocular skin, and creases. The use of TCIs is limited by their cost and their tendency to cause a burning sensation. Sedating antihistamines may be used for intractable nocturnal pruritus, although their use is declining due to concerns over cognitive impairment in children. Topical antibiotics are also used in cases of chronic impetiginization, usually fusidic acid and mupirocin, and systemic antibiotics may be used in cases of more serious infection. In cases of inadequate response, patients may move on to phototherapy (if available) and if topical therapy and phototherapy still do not elicit an adequate response, then they move on to systemic therapies. Methotrexate is a first-line option among systemic drugs, while cyclosporine would be an option for patients who experience methotrexate failure or intolerance. For patients who fail or are intolerant to methotrexate and cyclosporine, dupilumab would be next in line, ahead of mycophenolate mofetil or azathioprine.

Issues specific to adolescents include concerns over adherence to therapies and the impact of the disease on the adolescent psyche and the family. While community dermatologists are often uncomfortable prescribing systemic immunosuppressants for children and adolescents, pediatric dermatologists are unlikely to have the same reluctance, according to the clinical expert consulted by CADTH.

Treatment Goals

An ideal treatment would have a proven long-term safety record, completely reverse barrier dysfunction and immunologic abnormalities that characterize AD, and be cost-effective. Such a treatment, which does not yet exist, would also maintain complete clearance without ongoing therapy, eliminate pruritus, and resolve all visible dermatitis.

Unmet Needs

Patients with suboptimal response to topical therapies and disease-specific skin measures have to use systemic therapies. Some patients are ineligible for these therapies due to contraindications or toxicities that limit their use.

Place in Therapy

Dupilumab may prove a useful option in patients who have contraindications, experience adverse effects, or are unresponsive to immunosuppressives, yet require continuous long-term systemic therapy. All patients with AD who are prescribed dupilumab are likely to continue with emollients, TCIs and TCS treatment, but dupilumab is unlikely to be combined with systemic immunosuppressives. Dupilumab is likely to be an addition to the armamentarium in managing AD rather than shifting the treatment paradigm in a significant way.

Patient Population

Before initiating treatment with dupilumab, it is appropriate to recommend trials of both methotrexate and cyclosporine. Both of these therapies are efficacious and dermatologists are experienced at calculating dosing and duration of therapy and appropriate monitoring periods for toxicities. In addition, many patients can be managed with intermittent immunosuppressives, which have likely been underutilized, due in part to a paucity of research.

Any patient with moderate-to-severe AD could potentially benefit from dupilumab. It is unclear whether this drug can be effectively used in patients who have failed methotrexate. There may be preference toward using dupilumab in patients with concomitant asthma, if in the opinion of the pediatrician or respirologist they might benefit from dupilumab for their asthma.

Dermatologists would be the clinicians to diagnose AD. Diagnosis can be complex because the differential diagnosis includes psoriasis, ichthyoses, allergic contact dermatitis, irritant contact dermatitis, and cutaneous T-cell lymphoma. Because the loss of barrier function of the skin predisposes patients to superimposed allergic contact dermatitis and dermatophytosis, patch tests and skin scrapings for potassium hydroxide and fungal culture may be beneficial in certain cases. Biopsies would normally be reserved for patients who are recalcitrant to all therapy and in whom cutaneous T-cell lymphoma is a consideration, or occasionally to distinguish AD from psoriasis. Dupilumab would never be considered for pre-symptomatic patients.

Patients least suitable include those with AD who are well controlled with topical therapy, phototherapy and/or conventional systemic therapy; patients with untreated and potentially serious helminth infections, and possibly those with a history of severe conjunctivitis or keratitis. It is not currently possible to predict those most likely to respond to dupilumab.

Assessing Response to Treatment

Outcomes used in clinical practice are aligned with those typically used in clinical trials. The Eczema Area and Severity Index (EASI) score is a benchmark for clinical assessment for reimbursement, and can be calculated and recorded at each patient visit. Physicians may

also assess treatment impact on quality of life using the age-appropriate version of the Dermatology Life Quality Index (DLQI). Reduction in pruritus will also be noted but not formally scored in practice. The patient's impression of overall improvement will also be recorded.

Achieving an EASI score improvement from baseline greater than or equal to 75% (EASI-75) with treatment would be clinically significant. Patients with severe disease recalcitrant to all previous therapies may find an EASI score reduction of between 50% and 75% to be clinically meaningful.

Patients placed on dupilumab will be re-evaluated at 16 weeks, and those who are responders will likely be seen at six-month intervals. Those who have not reached response targets at 16 weeks will be re-evaluated at 24 weeks following initiation of the drug, and a decision on whether to stop or continue therapy made at that 24-week visit.

Discontinuing Treatment

Factors to consider when deciding to discontinue therapy would include failure to achieve a clinically meaningful response at 16 weeks, failure to maintain adequate response on long-term maintenance, severe injection reactions, adverse effects such as severe keratitis, ectropion or alopecia areata, helminth infections that do not respond to appropriate therapy, and a generalized hypersensitivity response, such as severe urticaria, erythema nodosum, anaphylaxis, or serum sickness.

Prescribing Conditions

A dermatologist would be required to prescribe dupilumab, which will likely be self-injected or injected by a parent and/or caregiver. It is unlikely to be administered in a hospital or physician's office.

Additional Considerations

Retinoids are unlikely to be prescribed in adolescents with AD localized to the hands (hand dermatitis). Apremilast is unlikely to be prescribed to an adolescent, and its main application in AD is in adults with coexisting psoriasis and AD. Ustekinumab is indicated in Canada for adolescents with psoriasis, but is unlikely to be prescribed to an adolescent patient with AD who does not have psoriasis, except when all other therapies have failed.

Clinical Evidence

The clinical evidence included in the review of dupilumab is presented in three sections. The systematic review includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of dupilumab for the treatment of patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient population	Patients aged 12 and older diagnosed with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Subgroups: • severity (e.g., moderate, severe) • failure to respond/contraindication/intolerance to one or more systemic therapy • age (adolescents vs. adults)
Intervention	Dupilumab by subcutaneous injection, with dosing in adolescents based on weight: < 60 kg: initial dose of 400 mg followed by 200 mg given every other week ≥ 60 kg: initial dose of 600 mg followed by 300 mg every other week (this is also the adult dose)
Comparators	When used alone or in combination with topical therapy: • immune-modulating drugs (e.g., methotrexate, cyclosporine-A, azathioprine, mycophenolate mofetil) • retinoids (e.g., acitretin, alitretinoin) • biologics (e.g., ustekinumab) • small molecules (e.g., apremilast) • placebo
Outcomes	**Efficacy outcomes:** • Severity of AD and AD lesions[a] (e.g., IGA score, EASI, SCORAD) • Symptom reduction[a] (e.g., pruritus, pain, sleep disturbance) • Health-related quality of life[a] (e.g., EQ-5D score, CDLQI score) • Mood[a] (e.g., anxiety, depression) • Productivity[a] (e.g., days of missed work/school) • Withdrawal effects
	Harms outcomes: • AEs • SAEs • WDAEs • AEs of special interest (e.g., exacerbations/flares, injection-site reaction, hypersensitivity, conjunctivitis, alopecia areata, treatment-resistant helminth infections, eye ectropion)
Study design	Published and unpublished phase III and IV RCTs

AD = atopic dermatitis; AE = adverse events; CDLQI = Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D = EuroQol 5-Dimensions; IGA = Investigator's Global Assessment; RCT = randomized controlled trial; SAE = serious adverse events; SCORAD = Scoring Atopic Dermatitis; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Outcomes identified as important from patient input.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[7]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Dupixent (dupilumab) and atopic dermatitis. Clinical trial registries searched included

the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on November 19, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on March 18, 2020.

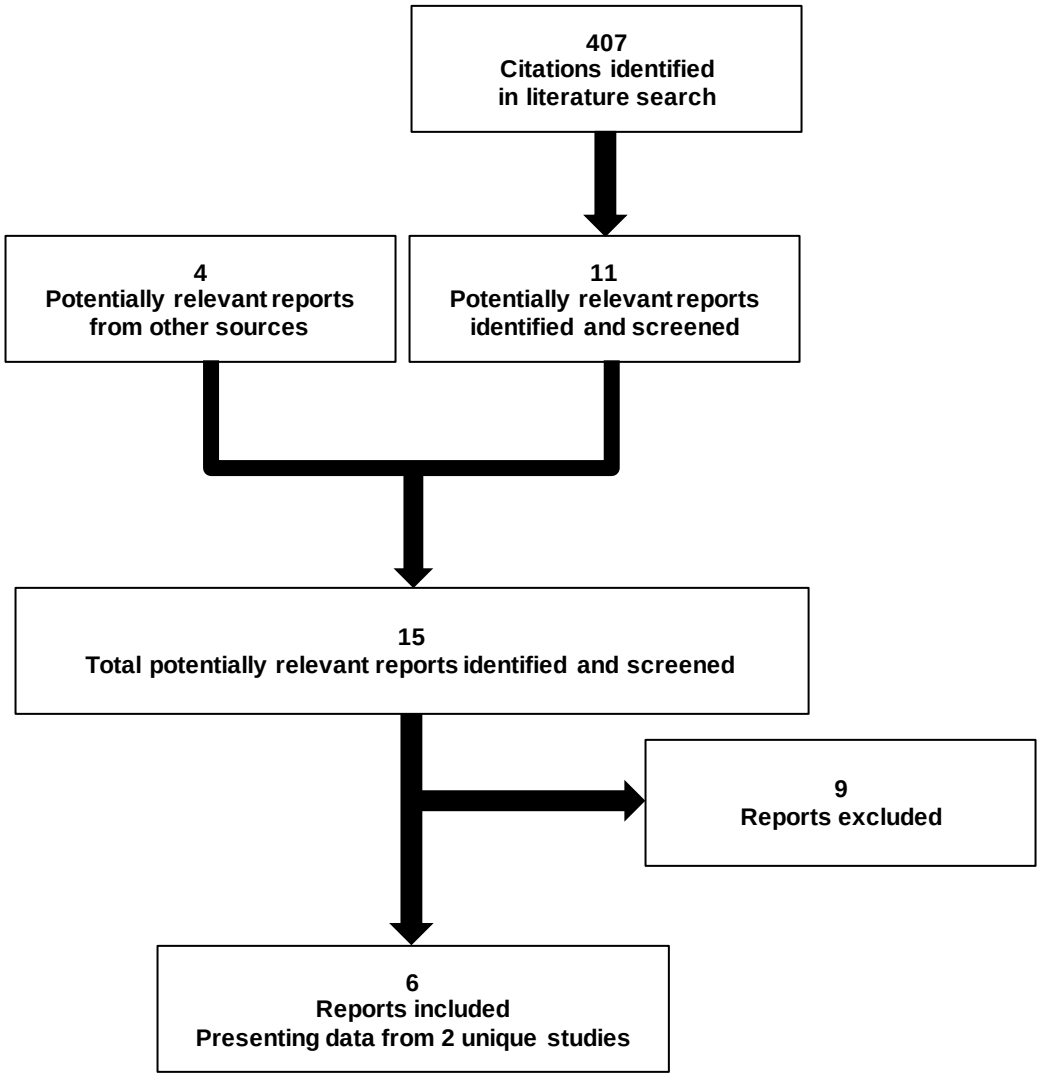
Relevant grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[8] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey-literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings from the Literature

Two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 6, Table 7, and Table 8. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Description of Studies

Adolescents (12 to < 18 years)

One pivotal sponsor-funded, phase III, DB randomized controlled trial (RCT), Study 1526, was included in this review. Study 1526 was a 16-week study that randomized 251 adolescent patients with moderate-to-severe AD 1:1:1 to either one of two different dose regimens of dupilumab, administered every four weeks or every two weeks, or to placebo administered every two weeks. The every two weeks regimen was the focus of this review, as it is the Health Canada–approved regimen. The primary outcome varied depending on geographic region: for patients in the US and US reference-market countries the primary outcome was patients with an Investigator's Global Assessment (IGA) of 0 or 1 at week 16, while European Union (EU) and EU reference-market countries added the co-primary outcome of patients with an EASI-75 at week 16. Because Health Canada appeared to use a co-primary outcome in its review, it was the approach taken in this report. Randomization was conducted using an interactive voice response system (IVRS) and was stratified by weight (< 60 kg or ≥ 60 kg) and by disease severity at baseline (moderate [IGA score of 3] or severe [IGA score of 4]). Aside from the data management committee, all individuals involved in the study remained blinded until the pre-specified unblinding. The study began with a screening period of up to five weeks during which patients were assessed for study eligibility, and when systemic and topical treatments for AD were washed out, according to eligibility requirements. Of the subgroups of interest for this review, only analyses on responses by baseline disease severity (IGA score of 3 versus 4) were conducted.

Adults

SOLO CONTINUE was a phase III, DB, placebo-controlled RCT that sought to determine which dosing regimens of dupilumab would be able to maintain a treatment response achieved in the initial 16-week studies, SOLO 1 and SOLO 2. Patients who had achieved an IGA score of 0 or 1 or achieved EASI-75 in these initial studies were randomized to either the same regimen they received in SOLO 1 or SOLO 2 (dupilumab every two weeks or once weekly) or dupilumab every four weeks, dupilumab once every eight weeks or placebo. Patients who had received placebo in the initial studies were eligible to enrol in SOLO CONTINUE to maintain blinding; however, they were not randomized, simply received placebo for the duration of the study, and were not included in efficacy analyses. An IVRS/interactive web response system (IWRS) was used and randomization was stratified by the original dupilumab regimen received in the parent study region (North America, Europe, Asia, Japan), and baseline IGA score (0 versus 1 versus > 1). Patients began treatment following randomization on day 1 (week 16 of the initial study) and underwent a 36-week treatment period and a 12-week follow-up period, and patients were also invited into an open-label extension following the 36-week treatment period.

Four phase III RCTs were identified by the sponsor in the original review of dupilumab. These included three 16-week trials (SOLO 1, SOLO 2, and LIBERTY AD CAFÉ) and one 52-week trial (LIBERTY AD CHRONOS).[4-7] SOLO 1, SOLO 2, and LIBERTY AD CHRONOS were classified as pivotal by the sponsor and Health Canada.

SOLO 1 and SOLO 2

These were two sponsor-funded phase-three trials of identical design. SOLO 1 and SOLO 2 were DB, placebo-controlled, parallel-group, randomized trials. Within the 35 days prior to randomization, patients were washed out for other treatments of AD. This included use of immunosuppressive and immunomodulating drugs and phototherapy, which could not be used within four weeks prior to baseline, treatment with a TCS or TCI within one week prior to baseline, and regular use (more than two visits per week) of a tanning booth or parlour within four weeks of baseline. Patients in the SOLO trials were randomized in a 1:1:1 ratio

for treatment with dupilumab 600 mg on day 1, followed by 300 mg, via subcutaneous injection weekly, for 16 weeks; or dupilumab 600 mg on day 1, followed by 300 mg, via subcutaneous injection, every other week for 16 weeks (and treatment with placebo in between weeks); or placebo. The dosing schedule for dupilumab once every other week was consistent with the Health Canada–recommended dose and was the focus of this review. Patients were randomized using a central randomization scheme provided by an IVRS/IWRS. The sequence was only accessible to the IVRS statistician and the independent data monitoring committee (IDMC). Randomization was stratified by baseline disease severity (moderate [IGA = 3] or severe [IGA = 4]) and by region (Asia Pacific, East Europe, West Europe, and North and South America). Blinding was conducted using coded drug kits with product lot numbers that were not accessible to individuals involved in the study. To ensure blinding, patients in the every two weeks treatment group received injections with placebo on alternate weeks to allow consistency with the patients in the weekly treatment group. End points were assessed at various pre-specified time points by patients and investigators who were blinded. The studies remained blinded to all individuals until the pre-specified unblinding to conduct the primary analyses. Patients were only unblinded during the study at the discretion of the investigator if they experienced a serious adverse event (SAE). In these studies, patients and/or caregivers were provided with training on subcutaneous injection protocol for the initial four visits or until they were competent. The option for clinical staff–administered injections throughout the entire trial was available for patients who preferred it.

SOLO 1 and SOLO 2 enrolled patients across North and South America, Europe, and Asia at approximately 160 sites. SOLO 1 recruited patients from October 28, 2014, to July 8, 2015; of these patients, 671 were randomized. SOLO 2 recruited patients from December 3, 2014, to June 17, 2015, and 708 patients were randomized. For both trials, patients were treated over the course of 16 weeks and either followed up for an additional 12 weeks or transitioned to an open-label or maintenance study.

Table 6: Details of Included Studies

		Study 1526
Designs and Populations	**Study design**	DB RCT
	Locations	Canada, US
	Study period	March 21, 2017, to April 5, 2018
	Randomized (N)	251
	Inclusion criteria	• Male or female ≥ 12 to < 18 years of age • Diagnosis of AD according to the American Academy of Dermatology consensus criteria (Eichenfield [2014]) at screening visit • Chronic AD diagnosed at least 1 year prior to the screening visit • IGA ≥ 3 at screening and baseline visits • EASI ≥ 16 at the screening and baseline visits • Baseline pruritus NRS average score for maximum itch intensity ≥ 4 • ≥ 10% BSA of AD involvement at the screening and baseline visits • With documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s) or for whom topical treatments were medically inadvisable (e.g., intolerance because of important side effects or safety risks) • Applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit (see exclusion criteria regarding restrictions on the kind of emollients permitted during the study)
	Exclusion criteria	• Treated with a TCS or TCI within 2 weeks before the baseline visit (patients were permitted to rescreen) • Used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, was likely to require such treatment(s) during the first 4 weeks of study treatment:

		Study 1526
		○ Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, ciclosporin, mycophenolate mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate) ○ Phototherapy for AD ○ Treated with biologics, as follows: ▪ Any cell-depleting agents, including but not limited to rituximab within 6 months before the baseline visit, or until lymphocyte and CD19+ lymphocyte counts return to normal, whichever was longer ▪ Other biologics within 5 half-lives (if known) or 16 weeks before the baseline visit, whichever was longer • Treatment with crisaborole within 2 weeks prior to the baseline visit • Body weight < 30 kg at baseline • Initiated treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients were permitted to continue using stable doses of such moisturizers if initiated before the screening visit) • Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study • Sexually active female of childbearing potential[a] who was unwilling to use adequate methods of contraception throughout the duration of the study and for 120 days after the last dose of the study drug
Drugs	**Intervention**	Dupilumab q.2.w. treatment: • if < 60 kg: SC injections of dupilumab, 400 mg loading dose on day 1, then 200 mg q.2.w. from week 2 to week 14, or • if ≥ 60 kg: SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg q.2.w. from week 2 to week 14 Dupilumab every four weeks treatment: SC injections of dupilumab, 600 mg loading dose on day 1, then 300 mg q.4.w. from week 4 to week 12; to maintain the blind, there was an SC injection of placebo in between dupilumab doses during the dosing period between week 2 and week 14 so the injection frequency matched the other 2 groups
	Comparator(s)	Placebo q.2.w.
Duration	**Phase**	
	Screening	Up to 5 weeks
	Double-blind	16 weeks
	Follow-up	12 weeks
Outcomes	**Primary end point**	Patients with IGA 0 or 1 (on a 5-point scale) at week 16. The co-primary end points in the study for EU and EU reference-market countries were: • Proportion of patients with EASI-75 (≥ 75% improvement from baseline) at week 16 • Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16 • Because Health Canada used co-primary outcomes in their analysis, this is the approach that will be taken in this Review.
	Other end points	Key secondary end points: • Patients with EASI-75 at week 16 (this was not a secondary end point for EU and EU reference-market countries as it was already a co-primary end point) • Percent change in EASI score from baseline to week 16 • Percent change from baseline to week 16 in weekly average of daily peak pruritus NRS • Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 3 from baseline at week 16 • Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 4 from baseline at week 16 Other secondary end points:

		Study 1526
		• Patients with EASI-50 at week 16 • Patients with EASI-90 at week 16 • Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 3 from baseline during the 16-week treatment period • Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 4 from baseline during the 16-week treatment period • Change from baseline to week 16 in percent BSA affected by AD • Percent change from baseline to week 16 in SCORAD • Change from baseline to week 16 in CDLQI • Change from baseline to week 16 in POEM • Change from baseline to week 16 in weekly average of daily peak pruritus NRS • Percent change from baseline to week 4 in weekly average of daily peak pruritus NRS • Change from baseline to week 16 in HADS • Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 4 from baseline to week 4 • Incidence of skin infection TEAEs (excluding herpetic infections) through week 16 [a] • Incidence of serious TEAEs through week 16
NOTES	**Publications**	Simpson (2019)

AD = atopic dermatitis; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DB = double-blind; EASI = Eczema Area and Severity Index; EASI-50 = Eczema Area and Severity Index score improvement from baseline ≥ 50%; EASI-75= Eczema Area and Severity Index score improvement from baseline ≥ 75%; EASI-90 = Eczema Area and Severity Index score improvement from baseline ≥ 90%; EU = European Union; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; q.2.w. = every two weeks; q.4.w. = every four weeks; RCT = randomized controlled trial; SC = subcutaneous;
SCORAD = Scoring Atopic Dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; TEAE = treatment-emergent adverse event.

Note: Four additional reports were included: Clinical Study Report for Study 1526,[9] Health Canada Reviewer's Report,[10] FDA Clinical Review,[11] and sponsor's submission.[12]

Source: Clinical Study Report for Study 1526.

Table 7: Details of Included Studies (Adult Population)

		SOLO CONTINUE
Designs & Populations	**Study design**	DB RCT
	Locations	Patients enrolled in SOLO 1 and SOLO 2
	Study period	March 25, 2015, to October 18, 2016
	Randomized (N)	
	Inclusion criteria	Completed the treatment phase in 1 of the two 16-week initial-treatment studies (SOLO 1 or SOLO 2). Achieved at least 1 of the following 2 treatment success criteria: IGA = 0 or 1 (clear or almost clear) at week 16 **OR** EASI-75 from baseline to week 16
	Exclusion criteria	• Receipt of rescue medication for AD in the initial-treatment study (i.e., the parent studies SOLO 1 or SOLO 2) • Any conditions that required permanent discontinuation of study treatment in either initial-treatment study • Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during this study • Women unwilling to use adequate birth control, if of reproductive potential and sexually active
Drugs	**Intervention**	Patients who received 300 mg q.w. in the initial-treatment studies were randomized 2:1:1:1 to receive 1 of the following 4 treatment regimens: • Dupilumab 300 mg q.w. • Dupilumab 300 mg q.4.w. • Dupilumab 300 mg q.8.w. • Placebo Patients who received 300 mg q.2.w. in the initial-treatment studies were randomized 2:1:1:1 to receive 1 of the following 4 treatment regimens: • Dupilumab 300 mg q.2.w. • Dupilumab 300 mg q.4.w. • Dupilumab 300 mg q.8.w. • Placebo
	Comparator(s)	Placebo weekly
Duration	**Phase**	
	Screening	NA
	Double-blind	36 weeks
	Follow-up	12 weeks
Outcomes	**Primary end point**	• Difference between baseline (week 0) and week 36 in percent change in EASI from the baseline in the parent study (SOLO 1 or SOLO 2) for all randomized patients • Patients with EASI-75 at week 36 in randomized patients with EASI-75 at baseline (of the current study)
	Other end points	*Key secondary end points* • Patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with IGA 0 or 1 at baseline (of the current study) • Patients with IGA 0 or 1 at week 36 in the subset of patients with IGA 0 or 1 at baseline *Note: Baseline IGA score (0, 1, or > 1) was used as one of the stratification criteria for randomization. Therefore, this subset contained balanced randomized analysis groups with respect to IGA.*

		SOLO CONTINUE
		Patients whose pruritus NRS increased by 3 or more points from baseline to week 36 in the subset of patients with pruritus NRS ≤ 7 at baseline *Other secondary end points* • Time to first IGA increase of ≥ 2 points from baseline in the subset of patients with IGA 0 or 1 at baseline • Patients with IGA scores 3 or 4 at week 36 in the subset of patients with IGA 0 or 1 at baseline • Patients with EASI-50 (≥ 50% reduction in EASI score from baseline of the parent study) through week 36 • Absolute change in EASI from baseline through week 36 • Absolute change in SCORAD score from baseline through week 36 • Absolute change in peak pruritus NRS from baseline through week 36 • Absolute change in BSA affected by AD from baseline through week 36 • Absolute change in POEM from baseline through week 36 • Absolute change in DLQI from baseline through week 36 • Absolute change in HADS from baseline through week 36 • Difference between baseline and time points through week 36 in percent change in SCORAD from the baseline of parent study • Difference between current study baseline and time points through week 36 in percent change in pruritus NRS from the baseline of the parent study • Annualized event rate of flares during the on-treatment period • Proportion of well-controlled weeks during the on-treatment period (refers to control of AD) • Annualized event rate of skin infection treatment-emergent adverse events (excluding herpetic infections) during the on-treatment period
NOTES	**Publications**	Worm (2019)[13]

AD = atopic dermatitis; BSA = body surface area; DB = double-blind; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-50 = Eczema Area and Severity Index score improvement from baseline ≥ 50%; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; q.2.w. = every two weeks; q.4.w.= every four weeks; q.8.w. = every eight weeks; q.w. = every week; RCT = randomized controlled trial; SCORAD = Scoring Atopic Dermatitis.

Note: One additional source was included: Clinical Study Report for SOLO CONTINUE.[14]

Source: Clinical Study Report for SOLO CONTINUE.[14]

Table 8: Details of Included Studies (Adult Population, Original Review)

		SOLO 1	SOLO 2	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
Designs & Populations	**Study design**	DB RCT	DB RCT	DB RCT	DB RCT
	Locations	North America, South America, Europe, Asia	North America, South America, Europe, Asia	North America, Europe, Asia	Europe
	Randomized (N)	671	708	740	325
	Inclusion criteria	Male and female patients ≥ 18 years of age, with moderate-to-severe AD with an IGA score ≥ 3, EASI score ≥ 16, ≥ 10% BSA with AD, for whom topical treatment was inadvisable or provided inadequate treatment Patients had to have chronic AD for a minimum of 3 years	Male and female patients ≥ 18 years of age, with moderate-to-severe AD with an IGA score ≥ 3, EASI score ≥ 16, ≥ 10% BSA with AD, for whom topical treatment was inadvisable or provided inadequate treatment Patients had to have chronic AD for a minimum of 3 years	Male and female patients ≥ 18 years of age, with moderate-to-severe AD with an IGA score ≥ 3, EASI score ≥ 16, ≥ 10% BSA with AD, where topical treatment was provided inadequate treatment Patients had to have chronic AD for a minimum of 3 years	Male and female patients ≥ 18 years of age, with chronic AD with an IGA score ≥ 3, EASI score ≥ 20, ≥ 10% BSA with AD, for whom treatment with potent TCS was indicated, but had inadequate response to TCS History of: • Prior CSA exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or • CSA-naive and not eligible for CSA due to medical contraindications, use of prohibited concomitant medications, increased susceptibility to CSA-induced renal damage and/or liver damage, increased risk of serious infection, or hypersensitivity to CSA-active substances or excipients
	Exclusion criteria	Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, treatment with immunosuppressive and/or immunomodulating drugs or	Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, treatment with immunosuppressive and/or immunomodulating drugs or	Participation in prior dupilumab clinical study, important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions,	Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, hypersensitivity/ intolerance to a TCS, treatment

		SOLO 1	SOLO 2	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
		phototherapy within 4 weeks of baseline visit, treatment with a TCS or TCI within 1 week before baseline visit, treatment with biologics within 6 months of the baseline visit	phototherapy within 4 weeks of baseline visit, treatment with a TCS or TCI within 1 week before baseline visit, treatment with biologics within 6 months of the baseline visit	significant skin atrophy, systemic effects), as assessed by the investigator or the patient's treating physician, ≥ 30% of the total lesional surface located on areas of thin skin that could not be safely treated with a medium or higher-potency TCS; treatment with a TCS or a TCI within 1 week before the baseline visit	with systemic CSA, systemic corticosteroids, or phototherapy within 4 weeks of screening, treatment with a TCI within 1 week before screening visit
DRUGS	**Intervention**	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.2.w. for 16 weeks	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.2.w. for 16 weeks	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. plus TCS for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.2.w. plus TCS for 16 weeks	Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. plus TCS for 16 weeks Dupilumab 600 mg on day 1, followed by 300 mg SC q.w. plus TCS for 16 weeks
	Comparator(s)	Placebo	Placebo	Placebo plus TCS	Placebo plus TCS
DURATION	Run-in	35 days	35 days	35 days	28 days
	Double-blind	16 weeks	16 weeks	52 weeks	16 weeks
	Follow-up	Week 16, 28	Week 16, 28	Week 16, 52, 64	Week 16, 28
END POINTS	**Primary end points**	Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥ 2 points at week 16. Proportion of patients with ≥ 75% improvement on the EASI at week 16.	Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥ 2 points at week 16. Proportion of patients with ≥ 75% improvement on the EASI at week 16.	Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥ 2 points at week 16. Proportion of patients with ≥ 75% improvement on the EASI at week 16.	Proportion of patients with ≥ 75% improvement on the EASI at week 16.
	Other end points	The proportion of patients with improvement (reduction ≥ 3 and ≥ 4 points) of weekly average of peak daily pruritus NRS from baseline to week 16	The proportion of patients with improvement (reduction ≥ 3 and ≥ 4 points) of weekly average of peak daily pruritus NRS from baseline to week 16	The proportion of patients with improvement (reduction ≥ 3 and ≥ 4 points) of weekly average of peak daily pruritus NRS from baseline to week 16 and week 52	Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥ 2 points at week 16 The proportion of patients with improvement (reduction ≥ 3 and

		SOLO 1	SOLO 2	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
		The change from baseline to week 16 in the SCORAD; DLQI; POEM; HADS; EQ-5D Sick leave/missed school days assessment	The change from baseline to week 16 in the SCORAD; DLQI; POEM; HADS; EQ-5D Sick leave/missed school days assessment	Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥ 2 points at week 52 Proportion of patients with EASI-75 response at week 52 Percent change from baseline to week 16 in weekly average of peak daily pruritus NRS The change from baseline to week 16 and 52 in the SCORAD; DLQI; POEM; HADS.	≥ 4 points) of weekly average of peak daily pruritus NRS from baseline to week 16 The change from baseline to week 16 for SCORAD, DLQI, POEM, and HADS.
NOTES	**Publications**	Simpson (2016)	Simpson (2016)	Blauvelt (2017)	De Bruin-Weller (2017)

AD = atopic dermatitis; BSA = body surface area; CSA = cyclosporine-A; DB = double-blind; DLQI = Dermatology Life Quality Index; DB = double-blind; ESAI = Eczema Area and Severity Index; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; EQ-5D = EuroQol 5-Dimensions; IGA = Investigator's Global Assessment; HADS = Hospital Anxiety and Depression Scale; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; TCS = topical corticosteroid; q.2.w. = every two weeks; q.w. = every week; RCT = randomized control trial; SCORAD = Scoring Atopic Dermatitis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Note: Two additional reports were included (CADTH Clinical Drug Review submission and Health Canada reviewer's report).

Source: Clinical Study Reports for SOLO 1, SOLO 2, LIBERTY AD CHRONOS and LIBERTY AD CAFÉ.

Populations

Inclusion and Exclusion Criteria

Adolescents (12 to < 18 years old)

Study 1526 included males or females between 12 and 18 years of age, with an IGA score of at least 3 (moderate AD) and an EASI score of at least 16. They were to have demonstrated a recent history of inadequate response to topical treatments or for whom topicals were not advised (due to intolerance, side effects, or safety risks). Patients had to apply a stable dose of an emollient twice daily for the seven consecutive days immediately prior to baseline. Patients who had been treated with a TCS or TCI within two weeks of the baseline visit, or used immunosuppressives, immunomodulators, or phototherapy within four weeks of baseline were excluded, as were those receiving cell-depleting drugs within six months of baseline or other biologics within five half-lives or 16 weeks of baseline, whichever was longer.

Adults

SOLO CONTINUE enrolled patients who had completed the SOLO 1 and SOLO 2 studies, with an IGA score of 0 or 1 or had achieved an EASI-75. The study population for the SOLO studies, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ consisted of patients 18 years of age and older. The SOLO studies and LIBERTY AD CHRONOS required patients to have moderate-to-severe AD with a number of severity indicators (e.g., an EASI score ≥ 16 or an IGA score ≥ 3). The main unique inclusion criteria for the SOLO trials required patients for whom topical treatment was inadvisable or provided inadequate treatment; this is contrary to the criteria in the LIBERTY AD CHRONOS trial that only required patients for whom topical treatment provided inadequate treatment and excluded patients who experienced important side effects to topical medications (e.g., intolerance or hypersensitivity). These inclusion and exclusion criteria in LIBERTY AD CHRONOS were also reflected in criteria for LIBERTY AD CAFÉ, with the additional inclusion criteria of either a history of prior cyclosporine-A (CSA) exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or a history of being CSA-naive and not eligible for CSA due to medical contraindications or other reasons. The LIBERTY AD CAFÉ trial also required patients to have an EASI score greater than or equal to 20, contrary to a score of 16 or more required for the other three studies. The SOLO trials and LIBERTY AD CHRONOS excluded patients who received treatment with a TCS or TCI within one week prior to the baseline visit. Patients in LIBERTY AD CAFÉ were excluded if they received treatment with a TCI within one week prior to the screening visit. Across all trials patients were required to have applied topical emollient (without additives) twice daily for at least seven consecutive days prior to the baseline visit.

Baseline Characteristics

Adolescents (12 to < 18 years old)

Of the patients enrolled in Study 1526, over half were male, about 60% were Caucasian, and they were 14.5 years old on average. Patients had AD for approximately 12 years on average, and 47% had an IGA score of 3 (moderate AD) and 53% had an IGA score of 4 (severe AD). Approximately 40% had received prior corticosteroids or immunosuppressants for their AD.

Some differences in the baseline characteristics were evident between groups. For example, there were 10% fewer males in the dupilumab group compared to placebo (52% versus 62%, respectively), and approximately 9% more whites in the dupilumab group (66% versus 57%) and 9% fewer Africans/African-Americans (9% versus 18%) compared to

placebo. About 7% fewer patients in the dupilumab group had pruritus scores of 7 or more when compared to placebo (72% versus 65%).

Adults

In SOLO CONTINUE, patients were approximately 38 years old, 53% were male, and 71% were white. The majority of patients (77%) had an IGA score of 0 or 1 at baseline, as these were all patients who were responders in the SOLO 1 and 2 trials. There were 12% fewer males (49% versus 61%) in the dupilumab group than in the placebo group.

Across studies included in the original review, the mean (standard deviation) age of patients ranged from 36.6 (13.01) to 39.8 (14.68) years, the most common ethnicity was not Hispanic or Latino, with 92.5% to 97.2% identifying as such. The majority of patients, ranging from 65.2% to 97.2%, identified as white, and male patients represented 52.7% to 63.0% of the study population. The SOLO trials and the LIBERTY AD CHRONOS trial recruited patients globally, with 34.0% to 49.2% of patients originating from North and South America. The LIBERTY AD CAFÉ recruited patients from Europe, with approximately 62% originating from Western Europe and more than 96% identifying as white. Across trials the baseline disease characteristics were balanced between groups for each study. The majority of patients, ranging from 52.2% to 68.2%, were diagnosed with AD before the age of five. Despite varying inclusion criteria, baseline severity of disease was similar between studies for various measures including the EASI, IGA, weekly average of peak daily pruritus numerical rating scale (NRS), and Scoring Atopic Dermatitis (SCORAD).

Table 9: Summary of Baseline Characteristics (Adolescent Population)

Study 1526		
Characteristic	**Dupilumab q.2.w. N = 82**	**Placebo N = 85**
Mean (SD) age, years	14.5 (1.7)	14.5 (1.8)
Male, n (%)	43 (52)	53 (62)
Race, n (%)		
White	54 (66)	48 (57)
African-American/African	7 (9)	15 (18)
Asian	12 (15)	13 (15)
Other	7 (9)	6 (7)
Not reported/missing	2 (2)	3 (4)
Weight group, n (%)		
< 60 kg	43 (52)	43 (51)
≥ 60 kg	39 (48)	42 (49)
BMI in kg/m^2, mean (SD)	24.9 (7.87)	23.9 (6.03)
Mean duration of atopic dermatitis, years (SD)	12.5 (2.97)	12.3 (3.44)
EASI score mean (SD)	35.3 (13.84)	35.5 (13.97)
IGA score mean (SD)	3.5 (0.50)	3.5 (0.50)
Number n (%) of patients with IGA score		
IGA = 3	39 (48)	39 (46)
IGA = 4	43 (52)	46 (54)
Peak weekly averaged pruritus NRS mean (SD)	7.5 (1.52)	7.7 (1.62)
Patients with peak weekly averaged pruritus NRS, n (%)		
< 7	29 (35)	24 (28)
≥ 7	53 (65)	61 (72)

Study 1526		
Characteristic	**Dupilumab q.2.w. N = 82**	**Placebo N = 85**
Patients receiving prior systemic corticosteroids and/or systemic nonsteroidal immunosuppressants, n (%)	35 (43)	33 (39)
Patients receiving prior systemic corticosteroids	21 (26)	21 (25)
Patients receiving prior systemic nonsteroidal Immunosuppressants, n (%)	20 (24)	17 (20)
Azathioprine	0	1 (1)
Cyclosporine	14 (17)	12 (14)
Methotrexate	10 (12)	6 (7)
Mycophenolate	2 (2)	0

BMI = body mass index; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numerical rating scale; q.2.w. = every two weeks; SD = standard deviation.

Source: Clinical Study Report for Study 1526.[9]

Table 10: Summary of Baseline Characteristics (Adult Population)

SOLO CONTINUE		
Characteristic	**Dupilumab q.2.w./q.w. N = 167**	**Placebo N = 83**
Mean (SD) age, years	38.5 (13.94)	38.1 (13.64)
Male, N (%)	82 (49)	51 (61)
Race, n (%)		
White	124 (73)	54 (65)
Black/African-American	7 (4)	7 (8)
Asian	31 (18)	17 (21)
Other	5 (3)	2 (2)
Not reported/missing	2 (1)	3 (4)
BMI in kg/m^2, mean (SD)	26.4 (5.52)	26.8 (4.79)
EASI score mean (SD)	2.6 (2.9)	2.5 (2.3)
Number n (%) of patients with IGA score		
IGA = 0	18 (11)	8 (10)
IGA = 1	111 (66)	55 (66)
IGA = 2	37 (22)	19 (23)
IGA = 3	3 (2)	1 (1)
IGA = 4	0	0
Peak weekly averaged pruritus NRS mean (SD)	2.8 (1.92)	2.8 (2.11)
Patients with peak weekly averaged pruritus NRS, n (%)		
≤ 7	168 (99)	80 96)
> 7	1 (1)	3 (4)

BMI = body mass index; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numerical rating scale; q.2.w. = every two weeks; q.w. = weekly; SD = standard deviation.

Source: Clinical Study Report for SOLO CONTINUE.[14]

Table 11: Summary of Baseline Characteristics (Adult Population, Original Studies)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Age, years mean (SD)	39.8 (14.7)	39.5 (13.9)	36.9 (14.0)	37.4 (14.1)	39.6 (14.0)	36.6 (13.0)	37.5 (12.9)	38.9 (13.4)
Ethnicity, n (%)								
Not Hispanic or Latino	215 (96.0)	212 (94.6)	218 (93.6)	219 (92.8)	103 (97.2)	299 (94.9)	99 (92.5)	101 (93.5)
Hispanic or Latino	6 (2.7)	11 (4.9)	7 (3.0)	8 (3.4)	2 (1.9)	10 (3.2)	1 (0.9)	3 (2.8)
Not reported/missing	3 (1.3)	1 (0.4)	8 (3.4)	9 (3.8)	1 (0.9)	6 (1.9)	7 (6.5)	4 (3.7)
Race, n (%)								
White	155 (69.2)	146 (65.2)	165 (70.8)	156 (66.1)	74 (69.8)	208 (66.0)	104 (97.2)	104 (96.3)
Asian	54 (24.1)	56 (25.0)	44 (18.9)	50 (21.2)	29 (27.4)	83 (26.3)	2 (1.9)	2 (1.9)
Black or African-American	10 (4.5)	16 (7.1)	13 (5.6)	20 (8.5)	2 (1.9)	19 (6.0)	0	0
Other	5 (2.2)	6 (2.7)	5 (2.1)	3 (1.3)	1 (0.9)	5 (1.6)	0	2 (1.9)
Not reported/missing			6 (2.6)	7 (3.0)			1 (0.9)	0
Male, n (%)	130 (58.0)	118 (52.7)	137 (58.8)	132 (55.9)	62 (58.5)	193 (61.3)	65 (60.7)	68 (63.0)
Region, n (%)								
North and South America	95 (42.4)	95 (42.4)	114 (48.9)	116 (49.2)	36 (34.0)	108 (34.3)	NA	NA
Asia Pacific	42 (18.8)	40 (17.9)	28 (12.0)	28 (11.9)	27 (25.5)	81 (25.7)	NA	NA
Eastern Europe	22 (9.8)	23 (10.3)	37 (15.9)	38 (16.1)	29 (27.4)	83 (26.3)	41 (38.0)	41 (38.0)
Western Europe	65 (29.0)	66 (29.5)	54 (23.2)	54 (22.9)	14 (13.2)	43 (13.7)	66 (61.7)	67 (62.0)
Inadequate response to topical corticosteroid treatment, n (%)								
No	5 (2.2)	4 (1.8)	4 (1.7)	6 (2.5)	NA	NA	NA	NA
Significant skin atrophy	0	2 (0.9)	2 (0.9)	4 (1.7)	NA	NA	NA	NA
Hypersensitivity reactions	1 (0.4)	2 (0.9)	2 (0.9)	2 (0.8)	NA	NA	NA	NA
Systemic effects	2 (0.9)	1 (0.4)	1 (0.4)	0	NA	NA	NA	NA
Other	2 (0.9)	0	1 (0.4)	1 (0.4)	NA	NA	NA	NA
Chronic AD diagnosis age, n (%)								
Before 5 years	117 (52.2)	118 (52.7)	122 (52.4)	131 (55.5)	61 (57.5)	180 (57.1)	73 (68.2)	67 (62.0)
Between 5 and 9 years	30 (13.4)	37 (16.5)	31 (13.3)	30 (12.7)	9 (8.5)	45 (14.3)	5 (4.7)	9 (8.3)
Between 10 and 19 years	32 (14.3)	23 (10.3)	31 (13.3)	37 (15.7)	19 (17.9)	37 (11.7)	12 (11.2)	11 (10.2)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Between 20 and 29 years	14 (6.3)	16 (7.1)	24 (10.3)	12 (5.1)	7 (6.6)	20 (6.3)	6 (5.6)	7 (6.5)
Between 30 and 39 years	12 (5.4)	10 (4.5)	9 (3.9)	11 (4.7)	2 (1.9)	12 (3.8)	6 (5.6)	6 (5.6)
40 years and above	19 (8.5)	18 (8.0)	13 (5.6)	12 (5.1)	8 (7.5)	21 (6.7)	5 (4.7)	8 (7.4)
Unsure	0	1 (0.4)	3 (1.3)	3 (1.3)	0	0		
Missing	0	1 (0.4)						
Duration of AD, years mean (SD)	28.5 (16.1)	29.5 (14.5)	27.2 (14.2)	28.2 (14.4)	30.1 (15.5)	27.5 (14.3)	29.6 (15.6)	29.2 (14.7)
EASI score, mean (SD)	33.0 (13.6)	34.5 (14.5)	31.8 (13.1)	33.6 (14.3)	33.6 (13.3)	32.6 (12.9)	33.5 (10.5)	34.4 (10.1)
IGA score, mean (SD)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)	3.5 (0.5)
Patients IGA = 3, n (%)	234 (50.9) pooled SOLO 1/2	234 (51.2) pooled SOLO 1/2	234 (50.9) pooled SOLO 1/2	234 (51.2) pooled SOLO 1/2				
Patients IGA = 4, n (%)	225 (48.9) Pooled SOLO 1/2	223 (48.8) SOLO 1/2	225 (48.9) Pooled SOLO 1/2	223 (48.8) SOLO 1/2				
Weekly average of peak daily pruritus NRS[a], mean (SD)	7.2 (1.9)	7.4 (1.8)	7.6 (1.60)	7.5 (1.8)	7.4 (1.7)	7.3 (1.8)	6.4 (2.2)	6.4 (2.2)
SCORAD score, mean (SD)	66.9 (14.0)	68.3 (14.0)	67.2 (13.5)	69.2 (14.9)	69.3 (15.2)	66.0 (13.5)	68.4 (10.5)	68.8 (11.1)
DLQI score, mean (SD)	13.9 (7.4)	14.8 (7.2)	15.4 (7.1)	15.4 (7.7)	14.5 (7.3)	14.7 (7.4)	13.3 (7.8)	13.0 (6.8)
PGADS, n (%)								
Poor (scale = 1)	87 (38.8)	109 (48.7)	95 (40.8)	111 (47.0)	49 (46.2)	139 (44.1)	15 (23.1)	21 (30.9)
Fair (scale = 2)	86 (38.4)	75 (33.5)	85 (36.5)	67 (28.4)	35 (33.0)	117 (37.1)	25 (38.5)	28 (41.2)
Good (scale = 3)	39 (17.4)	33 (14.7)	45 (19.3)	46 (19.5)	21 (19.8)	46 (14.6)	21 (32.3)	14 (20.6)
Very good (scale = 4)	11 (4.9)	6 (2.7)	8 (3.4)	9 (3.8)	1 (0.9)	12 (3.8)	3 (4.6)	5 (7.4)
Excellent (scale = 5)	1 (0.4)	0	0	3 (1.3)	0	1 (0.3)	1 (1.5)	0
Missing	0	1 (0.4)						
POEM, mean (SD)	19.8 (6.4)	20.3 (5.9)	20.8 (5.5)	21.0 (5.9)	20.3 (5.7)	20.0 (6.0)	18.7 (6.5)	19.5 (5.6)
EQ-5D visual analogue scale, mean (SD)	56.8 (23.3)	54.7 (24.8)	55.4 (23.0)	57.0 (24.4)	57.9 (22.6)	56.5 (23.7)	57.4 (21.7)	53.0 (22.3)
EQ-5D utility, mean (SD)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.7(0.3)	0.6 (0.3)	0.8 (0.2)	0.7 (0.2)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Total HADS, mean (SD)	12.2 (7.3)	12.6 (8.3)	13.7 (7.5)	13.7 (8.3)	12.9 (7.7)	12.6 (8.1)	11.7 (8.5)	12.4 (7.2)
HADS-A, mean (SD)	7.0 (4.1)	7.0 (4.5)	7.5 (4.1)	7.8 (4.5)	7.4 (4.2)	7.0 (4.4)	6.4 (4.5)	6.8 (4.2)
HADS-D, mean (SD)	5.2 (3.9)	5.6 (4.7)	6.2 (4.2)	5.9 (4.5)	5.5 (4.3)	5.5 (4.3)	5.3 (4.8)	5.6 (3.9)

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D = EuroQol 5-Dimensions; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale–Anxiety; HADS-D = Hospital Anxiety and Depression Scale–Depression; IGA = Investigator's Global Assessment; NRS = numerical rating scale; PGADS = Patient Global Assessment of Disease Status; POEM = Patient-Oriented Eczema Measure; q.2.w. = every two weeks; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; TCS = topical corticosteroid.

[a] Weekly average obtained in the seven-day period before the baseline visit.

Source: Clinical Study Report for SOLO 1,[4] SOLO 2,[5] LIBERTY AD CHRONOS,[6] and LIBERTY AD CAFÉ.[7]

Interventions

Adolescents (12 to < 18 years)

Dosing of dupilumab was weight-based; those with a body weight < 60 kg received the 200 mg dose of dupilumab, whether they were in the every two weeks or every four weeks group, and those with body weight ≥ 60 kg received the 300 mg strength. Patients in the every four weeks group received a placebo injection to keep them on the same administration schedule as the every two weeks group. Those receiving the 200 mg dose received an initial loading dose of 400 mg while those receiving 300 mg started with 600 mg as a loading dose. All injections were administered subcutaneously and dose modifications were not allowed. Patients in the placebo group received injections of placebo on the same administration schedule as the intervention groups, including loading doses.

With respect to background treatment, patients were to apply non-prescription moisturizers twice daily for at least seven consecutive days prior to randomization and then throughout the study. Rescue treatment to control intolerable symptoms was to be provided at the discretion of the investigator. Investigators were encouraged to try topical treatments (medium- to high-potency corticosteroids) first, for at least seven days, before moving to systemic therapies. A TCI was permitted as a rescue but only for specific problem areas (e.g., face or neck). Any patients who received systemic therapies (corticosteroids or immunosuppressants) as rescue treatments were permanently discontinued from the study drug. The use of a rescue was less common with dupilumab (20.7%) than with placebo patients (58.8%) and only a small number used systemic corticosteroids (2.4% dupilumab and 5.9% placebo) or immunosuppressants (none with dupilumab, 3.5% with placebo). See Appendix 3 for further details regarding rescue treatments used.

Adults

In SOLO CONTINUE, patients were assigned to one of dupilumab every week/every two weeks, every four weeks, every eight weeks, or placebo groups, and treatment was carried out in a manner similar to that of the parent SOLO trials with respect to the use of placebo injections to match the administration schedule of the once weekly/every two weeks group. In the SOLO 1 and SOLO 2 trials, patients received treatment with subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day 1. Patients received treatment with dupilumab weekly or once every two weeks. For patients in the every two weeks treatment group, subcutaneous injections with placebo on the alternate weeks were

administered to maintain blinding. The trials were placebo-controlled, with patients in the placebo group receiving weekly subcutaneous injections with placebo following placebo given on day 1 to match the loading dose. The SOLO 1 and SOLO 2 studies were 16 weeks in duration. Throughout the SOLO trials, patients were required to apply moisturizers (emollients) at least twice daily. Patients were not permitted to use any prescription moisturizers or moisturizers containing additives. Treatments with the following concomitant medications were prohibited throughout the study: live (attenuated) vaccine, immunomodulating biologics, other investigational drugs, systemic corticosteroids, or nonsteroidal systemic immunosuppressive drugs. A TCS or TCI could be administered during the study if required for rescue therapy. Other concomitant medications and procedures for AD that were permitted included basic skin care (cleansing and bathing, including bleach baths), topical anesthetics, antihistamines, and anti-infective medications. Medications used to treat chronic disease such as diabetes, hypertension, and asthma were also permitted. Patients treated with rescue medication, systemic corticosteroids, systemic non-steroid immunosuppressants, or phototherapy were to temporarily stop the study drug. However, treatment could resume when approved by the investigator no sooner than five half-lives after the last dose of the systemic rescue medication.

The LIBERTY AD CHRONOS trial involved interventions similar to those of the SOLO trials with one major difference. In addition to treatment with dupilumab weekly, every two weeks, or placebo, patients were required to initiate treatment with a medium-potency TCS applied once daily to areas with active lesions initiating on day 1. If the lesion was present on an area of thin skin (e.g., face, neck, intertriginous, genital areas, or areas of skin atrophy) patients were required to use a low-potency TCS instead. Once lesions became clear or almost clear, treatment was switched from a medium- to low-potency TCS and applied once daily for seven days. This process could be repeated if lesions returned. The LIBERTY AD CHRONOS trial was 52 weeks in duration. As in the SOLO trials, patients in LIBERTY AD CHRONOS were required to apply moisturizers (emollients) at least twice daily throughout the study. Patients were not permitted to use any prescription moisturizers or moisturizers containing additives. Treatment with the following concomitant medications and procedures were prohibited throughout the study: live (attenuated) vaccine, immunomodulating biologics, other investigational drugs, wet wraps, other medications for AD that could have interfered with efficacy end points, major elective surgical procedures, tanning in a booth/bed, and live vaccines for approximately three months after stopping treatment with dupilumab. Concomitant medications and procedures for AD that were permitted included basic skin care (cleansing and bathing, including bleach baths), topical anesthetics, and antihistamines. TCI could be used for problem areas (e.g., face, intertriginous, and genital areas) but not concomitantly with TCS for the same area. Medications used to treat chronic disease such as diabetes, hypertension, and asthma were also permitted. As with other studies, patients treated with rescue medication, systemic corticosteroids, systemic non-steroid immunosuppressants, or phototherapy were to temporarily stop the study drug. However, treatment could be resumed when approved by the investigator no sooner than five half-lives after the last dose of the systemic rescue medication.

The LIBERTY AD CAFÉ trial had the same interventions as the LIBERTY AD CHRONOS trial with the following exception: patients initiated treatment with a TCS on active lesions starting on day −14. The LIBERTY AD CAFÉ trial was 16 weeks in duration. Background treatment with moisturizers, and both prohibited and permitted concomitant medications, were consistent with the other trials, with the addition of prohibition of phototherapy. Patients treated with rescue medications, systemic corticosteroids, or systemic non-steroid immunosuppressants were to temporarily stop the study drug. However, treatment could be resumed when approved by the investigator no sooner than five half-lives after the last dose of the systemic rescue medication.

Outcomes

The co-primary outcomes in Study 1526 were patients with an IGA score of 0 or 1 at week 16 and patients who had achieved EASI-75 at week 16. The IGA is a five-point scale that provides a global clinical assessment of AD severity ranging from 0 to 4, in which "0" indicates clear, and "4" indicates severe AD.[15] A decrease in score reflects improvement in signs and symptoms. No information was found on what would constitute a MID in patients with AD.

The primary outcome of SOLO CONTINUE was percent change in EASI from baseline to week 36. The EASI is a scale used in clinical trials to assess the severity and extent of AD.[16-19] In the EASI, the severity of four disease characteristics of AD (erythema, infiltration/papulation, excoriations, and lichenification) are assessed by the investigator on a scale of "0" (absent) to "3" (severe). The scores are added up for each of the four body regions (head, arms, trunk, and legs). The assigned percentages of body surface area (BSA) for each section of the body are 10% for head, 20% for arms, 30% for trunk, and 40% for legs. Each subtotal score is multiplied by the BSA represented by that region. In addition, the affected area of AD assessed as a percentage by each body region is converted to a score of 0 to 6, where the area is expressed as 0 (none), 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Each of the body area scores are multiplied by the area affected. The total EASI score therefore ranges from 0 to 72 points, with the highest score indicating worse severity of AD.[17] It has been suggested that the severity of AD based on the EASI can be categorized as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; 50.1 to 72.0 = very severe.[20] EASI-75 indicates ≥ 75% improvement from baseline.[15] The validity and reliability of the EASI was examined in several studies.[16-19,21] The overall MID was 6.6, based on results from one study.[16]

Patient Global Assessment of Disease Status (PGADS), a secondary outcome across many of the included studies, is measured on a five-point Likert scale. A higher score indicates a better overall condition. In the pivotal clinical studies,[15,22,23] patients rated their overall well-being based on scale from poor to excellent. Patients were asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices were: "Poor," "Fair," "Good," "Very Good," and "Excellent."[4] No information was found for the MID of PGADS in AD.

The SCORAD is a tool used in clinical research that was developed to standardize the evaluation of the extent and severity of AD.[15,24] SCORAD was a secondary outcome of many of the studies included in this review. It assesses three components of AD: the affected BSA, severity of clinical signs, and symptoms. The severity of six specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using a four-point scale (i.e., none = 0, mild = 1, moderate = 2 and or severe = 3) with a maximum of 18 total points. The symptoms (itch and sleeplessness) are recorded by the patient or a relative on a visual analogue scale in which 0 is no symptom and 10 is the worst imaginable symptom, with a maximum possible score of 20. The SCORAD is calculated based on the previously discussed three components of AD. The maximum possible total score is 103, with a higher score indicating a poorer or more-severe condition.[15] A difference of 8.7 points in the SCORAD was estimated as the MID for the patients with atopic eczema (also known as AD).[16]

The pruritus NRS is a tool that patients used to report the intensity of itch during a daily recall period using an IVRS. It was a secondary outcome of the included studies. Patients were asked to rate the overall (average) and maximum intensity of itch experienced during the past 24 hours based on a scale of 0 to 10 (0 = "no itch" and 10 = "worst itch

imaginable").[15] The proportion of patients with improvement (reduction ≥ 3 or ≥ 4 points) in the weekly average of peak daily pruritus NRS from baseline to week 16 was reported in the pivotal studies.[15] Additional information provided by the sponsor reported the validity and reliability of the NRS based on three phase III and one phase IIb RCTs.[25,26] In the aforementioned RCTs, the NRS item was completed daily from baseline through week 16 and weekly from week 17 to week 52.[25,26] The most appropriate definition of a responder on the pruritus NRS was in the range of 3 to 4 points.

The DLQI is a dermatology-specific quality-of-life instrument. It is a 10-item questionnaire that assesses six different aspects that can affect quality of life: symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[27,28,29] The maximum score per aspect is either 3 (with a single question) or 6 (with two questions) and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much) and the overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30).[27,28] The higher the score, the more quality of life is impaired. The meaning of the DLQI scores on a patient's life is as follows:[30]

- 0 to 1 = no effect
- 2 to 5 = small effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect.

Estimates of the MID have ranged from 2.2 to 6.9.[27,30]

The Children's Dermatology Life Quality Index (CDLQI) is a 10-item, validated questionnaire widely used in clinical practice and clinical trials to measure the impact of skin disease on the quality of life in children.[31,32] It was a secondary outcome of Study 1526. The CDLQI can be completed by the child alone and/or with help from the parents or guardian.[31] It covers six areas of daily activities, including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The questions are answered using a four-point Likert scale (scored from 0 to 3 for each question) based on recall of the past week's experiences. Total scores range from 0 to 30. A higher CDLQI score indicates greater degree of quality-of-life impairment.[31] No minimal clinically important difference was identified in the literature.

The Hospital Anxiety and Depression Scale (HADS) is a patient-reported survey tool designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions. Repeated administration also provides information about changes in a patient's emotional state.[33-35] The HADS questionnaire contains 14 items that assess symptoms experienced in the previous week, among which seven items are related to anxiety and seven items are related to depression. Patients provide responses to each item on a four-point Likert scale, from 0 (the best) to 3 (the worst); a patient can therefore score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. Scores of 11 or more on either subscale were considered to be a "definite case" of psychological morbidity, while scores of 8 to 10 represented a "probable case" and 0 to 7 "not a case."[33] No information on MID was found in the literature.

The Patient-Oriented Eczema Measure (POEM) is a seven-item questionnaire used in clinical trials to assess disease symptoms in children and adults.[36] Based on frequency of occurrence during the past week, the seven items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) are assessed on a five-point scale. The possible scores for each question were: 0 for no days, 1 for one to two days, 2 for three to four days, 3 for five

to six days, and 4 for every day. The maximum total score was 28; a high score was indicative of poor quality of life (0 to 2 indicates clear or almost clear conditions, 3 to 7 mild eczema, 8 to 16 moderate eczema, 17 to 24 severe eczema, and 25 to 28 very severe eczema).[36] One study[16] reported that the overall mean MID of the POEM was 3.4 points (standard deviation [SD] = 4.8), when IGA scores improved, with one point used as anchor. In 2018, the minimally important change in the POEM children (N = 300) with moderate-to-severe atopic eczema was calculated in one study.[37] The authors recommended the following thresholds be used to interpret changes in POEM scores in children: a score of 3 to 3.9 indicates a probably clinically important change and a score of 4 or greater indicates a very likely clinically important change.[37]

Statistical Analysis

Adolescents (12 to < 18 years old)

Power calculations were performed based on both the co-primary and the key secondary outcome of patients with an improvement in pruritus NRS of ≥ 4 from baseline to week 16. With respect to patients who achieved an IGA score of 0 to 1, with a sample of 80, for the dupilumab every two weeks group, there was a 98% power to detect a difference of 28% between it and placebo, and for the dupilumab every four weeks group, there was an 88% power to detect a 20% difference between it and placebo. For the outcome of patients with an EASI-75 response at week 16, there was a 99% power to detect a 35% difference between dupilumab every two weeks and placebo and a 32% difference between dupilumab every four weeks and placebo. For the key secondary outcome, there was a 97% power at a 0.05 level to detect a 27% difference between dupilumab every two weeks and placebo and a 95% power to detect a 25% difference between every four weeks and placebo. The assumptions were based on studies in adults (Studies 1334, 1416, and 1021).

The co-primary outcomes, patients with an IGA score of 0 or 1 at week 16 and EASI-75 at week 16, were analyzed using the Cochran-Mantel-Haenszel method and adjusted for the randomization strata. Patients who discontinued study treatment but remained in the study were included in the analysis. For dichotomous outcomes, if a patient withdrew from the study they were counted as a nonresponder for all subsequent time points after withdrawal. A similar method was used to account for patients who received rescue therapy; from the point of receiving rescue the patient was designated as a nonresponder. Those with missing values at week 16 were also counted as nonresponders at week 16. Sensitivity analyses were performed using the post-baseline last observation carried forward (LOCF) approach after censoring for rescue or study withdrawal, and all observed data, regardless of rescue or whether data were collected after withdrawal from study treatment.

Continuous variables were analyzed using analysis of covariance (ANCOVA) with multiple imputation for missing values. Results comparing the treatment groups were reported as LSMD for these analyses. Patients who received rescue had data imputed using the multiple imputation method. Data were imputed 40 times to generate 40 complete datasets using the SAS software procedure for multiple imputation. ANCOVA was used to analyze each of the 40 complete datasets with treatment, randomization strata, and relevant baseline included in the model. The SAS MIANALYZE procedure was used to generate valid statistical inferences by combining results from the 40 analyses using Rubin's formula. The imputation model covariates in the ANCOVA model included treatment group, baseline value, and randomization strata, and measured input values at every clinic visit (i.e., weeks 1, 2, 3, 4, 8, 12, and 16). The categorical variables included in the model (treatment group and randomization strata) were not expected to be missing.

A hierarchical approach was employed to account for multiple statistical comparisons, where each subsequent hypothesis was only formally tested if the previous hypothesis in

the hierarchy proved statistically significant. Comparisons for the co-primary outcomes, key secondary outcomes and the first two other secondary outcomes (patients with EASI-50 and EASI-90) were all tested in sequence, first in the dupilumab every two weeks group, before proceeding to testing this list in the dupilumab every four weeks group. Testing then proceeded for the next 12 other secondary outcomes in the dupilumab every two weeks group before moving on to those 12 outcomes in the dupilumab every four weeks group. In total, 40 outcomes were tested in the hierarchy.

Adults

In SOLO CONTINUE, the assumptions behind the power calculations for the co-primary outcomes were based on data from previously completed studies of dupilumab. With 170 patients in the dupilumab 300 mg every week or every two weeks group and 84 patients in the placebo group, it was estimated that the study would provide a 99% power at a two-sided 5% level of significance to detect the expected differences between dupilumab and placebo for the co-primary outcomes.

Multiplicity was accounted for using a hierarchical testing procedure. The co-primary outcome, percent change in EASI at week 36 relative to baseline, was tested, followed by patients who had achieved EASI-75 at week 36 among randomized patients with EASI-75 at baseline, patients whose IGA response at week 36 was maintained within 1 point of baseline in the subset of patients with an IGA score of 0 or 1 at baseline, patients with an IGA score of 0 or 1 at week 36 in the subset of patients with an IGA score of 0 or 1 at baseline, and patients whose pruritus NRS increased by 3 or more points from baseline to week 36 in the subset of patients with a pruritus NRS score of ≤ 7 at baseline. Once statistical significance was not met, testing was halted. Testing within this sequence of outcomes began with the highest dosage (dupilumab every week and every two weeks.), followed by dupilumab every four weeks, and then the every eight weeks dosage.

The percent change in EASI at week 36 was analyzed using multiple imputation with the ANCOVA model. Efficacy data that were missing through week 36, either because of early discontinuation or use of rescue medication, were treated as missing and imputed by the multiple imputation method described in Study 1526.

The four included trials from the previous review (SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ) used similar methods for statistical analysis for the assessment of the primary efficacy end points. The SOLO trials and LIBERTY AD CHRONOS evaluated different end points depending on the requesting health authority. For the US and the US reference-market countries, the primary end point was the proportion of patients with an IGA score of 0 or 1 (on a five-point scale) and a reduction from baseline of 2 or more points at week 16. For the EU, the EU reference-market countries, and Japan, the co-primary end points were the proportion of patients who had achieved EASI-75 at week 16, and the proportion of patients with an IGA score of 0 or 1 (on a five-point scale) and a reduction from baseline of 2 or more points at week 16. LIBERTY AD CAFÉ assessed the proportion of patients with EASI-75 as the only primary efficacy end point.

A number of secondary end points were included in the trials. Secondary end points relevant to this review included the following:

- The proportion of patients with improvement (reduction ≥ 4 and ≥ 3 points) in weekly average of peak daily pruritus NRS from baseline to week 16
- The proportion of patients with EASI-50 at week 16
- The percent change from baseline to week 16 in the SCORAD
- The change from baseline to week 16 in the DLQI
- The change from baseline to week 16 in the POEM
- The change from baseline to week 16 in the HADS
- The percent change from baseline to week 16 in the EuroQol 5-Dimensions (EQ-5D) questionnaire.

The studies assessed multiple end points; to protect against increased type I error a serial gatekeeping procedure was used for the primary and secondary end points. For the US and US reference-market countries for each test within each dose regimen, if the primary end point was significant at the 0.025 level, the secondary end points were tested following a hierarchical testing procedure with a pre-specified order unique to each trial.

The EU, EU reference-market countries, and Japan also used a serial gatekeeping procedure to control the overall type I error rate at 0.05 for the two co-primary end points and the secondary end points. For each dosage regimen, an intersection-union method was applied to the co-primary end points, which required statistical significance of both co-primary end points at the two-sided 0.025 level. If both co-primary end points were significant, the secondary end points were tested following the same hierarchical testing procedure used for the US.

In the SOLO trials and LIBERTY AD CHRONOS, primary efficacy analysis was conducted using the Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity). In the LIBERTY AD CAFÉ trial, the Cochran-Mantel-Haenszel test adjusted by randomization strata (disease severity and prior CSA use) was used. Patients were classified as nonresponders for the time points following study withdrawal or use of rescue treatment. Patients with a missing value at week 16 were counted as nonresponders at week 16. Sensitivity analyses were included that utilized alternative methods to account for missing data (LOCF), and to assess all patient data regardless of use of rescue medication with and without imputation (via multiple imputation methodology).

For continuous end points the studies all used multiple imputation using the Markov-chain Monte Carlo algorithm and ANCOVA to account for missing data. The covariates included in the ANCOVA model included treatment group, baseline value, and randomization strata. Hierarchical testing was applied to secondary end points at a two-sided significance level of 0.025 for the comparison between each dupilumab dosage regimen and placebo. Sensitivity analyses for secondary end points included analysis based on all observed data regardless of whether rescue treatment was used or if data were collected after withdrawal using the multiple imputation method, mixed-effect model repeated measures, including factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. Sensitivity analyses using alternate methods to handle missing data were also conducted; these included the worst observation carried forward (WOCF) method, the LOCF method, and no imputation.

For the primary efficacy end point(s) and some secondary end points, subgroup analysis was presented. With relevance to this CDR, subgroups for baseline disease severity (moderate [IGA = 3] and severe [IGA = 4]) were included a priori and subgroups for

geographic region (North and South America, Asia Pacific, Eastern Europe, and Western Europe) were included a posteriori.

In the SOLO trials, sample sizes were estimated to provide 90% power. To ensure adequate power, the sample size was increased to 200 patients per group to yield 99% in both of the comparisons (dupilumab every week or every two weeks) while adjusting the significance level to account for multiplicity. In LIBERTY AD CHRONOS, the use of 300, 100, and 300 patients in the dupilumab 300 mg every week, dupilumab 300 mg every two weeks, and placebo groups, respectively, was estimated to provide 99% power in both comparisons with placebo. In LIBERTY AD CAFÉ, 110 patients per arm were required to provide 99% power for both the primary efficacy end point and the secondary end point for the proportion of patients with improvement (reduction ≥ 4 points) of weekly average of peak daily pruritus NRS from baseline to week 16. The power calculations were based on assumptions of efficacy in the placebo and treatment groups from phase II studies on dupilumab (R668-AD-1117, R668-AD-1021). The power calculation for LIBERTY AD CAFÉ differed as it required additional assumptions for the proportion of patients with prior CSA use based on assumptions from prior RCTs.

Analysis Populations

Adolescents (12 to < 18 years)

In Study 1526, the full analysis set included all randomized patients, while the per-protocol set included all members of the full analysis set except those excluded due to protocol violations. The safety analysis set included all patients who received at least one dose of the study drug, and these patients were analyzed based on the actual treatment they received rather than the group to which they were assigned.

Adults

The full analysis set/intention-to-treat (ITT) population included all patients that were randomized using the IVRS/IWRS. The primary efficacy analysis was conducted using this set of patients.

The per-protocol set included all of the patients in the ITT set except patients who had been excluded due to major efficacy-related protocol violations. Such violations included patients who were randomized more than once, patients who received less than 80% or greater than 120% of the scheduled doses during the study treatment period, and any major violations of the efficacy-related entry criteria.

The safety analysis set included all randomized patients who received any study drug, and was analyzed as treated.

The pharmacokinetic analysis set included all patients from the safety analysis set who had at least one non-missing post-baseline measurement of functional dupilumab available for statistical analysis. Treatment assignments were based on the treatment received.

The anti-drug antibody analysis set included all patients from the safety analysis set who also had at least one non-missing screening measurement of anti-dupilumab antibody following the first study treatment. Treatment assignments were based on the treatment received.

LIBERTY AD CHRONOS included the following additional analysis populations:

- The concentration-response population included all patients from the pharmacokinetic population with at least one non-missing functional dupilumab concentration following the first dose of the study drug and at least one non-missing IGA, EASI, or pruritus NRS value.

- The neutralizing anti-drug antibody population included all treated patients who received any study drug, and either tested negative for anti-drug antibodies or tested positive for anti-drug antibodies with at least one non-missing neutralizing anti-drug antibody result after the first dose of the study drug.

Results

Patient Disposition

Adolescents (12 to < 18 years)

Overall, 92% of patients completed study treatment, with the highest number of those not completing in the placebo group (11%). The most common reason for non-completion was lack of efficacy in that group (7%).

Adults

In SOLO CONTINUE, 8.3% of patients in the dupilumab group did not complete study treatment versus 16.9% of those in the placebo group. The most common reason for discontinuation was an AE and study drug supply issues (4.8% for each) with placebo, and the most common reasons for discontinuation with dupilumab were protocol violation, withdrawn consent, and study drug supply issues (1.8% for each).

The proportion of patients who discontinued from each study from the original review was highest for the placebo groups and ranged from 4.6% to 19.5%. Patients in LIBERTY AD CAFÉ had the lowest proportion of patients who discontinued the study, with a range from 0% to 4.6% across treatment groups. AEs, including those related to the disease itself (i.e., AD flares and withdrawal by patient), were cited as the main reason for discontinuation.

Table 12: Patient Disposition (Adolescent Population)

Aged 12 to 18: Study 1526		
	Dupilumab every 2 weeks N = 82	**Placebo N = 85**
Screened	295	
Randomized, n	82	85
Randomized and treated, n (%)	82 (100)	85 (100)
Completed study treatment, n (%)	76 (93)	76 (89)
Did not complete study treatment, n (%)	6 (7)	9 (11)
• adverse events	2 (2)	1 (1)
• lack of efficacy	0	6 (7)
• protocol violation	0	0
• lost to follow-up	1 (1)	0
• use of prohibited medication	1 (2)	0
• withdrawal by patient	2 (2)	2 (2)
Analysis sets, n (%)		
Full analysis set	82 (100)	85 (100)
Safety set	82 (100)	85 (100)
Per protocol	79 (96)	84 (99)
Patients with at least one rescue medication, n (%)	17 (21)	50 (59)
• corticosteroids, dermatological preparations	14 (17)	47 (55)
• agents for dermatitis, excluding corticosteroids	3 (4)	7 (8)
• corticosteroids for systemic use	2 (2)	5 (6)
• immunosuppressants	0	3 (4)
Calcineurin inhibitors	0	2 (2)
Selective immunosuppressants	0	1 (1)

Table 13: Patient Disposition (Adult Population)

SOLO CONTINUE		
Characteristic	**Dupilumab q.2.w./q.w. N = 169**	**Placebo N = 83**
Randomized, n	169	83
Randomized and treated, n (%)	169 (100)	82 (98.8)
Completed study treatment, n (%)	155 (91.7)	69 (83.1)
Did not complete study treatment, n (%)	14 (8.3)	14 (16.9)
• adverse event	0	4 (4.8)
• lack of efficacy	1 (0.6)	1 (1.2)
• protocol violation	3 (1.8)	1 (1.2)
• consent withdrawn with no reason	2 (1.2)	1 (1.2)
• consent withdrawn for personal or administrative reason	3 (1.8)	0
• study drug supply issue	3 (1.8)	4 (4.8)
• lost to follow-up	0	0
• pregnancy	0	0
• sponsor decision	1 (0.6)	2 (2.4)
• other	1 (0.6)	1 (1.2)
Analysis populations, n (%)		
• full analysis set	169 (100)	83 (100)
• safety set	167 (98.8)	82 (98.8)
• per-protocol set	161 (95.3)	81 (97.6)

q.2.w. = every two weeks; q.w. = every week.

Source: Clinical Study Report for SOLO CONTINUE.[14]

Table 14: Patient Disposition for SOLO 1 and SOLO 2 (Adult Population, Original Review)

	SOLO 1			SOLO 2		
	DUP 300 mg q.2.w.	**DUP 300 mg q.w.**	**Placebo**	**DUP 300 mg q.2.w.**	**DUP 300 mg q.w.**	**Placebo**
Screened, N	917			962		
Not randomized, N	246			254		
Randomized, N	224	223	224	233	239	236
Discontinued, N (%)	16 (7.1)	26 (11.7)	40 (17.9)	13 (5.6)	18 (7.5)	46 (19.5)
Adverse event	6 (2.7)	6 (2.7)	10 (4.5)	2 (0.9)	4 (1.7)	14 (5.9)
Lack of efficacy	4 (1.8)	3 (1.3)	11 (4.9)	0	4 (1.7)	17 (7.2)
Protocol violation	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.3)	5 (2.1)	3 (1.3)
Other[a]	5 (2.2)	16 (7.2)	18 (8.0)	8 (3.4)	5 (2.1)	12 (5.1)
Full analysis set, N (%)	224 (100)	223 (100)	224 (100)	233 (100)	239 (100)	236 (100)
Per-protocol, N (%)	216 (96.4)	215 (96.4)	215 (96.0)	224 (96.1)	231 (96.7)	225 (95.3)
Safety, N (%)	229 (102.2)	218 (97.8)	222 (99.1)	236 (101.3)	237 (99.2)	234 (99.2)

DUP = dupilumab; q.2.w. = every two weeks; q.w. = every week.

Note: Percentages are based on the number of randomized patients.

[a] Other reasons were withdrawal of consent, death, lost to follow-up, missed last injection, rescue medication, and other.

Source: Simpson (2016),[10] Clinical Study Reports for SOLO 1[4] and SOLO 2.[5]

Table 15: Patient Disposition for LIBERTY AD CHRONOS and LIBERTY AD CAFÉ (Adult Population, Original Review)

	LIBERTY AD CHRONOS			LIBERTY AD CAFÉ		
	DUP + TCS 300 mg q.2.w.	DUP + TCS 300 mg q.w.	Placebo + TCS	DUP + TCS 300 mg q.2.w.	DUP + TCS 300 mg q.w.	Placebo + TCS
Screened, N	957			390		
Not randomized, N	217			65		
Randomized, N	106	319	315	107	110	108
Discontinued, N (%)	9 (8.5)	33 (10.3)	52 (16.5)	0	2 (1.8)	5 (4.6)
Adverse event	1 (0.9)	8 (2.5)	10 (3.2)	0	2 (1.8)	2 (1.9)
Death	0	1 (0.3)	0	0	0	0
Lack of efficacy	1 (0.9)	0	6 (1.9)	0	0	3 (2.8)
Lost to follow-up	0	4 (1.3)	6 (1.9)	0	0	0
Physician decision	2 (1.9)	4 (1.3)	3 (1.0)	0	0	0
Protocol violation	1 (0.9)	4 (1.3)	2 (0.6)	0	0	0
Withdrawal by patient	4 (3.8)	11 (3.4)	22 (7.0)	0	0	0
Other	0	1 (0.3)	3 (1.0)	0	0	0
Full analysis set, N (%)	106 (100)	319 (100)	315 (100)	107 (100)	110 (100)	108 (100)
Per-protocol, N (%)	100 (94.3)	309 (96.9)	301 (95.6)	107 (100)	110 (100)	108 (100)
Safety, N (%)	110 (103.8)[a]	315 (98.7)	315 (100.0)	107 (100)	110 (100)	108 (100)

DUP = dupilumab; q.2.w. = every two weeks; q.w. = every week; TCS = topical corticosteroid.

Note: Percentages are based on the number of randomized patients.

[a] Four patients randomized to dupilumab 300 mg q.w. + TCS received ≥ 3 less injections than planned through week 16. These 4 patients were counted in the dupilumab 300 mg every two weeks + TCS group for the safety analysis set.

Source: Blauvelt (2017),[9] De Bruin-Weller (2017),[11] Clinical Study Reports for LIBERTY AD CHRONOS[6] and LIBERTY AD CAFÉ.[7]

Exposure to Study Treatments

Adolescents (12 to < 18 years)

The mean (SD) number of doses administered was 8.7 (1.1) in the dupilumab group, and 8.5 (1.5) in the placebo group. Compliance with injections was > 99% in all groups in study 1526.

Adults

In SOLO CONTINUE, the mean injection compliance was 97.1% with dupilumab and 96.1% with placebo, and the mean (SD) number of doses administered was 33.7 (6.1) with dupilumab and 32.3 (7.4) with placebo. In the trials included in the original review, the mean injection compliance ([number of injections during the exposure period]/[number of planned injections during the exposure period] x 100%) was similar across treatment groups and trials in a range of 96.7% to 100%. Compliance with background treatment (application of moisturizers at least twice daily) was consistent across treatment groups in the 16-week studies (SOLO 1, SOLO 2, and LIBERTY AD CAFÉ) in a range of 70.1% to 88.9%. LIBERTY AD CHRONOS reported a background treatment compliance of 39.2% for the placebo group and 36.3% for the dupilumab group. The difference in background treatment compliance is likely attributable to the length of the trial and the daily frequency of the treatment.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

Disease Severity

Investigator's Global Assessment

Adolescents (12 to < 18 years)

The primary outcome in US and US reference-market countries was patients with an IGA of 0 or 1 and a reduction from baseline of 2 or more points at week 16. In the dupilumab group 24.4% of patients achieved an IGA score of 0 or 1 versus 2.4% in placebo. The differences between dupilumab and placebo (22.0%; 95% confidence interval [CI], 12.2 to 31.9; P < 0.0001) was statistically significant (Table 16). Sensitivity analyses were performed using all observed values, with missing values counted as nonresponders (24.4% versus 4.7%, difference versus placebo of 19.7%; 95% CI, 9.36 to 30.01; P = 0.0003), and using LOCF (24.4% versus 2.4%), and those results were consistent with that of the primary analysis (Table 27).

Subgroup analyses of the primary outcome results were provided for baseline severity (based on IGA scores). In patients with moderate disease (baseline IGA = 3), 30.8% of dupilumab and 2.6% of placebo patients achieved an IGA score of 0 or 1, and in patients with severe disease (baseline IGA = 4), 18.6% of dupilumab and 2.2% placebo achieved a response (Table 27).

Adults

In SOLO CONTINUE, 70.6% of patients in the dupilumab group maintained an IGA within 1 point of baseline at week 36, compared to 28.6% of placebo patients (difference versus placebo of 42.1; 95% CI, 28.36 to 55.76; P < 0.0001). With respect to the patients whose IGA score increased (worsened) to 3 or 4 at week 36, this occurred in 26.2% of dupilumab patients and 66.7% of placebo (−40.5; 95% CI, −54.42 to −26.53; P < 0.0001).

The proportion of patients with an IGA score of 0 or 1 and a reduction from baseline of 2 or more points at week 16 was a co-primary end point for SOLO 1, SOLO 2, and LIBERTY AD CHRONOS and a secondary end point for LIBERTY AD CAFÉ. This proportion was consistently greater in the dupilumab group (36.1% to 40.2%) compared to the placebo group (8.5% to 13.9%), with a range in difference of proportion of 26.3% (95% CI, 14.95 to 37.65) to 27.7% (95% CI, 20.18 to 35.17). The difference in the proportion of patients with an IGA score of 0 or 1 and reduction from baseline of 2 or more points was statistically significant (P < 0.0001) across all trials at week 16. Greater improvement from baseline to week 16 in the placebo group was seen in the LIBERTY trials compared to the SOLO trials.

Eczema Area and Severity Index

Adolescents (12 to < 18 years)

EASI-75 responses occurred in 41.5% of dupilumab and 8.2% of placebo patients, and the differences between dupilumab and placebo groups (33.2%; 95% CI, 21.1 to 45.4; P < 0.0001) was statistically significant (Table 16). Results from a sensitivity analysis performed using all observed values, with patients with missing values counted as nonresponders, were consistent with that of the primary analysis (dupilumab: 45.1% and placebo: 15.3%), with a difference versus placebo of 29.8 (95% CI, 16.62 to 43.04) (Table 27). Subgroup data for EASI-75 responses based on disease severity (IGA of 3 versus 4) were reported. In patients with moderate disease (IGA = 3), 43.6% of dupilumab and 10.3%

of placebo patients achieved an EASI-75, and for patients with severe disease (IGA = 4), 39.5% of dupilumab and 6.5% of placebo patients achieved an EASI-75 at week 16.

Mean percent EASI scores were reduced (improved) from baseline to week 16 to a greater extent with dupilumab compared to placebo (LSMD versus placebo of −42.3%; 95% CI, −55.6 to −29.0; P < 0.0001) and this difference was statistically significant (Table 16). Sensitivity analyses performed on the full analysis set regardless of treatment rescue (LSMD versus placebo of −34.9%; 95% CI, −44.76 to −25.11; P < 0.0001) and sensitivity analyses based on LOCF and WOCF were all consistent with the primary analysis (Table 27).

The percentage of patients with an EASI score reduction of ≥ 50% at week 16 was 61.0% with dupilumab and 12.9% with placebo. Compared to placebo, this was statistically significant (a difference of 48.0%; 95% CI, 35.3 to 60.8; P < 0.0001). The percent of patients with EASI score reduction of ≥ 90% at week 16 was 23.2% with dupilumab and 2.4% with placebo. When compared to placebo, these differences were considered statistically significant (a difference of 20.8%; 95% CI, 11.1 to 30.5; P < 0.0001) (Table 16).

Adults

In SOLO CONTINUE, 71.6% of patients in the dupilumab group had an EASI-75 at baseline and then at week 36, compared to 30.4% of placebo-treated patients (difference versus placebo of 41.2; 95% CI, 28.93 to 53.52; P < 0.0001). There was a mean (SD) percent change in EASI from current study baseline to week 36 of 0.06 (1.736) with dupilumab and 21.67 (3.134) with placebo, and this difference was statistically significant (LSMD versus placebo of −21.61; 95% CI, −28.36 to −14.87; P < 0.0001). A sensitivity analysis that included all observed values yielded results that were consistent with the primary analysis (LSMD versus placebo of −24.02; 95% CI, −29.41 to −18.63; P < 0.0001).

The proportion of patients who achieved EASI-75 at week 16 was the co-primary end point in the SOLO trials and LIBERTY AD CHRONOS, and the primary end point in LIBERTY AD CAFÉ (Table 18). This proportion was consistently greater in the dupilumab group (44.2% to 68.9%) compared to the placebo group (11.9% to 29.6%), with a range in difference of proportion from 32.3% (95% CI, 24.75 to 39.94) to 45.7% (95% CI, 35.72 to 55.66). The difference in the proportion of patients who achieved EASI-75 was statistically significant (P < 0.0001) across all trials at week 16. Greater improvement from baseline to week 16 was evident in both the placebo and dupilumab groups in the LIBERTY trials compared to the SOLO trials. As a secondary end point, the proportion of patients who achieved 50% improvement from baseline in the EASI also yielded statistically significant results (P < 0.0001) across all trials, with a trend similar to that of EASI-75 efficacy results.

Consistently across all trials, the severity of AD showed a statistically significant (P < 0.0001) decrease in the dupilumab group compared to the placebo group regardless of which measure was used. The LIBERTY AD CHRONOS trial included an additional end point at week 52; all efficacy results remained consistent and statistically significant (P < 0.0001). Patients were classified as nonresponders for the time points following study withdrawal or use of rescue treatment. Patients with a missing value at week 16 were counted as nonresponders at week 16. Sensitivity analyses were included that utilized alternative methods to account for missing data (i.e., LOCF, no multiple imputation), and to assess all patient data regardless of use of rescue medication with and without imputation (via multiple imputation methodology) and statistical significance remained consistent across all sensitivity analyses. In the subgroup analysis for moderate AD and severe AD, greater efficacy was seen for the IGA and EASI end points in the dupilumab groups compared to placebo.

Scoring Atopic Dermatitis

Adolescents (12 to < 18 years)

An improvement (reduction) in mean SCORAD scores from baseline to week 16 was seen for dupilumab compared to placebo (LSMD between dupilumab and placebo of −34.0; 95% CI, −43.4 to −24.6; P < 0.0001) and this difference was statistically significant (Table 16). In sensitivity analyses performed regardless of whether rescue was used (LSMD of −27.7%; 95% CI, −35.37 to −20.09; P < 0.0001), LOCF and WOCF were consistent with the primary analysis.

Adults

In SOLO CONTINUE, the least squares mean (standard error [SE]) percent change from current study baseline to week 36 in the SCORAD was 0.33 (2.092) with dupilumab and 28.97 (3.683) with placebo, and this difference was statistically significant (−28.64; 95% CI, −36.56 to −20.72; P < 0.0001) (Table 17).

The percent change in the SCORAD from baseline to week 16 was a secondary end point across the four adult trials. The least squares mean percent change from baseline was greater in the dupilumab group (51.1% to 63.9% reduction) compared to the placebo group (19.7% to 36.2% reduction). Across trials the least squares mean percent difference of SCORAD scores between dupilumab and placebo groups ranged from −27.7% (95% CI, −33.46 to −21.90) to −32.9% (95% CI, −39.70 to −26.06) and was statistically significant (P < 0.0001) across all trials at week 16 (Table 18).

Symptoms

Pruritus

Adolescents (12 to < 18 years)

Mean percent change in daily peak pruritus NRS was reduced (improved) from baseline to week 16 in the dupilumab group compared to placebo (LSMD of −29.0%; 95% CI, −39.5 to −18.4; P < 0.0001) and this difference was statistically significant (Table 16).

The percentage of patients at week 16 achieving a reduction of at least 3 points from baseline in weekly average of daily peak pruritus NRS was 48.8% with dupilumab and 9.4% with placebo. The difference in percentages versus placebo was statistically significant (difference between dupilumab and placebo of 39.4%; 95% CI, 26.9 to 51.8; P < 0.0001). Sensitivity analyses using all observed values regardless of rescue were consistent with that of the primary analysis (58.5% dupilumab versus 22.4% placebo, difference versus placebo of 36.2%; 95% CI, 22.32 to 50.05; P < 0.0001). The percentage of patients with a reduction of at least 4 points from baseline was 36.6% with dupilumab and 4.8% with placebo. The differences in percentages versus placebo were statistically significant (difference of 31.8%: 95% CI, 20.5 to 43.2; P < 0.0001) (Table 16). There was an improvement (reduction) in weekly average of daily peak pruritus scores from baseline to week 16 for dupilumab versus placebo in the dupilumab group (LSMD between dupilumab and placebo of −2.2; 95% CI, −2.9 to −1.4; P < 0.0001), and this difference was statistically significant. The percent change in weekly average of daily peak pruritus scores from baseline to week 16 was a least squares mean (SE) of −47.9% (3.4) with dupilumab and 19.0% (4.1) with placebo, for a LSMD between groups of −29.0% (95% CI, −39.5 to 18.4; P < 0.0001). In a sensitivity analysis using all observed data regardless of rescue, results were consistent with that of the primary analysis (LSMD between groups of −27.3; 95% CI, 36.3 to −18.2; P < 0.0001). The percent change from baseline to week 4 in weekly average of daily peak pruritus NRS scores was also assessed, and again there were improvements

from baseline for dupilumab versus placebo (LSMD between dupilumab and placebo of −22.2%; 95% CI, −30.6 to −13.9; P < 0.0001) and this difference was statistically significant. Sensitivity analyses using all observed values, LOCF, and/or WOCF were also consistent with that of the primary analysis.

Adults

In SOLO CONTINUE, with dupilumab, 33.9% of patients' peak weekly pruritus NRS scores increased (worsened) by 3 or more points from baseline to week 35, compared to 70.0% with placebo, and this difference was statistically significant (difference versus placebo of −36.1%; 95% CI, −48.40 to −23.74; P < 0.0001). The least squares mean (SE) change from current study baseline to week 35 in pruritus NRS was −0.1 (3.05) with dupilumab and 35.6 (4.32) with placebo (LSMD versus placebo of −35.8; 95% CI, −45.4 to −26.1;P < 0.0001) (Table 17).

The proportion of patients experiencing an improvement (reduction) in weekly average of peak daily pruritus NRS scores of 4 or more points from baseline to week 16 was one of the secondary end points in all of the studies in the original review. Compared to placebo, the proportion of patients in the dupilumab group was statistically greater (P < 0.0001) across all trials, with a range in difference between groups of 26.5% (95% CI, 19% to 33.87%) to 39.1% (95% CI, 28.53% to 49.65%). Similar findings were seen for the proportion of patients with improvement (reduction) of weekly average of peak daily pruritus NRS scores of 3 or more points from baseline to week 16 (Table 18). The LIBERTY AD CHRONOS trial included an additional end point at week 52 for the pruritus NRS end points, which resulted in consistent and statistically significant (P < 0.0001) findings.

Patient-Oriented Eczema Measure

Adolescents (12 to < 18 years)

The mean change in POEM scores from baseline to week 16 was a secondary end point in study 1526. An improvement (reduction) in POEM scores was seen from baseline to week 16 with dupilumab (least squares mean [SE]: −10.1 [0.76]) versus placebo (−3.8 [0.96]) for an LSMD between dupilumab and placebo of −6.3 (95% CI, −8.6 to –4.0; P < 0.0001) and these differences were statistically significant (Table 16). In sensitivity analyses performed regardless of whether rescue was used (LSMD of −5.3; 95% CI, −7.39 to −3.17; P < 0.0001), LOCF and WOCF were consistent with the primary analysis.

Adults

The percent change in POEM from baseline to week 16 was an additional secondary end point across all four trials in the original review. The least squares mean change from baseline was greater in the dupilumab group (a reduction of 10.2 to 12.7 points) compared to the placebo group (a reduction of 3.3 to 5.3 points). Across trials the LSMD of POEM scores between dupilumab and placebo groups ranged from −6.5 (95% CI, −8.02 to −5.01) to −7.6 (95% CI, −9.29 to −5.97), a difference that was statistically significant (P < 0.0001) and clinically significant (MID = 3.4[8]) across all trials (Table 18).

Health-Related Quality of Life

Adolescents (12 to < 18 years)

A larger improvement (reduction) in least squares mean (SE) CDLQI scores from baseline to week 16 was seen with dupilumab (−8.5 [0.50]) compared to placebo (−5.1 [0.62]) for an LSMD between dupilumab and placebo of −3.4 (95% CI, −5.0 to −1.8; P < 0.0001) and this difference was statistically significant (Table 16). The minimum clinically important difference on this scale could not be found. In sensitivity analyses performed regardless of

whether rescue was used (LSMD of −2.8; 95% CI, −4.2 to −1.4), LOCF and WOCF were consistent with the primary analysis.

Adults

The change in DLQI from baseline to week 16 was a secondary end point across SOLO 1 and 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ. The least squares mean change from baseline was greater in the dupilumab group (a reduction of 9.3 to 10.0 points) compared to the placebo group (a reduction of 5.8 to 7.2 points). Across trials the LSMD of DLQI scores between dupilumab and placebo groups ranged from −4.0 (95% CI, −5.16 to −2.80) to −5.7 (95% CI, −6.86 to −4.47) and were statistically significant (P < 0.0001) but not clinically significant (MID of 2.2 to 6.9. points) across all trials (Table 18). The LIBERTY AD CHRONOS trial included an additional DLQI end point at week 52, which resulted in consistent and statistically significant (P < 0.0001) findings.

The change in EQ-5D index utility scores from baseline to week 16 was a secondary end point across all four trials. The least squares mean change from baseline was numerically greater in the dupilumab group (0.22 to 0.24) compared to the placebo group (0.06 to 0.16) in the SOLO trials and LIBERTY AD CHRONOS. Across the three trials the LSMD of EQ-5D index utility scores between dupilumab and placebo groups ranged from 0.060 (95% CI, 0.02 to 0.10) to 0.17 (95% CI, 0.12 to 0.21). While no AD-specific MID existed, the EQ-5D results in the trials were clinically relevant using the general MID, which ranged from 0.033 to 0.074. The LSMD was statistically significant (P < 0.0001) in SOLO 1 and SOLO 2. The change in EQ-5D visual analogue scale score from baseline to week 16 was statistically significant (P < 0.0001) in SOLO 1, SOLO 2, and LIBERTY AD CHRONOS.

Mood

Adolescents (12 to < 18 years)

The mean improvement (reduction) in HADS total scores from baseline to week 16 was not statistically larger in the dupilumab group compared to placebo (LSMD between groups of −1.3; 95% CI, −3.30 to 0.76) P = 0.2203) (Table 16). The change from baseline to week 16 in HADS anxiety and depressions scores was not statistically significant between dupilumab and placebo groups.

Adults

The HADS and its subscales for anxiety and depression were used to assess mood at week 16. For the total HADS score, statistical significance (P < 0.0001) was found for the LSMD between dupilumab and placebo in SOLO 2 and LIBERTY AD CAFÉ. SOLO 1 had a P value of 0.0006, and LIBERTY AD CHRONOS had P values of 0.1596 and p = 0.0337 at weeks 16 and 52, respectively.

Productivity

Adolescents (12 to < 18 years)

Patients in each of the dupilumab groups missed an average of one day of school through 16 weeks versus two days in the placebo group. There were 24% of patients in the dupilumab group and 30% of patients in the placebo group who had missed a day of school through 16 weeks (Table 16).

Adults

Productivity was assessed though the measurement of days missed from school or sick leave from work. Patients in the placebo group missed 1.8 to 6.2 days of school or work, while patients in the dupilumab group missed 0.1 to 1.2 days, although these data were only available for a subset of the patients.

Table 16: Key Efficacy Outcomes (Adolescent Population)

Aged 12 to < 18: Study 1526		
	Dupilumab q.2.w. N = 82	Placebo N = 85
Disease severity		
Patients with IGA score of 0 or 1 at week 16, n (%)	20 (24)	2 (2)
Difference vs. placebo, % (95% CI)[a]	22.0 (12.20 to 31.87; P < 0.0001)	
Patients with EASI-75 at week 16, n (%)	34 (42)	7 (8)
Difference vs. placebo, % (95% CI)[a]	33.2 (21.07 to 45.39; P < 0.0001)	
Mean (SD) baseline EASI	35.26 (13.836)	35.53 (13.971)
LSM (SE) % change in EASI score; baseline to week 16 (sample observed/imputed)	−65.9 (3.99) (66/16)	−23.6 (5.49) (33/52)
LSMD (95% CI)[b]	−42.3 (−55.60 to −29.04; P < 0.0001)	
Patients with EASI-50 at week 16, n (%)	50 (61.0)	11 (12.9)
Difference vs. placebo, % (95% CI)[a]	48.0 (35.29 to 60.78; P < 0.0001)	
Patients with EASI-90 at week 16, n (%)	19 (23.2)	2 (2.4)
Difference vs. placebo, % (95% CI)[a]	20.8 (11.13 to 30.50; P < 0.0001)	
Symptom: pruritus		
Mean (SD) baseline	7.52 (1.52)	7.73 (1.62)
LSM (SE) % change from baseline to week 16 in weekly average of daily peak pruritus NRS (sample observed/imputed)	−47.9 (3.43) (66/16)	−19.0 (4.09) (31/54)
LSMD (95% CI)[b]	−29.0 (−39.54 to −18.38; P < 0.0001)	
Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 3 from baseline to week 16, n/N (%)	40/82 (48.8)	8/85 (9.4)
Difference vs. placebo, % (95% CI)[a]	39.4 (26.90 to 51.84; P < 0.0001)	
Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 4 from baseline to week 16, n (%)	30/82 (36.6)	4/84 (4.8)
Difference vs. placebo, % (95% CI)[a]	31.8 (20.45 to 43.20; P < 0.0001)	
Mean (SD) baseline weekly average of daily peak pruritus NRS	7.52 (1.519)	7.73 (1.624)
LSM (SE) change from baseline to week 16 in weekly average of daily peak pruritus NRS (sample observed/imputed)	−3.70 (0.250) (66/16)	−1.54 (0.303) (31/54)
LSMD (95% CI)[b]	−2.16 (−2.935 to −1.389; P < 0.0001)	
LSM (SE) % change from baseline to week 4 in weekly average of daily peak pruritus NRS	−34.7 (2.99)	−12.5 (3.06)
LSMD (95% CI)[b]	−22.2 (−30.55 to −13.85; P < 0.0001)	
Patients with improvement (reduction) of weekly average of daily peak pruritus NRS ≥ 4 from baseline to week 4, n/N (%)	18/82 (22.0)	4/84 (4.8)
Difference vs. placebo, % (95% CI)[a]	17.2 (7.14 to 27.24; P = 0.0009)	

Aged 12 to < 18: Study 1526		
	Dupilumab q.2.w. N = 82	Placebo N = 85
Body surface area		
Mean (SD) baseline BSA	55.99 (21.40)	56.41 (24.13)
LSM (SE) change from baseline to week 16 in percent BSA affected by AD (sample observed/imputed)	−30.11 (2.337) (67/15)	−11.66 (2.720) (33/52)
LSMD (95% CI)[b]	−18.44 (−25.117 to −11.770; P < 0.0001)	
SCORAD		
Mean (SD) baseline SCORAD	70.60 (13.89)	70.44 (13.25)
LSM (SE) percent change from baseline to week 16 in SCORAD (sample observed/imputed)	−51.6 (3.23) (67/15)	−17.6 (3.76) (33/52)
LSMD (95% CI)[b]	−34.0 (−43.41 to −24.58; P < 0.0001)	
Patients with SCORAD-50 at week 16, n (%)	36 (43.9)	6 (7.1)
Difference vs. placebo, % (95% CI)	36.8 (24.80 to 48.89)	
Patients with SCORAD-75 at week 16, n(%)	13 (15.9)	2 (2.4)
Difference vs. placebo, % (95% CI)	13.5 (4.96 to 22.04)	
Patients with SCORAD-90 at week 16, n (%)	2 (2.4)	1 (1.2)
Difference vs. placebo, % (95% CI)	1.3 (−2.79 to 5.31)	
Health-related quality of life: CDLQI		
Mean (SD) baseline CDLQI	13.0 (6.2)	13.1 (6.7)
LSM (SE) change from baseline to week 16 in CDLQI (sample observed/imputed)	−8.5 (0.50) (66/16)	−5.1 (0.62) (33/52)
LSMD (95% CI)[b]	−3.4 (−5.01 to −1.80; P < 0.0001)	
POEM		
Mean (SD) baseline POEM	21.0 (5.0)	21.1 (5.4)
LSM (SE) change from baseline to week 16 in POEM (sample observed/imputed)	−10.1 (0.76) (67/15)	−3.8 (0.96) (33/52)
LSMD (95% CI)[b]	−6.3 (−8.63 to −4.01; P < 0.0001)	
Mood: HADS		
Mean (SD) baseline HADS total score	12.6 (8.0)	11.6 (7.8)
LSM (SE) change from baseline to week 16 in HADS total score (sample observed/imputed)	−3.8 (0.68) (67/15)	−2.5 (0.80) (33/52)
LSMD (95% CI)[b]	−1.3 (−3.30 to 0.76; P = 0.2203)	
Mean (SD) baseline HADS anxiety	8.1 (4.6)	7.4 (4.4)
LSM (SE) change from baseline to week 16 in HADS anxiety (sample observed/imputed)	−2.3 (0.42) (67/15)	−1.6 (0.50) (33/52)
LSMD (95% CI)[b]	−0.7 (−1.92 to 0.59; P = 0.2980)	
Mean (SD) baseline HADS depression	4.4 (4.2)	4.3 (3.9)
LSM (SE) change from baseline to week 16 in HADS depression (sample observed/imputed)	−1.4 (0.33) (67/15)	−0.8 (0.39) (33/52)
LSMD (95% CI)[b]	−0.7 (−1.67 to 0.29) P = 0.1691	

Aged 12 to < 18: Study 1526		
	Dupilumab q.2.w. N = 82	Placebo N = 85
Patient global assessment of disease: PGADS		
Patients with PGADS no or mild symptoms (scale = 1 or 2) at week 16, n (%)	42 (51.2)	11 (12.9)
Difference vs. placebo, % (95% CI)	38.3 (25.32 to 51.24)	
No symptoms (scale = 1), n (%)	8 (9.8)	2 (2.4)
Difference vs. placebo, % (95% CI)	7.4 (0.22 to 14.59)	
Mild symptoms (scale = 2), n (%)	34 (41.5)	9 (10.6)
Difference vs. placebo, % (95% CI)	30.9 (18.37 to 43.38)	
Moderate symptoms (scale = 3), n (%)	19 (23.2)	9 (10.6)
Difference vs. placebo, % (95% CI)	12.6 (1.35 to 23.82)	
Severe symptoms (scale = 4), n (%)	6 (7.3)	10 (11.8)
Difference vs. placebo, % (95% CI)	−4.4 (−13.32 to 4.42)	
Very severe symptoms (scale = 5), n (%)	0 (0.0)	3 (3.5)
Difference vs. placebo, % (95% CI)	−3.5 (−7.45 to 0.39)	
Productivity: missed school		
Cumulative missed school days through week 16 for patients attending school full-time, mean (SD)	1.01 (3.323) N = 79	2.00 (8.598) N = 84
Patients with any day missed, n (%)	19 (24.1)	25 (29.8)

BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; CI = confidence interval; EASI = Eczema Area and Severity Index; EASI-50 = Eczema Area and Severity Index score improvement from baseline ≥ 50%; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; EASI-90 = Eczema Area and Severity Index score improvement from baseline ≥ 90%; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; LSM = least squares mean; LSMD = least squares mean difference; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; q.2.w. = every two weeks; SCORAD = Scoring Atopic Dermatitis; SCORAD-75 = Scoring Atopic Dermatitis score ≥ 75; SCORAD-90 = Scoring Atopic Dermatitis score ≥ 90; SD = standard deviation; SE = standard error; vs. = versus.

[a] P values were derived by Cochran-Mantel-Haenszel tests stratified by baseline disease severity (IGA = 3 vs. IGA = 4] and baseline weight group (< 60 kg vs. ≥ 60 kg).

[b] Confidence intervals with a P value are based on treatment difference (dupilumab group vs. placebo) of the LSM percent change using an analysis of covariance model with baseline measurement as the covariate and the treatment, randomization strata (baseline disease severity [IGA = 3 vs. IGA = 4]) and baseline weight group (< 60 kg vs. ≥ 60 kg) as fixed factors.

Source: Clinical Study Report for Study 1526.[9]

Table 17: Key Efficacy Outcomes (Adult Population)

	SOLO CONTINUE	
	Dupilumab q.2.w./q.w. N = 167	Placebo N = 85
EASI		
Mean (SD) % change in EASI from parent study baseline to current study baseline	−91.27 (9.344)	−91.17 (8.207)
Difference between current study baseline and week 36 in LSM % change in EASI from parent study baseline (SE), %	0.06 (1.736)	21.67 (3.134)
LSMD vs. placebo (95% CI)[a]	−21.61 (−28.36 to −14.87; P < 0.0001)	
Patients with EASI-75 at week 36 for patients with EASI-75 at baseline – patients considered nonresponders after rescue, n (%)	116 (71.6)	24 (30.4)
Difference vs. placebo, % (95% CI)[b]	41.2 (28.93 to 53.52; P < 0.0001)	
Patients with EASI-50 at week 36 – patients considered nonresponders after rescue, n (%)	124 (73.4)	33 (39.8)
Difference vs. placebo, % (95% CI)[b]	33.6 (21.15 to 46.07; P < 0.0001)	
Mean (SD) baseline EASI	2.61 (2.922)	2.49 (2.306)
LSM (SE) change from baseline in EASI at week 36 – multiple imputation method with data set to missing after rescue treatment	0.09 (0.511)	6.61 (0.799)
LSMD (95% CI)[a]	−6.52 (−8.22 to −4.82; P < 0.0001)	
IGA		
Patients whose IGA scores were maintained within 1 point of baseline at week 36 – patients considered nonresponder after rescue, n (%)	89 (70.6)	18 (28.6)
Difference vs. placebo, % (95% CI)[b]	42.1 (28.36 to 55.76; P < 0.0001)	
Patients whose IGA score increased to 3 or 4 at week 36 – patients considered responder after rescue, n (%)	33 (26.2)	42 (66.7)
Difference vs. placebo, % (95% CI)[b]	−40.5 (−54.42 to −26.53; P < 0.0001)	
Symptom: pruritus		
Patients with peak weekly pruritus NRS increased by 3 or more points from baseline at week 35, excluding patients whose peak weekly NRS scores are more than 7 at baseline, patients considered a responder after rescue, n (%)	57 (33.9)	56 (70.0)
Difference vs. placebo, % (95% CI)[b]	−36.1 (−48.40 to −23.74; P < 0.0001)	
Analysis of difference between current study baseline and week 35 in percent change in peak weekly pruritus NRS from parent study baseline – multiple imputation method with data set to missing after rescue		
Mean (SD) % change in pruritus NRS, parent study baseline to current study baseline	−60.1 (26.82)	−59.6 (29.95)
Difference between current study baseline and week 35 in LSM % change in pruritus NRS from parent study, SE (%)	−0.1 (3.05)	35.6 (4.32)
Difference vs. placebo of LSM of the end point (95% CI)[b]	−35.8 (−45.4 to −26.1; P < 0.0001)	
SCORAD		
Difference between current study baseline and week 36 in % change in SCORAD from parent study baseline, multiple imputation method with data set to missing after rescue		

	SOLO CONTINUE	
	Dupilumab q.2.w./q.w. N = 167	Placebo N = 85
Mean (SD) baseline	−73.71 (15.931)	−73.12 (16.751)
LSM change (SE)	0.33 (2.092)	28.97 (3.683)
LSMD (95% CI)[a]	−28.64 (−36.56 to −20.72; P < 0.0001)	

CI = confidence interval; EASI = Eczema Area and Severity Index; EASI-50 = Eczema Area and Severity Index score improvement from baseline ≥ 50%; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; IGA = Investigator's Global Assessment; LSM = least squares mean; LSMD = least squares mean difference; NRS = numerical rating scale; q.2.w. = every two weeks; q.w. = every week; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; SE = standard error; vs. = versus.

[a] Confidence intervals with P values are based on treatment difference (dupilumab group vs. placebo) of the LSM change using an analysis of variance model with baseline measurement as the covariate and the treatment, region, baseline IGA strata (0, 1, > 1), and dupilumab regimen received in parent studies as fixed factors.

[b] For dupilumab vs. placebo P values were derived by Cochran-Mantel-Haenszel tests stratified by baseline disease severity (IGA = 0 vs. 1), region and dupilumab regimen received in parent studies.

Table 18: Key Efficacy Outcomes (Adult Population, Original Review)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
IGA score of 0 or 1 and reduction from baseline of ≥ 2 points										
N (%)	85 (37.9)	23 (10.3)	84 (36.1)	20 (8.5)	41 (38.7)	39 (12.4)	32 (36.0)	33 (12.5)	43 (40.2)	15 (13.9)
Difference, % (95% CI)[a]	27.7 (20.2 to 35.2)		27.6 (20.5 to 34.7)		26.3 (16.3 to 36.3)		23.5 (12.7 to 34.2)		26.3 (15.0 to 37.6)	
P value[b]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
EASI-75										
N (%)	115 (51.3)	33 (14.7)	103 (44.2)	28 (11.9)	73 (68.9)	73 (23.2)	58 (65.2)	57 (21.6)	67 (62.6)	32 (29.6)
Difference, % (95% CI)[a]	36.6 (28.6 to 44.6)		32.3 (24.8 to 39.9)		45.7 (35.7 to 55.7)		43.6 (32.5 to 54.6)		33.0 (20.4 to 45.6)	
P value[b]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
EASI-75 for patients with prior CSA use[c]										
N (%)	NA	NA	NA	NA	NA	NA	NA	NA	40 (58.0)	19 (26.4)
Difference, % (95% CI)[a]	NA		NA		NA		NA		31.6 (16.1 to 47.0)	
P value[b]	NA		NA		NA		NA		0.0001	
EASI-50										
N (%)	154 (68.8)	55 (24.6)	152 (65.2)	52 (22.0)	85 (80.2)	118 (37.5)	70 (78.7)	79 (29.9)	91 (85.0)	47 (43.5)
Difference, % (95% CI)[a]	44.2 (35.9 to 52.5)		43.2 (35.1 to 51.3)		42.7 (33.4 to 52.0)		48.7 (38.6 to 58.9)		41.5 (30.0 to 53.1)	
P value[b]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
SCORAD										
Baseline mean (SD)	66.94 (13.9)	68.3 (13.9)	67.2 (13.4)	69.2 (14.8)	69.3 (15.2)	66.0 (13.5)	69.9 (15.1)	65.7 (13.3)	68.6 (11.9)	67.0 (12.196)
N observed/imputed	172/52	97/127	193/40	105/131	92/14	188/127	71/18	101/163	103/4	89/19
LSM % change (SE)	−57.7 (2.1)	−29.0 (3.2)	−51.1 (2.0)	−19.7 (2.5)	−63.9 (2.5)	−36.2 (1.7)	−69.7 (3.1)	−47.3 (2.2)	-62.4 (2.5)	−29.5 (2.6)
LSM, % difference (95% CI)[c]	−28.7 (−35.8 to −21.5)		−31.4 (−37.4 to −25.4)		−27.7 (−33.5 to −21.9)		−22.4 (−29.4 to −15.3)		−32.9 (−39.7 to −26.1)	

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
P value[c]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
Peak daily pruritus NRS score reduction of ≥ 4										
N/N1 (%)	87/213 (40.8)	26/212 (12.3)	81/225 (36.0)	21/221 (9.5)	60/102 (58.8)	59/299 (19.7)	44/86 (51.2)	32/249 (12.9)	43/94 (45.7)	13/91 (14.3)
Difference, % (95% CI)[a]	28.6 (20.6 to 36.5)		26.5 (19.1 to 33.9)		39.1 (28.5 to 49.7)		38.3 (27.0 to 49.7)		31.5 (19.1 to 43.8)	
P value[b]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
Peak daily pruritus NRS score reduction of ≥ 3										
N/N1 (%)	103/220 (46.8)	38/221 (17.2)	117/231 (50.6)	29/226 (12.8)	69/105 (65.7)	85/306 (27.8)	49/88 (55.7)	40/256 (15.6)	57/99 (57.6)	20/98 (20.4)
Difference, % (95% CI)[a]	29.6 (21.4 to 37.9)		37.8 (30.0 to 45.6)		37.9 (27.6 to 48.3)		40.1 (28.8 to 51.4)		37.2 (24.6 to 49.8)	
P value[b]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
POEM										
Baseline mean (SD)	19.8 (6.4)	20.3 (5.9)	20.8 (5.5)	21.0 (5.9)	20.3 (5.7)	20.0 (6.0)	20.6 (5.7)	20.1 (6.0)	19.3 (6.2)	19.1 (6.0)
N observed/imputed	173/51	96/128	196/37	104/132	92/14	187/128	71/18	99/165	103/4	88/20
LSM change (SE)	–11.6 (0.5)	–5.1 (0.7)	–10.2 (0.5)	–3.3 (0.6)	–12.7 (0.6)	–5.3 (0.4)	–14.2 (0.8)	–7.0 (0.6)	–11.9 (0.6)	–4.3 (0.6)
LSMD (95% CI)[c]	–6.5 (–8.0 to –5.0)		–7.0 (–8.4 to –5.6)		–7.4 (–8.8 to –5.9)		–7.2 (–9.0 to –5.4)		–7.6 (–9.3 to –6.0)	
P value[c]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	
DLQI										
Baseline mean (SD)	13.9 (7.4)	14.8 (7.2)	15.4 (7.1)	15.4 (7.7)	14.5 (7.3)	14.7 (7.4)	15.0 (7.3)	15.2 (7.4)	14.5 (7.6)	13.2 (7.6)
N observed/imputed	173/51	97/127	197/36	105/131	92/14	187/128	71/18	101/163	103/4	89/19
LSM change (SE)	–9.3 (0.4)	–5.3 (0.5)	–9.3 (0.4)	–3.6 (0.5)	–10.0 (0.5)	–5.8 (0.3)	–11.4 (0.6)	–7.2 (0.4)	–9.5 (0.5)	–4.5 (0.5)
LSMD (95% CI)[c]	–4.0 (–5.2 to –2.8)		–5.7 (–6.9 to –4.5)		–4.2 (–5.3 to –3.0)		–4.2 (–5.5 to –2.9)		–5.0 (–6.3 to –3.7)	
P value[c]	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
EQ-5D utility score										
Baseline mean (SD)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	NA	NA	0.7 (0.3)	0.7 (0.3)
N observed/imputed	173/51	96/128	197/36	105/131	92/14	188/127	NR	NR	103/4	89/19
LSM change (SE)[e]	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	NR	NR	–8.2 (79.2)	–90.0 (79.0)
LSMD (95% CI)[c,e]	0.1 08 (0.06 to 0.15)		0.17 (0.12 to 0.21)		0.06 (0.02 to 0.10)		NR		81.8 (–134.0 to 297.6)	
P value[c,d]	< 0.0001		< 0.0001		0.0058		NR		0.4577	
EQ–5D VAS score										
Baseline mean (SD)	56.8 (23.4)	54.6 (24.8)	55.4 (23.0)	56.9 (24.3)	57.8 (22.5)	56.5 (23.7)	NA	NA	55.5 (22.8)	53.4 (24.5)
N observed/imputed	173/51	97/127	196/37	105/131	91/15	188/127	NR	NR	103/4	89/19
LSM change (SE)[e]	19.5 (1.5)	7.1 (1.8)	14.9 (1.4)	3.9 (1.7)	20.4 (1.7)	9.5 (1.2)	NR	NR	111.7 (23.1)	58.9 (23.2)
LSMD (95% CI)[c,e]	12.5 (8.2 to 16.7)		10.9 (7.0 to 14.8)		10.9 (6.9to 14.8)		NR		52.8 (–10.3 to 115.9)	
P value[c,d]	< 0.0001		< 0.0001		< 0.0001		NR		0.1008	
Patients who responded “very good” or “excellent” on PGADS										
N (%)	85 (37.9)	25 (11.2)	89 (38.2)	28 (11.9)	53 (50.0)	49 (15.6)	NR	NR	55 (51.4)	17 (15.7)
Difference, % (95% CI)[a]	26.8 (19.2 to 34.4)		26.3 (18.8 to 33.8)		34.4 (24.1 to 44.8)		NR		35.7 (24.0 to 47.4)	
P value[b,d]	< 0.0001		< 0.0001		< 0.0001		NR		< 0.0001	
HADS total										
Baseline mean (SD)	12.0 (7.03)	12.4 (8.01)	13.7 (7.43)	13.7 (8.23)	12.9 (7.73)	12.6 (8.06)	13.5 (7.74)	13.1 (8.05)	12.8 (8.01)	13.0 (7.85)
N observed/imputed	159/65	82/142	191/42	103/133	92/14	188/127	71/18	101/163	103/4	89/19

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
LSM change (SE)	–5.2 (0.54)	–3.0 (0.65)	–5.1 (0.39)	–0.8 (0.44)	–4.9 (0.58)	–4.0 (0.37)	–5.5 (0.71)	–3.8 (0.47)	–6.1 (0.54)	–2.3 (0.56)
LSMD (95% CI)[c]	–2.2 (–3.44 to –0.95)		–4.2 (–5.34 to –3.09)				–1.7 (–3.28 to –0.13)		–3.9 (–5.38 to –2.40)	
P value[c]	0.0006		< 0.0001		0.1596		0.0337		< 0.0001	
HADS-A										
Baseline mean (SD)	7.0 (3.98)	6.9 (4.32)	7.5 (4.09)	7.8 (4.46)	7.4 (4.23)	7.0 (4.40)	7.7 (4.12)	7.5 (4.42)	7.0 (4.33)	7.3 (4.54)
N observed/imputed	159/65	82/142	191/42	103/133	92/14	188/127	71/18	101/163	103/4	89/19
LSM change (SE)	–2.9 (0.31)	–2.2 (0.37)	–2.8 (0.22)	–0.8 (0.26)	–2.8 (0.32)	–2.3 (0.22)	–3.2 (0.40)	–2.3 (0.30)	–3.4 (0.31)	–1.5 (0.31)
LSMD (95% CI)[c]	–0.7 (–1.48 to 0.02)		–2.0 (–2.66 to –1.37)		–0.5 (–1.24 to 0.21)		–0.8 (–1.79 to 0.09)		–1.9 (–2.74 to –1.06)	
P value[c]	0.0565		< 0.0001		0.1662		0.0768		< 0.0001	
HADS-D										
Baseline mean (SD)	5.1 (3.78)	5.4 (4.50)	6.2 (4.14)	5.9 (4.42)	5.5 (4.33)	5.5 (4.29)	5.8 (4.39)	5.7 (4.24)	5.8 (4.37)	5.7 (4.09)
N observed/imputed	159/65	82/142	191/42	103/133	92/14	188/127	71/18	101/163	103/4	89/19
LSM change (SE)	–2.4 (0.28)	–1.0 (0.32)	–2.2 (0.22)	–0.1 (0.25)	–2.1 (0.31)	–1.7 (0.20)	–2.4 (0.36)	–1.5 (0.27)	–2.8 (0.28)	–0.8 (0.29)
LSMD (95% CI)[c]	–1.4 (–2.03 to –0.73)		–2.1 (–2.70 to –1.44)		–0.4 (–1.15 to 0.27)		–0.9 (–1.77 to –0.09)		–2.0 (–2.76 to –1.21)	
P value[c]	< 0.0001		< 0.0001		0.2286		0.0301		< 0.0001	
Sick leave/missed school days – full-time status										
N	167	151	165	168	NR	NR	87	263	83	85
Mean days missed (SD)	0.5 (1.9)	1.8 (6.9)	1.2 (6.4)	2.6 (7.4)	NR	NR	0.43 (2.5)	2.3 (9.7)	0.14 (0.5)	6.16 (21.3)
Patients with any day missed, N (%)	26 (15.6)	31 (20.5)	27 (16.4)	54 (32.1)	NR	NR	8 (9.2)	72 (27.4)	7 (8.4)	14 (16.5)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-up at week 16)		LIBERTY AD CHRONOS (Follow-up at week 52)		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 236	Dupilumab 300 mg q.2.w + TCS N = 106	Placebo N = 315	Dupilumab 300 mg q.2.w + TCS N = 89	Placebo N = 264	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Sick leave/missed school days – part-time status										
N	35	37	45	34	NR	NR	21	61	12	9
Mean days missed (SD)	0.1 (0.6)	4.9 (18.2)	0.5 (1.6)	4.3 (8.0)	NR	NR	1.0 (2.9)	2.4 (6.8)	0.4 (1.2)	1.1 (3.3)
Patients with any day missed, N (%)	2 (5.7)	10 (27.0)	6 (13.3)	14 (41.2)	NR	NR	3 (14.3)	13 (21.3)	2 (16.7)	1 (11.1)

CI = confidence interval; CSA = cyclosporine-A; EASI = Eczema Area and Severity Index; EASI-50 = Eczema Area and Severity Index score improvement from baseline ≥ 50%; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; EQ-5D = EuroQol 5-Dimensions; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale–Anxiety; HADS-D = Hospital Anxiety and Depression Scale–Depression; IGA = Investigator's Global Assessment; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; NR = not reported; NRS = numerical rating scale; PGADS = Patient Global Assessment of Disease Status; POEM = Patient-Oriented Eczema Measure; q.2.w. = every two weeks; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; SE = standard error; TCS = topical corticosteroid; VAS = visual analogue scale.

Note: PGADS and the EQ-5D were not adjusted for multiplicity.

[a] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.

[b] P values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 versus IGA = 4).

[c] Confidence intervals with P value is based on treatment difference (dupilumab group versus placebo) of the LSM change using an analysis of variance model with baseline measurement as the covariate and the treatment, region and baseline IGA strata as fixed factors.

[d] The P value is not adjusted for multiplicity and is presented for descriptive purposes only.

[e] The percent LSM change/difference in LIBERTY AD CAFÉ.

Source: Clinical Study Reports for SOLO 1,[4] SOLO 2,[5] LIBERTY AD CHRONOS,[6] and LIBERTY AD CAFÉ.[7]

Harms

Only those harms identified in the review protocol are reported below.

Adverse Events

Adolescents (12 to < 18 years old)

Adverse events were reported in 72.0% (n = 59) of dupilumab and 69.4% (n = 59) of placebo patients (Table 19). The most common AEs were upper respiratory tract infections, in 12.2% (n = 10) of dupilumab and 17.6% (n = 15) of placebo patients, AD in 18.3% (n = 15) of dupilumab and 24.7% (n = 21) of placebo patients, and headache in 11.0% (n = 9) of dupilumab and 10.6% (n = 9) of placebo patients. Few SAEs were reported in the 16-week study, none with dupilumab and 1.2% (n = 1) of patients treated with placebo. No dupilumab-treated patients discontinued the study drug due to an AE and 1.2% (n = 1) of placebo patients discontinued. Among notable harms, conjunctivitis occurred in 4.9% (n = 4) of dupilumab and 1.2% (n = 1) of placebo patients, injection-site pain/swelling occurred in 3.7% (n = 3) of dupilumab and 1.2% (n = 1) of placebo patients, injection-site erythema in 2.4% (n = 2) of dupilumab and 1.2% (n = 1) of placebo patients, and injection-site pruritus in 2.4% (n = 2) of patients in each group.

Adults

In SOLO CONTINUE, AEs occurred in 71% (n = 118) of dupilumab versus 82% (n = 67) of placebo patients after 36 weeks (Table 20). In the four trials included in the original review, AEs were reported in 65.3% to 73.6% of patients in the dupilumab group and 65.3% to 71.8% in the placebo group across trials at week 16. The most common AE was under a class of infections and infestations that affected between 27.5% and 45.8% of patients in the dupilumab group and 28.4% to 40.7% of patients in the placebo group. Across all studies, nasopharyngitis was the most common infection/infestation, affecting between 8.5% and 20.6% of patients in the dupilumab group and 7.7% to 16.7% of patients in the placebo group. Patients enrolled in the LIBERTY AD CAFÉ trial had the highest prevalence of infections and infestations, and nasopharyngitis. Across all trials, patients in the dupilumab group had higher occurrences of eye disorders (including conjunctivitis), injection-site reactions, and herpes simplex infections. AEs that occurred in 2% or more of the population are presented in Table 21.

Serious Adverse Events

Adolescents (12 to < 18 years)

Few SAEs were reported in the 16-week study, none with dupilumab and in 1.2% (n = 1) of placebo patients (Table 19).

Adults

In SOLO CONTINUE, SAEs occurred in 3.6% (n = 6) of dupilumab patients and 1.2% (n = 1) of placebo patients after 36 weeks (Table 21). In the four trials included in the previous review, SAEs were reported in 1.7% to 4.7% of patients in the dupilumab group and 3.5% to 9.3% in the placebo group across trials at week 16 (Table 21). Regardless of treatment group, patients in LIBERTY AD CAFÉ had the highest frequency of SAEs. The most common severe AE was related to an AD flare worsening or aggravation that required or prolonged hospitalization (reported as “dermatitis atopic”) and affected 0.4% to 1.9% of patients in the dupilumab group, and 1.4% to 5.6% of patients in the placebo group.

Withdrawals Due to Adverse Events

Adolescents (12 to < 18 years)

No dupilumab-treated patients discontinued the study drug due to an AE and 1.2% (n = 1) of placebo patients discontinued. (Table 19).

Adults

In SOLO CONTINUE, no dupilumab patients permanently discontinued the study drug, and 3.7% (n = 3) in the placebo group discontinued (Table 20). In the four trials from the original review, withdrawals due to AEs were reported in 0 to 1.7% of patients in the dupilumab group, and 0.9% to 4.8% of patients in the placebo group at week 16 (Table 21). The greatest number of withdrawals due to AEs was found in LIBERTY AD CHRONOS, in which 4.8% of patients in the placebo group and 0.9% of patients in the dupilumab group withdrew by week 16.

Mortality

Adolescents (12 to < 18 years)

There were no deaths in the study.

Adults

In SOLO CONTINUE, no deaths occurred in either the dupilumab or placebo group. In the four trials included in the original review, two deaths occurred in the dupilumab group in SOLO 2 (one in each dupilumab group, weekly and every other week), one death occurred in LIBERTY AD CHRONOS (in the dupilumab every-other-week group). The deaths were reportedly unrelated to the study drug.

Notable Harms

Adolescents (12 to < 18 years)

Among notable harms, conjunctivitis occurred in 4.9% (n = 4) of dupilumab and 1.2% (n = 1) of placebo patients, injection-site pain or swelling occurred in 3.7% (n = 3) of dupilumab and 1.2% (n = 1) of placebo patients, injection-site erythema in 2.4% (n = 2) of dupilumab and 1.2% (n = 1) of placebo patients, and injection-site pruritus in 2.4% (n = 2) of patients in each group (Table 19).

Adults

In SOLO CONTINUE, conjunctivitis was the most common notable harm, occurring in 3.6% (n = 6) of dupilumab and 2.4% (n = 2) of placebo patients (Table 20). The prevalence of AD flares worsening or aggravation that required or prolonged hospitalization (reported as “dermatitis atopic”) was greater in the placebo group, in which 14.8% to 35% of patients in the placebo group were affected compared to 7.5% to 14% of patients in the dupilumab group for SOLO 1, SOLO 2, and LIBERTY AD CAFÉ (Table 21). At week 52 in LIBERTY AD CHRONOS, 46% of patients in the placebo group and 18% of patients in the dupilumab group experienced AD flare–related AEs. Trials without use of TCS (SOLO 1 and SOLO 2) had the highest proportion of patients who experienced AD flares worsening or aggravation that required or prolonged hospitalization. Consistently across trials, conjunctivitis (and general eye disorders) affected more patients in the dupilumab group (conjunctivitis: 3.8% to 15.0%) compared to the placebo group (conjunctivitis: 0.4% to 6.5%).

Table 19: Summary of Harms (Adolescent Population)

Aged 12 to < 18: Study 1526		
	Dupilumab q.2.w. N = 84	Placebo N = 85
Adverse events		
Any treatment-emergent adverse event, n (%)	59 (72.0)	59 (69.4)
Most common, 10% in any group, n (%)		
Upper respiratory tract infection	10 (12.2)	15 (17.6)
Nasopharyngitis	3 (3.7)	4 (4.7)
Dermatitis atopic	15 (18.3)	21 (24.7)
Headache	9 (11.0)	9 (10.6)
Withdrawal due to adverse event		
Any treatment-emergent AE leading to permanent discontinuation of study drug, n (%)	0	1 (1.2)
Serious adverse event		
Patients with a serious adverse event, n (%)	0	1 (1.2)
Notable harms		
Infection, n (%)		
Conjunctivitis	4 (4.9)	1 (1.2)
Conjunctivitis viral	1 (1.2)	0
Conjunctivitis bacterial	0	0
General, n(%)		
Injection-site pain	3 (3.7)	1 (1.2)
Injection-site swelling	3 (3.7)	1 (1.2)
Injection-site pruritus	2 (2.4)	2 (2.4)
Injection-site erythema	2 (2.4)	1 (1.2)
Injection-site warmth	2 (2.4)	0
Keratitis viral	0	0
Alopecia areata	0	0
Treatment-resistant helminth infections	0	0

AE = adverse event; q.2.w. = every two weeks.

Source: Clinical Study Report for Study 1526.[9]

Table 20: Summary of Harms (Adult Population)

	SOLO CONTINUE	
	Dupilumab q.2.w./q.w. N = 167	Placebo N = 85
Adverse event		
Patients with any treatment-emergent AE, n (%)	118 (71)	67 (82)
Most common, 10% in any group, n (%)		
Nasopharyngitis	32 (19.2)	11 (13.4)
Dermatitis atopic	34 (20.4)	40 (48.8)
Withdrawal due to adverse event		
Any treatment-emergent AE leading to permanent discontinuation of study drug, n (%)	0	3 (3.7)
Serious adverse event		
Patients with a serious adverse event, n (%)	6 (3.6)	1 (1.2)
Notable harms		
Conjunctivitis	6 (3.6)	2 (2.4)
Conjunctivitis allergic	2 (1.2)	1 (1.2)
Conjunctival hyperaemia	2 (1.2)	0
Dry eye	2 (1.2)	0
Eye pruritus	1 (0.6)	1 (1.2)
Conjunctivitis bacterial	1 (0.6)	1 (1.2)
Acute allergic reactions	*3 (1.8)*	*1 (1.2)*
Anaphylactic reaction	1 (0.6)	0
Urticaria	2 (1.2)	0
Angioedema	1 (0.6)	0
Drug eruption	0	1 (1.2)

AE = adverse event; q.2.w. = every two weeks; q.w. = every week.

Source: Clinical Study Report for SOLO CONTINUE.[14]

Table 21: Summary of Harms (Adult Population, Original Review)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 236	Placebo N = 234	Dupilumab 300 mg q.2.w + TCS N = 110	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
AEs								
Patients with > 0 AEs, N (%)	167 (72.9)	145 (65.3)	154 (65.3)	168 (71.8)	81 (73.6%)	214 (67.9%)	77 (72.0%)	75 (69.4%)
Most common AEs[a]								
Infections and infestations	80 (34.9)	63 (28.4)	65 (27.5)	76 (32.5)	39 (35.5)	111 (35.2)	49 (45.8)	44 (40.7)
Nasopharyngitis	22 (9.6)	17 (7.7)	20 (8.5)	22 (9.4)	15 (13.6)	33 (10.5)	22 (20.6)	18 (16.7)
Conjunctivitis	11 (4.8)	2 (0.9)	9 (3.8)	1 (0.4)				

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 236	Placebo N = 234	Dupilumab 300 mg q.2.w + TCS N = 110	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Upper respiratory tract infection	6 (2.6)	5 (2.3)	7 (3.0)	5 (2.1)	7 (6.4)	20 (6.3)		
Oral herpes	9 (3.9)	4 (1.8)	8 (3.4)	4 (1.7)			1 (0.9)	3 (2.8)
Herpes simplex	7 (3.1)	3 (1.4)			3 (2.7)	5 (1.6)	3 (2.8)	0
Sinusitis	NA	NA	NA	NA	0	3 (1.0)	NA	NA
Viral upper respiratory tract infection	NA	NA	NA	NA	2 (1.8)	4 (1.3)	NA	NA
Skin infection	NA	NA	NA	NA	0	7 (2.2)	NA	NA
Gastroenteritis	NA	NA	NA	NA	NA	NA	2 (1.9)	1 (0.9)
Pharyngitis	NA	NA	NA	NA	NA	NA	1 (0.9)	3 (2.8)
General disorders and administration conditions	39 (17.0)	20 (9.0)	41 (17.4)	32 (13.7)	20 (18.2)	32 (10.2)	9 (8.4)	12 (11.1)
Injection-site reaction	19 (8.3)	13 (5.9)	32 (13.6)	15 (6.4)	11 (10.0)	18 (5.7)	NA	NA
Fatigue	5 (2.2)	1 (0.5)	6 (2.5)	3 (1.3)	1 (0.9)	7 (2.2)	4 (3.7)	1 (0.9)
Skin and subcutaneous tissue disorders	47 (20.5)	78 (35.1)	49 (20.8)	93 (39.7)	20 (18.2)	110 (34.9)	22 (20.6)	21 (19.4)
Dermatitis atopic[b]	30 (13.1)	67 (30.2)	32 (13.6)	81 (34.6)	12 (10.9)	84 (26.7)	8 (7.5)	16 (14.8)
Pruritus	0	5 (2.3)	1 (0.4)	5 (2.1)	NA	NA	NA	NA
Alopecia	NA	NA	1 (0.4)	3 (1.3)	NA	NA	NA	NA
Urticaria	NA	NA	NA	NA	1 (0.9)	8 (2.5)	NA	NA
Nervous system disorders	30 (13.1)	20 (9.0)	29 (12.3)	23 (9.8)	9 (8.2)	27 (8.6)	14 (13.1)	12 (11.1)
Headache	21 (9.2)	13 (5.9)	19 (8.1)	11 (4.7)	4 (3.6)	15 (4.8)	10 (9.3)	9 (8.3)
Dizziness	NA	NA	3 (1.3)	6 (2.6)	NA	NA	NA	NA
Eye disorders	18 (7.9)	4 (1.8)	NA	NA	23 (20.9)	19 (6.0)	21 (19.6)	15 (13.9)
Conjunctivitis allergic	12 (5.2)	2 (0.9)	NA	NA	7 (6.4)	10 (3.2)	16 (15.0)	7 (6.5)
Blepharitis	NA	NA	NA	NA	5 (4.5)	2 (0.6)	NA	NA
Eye pruritus	NA	NA	NA	NA	2 (1.8)	2 (0.6)	NA	NA
Gastrointestinal disorders	21 (9.2)	9 (4.1)	22 (9.3)	18 (7.7)	11 (10.0)	33 (10.5)	9 (8.4)	16 (14.8)
Diarrhea	7 (3.1)	4 (1.8)	9 (3.8)	3 (1.3)	0	7 (2.2)	3 (2.8)	2 (1.9)
Nausea	5 (2.2)	1 (0.5)	5 (2.1)	3 (1.3)	2 (1.8)	7 (2.2)	NA	NA
Abdominal pain	NA	NA	NA	NA	NA	NA	0	4 (3.7)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 236	Placebo N = 234	Dupilumab 300 mg q.2.w + TCS N = 110	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Musculoskeletal and connective tissue	19 (8.3)	13 (5.9)	27 (11.4)	15 (6.4)	10 (9.1)	27 (8.6)	4 (3.7)	12 (11.1)
Arthralgia	6 (2.6)	3 (1.4)	6 (2.5)	6 (2.6)	2 (1.8)	8 (2.5)	1 (0.9)	3 (2.8)
Back pain	2 (0.9)	4 (1.8)	7 (3.0)	5 (2.1)	NA	NA	NA	NA
Investigations	13 (5.7)	9 (4.1)	NA	NA	8 (7.3)	26 (8.3)	NA	NA
Blood creatine phosphokinase increased	5 (2.2)	4 (1.8)	NA	NA	1 (0.9)	6 (1.9)	NA	NA
Blood lactate dehydrogenase increased	NA	NA	NA	NA	4 (3.6)	4 (1.3)	NA	NA
Respiratory, thoracic and mediastinal disorders	NA	NA	17 (7.2)	16 (6.8)	8 (7.3)	33 (10.5)	14 (13.1)	14 (13.0)
Oropharyngeal pain	NA	NA	5 (2.1)	4 (1.7)	1 (0.9)	7 (2.2)	3 (2.8)	2 (1.9)
Asthma	NA	NA	NA	NA	3 (2.7)	11 (3.5)	1 (0.9)	3 (2.8)
Rhinitis allergic	NA	NA	NA	NA	NA	NA	7 (6.5)	1 (0.9)
Cough	NA	NA	NA	NA	NA	NA	4 (3.7)	1 (0.9)
Rhinorrhea	NA	NA	NA	NA	NA	NA	0	3 (2.8)
Vascular disorders	NA	NA	NA	NA	NA	NA	4 (3.7)	1 (0.9)
Blood and lymphatic system disorders	NA	NA	NA	NA	NA	NA	4 (3.7)	4 (3.7)
Lymphadenopathy	NA	NA	NA	NA	NA	NA	2 (1.9)	4 (3.7)
Psychiatric disorders	NA	NA	6 (2.5)	17 (7.3)	NA	NA	NA	NA
Depression	NA	NA	0	5 (2.1)	NA	NA	NA	NA
Vascular disorders	NA	NA	7 (3.0)	6 (2.6)	NA	NA	NA	NA
Hypertension	NA	NA	5 (2.1)	4 (1.7)	NA	NA	NA	NA
SAEs								
Patients with > 0 SAEs, N (%)	7 (3.1)	11 (5.0)	4 (1.7)	17 (7.3)	4 (3.6)	11 (3.5)	5 (4.7)	10 (9.3)
Most common reasons	7 (3.1)	11 (5.0)	4 (1.7)	17 (7.3)	4 (3.6)	11 (3.5)	5 (4.7)	10 (9.3)
Skin and subcutaneous tissue disorders	2 (0.9)	3 (1.4)	2 (0.8)	12 (5.1)	2 (1.8)	5 (1.6)	2 (1.9)	8 (7.4)
Dermatitis atopic[b]	2 (0.9)	3 (1.4)	1 (0.4)	11 (4.7)	2 (1.8)	5 (1.6)	2 (1.9)	6 (5.6)
Psychiatric disorders	0	3 (1.4)	NA	NA	NA	NA	NA	NA
Infections and infestations	NA	NA	1 (0.4)	4 (1.7)	NA	NA	NA	NA
WDAEs								
WDAEs, N (%)	4 (1.7)	2 (0.9)	2 (0.8)	5 (2.1)	1 (0.9)	15 (4.8)	0	1 (0.9)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 236	Placebo N = 234	Dupilumab 300 mg q.2.w + TCS N = 110	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w + TCS N = 107	Placebo + TCS N = 108
Most common reasons	NA	NA	NA	NA			NA	NA
Skin and subcutaneous tissue disorders	NA	NA	NA	NA	1 (0.9)	10 (3.2)	NA	NA
Dermatitis atopic[b]	NA	NA	NA	NA	0	8 (2.5)	NA	NA
Deaths								
Deaths, N (%)	0	0	1 (0.4)	0	0	0	0	0

AE = adverse event; NA = not applicable; q.2.w. = every two weeks; SAE = serious adverse event; TCS = topical corticosteroid; WDAE = withdrawal due to adverse event.

[a] Frequency greater than or equal to 2% during a 16-week period.

[b] Reported as flare worsening or aggravation that required or prolonged hospitalization.

Source: Clinical Study Reports for SOLO 1,[4] SOLO 2,[5] LIBERTY AD CHRONOS,[6] and LIBERTY AD CAFÉ.[7]

Critical Appraisal

Internal Validity

Study 1526, as well as all the included trials in adults, was a randomized, DB, placebo-controlled, and parallel-group. Each trial was clearly described with specific objectives, end points, and interventions. Patients in each trial were randomized using a central randomization scheme provided by an IVRS/IWRS. As well, the baseline demographics and disease characteristics were generally similar between treatment groups in each trial, suggesting adequate randomization. The use of a centralized IVRS/IWRS allowed for allocation concealment. In each study all individuals were blinded with the exception of the IVRS statistician who reviewed and approved the IVRS randomization sequence, the IDMC statistician, and the IDMC members. Measures were taken to ensure blinding throughout the studies, including the use of coded drug kits, subcutaneous placebo-matched injections, and blinding of end-point assessors. Certain adverse effects (e.g., injection-site/hypersensitivity reactions, and conjunctivitis) would be known to be at higher risk with dupilumab and therefore may have resulted in unblinding if patients experiencing these harms surmised that they were assigned to dupilumab. However, the occurrence of these events was relatively infrequent (< 5% of patients) and this is unlikely to have affected blinding to a significant degree.

The greatest number of patients that discontinued was within the placebo groups in all trials. This presents the potential for bias toward inflated efficacy of dupilumab as non-response imputation was used to account for missing data. The difference in discontinuations in Study 1526 was relatively small: 7% in the dupilumab group and 11% with placebo. The difference is likely accounted for by lack of efficacy, which accounted for 7% of discontinuations in the placebo group and this does support the use of non responder imputation to account for missing data. Sensitivity analyses performed appeared to support the conclusions of the primary analyses.

The primary outcomes assessed in the trial were based on the IGA and EASI scores. The EASI has been determined to be both reliable[8,20-22,22] and valid[12,20] for the assessment of severity and extent of AD.[12,20] Validity was determined using the correlation coefficient

between EASI and SCORAD, where high correlation was found.[21] The MID for the EASI was 6.6 points.[8] Reliability, validity, and MID for the assessment of AD using the IGA were not identified in the literature search. A lack of MID for the IGA and CDLQI restricts the ability to determine clinical relevance of the IGA outcome for disease severity.

Several subgroup analyses were specified a priori and conducted across the trials (i.e., age, sex, ethnicity, race, duration of AD, geographic region, and baseline disease severity). In Study 1526 randomization was stratified by weight (< 60 kg or ≥ 60 kg) and by baseline disease severity. In the SOLO trials and LIBERTY AD CHRONOS, randomization was stratified by geographic region and baseline disease severity. In the LIBERTY AD CAFÉ trial, randomization was stratified by baseline disease severity and prior CSA use.

The main analysis was conducted on all randomized patients based on the treatment allocated at the time of randomization for each trial. This ITT analysis was appropriate as it preserved statistical power and better reflected clinical practice by including patients who were non-compliant or violated the protocol. The primary efficacy analysis for each trial was conducted using the Cochran-Mantel-Haenszel test adjusted by randomization strata (i.e., geographic region, baseline disease severity, and prior experience with CSA). For comparative purposes the trials also included a per-protocol analysis set.

The studies used multiple imputation and the Markov-chain Monte Carlo algorithm and ANCOVA to account for missing data for continuous end points. All primary efficacy end points across the trials had less than 10% missing data, with the majority missing less than 5%. The numbers of patients with imputed data were provided for secondary efficacy end points, with some end points reporting more than 50% of data as missing. These missing or imputed values appear to be largely accounted for by patient data being excluded from analysis due to use of rescue medication. For the primary analysis, patients who used rescue medication were treated as nonresponders, which may not be consistent with the ITT principle. However, sensitivity analyses were included that utilized alternative methods (e.g., LOCF) to account for missing data, and to assess all patient data regardless of use of rescue medication with and without imputation, and the results were consistent with that of the primary analysis.

A hierarchical testing procedure was used to account for multiplicity in Study 1526 and SOLO CONTINUE. Approximately a dozen outcomes were included in the hierarchy and the investigators appeared to adhere to their hierarchy, suggesting a thorough accounting for multiplicity. The hierarchy also accounted for multiple testing due to the use of two different dosage regimens in the trial, only one of which was Health Canada–approved and is therefore reported in this CDR review. Subgroup analyses do not appear to have been adjusted for multiple comparisons, and should be considered hypothesis-generating as they are at higher risk of type I error.

SOLO CONTINUE re-randomized patients who had responded to dupilumab in SOLO 1 or SOLO 2 to either dupilumab (one of three different dosage regimens) or placebo. A limitation of this study was that no patients were included in the analysis who received placebo through the parent study and this long-term extension. Patients in the placebo group in SOLO CONTINUE therefore may have experienced withdrawal effects from no longer being on dupilumab, exaggerating any worsening in their AD they experienced from being on placebo. Patients who were in the placebo group in SOLO 1 or 2 who were eligible were enrolled into SOLO CONTINUE but were not included in the efficacy analysis. This was done to maintain blinding. However, it is not clear why these patients were not included in the analysis if they were followed during the study.

External Validity

The population in Study 1526 appeared to be generalizable to an adolescent Canadian population suffering from AD, and the study included Canadian sites. The population in Study 1526 appeared to have slightly more severe AD than in the SOLO 1 and SOLO 2 studies in adults, as mean EASI scores were slightly higher (35.5 versus 33.2) and a higher percent of patients in Study 1526 had an IGA score of 4 than in SOLO 1 and 2 (53.8% versus 48.9%). In SOLO 1, SOLO 2, and LIBERTY AD CHRONOS, patients were recruited globally, with 7.2%, 15.3%, and 15.5% of patients recruited from Canada, respectively. Despite the relatively small contribution of Canadians in these studies, the clinical expert consulted for this review suggested that the study population was generally representative of Canadian adult patients seen in clinical practice. All patients in LIBERTY AD CAFÉ were recruited from Europe and more than 96% of patients identified their race as white.

The inclusion and exclusion criteria for each study were clearly described and differed slightly between studies. Among other criteria, the SOLO studies required patients for whom topical treatment was inadvisable or provided inadequate treatment, while the LIBERTY AD CHRONOS trial only required patients for whom topical treatment provided inadequate treatment and excluded patients who experienced important side effects to topical medications (e.g., intolerance and hypersensitivity). The latter inclusion and exclusion criteria were also reflected in LIBERTY AD CAFÉ, with the additional inclusion criteria of either a history of prior CSA exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or a history of being CSA-naive and not eligible for CSA due to medical contraindications or other reasons. This range of patient characteristics is useful in providing an extensive view of patients who would be seeking second-line treatment. The SOLO trials and LIBERTY AD CHRONOS excluded patients who received treatment with a TCS or TCI within one week prior to the baseline visit. Patients in LIBERTY AD CAFÉ were excluded if they received treatment with TCI within one week prior to the screening visit. These inclusion criteria among others relating to AD therapies used within specific time frames created a study population that may be inconsistent with the Canadian population and may have contributed to the share of patients (approximately 25%) who failed screening.

No head-to-head comparative data were available to compare dupilumab to other active treatments. The indirect treatment comparisons (ITCs) found in the literature were of poor methodological quality and cannot be relied upon when drawing conclusions about the relative efficacy or harms of dupilumab to other systemic therapies for AD. Overall, there is a lack of comparative evidence between dupilumab and systemic therapies, in both adolescents and in adults.

The IGA and EASI, the primary and (depending on region) co-primary outcomes of study 1526, were also typically the primary or co-primary outcomes in the adult studies. While these instruments appear to be standard tools used in clinical trials, they are not currently used in clinical practice. In practice, severity of AD is typically assessed over the long term at the physician's discretion, without using a specific instrument.

Dupilumab employs a novel mechanism of action and thus it would be prudent to have a thorough assessment of its longer-term safety, particularly in children. Study 1526 was 16 weeks in duration, as were the majority of trials in adults (LIBERTY AD CHRONOS was 52 weeks), and this is unlikely to be of sufficient duration to assess long-term harms. SOLO CONTINUE was a longer-duration trial in adults that provided an additional 36 weeks of follow-up, beyond the 16 weeks in the parent trials. However, the lack of a group that received placebo throughout limits conclusions that can be drawn from this study regarding long-term efficacy and harms. Additionally, long-term effects of dupilumab in patients for

whom treatment with TCS was inadvisable, or in patients who were not eligible for treatment with CSA or had inadequate response to CSA or intolerance and/or unacceptable toxicity, are unknown. It should be noted that in LIBERTY AD CHRONOS, the end point assessment at week 52 included data for 623 patients (out of 740 patients) as only these patients had week-52 data by the pre-specified cut-off date of April 27, 2016.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

In this review, no head-to-head trials provide direct evidence to compare dupilumab with other existing treatments for AD. The sponsor did not submit an ITC for this review.

Description of Indirect Comparison(s)

A CADTH literature search identified three potentially relevant ITCs[2-4] that compared dupilumab to other agents used for the treatment of patients with moderate-to-severe AD. The population, intervention, comparators, outcomes, and design of studies included in the three ITCs are presented in Table 22.

Table 22: Study Selection Criteria and Methods for Indirect Treatment Comparisons

	ITC by Ariens (2019)[3]	ITC by Alexander (2019)[4]	ITC by NICE (2018)[2]
Population	Adult patients with moderate-to-severe AD	Adult patients with AD	Patients (≥ 15 years) with moderate-to-severe AD
Intervention	Dupilumab	Dupilumab	Dupilumab
Comparator	Cyclosporine	Immune-modulating drugs (e.g., methotrexate, cyclosporine-A, azathioprine, mycophenolate mofetil), ustekinumab, nemolizumab, fezakinumab, lebrikizumab, baricitinib, tralokinumab	Cyclosporine
Outcome	EASI	EASI, SCORAD, POEM, and harm outcomes	EASI, SCORAD, POEM, pruritus NRS, DLQI, and harm outcomes
Study design	RCTs	RCTs	RCTs and other phase I, II, III, or IV clinical trials
Publication characteristics	Publication in English	Publication in English	Publication in English
Exclusion criteria	NR	NR	Conference papers published before 2015
Databases searched	NR, no systemic search was reported	NR	Nine bibliographic databases and eight conferences were searched between May 22 and 23, 2017 to identify relevant studies. The major relevant databases were: MEDLINE, Embase, Cochrane Central Register of Controlled Trial and the Cochrane Database for Systematic Reviews
Selection process	NR	NR	Done by two reviewers independently
Data extraction process	NR	NR	Done by two reviewers independently

	ITC by Ariens (2019)[3]	ITC by Alexander (2019)[4]	ITC by NICE (2018)[2]
Quality assessment	NR	NR	Two reviewers independently assessed the risk of bias of the four main RCTs[15,22,23,38] (i.e., 4 pivotal studies in adult patients) using the Cochrane risk of bias tool.

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; ESAI = Eczema Area and Severity Index; NR = not reported; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; RCT = randomized control trial; SCORAD = Scoring Atopic Dermatitis.

Source: NICE (2018),[2] Ariens et al. (2019),[3] Alexander et al. (2019).[4]

Methods of Three ITCs

Objectives

The aim of the ITC by Ariens et al.[3] was to assess the relative efficacy and safety of dupilumab versus cyclosporine in adult patients with moderate-to-severe AD.

The aim of the ITC by Alexander et al.[4] was to review the current systemic therapies in AD and to assess relative efficacy and safety of dupilumab versus other existing treatments for adult patients with AD.

The aim of ITC by NICE 2018[2] was to assess the relative efficacy and safety of dupilumab versus cyclosporine in patients (≥ 15 years of age) with moderate-to-severe AD.

Study Selection Methods

In the ITC by Ariens et al.,[3] no systematic review was conducted. Patient-level data on dupilumab and cyclosporine in the treatment of patients with AD were collected from two different data sources. Data on dupilumab were collected from the pivotal phase III trial LIBERTY AD CHRONOS.[22] Data on cyclosporine were collected from patients treated with cyclosporine at the Department of Dermatology and Allergology, University Medical Center, Utrecht, the Netherlands.[3]

In the ITC by Alexander et al.,[4] no detailed methodologic information about the systematic review was reported. However, the ITC reviewed the systemic therapies for patients with AD and an indirect comparison of systemic AD treatments was performed using effectiveness and safety data from published RCTs (Table 23).

In the ITC by NICE 2018,[2] a systematic literature review was conducted to identify evidence for the clinical efficacy and safety of dupilumab and other conventional treatments for moderate-to-severe AD (e.g., systemic immunosuppressants, phototherapy, or other systemic therapies) in patients with AD (≥ 15 years old). Only the results comparing dupilumab with cyclosporine were reported. The study selection criteria and methods for ITC are presented in Table 23.

Indirect Treatment Comparison Analysis Methods

The ITC methods are briefly summarized in Table 23.

In the ITC by Ariens et al.,[3] the dupilumab and cyclosporine treatment groups were compared using t-tests for continuous outcomes and chi-square tests for categorical outcomes. The efficacy outcomes were assessed using logistic regression analysis. Missing values were imputed by the LOCF method. The other regressors in the model included sex and baseline EASI.[3] Standard errors for EASI responders were calculated using a bootstrapping technique with re-sampling (number of iterations = 1,000). The

relative improvement in efficacy of dupilumab compared with cyclosporine over time between weeks 12–16 and weeks 24–30 was tested by a bootstrap method with 1,000 iterations.[3] A threshold of $P < 0.05$ was used to define statistical significance.[3]

In the ITC by Alexander et al.,[4] no details of statistical analysis were described.

The ITC by NICE 2018[2] reported that a standard approach (a network meta-analyses or Bucher comparison) was infeasible because no common comparators were available. Therefore, the matching-adjusted indirect comparison (MAIC) approach was used, in which patient-level data were used along with published aggregate-study-level data for the comparator. The method matched patient baseline characteristics between dupilumab and cyclosporine.[2] After matching, the baseline characteristics between the two treatment groups were balanced on measured characteristics, and outcomes were compared across the balanced trial populations in a hypothetical head-to-head trial.[2]

Table 23: Indirect Treatment Comparison Analysis Methods

	ITC by Ariens (2019)[3]	ITC by Alexander (2019)[4]	ITC by NICE (2018)[2]
ITC methods	Logistic regression analysis	NR	MAIC
Priors	NR	NR	NR
Assessment of model fit	NR	NR	Goodness-of-fit was assessed using diagnostic plots, AIC and BIC statistics.
Assessment of consistency	NR	NR	Yes, only for four pivotal RCTs[15,22,23,38]
Assessment of convergence	NR	NR	NR
Outcomes	EASI	EASI, SCORAD, POEM, and harms outcomes.	EASI, SCORAD, POEM, pruritus NRS, DLQI, and harms outcomes
Follow-up time points	12 to 30 weeks	8 to 260 weeks	Range: ≥ 1 year to ≥ 2 years
Construction of nodes	NR	NR	NR
Sensitivity analyses	NR	NR	Several sensitivity analyses reported
Subgroup analysis	NR	NR	Several subgroup analyses reported
Methods for pairwise meta-analysis	NR	NR	NR

AIC = Akaike's information criterion (lower AIC values indicate better fit); BIC = Bayesian information criterion (lower BIC values indicate better fit); DLQI = Dermatology Life Quality Index; ESAI = Eczema Area and Severity Index; ITC = indirect treatment comparison; NR = not reported; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; RCT = randomized control trial; SCORAD = Scoring Atopic Dermatitis.

Source: NICE (2018),[2] Ariens et al. (2019),[3] Alexander et al. (2019).[4]

Results of Three ITCs

The results of the three ITCs were not summarized because the findings were associated with significant uncertainty due to their critical methodological limitations.

Critical Appraisal of Three ITCs

The ITC by Ariens et al.[3] was not based on a systematic review. Only two studies were chosen and the ITC only compared dupilumab with cyclosporine. In the ITC by Alexander et al.,[4] no detailed methodological information about the systematic review was reported. Insufficient information was available to adequately assess the methodological quality and the risk of bias. The ITC by NICE 2018,[2] was a MAIC based on a systematic review. However, the body of evidence was limited by small sample sizes and heterogeneity in terms of study design of the included studies. The validity of the findings reported in the above three ITCs is therefore highly uncertain.

In addition, in the three ITCs, no subgroup results were reported for adolescent patients with AD.

Summary

The findings of the three ITCs were associated with significant uncertainty due to their potentially critical methodological limitations, which prevent drawing any conclusions.

Other Relevant Studies

Long-Term Extension Studies

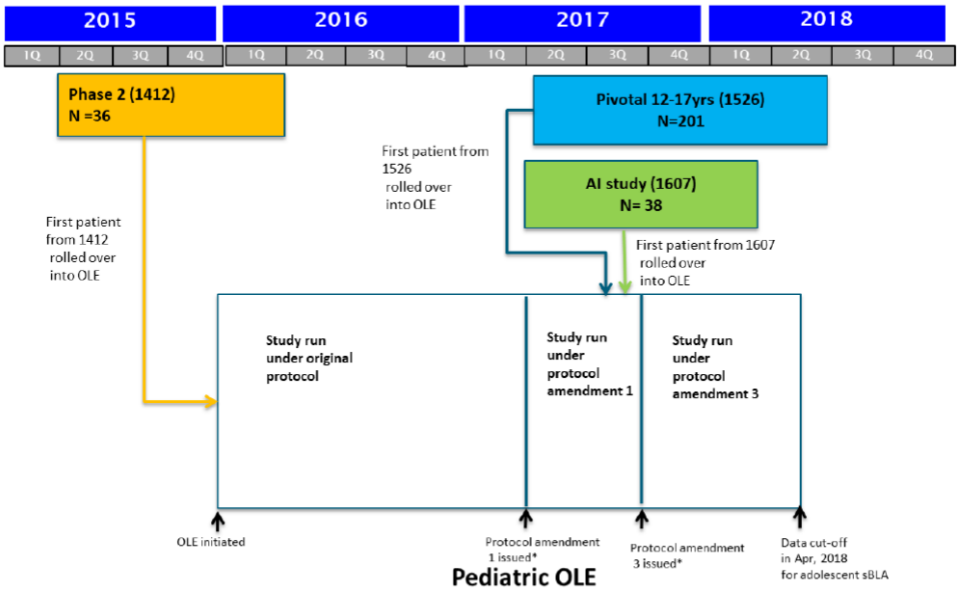
This section includes a summary and critical appraisal of the long-term extension periods for Study 1434[39] and Study 1225.[14] The primary objective of Study 1343 was to assess the long-term safety of dupilumab in pediatric patients with AD. The objective of Study 1225 was to assess long-term safety and efficacy of dupilumab in adult patients with AD. For the purpose of this review, only safety outcomes are presented in this summary.

Methods

Study 1434 is ongoing (October 2015 to November 2023; data cut-off date for this review: April 21, 2018).[12,39] Study 1434 is a global, multi-centre, non-randomized, phase III open-label extension (OLE), single-group interventional trial (N = 765) in adolescents (≥ 12 to < 18 years) with moderate-to-severe AD.[39] Enrolled patients were adolescent patients who participated in one of the three previous parent studies on dupilumab in children with AD. The three parent studies included the pivotal phase III Study 1526,[9] Study 1412 (phase IIa),[40] and Study 1607 (phase I)[41,12] (Figure 2). The Study 1434 consisted of three periods: a screening period, a treatment period that lasted until regulatory approval of the product for the age group of the patient (until the end of week 260; see Figure 3 below), and a 12-week follow-up period (Figure 3). Patients who had a sustained remission of the disease, as defined by maintenance of an IGA score of 0 or 1 continuously for a 12-week period after week 40, were discontinued from dupilumab.[39] Disease activity was closely monitored in these patients during the remaining study visits and treatment with the study drug was re-initiated in case these patients suffered from relapse of disease (IGA score ≥ 2). Patients who turned 18 years of age during the study (in a geographic region where the drug was commercially available for treatment of AD in adults) were provided treatment with the study drug only until their 18th birthday. The primary outcome was the incidence and rate (events per patient-year) of treatment-emergent adverse events (TEAEs). Results presented in this document were based on a pre-specified first-step analysis (data cut-off on April 21, 2018).[39]

Study 1225 is ongoing (October 2013 to November 2022; data cut-off date for this review: April 11, 2016).[14,12] It is a multi-centre, non-randomized OLE, single-group interventional trial (N = 2,678) that included screening and treatment periods (Figure 4). Study 1225 evaluated long-term dupilumab treatment in adults with AD who had previously participated in one of the 12 parent phase I, II, or III dupilumab clinical trials (Figure 5). The 12 parent studies included four pivotal phase III trials (SOLO 1 [Study 1334],[15] SOLO 2 [Study 1416],[23] LIBERTY AD CHRONOS [Study 1224],[22] and SOLO CONTINUE [Study 1415][42]) and the other eight were phase I or phase II trials[14] (Figure 5). The primary outcome was incidence and rate (events per 100 patient-years) of AEs. The results reported in this summary were based on a pre-specified first-step analysis of the data up to the cut-off date of April 11, 2016, on patients given 300 mg dupilumab weekly for up to 76 weeks.

Figure 2: Study 1434 – Timeline of Patients Feeding Into the OLE from Parent Studies

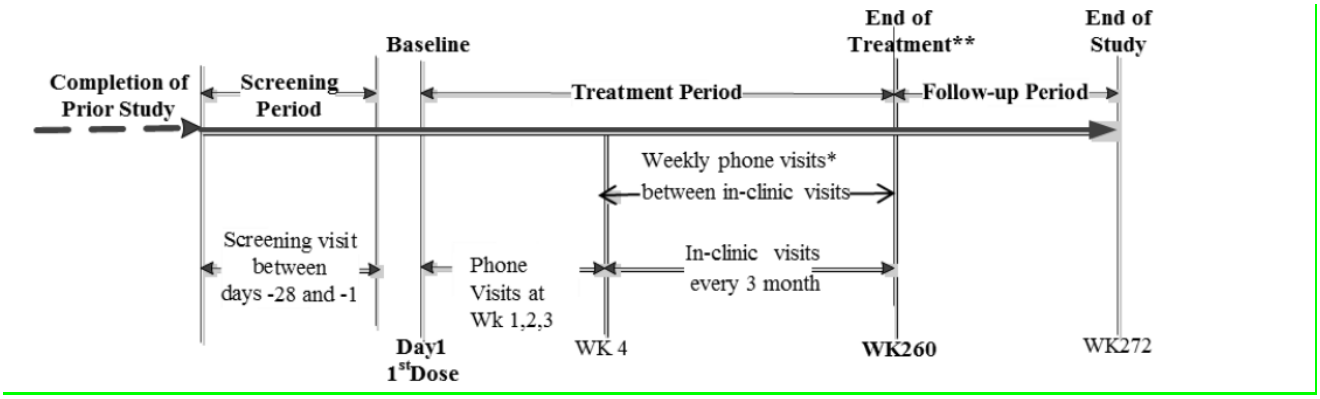


1412 = Study 1412; 1526 = Study 1526; 1607 = Study 1607; OLE = open-label extension.

Note: Date refers to the date when the protocol amendment was finalized by the sponsor. The actual time for implementation varied from site to site. Protocol amendment 2, which was specific for Germany, is not shown in this schematic for the sake of simplicity, as this included all the changes to Study 1434 amendment 1 global, except for one of the eligibility criteria. The first dose of dupilumab was administered to the first patient who rolled over into the OLE from Study 1412 on October 22, 2015, from Study 1607 on 12 September 2017, and from Study 1526 on August 29, 2017. The first dose of dupilumab was administered to the last patients who rolled over into the OLE prior to the database cut-off from Study 1412 on June 27, 2016, from Study 1607 on March 19, 2018, and from Study 1526 on April 20, 2018.

Source: Clinical Study Report for Study 1434.[39]

Figure 3: Study Flow Diagram for Study 1434



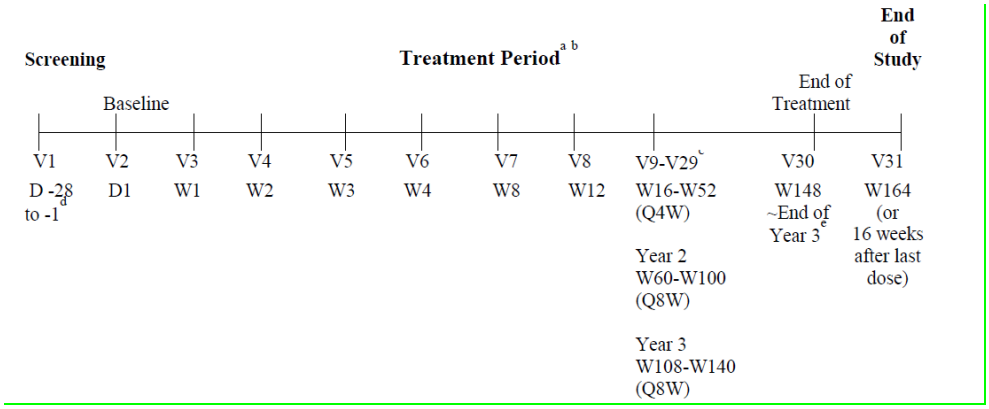
* On visits in which study drug administration was planned, patients had the option to come to the clinic to have it administered by site staff.

** The end of treatment has been depicted as happening at week 260 in Figure 3 just for illustrative purposes. The actual treatment period will last until regulatory approval.

Note: A few patients may have completed the two-year treatment period (as per protocol Study 1434.01) and were in the 12-week follow-up period before or at the time of implementation of amendment three. Under the amended protocol Study 1434.03, these patients could be re-initiated on study drug once Study 1434.03 was approved at their site. These patients were to be transitioned to the updated schedule of events as per Study 1434.03. There could also have been a few patients who had completed the study (as per protocol for Study 1434.01). These patients would be re-screened to confirm their eligibility for the study.

Source: Clinical Study Report for Study 1434.[39]

Figure 4: Study Flow Diagram for Study 1225



D = day; Q4W = every 4 weeks; Q8W = every 8 weeks; V = visit; W = week.

[a] Patients received 600 mg SC dupilumab loading dose on day 1 (unless the last dose administered in the previous AD study was given less than 4 weeks before their first dose in the current study, in which case patients received 300 mg dupilumab; the first dose of 300 mg was to be at least one week after the last dose in the previous dupilumab parent study) and then 300 mg dupilumab every week, starting at day 8.

[b] Patients were monitored at the study site for a minimum of 30 minutes after each dose of study drug from day 1 through week 2.

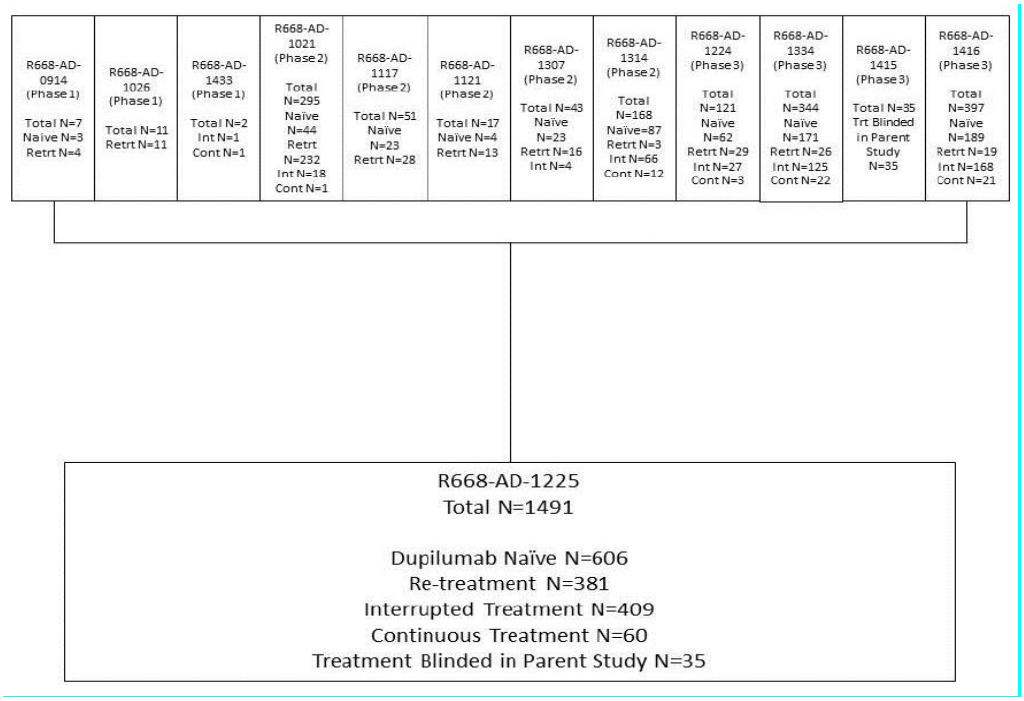
[c] Visits occurred every four weeks from week four to week 52, and then every eight weeks from week 60 onward.

[d] Patients who failed screening or who failed to complete the baseline visit within 28 days of screening could be re-screened upon approval by the medical monitor.

[e] The duration for each patient was up to 3 years or until the product was commercially available in the geographic region of the patient (whichever came first). In Great Britain, the duration was modified to up to 2 years.

Source: Clinical Study Report for Study R668-AD-1225.[14]

Figure 5: Schematic of Enrolment in Study 1225



Cont = continuous treatment (< 6 weeks between last dupilumab injection in parent study and first injection in current study); Int = interrupted-treatment (≥ 6 weeks but < 13 weeks between the last dupilumab injection in the parent study and first injection in current study); Naive = dupilumab-naive patients (received placebo or were enrolled but not treated due to enrolment closure in parent study); Retrt = re-treatment (≥ 13 weeks from last dupilumab injection in parent study and first injection in current study).

Source: Clinical Study Report for Study 1225.[14]

Populations

In Study 1434, adolescent patients (≥ 12 to < 18 years old) with AD (N = 275) were enrolled from three previous parent studies, including Study 1526,[9] Study 1412,[40] and Study 1607 [41] (Table 24). Mean age (SD) was 14.6 (1.70). A total of 206 (74.9%) patients received dupilumab in a previous parent study and 69 (25.1%) received placebo (Table 24 and Table 25).

In Study 1225, adult patients (> 18 years old) with AD (N = 1491) were enrolled from 12 previous parent studies, including four pivotal phase III trials (SOLO 1 [Study 1334],[15] SOLO 2 [Study 1416],[23] LIBERTY AD CHRONOS [Study 1224],[22] and SOLO CONTINUE [Study 1415][42]) and other eight phase I or II trials[14] (Figure 5). Mean age (SD) was 39.7 (13.41). A total of 850 (57.0%) patients received dupilumab in a previous parent study and 577 (38.7%) received placebo.

Table 24: Treatment Received in a Previous Parent Study (Study 1434)

	Study 1434 (N = 275)
Treatment in previous parent study, n (%)	
Dupilumab	206 (74.9)
Placebo	69 (25.1)
Duration of off-dupilumab period (days) before baseline of OLE	N = 206
Mean days (SD)	61.8 (50.1)
< 6 weeks, n (%)	93 (45.1)
≥ 6 to ≤ 13 weeks, n (%)	73 (35.4)
> 13 weeks, n (%)	40 (19.4)
Patients enrolled from the previous parent study, n (%)	
Study 1412, n (%)	36 (13.1)
Dupilumab: 2 mg/kg q.w.	17 (6.2)
Dupilumab: 4 mg/kg q.w.	19 (6.9)
Study 1526, n (%)	201 (73.1)
Placebo	69 (25.1)
Dupilumab: 200 mg q.2.w.	36 (13.1)
Dupilumab: 300 mg q.4.w.	67 (24.4)
Dupilumab: 300 mg q.2.w.	29 (10.5)
Study 1607, n (%)	38 (13.8)
Dupilumab: 300 mg q.2.w.	27 (9.8)
Dupilumab: 200 mg q.2.w.	11 (4.0)

OLE = open-label extension; q.2.w. = every two weeks; q.4.w. = every four weeks; q.w. = every week; SD = standard deviation.

Source: Clinical Study Report for Study 1434.[39]

Table 25: Study 1434 Demographics

	Study 1434 (N = 275)
Age (years), n	
Mean (SD)	14.6 (1.70)
Race, n (%)	
White	191 (69.5)
Black or African-American	26 (9.5)
Asian	40 (14.5)
Other	18 (6.6)
Sex, n (%)	
Male	162 (58.9)
Female	113 (41.1)
Weight (kg), n	275
Mean (SD)	64.96 (20.6)
Weight group, n (%)	
< 60 kg	135 (49.1)
≥ 60 kg	140 (50.9)
BMI (kg/m^2), n	275
Mean (SD)	24.15 (6.1)

BMI = body mass index, SD = standard deviation.

Source: Clinical Study Report for Study 1434.[39]

Table 26: Baseline Disease Characteristics of Study 1434

	Study 1434 (N = 275)
IGA (N = 275)	
Mean (SD)	3.5 (0.50)
IGA Score, n (%)	
3 – Moderate disease	126 (45.8)
4 – Severe disease	149 (54.2)
Baseline EASI total score (n = 275)	
Mean (SD)	34.8 (14.5)
BSA involvement of AD (%) (n = 275)	
Mean (SD)	54.6 (23.61)
SCORAD score (n = 237)	
Mean (SD)	70.2 (13.47)
Pruritus NRS (n = 275)	
Mean (SD)	7.4 (1.75)
CDLQI (n = 201)	
Mean (SD)	13.9 (6.81)

AD = atopic dermatitis; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index Score; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numerical rating scores; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation.

Source: Clinical Study Report for Study 1434.[39]

Table 27: Baseline Demographics and Disease Characteristics of Study 1225

	Study 1225 (N = 1,491)
Mean age, years (SD)	39.7 (13.4)
Media duration of AD, years	29.0
Race, n (%)	
White	1,051 (70.5)
Black	106 (7.1)
Asian	300 (20.1)
Other	34 (2.2)
Sex, male, n (%)	894 (60.0)
Region, n (%)	
Americas	753 (50.5)
Asia Pacific	190 (12.7)
Europe	548 (36.8)
Body weight, mean (SD)	77.97 (18.6)
Treatment in parent study, n (%)	
Previously treated with dupilumab	850 (57.0)
Dupilumab 300 mg q.w., n	401 (26.8)
Dupilumab 300 mg q.2.w., n	274 (18.4)
Other dupilumab dosage,[a] n	175 (11.7)
Dupilumab-naive subgroup, n	606 (40.6)
Received placebo q.w. in parent study, n	577 (38.7)
Screen failure in parent study, n	29 (1.9)
Treatment blinded in parent study, n	35 (2.3)
Duration of off-dupilumab treatment period (days) before baseline of current study	
n	850

	Study 1225 (N = 1,491)
Mean (SD)	146.4 (201.9)
< 6 weeks, n (%)	60 (4.0)
≥ 6 weeks and ≤ 13 weeks, n (%)	409 (27.4)
>13 weeks, n (%)	381 (25.6)
Number of patients with current history of atopic/allergic conditions reported in parent study, n (%)	1,246 (84)
Allergic rhinitis	754 (51)
Asthma	637 (43)
Food allergy	568 (38)
Allergic conjunctivitis	380 (25)
Hives	229 (15)
Atopic keratoconjunctivitis	35 (2)
Eosinophilic esophagitis	6 (< 1)
Disease characteristics at baseline of current study (OLE)	Current study (OLE)
EASI, median	17.1
Patients with IGA score, n (%)	
0 – Clear	12 (0.8)
1 – Almost clear	56 (3.8)
2 – Mild disease	217 (14.6)
3 – Moderate disease	847 (56.8)
4 – Severe disease	359 (24.1)
Peak pruritus NRS score, median	6.0
POEM total score, median	17.0
DLQI total score, median	9.0

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index Score; EASI = Eczema Area and Severity Index; IGA = Investigator Global Assessment; NRS = numerical rating scores; OLE = open-label extension; POEM = Patient-Oriented Eczema Measure; q.2.w = every two weeks; q.4.w. = every four weeks; q.w.= every week.; SD = standard deviation.

[a] Includes the following dupilumab dosages in parent study: 75 mg weekly, 100 mg every four weeks, 150 mg every week, 200 mg every two weeks, 200 mg weekly, 300 mg every four weeks.

Note: Thirty-one patients had missing IGA at baseline of parent study; 117 patients had missing PGADS scores at baseline of parent study.

Source: Clinical Study Report for Study 1225.[14,43]

Interventions

In the original protocol of Study 1434, the dosage regimen was dupilumab 2 mg/kg every week or 4 mg/kg every week Starting from protocol amendment 1 (on March, 27, 2017),[39] the dosage regimen was changed from weight-based dosing to a fixed regimen of 300 mg every four weeks. The dose was up-titrated in case of inadequate clinical response at week 16 as follows:

- Patients weighing more than or equal to 60 kg: 300 mg every two weeks.
- Patients weighing less than 60 kg: 200 mg every two weeks.

Patients enrolled from Study 1412 received weight-based dosing (2 mg/kg every week or 4 mg/kg every week) under the original protocol until they were switched to a fixed dose (300 mg every four weeks). Patients from Study 1526 and Study 1607 received the fixed dosage regimen from the time they enrolled in the study because protocol amendment 1 was already established.

Rescue medication was permitted if it was medically necessary to control intolerable AD symptoms.[39]

In Study 1225, patients received subcutaneous 300 mg dupilumab weekly, including an initial loading dose of 600 mg (300 mg if the last dupilumab dose in a previous study was administered no more than four weeks before OLE baseline) administered on day 1. Patients enrolled in the early stage of the study (starting October 2013) received 200 mg every week (400 mg loading dose). The protocol was subsequently amended on December 12, 2013, to a 300 mg every week regimen based on the regimens selected for phase III studies.[14] Patients could be treated for up to three years. Concomitant topical treatments were allowed. Only systemic treatments for AD were considered rescues and required discontinuation of study treatment for the duration of the rescue.[14]

Outcomes

In both Study 1434 and Study 1225, the primary outcomes were incidence (percent) and rate (events per patient-year) of AEs. Secondary outcomes included incidence and rate of SAEs, AEs of special interest, efficacy up to week 52, and the proportion of patients requiring rescue treatment.[14,39] Given limitations with design, heterogeneous populations, and analyses, only safety data were reported in this summary.

Statistical Analysis

As neither Study 1434 nor Study 1225 included a statistical hypothesis, no formal sample size or power calculations were performed for this study. The safety analysis set included all patients who received any study drug.

In addition, Study 1225 defined four analysis subsets of the safety analysis set based on patients' prior experience of dupilumab in the parent studies: *dupilumab-naive*: patients who did not receive any dupilumab doses in their parent studies (e.g., placebo patients in the parent study or patients who were screened, but could not be randomized); *re-treatment* (treatment gap > 13 weeks): the gap period between the last dupilumab study drug injection in a parent study and the first study drug injection in the current study was > 13 weeks (> 91 days); *interrupted-treatment* (gap ≥ 6 weeks to ≤ 13 weeks): if the gap period between the last dupilumab study drug injection in the parent study and the first study drug injection in the current study was ≤ 13 weeks and ≥ 6 weeks (≥ 42 days); and *continuous treatment* (gap < 6 weeks): if the gap period between the last dupilumab study drug injection in the parent study and the first study drug injection in the current study was < 6 weeks (< 42 days). These different populations do not represent groups that were randomized at the initiation of this OLE study. Patients in the dupilumab-naive group came from the placebo groups of the phase I, II, or III studies and included patients screened but not randomized into the phase III study. Patients in the re-treatment and interrupted-treatment groups generally came from the phase I or II studies. Most patients in the continuous treatment group came from the dupilumab groups in the phase III studies (Study 1334 and Study 1416) who either did not qualify for the maintenance study (i.e., IGA scores of 0 and 1 and EASI-75 nonresponders) or who completed the maintenance study and received dupilumab during this study.

Patient Disposition

In Study 1434, a total of 279 patients were screened, of whom 275 (98.6%) were enrolled. Four patients (1.4%) were considered screen failures, three did not meet eligibility criteria, and, for one, the baseline visit could not be completed within the screening window. Four patients discontinued from the study prior to the date for data cut-off for this first-step analysis.[39] (Table 28).

In Study 1225, a total of 1,587 patients were screened, of whom 1,492 were enrolled and 1,491 received dupilumab in this study (i.e., 1,042.9 patient-years). Few patients (7.1%)

discontinued the study prematurely, and the majority (98.6%) were ≥ 80% adherent with study treatment.[14]

Table 28: Patient and Study Disposition – Adolescents (Study 1434)

	Study 1434 (N = 275)
Patients screened	279
Patients enrolled, n(%)	275 (98.6)
Patients screen failed, n(%)	4 (1.4)
Primary reason for screen failure, n(%)	
Inclusion criteria not met and/or exclusion criteria met	3/4 (75.0)
Baseline visit could not be completed within screening window	1/4 (25.0)
Patients who completed study, n (%)	1 (0.4)
Patients ongoing, n (%)	270 (98.2)
Patients who did not complete study, n (%)	4 (1.5)
Adverse event	0
Physician decision	1 (0.4)
Lost to follow-up	1 (0.4)
Withdrawal by patient	2 (0.7)
Death	0
WDAE	0

WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for Study 1434.[39]

Table 29: Patient Disposition (Study 1225)

	Study 1225 (N = 1492)
Patients screened	1,587
Patients enrolled, n (%)	1,492 (100)
Patients enrolled but not treated, n (%)	1 (< 0.1)
Reason not treated	
Protocol deviation, n (%)	1 (< 0.1)
Safety analysis set, n (%)	1,491 (99.9)

Source: Clinical Study Report for Study 1225.[14]

Exposure to Study Treatments

In Study 1434, the mean number of dupilumab injections administered to all patients during the OLE was 15.8 (SD: 28.56). The mean overall treatment exposure of all patients in the OLE was 26.44 weeks (SD: 30.37) and the median overall treatment exposure was approximately 16 weeks (range 4.0 to 120.1). A total of 152 patients had exposure for ≥ 16 weeks, 34 patients for ≥ 52 weeks, and 22 patients for ≥ 104 weeks. No patients had 130 or more weeks of treatment at the data cut-off date of April 21, 2018.[39]

In Study 1225, a total of 312 (20.9%) patients had received the dupilumab 200 mg doses prior to the change in dosing, including 55 (9.1%) patients in the dupilumab-naive subgroup and 237 patients (62.2%) in the re-treatment subgroup.[14] The mean overall treatment exposure of all patients in Study 1225 was 38.3 weeks (SD: 30.69) and the median overall treatment exposure was 24.4 weeks (range 1.0 to 125.0). Most patients (52.0%) had cumulative treatment durations of at least 24 weeks at the time of the interim analysis.[14]

Harms

In Study 1434, a total of 149 patients (54.2%; 283 patients per 100 patient-years) had at least one TEAE during the study, most commonly related to nasopharyngitis (13.8%) and AD (14.2%). Four patients (1.5%; 2.9 patients per 100 patient-years) experienced an SAE during the study. The most common notable harms were AD (14.2%), injection-site reaction (3.3%), and allergic conjunctivitis (2.2%). No patients discontinued the study drug due to AEs and no deaths were reported. (Table 30). In Study 1225, a total of 1,054 patients (70.7%; 279 patients per 100 patient-years) experienced at least one TEAE during the study. The most common TEAE was nasopharyngitis (20.5%). Seventy-four patients (5%; 7.3 patients per 100 patient-years) experienced an SAE. The most common notable harms were AD exacerbations (8.2%), injection-site reactions, (5.5%) and conjunctivitis (5.2%). A total of 27 (1.8%) patients discontinued the study drug due to AEs. No deaths were reported (Table 30).

Table 30: Overall Summary of Harms (Study 1434 and Study 1225)

	Study 1434 (adolescents with AD) (N = 275)	Study 1225 (adults with AD) (N = 1,491)
Patients with ≥ 1 AE, n (%)	149 (54.2)	1,054 (70.7)
WDAE, n (%)	0	27 (1.8)
Death, n (%)	0	0
SAE, n (%)	4 (1.5)	74 (5.0)

AD = atopic dermatitis; AE = adverse events; SAE = serious adverse events; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Reports for Study 1434[39] and Study 1225.[14]

Table 31: Treatment-Emergent Adverse Events Reported in Study 1434

	Study 1434	
	Number of patients with > 1 TEAE, n (%) (N = 275)	Number of TEAEs per 100 patient-years
TEAEs (≥ 5 %)	149 (54.2)	283.05
Nasopharyngitis	38 (13.8)	33.26
Upper respiratory tract infection	22 (8.0)	16.76
Atopic dermatitis	39 (14.2)	31.74
Headache	16 (5.8)	12.70
Injury, poisoning, and procedural complications[a]	20 (7.3)	16.15
General disorders and administration site conditions	18 (6.5)	14.49
SAEs	4 (1.5)	2.93
Patent ductus arteriosus	1 (0.4)	0.72
Food allergy	1 (0.4)	0.71
Injection-site cellulitis	1 (0.4)	0.71
Ankle fracture	1 (0.4)	0.71
Notable harms	3 (1.1)	2.154
Allergic conjunctivitis	6 (2.2)	4.40
Hypersensitivity	0	0
AD exacerbations (worsening or exacerbation)	39 (14.2)	31.74
Injection-site reaction	9 (3.3)	6.8
Alopecia areata	0	0

	Study 1434	
	Number of patients with > 1 TEAE, n (%) (N = 275)	Number of TEAEs per 100 patient-years
Helminth	0	0
Eye ectropion	0	0

AD = atopic dermatitis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Patients who experienced more than 1 TEAE were counted only once in each category. For patients with an event, the number of patient-years is calculated up to the date of the first event; for patients without an event, it corresponds to the length of study observation period.

[a] Including ligament strain (4 patients, 1.5%), muscle strain (3 patients, 1.1%), and joint injury (2 patients, 0.7%).

Source: Clinical Study Report for Study 1434.[39]

Table 32: Harms Reported in Study 1225

	Study 1225	
	Number of patients with ≥ 1 TEAE, n (%) (N = 1,494)	Number of TEAEs per 100 patient-years,
Most common TEAEs (≥ 5% of patients)		
Nasopharyngitis	306 (20.5)	35.8
Upper respiratory tract infection	142 (9.5)	14.5
Dermatitis atopic	123 (8.2)	15.3
Headache	106 (7.1)	19.6
Conjunctivitis	78 (5.2)	7.8
Injection-site reactions	82 (5.5)	8.2
SAEs (> 1 patient)		
Ligament rupture	2 (0.1)	0.192
Squamous cell carcinoma of skin	3 (0.2)	0.288
Syncope	2 (0.1)	0.192
Inguinal hernia	2 (0.1)	0.192
Osteoarthritis	3 (0.2)	0.288
Depression	2 (0.1)	0.192
Chronic obstructive pulmonary disease	2 (0.1)	0.192
Dermatitis atopic	3 (0.2)	0.384
Noncardiac chest pain	2 (0.1)	0.288
Notable harms	67 (4.5)	
Conjunctivitis	78 (5.2)	7.8
Injection-site reactions	82 (5.5)	8.2
Hypersensitivity	2 (0.1)	NR
AD exacerbations (worsening or exacerbation)	126 (8.2)	12.39
Alopecia areata	1 (< 0.1)	0.096
Helminth	0	0
Eye ectropion	0	0

AD = atopic dermatitis; AE = adverse event; NR = not reported; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Total patient-years were calculated as the sum of study observational periods over all patients.

Source: Clinical Study Report for Study 1225.[14]

Critical Appraisal

Study 1434 and Study 1225 included patients from phase I, II, and III parent studies. Heterogeneities were evident among those parent studies in terms of study design, patient populations, interventions (i.e., dose regimens), comparators, outcomes, and study duration. In both Study 1434 and 1225, dupilumab dosage regimens varied during the extension phase due to protocol amendments. Concomitant use of TCS was also allowed, but not standardized in either Study 1434 or Study 1225. In addition, the lack of a control arm limits interpretation of both studies' outcomes.

Summary of Study 1434 and Study 1225 Long-Term Extension Phase

The findings of the Study 1434 showed that the harm outcomes associated with long-term treatment with dupilumab in adolescent patients (≥ 12 to < 18 years old) was consistent with that seen with 16-week treatment in adolescents in the pivotal trial (Study 1526). No new safety signals were associated with long-term use of dupilumab in adolescent patients with moderate-to-severe AD. Similarly, the findings of Study 1225 indicated that the harm outcomes associated with long-term treatment with dupilumab were consistent with the known dupilumab safety profile observed in the pivotal trials (SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and SOLO CONTINUE). However, due to various limitations, the findings of Study 1434 and Study 1225 should be interpreted with caution.

Discussion

Summary of Available Evidence

Adolescents (12 to < 18 years)

One pivotal sponsor-funded phase III, DB RCT, Study 1526, which featured a population of adolescents with moderate-to-severe AD, was included in this review. Study 1526 was a 16-week study that randomized 251 patients 1:1:1 to either one of two different dosage regimens of dupilumab, administered every four weeks or every two weeks, or matching placebo. The primary outcome varied depending on geographic region; for patients in the US and US reference-market countries the primary was patients with an IGA of 0 or 1 at week 16, while EU and EU reference-market countries added the co-primary outcome of patients achieving EASI-75 at week 16. Randomization was conducted using an IVRS and was stratified by weight (< 60 kg or ≥ 60 kg) and disease severity at baseline (moderate [IGA score of 3] or severe [IGA score of 4]). Aside from the data management committee, all individuals involved in the study remained blinded until the pre-specified unblinding. The study began with a screening period of up to five weeks during which patients were assessed for study eligibility, and systemic and topical treatments for AD were washed out, according to eligibility requirements. Limitations in the evidence include a lack of active comparators and a lack of indirect comparisons of either efficacy or harm of dupilumab compared to other systemic therapies.

No ITCs were identified among studies that focused on an adolescent population.

One ongoing non-randomized study (Study 1434) was identified and reviewed for assessment of long-term safety in an adolescent population. In Study 1434 (N = 765), which was an extension of studies 1526, 1412, and 1607, the primary outcome was the incidence and rate (events per patient-year) of TEAEs. Results for Study 1434 presented in this document were based on a pre-specified first-step analysis (data cut-off on April 21, 2018).

Adults

SOLO CONTINUE is a study conducted in adults who met the inclusion criteria for the current review. It was a phase III, DB, placebo-controlled RCT that sought to determine which dosage regimens of dupilumab would be able to maintain the treatment response achieved in the initial 16-week studies, SOLO 1 and SOLO 2. Patients who had achieved an IGA score of 0 or 1 or EASI-75 in these initial studies were randomized to either the same regimen they received in SOLO 1 or SOLO 2 (dupilumab every two weeks or weekly) or dupilumab every four weeks, dupilumab every right weeks, or matched placebo. Patients who received placebo in the initial studies were eligible to enroll in SOLO CONTINUE to maintain blinding, but were not randomized. Instead, they simply received placebo for the duration of the study and were not included in efficacy analyses. An IVRS/IWRS was used and randomization was stratified by the original dupilumab regimen used in the parent study, region (North America, Europe, Asia, Japan), and baseline IGA (0 versus 1 versus > 1). Patients began treatment following randomization on day 1 (week 16 of the initial study) and underwent a 36-week treatment period and a 12-week follow-up period.

The evidence presented regarding adults in the previous review was acquired from four sponsor-funded phase III RCTs (SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ). In each trial, patients were randomized to receive treatment with weekly or bi-weekly subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, or weekly subcutaneous injections of placebo. Patients in the SOLO trials were included if topical AD treatment was inadvisable or provided inadequate

treatment. In LIBERTY AD CHRONOS, patients were included if topical treatment provided inadequate treatment and patients who experienced important side effects to topical medications (e.g., intolerance and hypersensitivity) were excluded. The inclusion and exclusion criteria in LIBERTY AD CHRONOS were also reflected in criteria for LIBERTY AD CAFÉ, with the additional inclusion criteria of either a history of prior CSA exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity, or patients had to have a history of being CSA-naive and not eligible for CSA due to medical contraindications or other reasons. All patients in LIBERTY AD CHRONOS and LIBERTY AD CAFÉ were required to use a medium-potency TCS on active lesions. In the SOLO trials, use of any TCS was classified as rescue. Across all studies the proportion of patients achieving EASI-75 at week 16 was the primary efficacy end point. The proportion of patients with an IGA score of 0 or 1 (on a five-point) scale and a reduction from baseline of 2 or more points at week 16 was an additional primary end point for the SOLO trials and LIBERTY AD CHRONOS, and a secondary end point for LIBERTY AD CAFÉ. Secondary end points assessing AD severity (i.e., SCORAD), AD symptoms (pruritus NRS, POEM), and health-related quality of life (DLQI and EQ-5D) were consistent across all trials.

A CADTH literature search identified three potentially relevant ITCs[2-4] that compared dupilumab to other agents used for the treatment of patients with moderate-to-severe AD. The results of the three ITCs were not summarized due to significant uncertainty associated with their critical methodological limitations.

Study 1125 (N = 2,678) is an extension of a dozen different parent studies in adults, including SOLO 1 and 2, LIBERTY AD CHRONOS, and SOLO CONTINUE. The primary outcome is the incidence and rate (events per patient-year) of TEAEs. The results reported for Study 1225 in this summary were based on a pre-specified first-step analysis (cut-off date of April 11, 2016).

Interpretation of Results

Efficacy

Dupilumab elicited a statistically significant improvement in markers of AD severity, such as IGA, EASI, and SCORAD scores in adolescents over the 16-week Study 1526, and these results were consistent with those observed in adults over a similar duration as reported in previous studies (SOLO 1 and SOLO 2). The adolescent population in Study 1526 may have had slightly more severe AD than adults in SOLO 1 and 2, as they had higher baseline EASI scores and a larger percentage had an IGA score of 4 than in SOLO 1 and 2. Dupilumab also improved symptoms in adolescents and in adults, most notably pruritus, inducing a clinically meaningful improvement in NRS scores in a larger percentage of patients than was achieved with placebo. Pruritus was identified as an important symptom of AD based on patient input as it interrupts sleep, can be painful if excoriation occurs, can potentially result in infection, and decreases quality of life. Health-related quality of life was also improved in adolescents using a disease-specific and age-appropriate scale, the CDLQI. However, as no MID for this instrument could be found, the clinical significance of this improvement is uncertain. Health-related quality of life was also improved in the studies involving adults on both the DLQI and the generic EQ-5D 3-Levels instruments. In summary, there is evidence that dupilumab can reduce AD severity, with commensurate improvements in symptoms and health-related quality of life, and these findings appear to be consistent across both adolescent and adult age groups.

The sponsor-submitted listing request, in addition to suggesting that it apply to patients who have failed or are ineligible for topical therapies, also includes patients who are ineligible for or are refractory to systemic immunosuppressants (due to contraindications, intolerance, or

need for long-term treatment). This latter group, those who for some reason are not eligible for systemic therapies, is not clearly represented in Study 1526. Approximately one-quarter of the patients in Study 1526 had received prior systemic corticosteroids, and slightly fewer had received a nonsteroidal systemic immunosuppressant. As a result, a minority of patients had experience with these therapies, and it was not clear whether they were unable to tolerate these prior therapies or whether they were refractory to these therapies. The clinical expert consulted by CADTH for this review noted that systemic therapies such as methotrexate and cyclosporine would likely be attempted first before dupilumab was considered. Data from LIBERTY AD CAFÉ, in which patients were to have tried and failed CSA before being enrolled, suggest that dupilumab improved disease severity (based on IGA and EASI scores), symptoms (pruritus) and health-related quality of life (DLQI) in a population of patients who had failed prior immunosuppressives, although the focus was on prior use of CSA in this study. These results appear to be consistent with those of the other pivotal studies in adults (SOLO 1 and 2 and LIBERTY AD CHRONOS). Dupilumab appeared to be efficacious regardless of disease severity, although in patients with severe disease (IGA score of 4 at baseline), IGA responses may have been reduced compared to those with moderate disease (score of 3), based on subgroup data from Study 1526, although this was not observed with EASI-75. Dupilumab also appears efficacious regardless of baseline disease severity in adults, based on results from the four studies included in the original review. However, these analyses suggested numerically greater efficacy for patients with moderate AD compared to severe AD for the IGA end point. Numerically greater efficacy for patients with moderate AD compared to severe AD for the proportion of patients achieving EASI-75 was found in the SOLO trials but not in LIBERTY AD CHRONOS or LIBERTY AD CAFÉ. Tests for interaction between subgroups were not reports in the adolescent or adult studies.

No RCTs included an active comparator for dupilumab, either in adolescents or in adults. CADTH conducted a systematic review of the literature and found three ITCs, but each contained significant methodological issues, and no analyses of their results were conducted. This lack of comparisons to active comparators, direct or indirect, remains a limitation of this review.

The durability of effect of dupilumab was assessed in SOLO CONTINUE, which sought to determine whether responses in adults achieved in the SOLO trials could be maintained beyond the original 16 weeks, for an additional 36 weeks. Patients who were on a dupilumab weekly or every two week regimen were able to maintain their EASI and SCORAD scores, while those who switched to placebo had scores that worsened over the course of the 36-week study. Similar results were seen for pruritus scores — no worsening of scores in the dupilumab group and a worsening in those who went on to placebo. A limitation of this study was that there was no group in which members took placebo throughout (i.e., placebo in the original study then placebo in SOLO CONTINUE), and it is therefore not clear to what extent worsening of placebo responses were due to a withdrawal effect or simply to a lack of active treatment. Although the worsening of response in the placebo group was much larger than in the original studies, these studies were 16 weeks in duration while SOLO CONTINUE lasted for 36 weeks. This study also found that increasing the dosing interval for dupilumab to either every four or eight weeks resulted in a diminishment of response.

Harms

No clear and consistent differences in overall risk of AEs, SAEs, or withdrawals due to AEs between dupilumab and placebo were seen in adolescents in Study 1526. These results were consistent with studies performed in adults. The notable harms identified in the product monograph that are potentially associated with the use of dupilumab include conjunctivitis, alopecia areata, and helminth infections, and only conjunctivitis occurred numerically more frequently with dupilumab versus placebo in Study 1526. Injection-site and hypersensitivity reactions are associated with monoclonal antibodies in general, but there were no clear numerical differences in the risk of these events between dupilumab and placebo. Results from longer-term comparative studies, such as SOLO CONTINUE, do not suggest an increasing risk of these or other harms with longer-term (total of approximately one year) therapy.

The precise cause of the conjunctivitis is unknown, and was not observed at the same frequency in trials of dupilumab in other indications such as asthma, according to a systematic review by Akinlade et al.[44] The conjunctivitis is typically mild to moderate in severity and tends to resolve without incident. Allergic conjunctivitis and other ocular disorders such as keratitis and blepharitis are more commonly seen in patients with AD than in the general population, though it is unclear why there appears to be an elevated risk of conjunctivitis with dupilumab treatment in AD. The authors of the review speculate that alterations in cytokines caused by dupilumab may increase *Demodex* mites (mites found around the eye that consume or irritate skin and conjunctiva), and disrupt immune responses and goblet cell function. Epithelial goblet cells facilitate mucus production on the eye, interfering with goblet cell function, causing instability of tear film, reducing its barrier function, and promoting inflammation.

Helminth infections have been observed with dupilumab, and it is recommended that patients who have a known helminth infection be treated and have it cleared before starting dupilumab. In patients already on dupilumab when diagnosed with a helminth infection and not responding to therapy to clear the helminth, it is recommended that they discontinue dupilumab until the infection clears. The link between helminth infections and dupilumab has not been established, beyond the fact that suppression of interleukin 4 or 13 may somehow limit the body's ability to clear the infection. The potential for dupilumab to cause alopecia areata is puzzling because dupilumab can also be used to treat this condition. A review by Marks et al. of post-marketing case reports of alopecia areata and dupilumab found five cases in which dupilumab appeared to cause alopecia areata and four in which it was used to successfully manage the condition. The authors proposed an explanation for these differing responses, suggesting that, in some patients T-helper type 2 (Th2) cells are a major contributing factor to alopecia areata, and dupilumab proves beneficial in these patients because it downregulates Th2 cells. In patients in whom Th2 cells play less of a role in pathogenesis of alopecia areata, downregulation of Th2 cells may result in a switch to T-helper type 1 cells, which in turn activate another pathway that contributes to the development of alopecia areata.[45]

Conclusions

Six DB RCTs in patients with moderate-to-severe AD — four in adults from the original review of dupilumab (SOLO 1 and 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ), one in adolescents (Study 1526), and one longer-term extension in adults (SOLO CONTINUE) — were included in this review. In adults and adolescents, dupilumab improved various measures of disease severity (IGA, EASI), symptoms (pruritus), and health-related quality of life (DLQI, CDLQI) versus placebo after 16 weeks (and 52 weeks with LIBERTY AD CHRONOS) of treatment. Where the minimum clinically important differences were known, these differences were clinically significant. Results from SOLO CONTINUE suggest durability of the effects after an initial 16-week treatment response; although longer-term studies are needed. No direct comparisons of dupilumab to other systemic therapies for AD have been reported, and published ITCs were inconclusive due to poor methodological quality and limitations with the base data. There were no direct comparisons of dupilumab to other systemic therapies for AD, and published ITCs were inconclusive due to poor methodological quality. There was no clear evidence of important harms occurring at greater risk with dupilumab than placebo, and longer-term safety extensions in both adolescents and adults revealed no new safety signals, with a mean follow-up of an additional 26 and 38 weeks, respectively.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946–) Embase (1974–) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 19, 2019
Alerts:	Bi-weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
MeSH	Medical Subject Heading
exp	Explode a subject heading
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(dupilumab* or dupixent* or REGN668 or REGN 668 or SAR231893 or SAR 231893 or 420K487FSG).ti,ab,kf,ot,hw,rn,nm.
2	Dermatitis, Atopic/ or exp Eczema/
3	eczema*.ti,ab,kf.
4	((dermatiti* or neurodermatiti*) adj3 (atopic* or disseminat* or constitutional*)).ti,ab,kf.
5	(sulzberger adj2 (disease* or syndrome*)).ti,ab,kf.
6	or/2-5
7	1 and 6
8	7 use medall
9	*dupilumab/
10	(dupilumab* or dupixent* or REGN668 or REGN 668 or SAR231893 or SAR 231893).ti,ab,kw,dq.
11	9 or 10
12	Atopic dermatitis/ or exp eczema/
13	eczema*.ti,ab,kw,dq.
14	((dermatiti* or neurodermatiti*) adj3 (atopic* or disseminat* or constitutional*)).ti,ab,kw,dq.
15	(sulzberger adj2 (disease* or syndrome*)).ti,ab,kw,dq.
16	or/12-15
17	11 and 16
18	17 use oemezd
19	18 not (conference review or conference abstract).pt.
20	8 or 19
21	remove duplicates from 20

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms: dupilumab* or dupixent* or REGN 668 or SAR 231893	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms: dupilumab* or dupixent* or REGN 668 or SAR 231893	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	November 14 to November 19, 2019
Keywords:	dupilumab* or dupixent* or REGN 668 or SAR 231893
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics

Appendix 2: Excluded Studies

Table 33: Excluded Studies

Reference	Reason for exclusion
Beck (2014)	Pooled analysis
Guttman-Yassky (2019)	Study design
Blauvelt (2019)	
Cork (2019)	
Deleuran (2019)	
Zhu (2019)	
Simpson (2016)	
Blauvelt (2017)	Included in previous review
De Bruin-Weller (2019)	

Appendix 3: Detailed Outcome Data

Table 34: Subgroup Analyses and Sensitivity Analyses: Study 1526

	Dupilumab q.2.w. N = 84	Placebo N = 85
OVERALL		
Patients with an IGA score of 0 or 1 at week 16, n (%)	20 (24)	2 (2)
Difference vs. placebo, % (95% CI)[a]	22.0 (12.20 to 31.87; P < 0.0001)	
Percentage of patients achieving IGA 0 or 1 by subgroup		
By baseline disease severity		
Moderate disease (IGA = 3), n/N (%)	12/39 (30.8)	1/39 (2.6)
Difference vs. placebo, % (95% CI)	28.2 (12.89 to 43.52)	
Severe disease (IGA = 4), n/N (%)	8/43 (18.6)	1/46 (2.2)
Difference vs. placebo, % (95% CI)	16.4 (4.06 to 28.80)	
OVERALL		
Patients with EASI-75 at week 16, n (%)	34 (42)	7 (8)
Difference vs. placebo, % (95% CI)[a]	33.2 (21.07 to 45.39; P < 0.0001)	
Percentage of patients achieving EASI-75 by subgroup		
By baseline disease severity		
Moderate disease (IGA = 3), n/N (%)	17/39 (43.6)	4/39 (10.3)
Difference vs. placebo, % (95% CI)	33.3 (15.09 to 51.58)	
Severe disease (IGA =4), n/N (%)	17/43 (39.5)	3/46 (6.5)
Difference vs. placebo, % (95% CI)	33.0 (16.75 to 49.28)	
Sensitivity analyses		
IGA		
Proportion of patients achieving IGA 0 or 1 at week 16 – all observed values regardless of rescue treatment use, FAS n/N (%)	20/82 (24.4)	4/85 (4.7)
Difference vs. placebo, % (95% CI)	19.7 (9.36 to 30.01; P = 0.0003)	
EASI		
Patients achieving EASI-75 at week 16 – all observed values regardless of treatment use, FAS n/N (%)	37/82 (45.1)	13/85 (15.3)
Difference vs. placebo, % (95% CI)	29.8 (16.62 to 43.04; P < 0.0001)	
LSM (SE) percent change from baseline in EASI score at week 16; multiple imputation method regardless of rescue treatment use; FAS (sample observed/imputed)	−66.2 (3.56) (78/4)	−31.3 (3.54) (82/3)
LSMD (95% CI)	−34.9 (−44.76 to −25.11; P < 0.0001)	
Pruritus		
LSM (SE) percent change from baseline in weekly average of peak pruritus NRS at week 16; multiple imputation method regardless of rescue treatment use; FAS (sample observed/imputed)	−48.1 (3.27) (78/4)	−20.9 (3.24) (76/9)
LSMD (95% CI)	−27.3 (−36.29 to −18.24; P < 0.0001)	
Patients achieving a reduction of ≥ 3 points from baseline in weekly average of daily peak pruritus NRS at week 16; all observed values regardless of rescue treatment use; missing considered as nonresponders; FAS n/N (%)	48/82 (58.5)	19/85 (22.4)

	Dupilumab q.2.w. N = 84	Placebo N = 85
Difference vs. placebo, % (95% CI)	36.2 (22.32 to 50.05; P < 0.0001)	
Patients achieving a reduction of ≥ 4 points from baseline in weekly average of daily peak pruritus NRS at week 16; all observed values regardless of rescue treatment use; missing considered as nonresponders, FAS n/N (%)	35/82 (42.7)	13/84 (15.5)
Difference vs. placebo, % (95% CI)	27.2 (14.00 to 40.41; P < 0.0001)	
Patients achieving a reduction of ≥ 3 points from baseline in weekly average of daily peak pruritus NRS at week 16; all observed values regardless of rescue treatment use; missing considered as nonresponders, FAS n/N (%)	48/82 (58.5)	19/85 (22.4)
Difference vs. placebo, % (95% CI)	36.2 (22.32 to 50.05; P < 0.0001)	
Patients achieving a reduction of ≥ 4 points from baseline in weekly average of daily peak pruritus NRS at week 16; all observed values regardless of rescue treatment use; missing considered as nonresponders, FAS n/N (%)	35/82 (42.7)	13/84 (15.5)
Difference vs. placebo, % (95% CI)	27.2 (14.00 to 40.41; P < 0.0001)	
CDLQI		
LSM (SE) change from baseline in CDLQI at week 16; multiple imputation method regardless of rescue treatment use; FAS	−8.4 (0.51)	−5.6 (0.50)
LSMD (95% CI)	−2.8 (−4.21 to −1.43; P < 0.0001)	
SCORAD		
LSM (SE) percent change from baseline to week 16 in SCORAD; multiple imputation method regardless of rescue treatment use; FAS	−51.6 (2.79)	−23.8 (2.73)
LSMD (95% CI)	−27.7 (−35.37 to −20.09; P < 0.0001)	
POEM		
LSM (SE) change from baseline to week 16 in POEM; multiple imputation method regardless of rescue treatment use, FAS	−10.1 (0.77)	−4.9 (0.75)
LSMD (95% CI)	−5.3 (−7.39 to −3.17; P < 0.0001)	
SOLO CONTINUE		
Sensitivity analyses		
Difference between current study baseline and week 36 in percent change from parent study baseline in EASI; no imputation for rescue; no imputation for missing data (all observed), LSM change from baseline (%)	−0.99 (1.854) N = 160	23.03 (2.458) N = 78
LS mean difference versus placebo, % (95% CI)	−24.02 (−29.41 to −18.63; P < 0.0001)	

CI = confidence interval; CDLQI = Children's Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = Eczema Area and Severity Index score improvement from baseline greater than or equal to 75%; FAS = full analysis set; IGA = Investigator's Global Assessment; LSM = least squares mean; LSMD = least squares mean difference; NRS = numeric rating scale; POEM = Patient-Oriented Eczema Measure; q.2.w.= every two weeks; SCORAD = Scoring Atopic Dermatitis; SE = standard error; vs. = versus.

Note: No subgroup data based on prior failure or intolerance.

Source: Clinical Study Report for Study 1526.[9]

Table 35: Key Efficacy End Points for SOLO 1 and SOLO 2 by Disease Severity

	SOLO 1				SOLO 2			
	Placebo N = 113	Dupilumab 300 mg q.2.w. N = 116	Placebo N = 110	Dupilumab 300 mg q.2.w. N = 108	Placebo N = 121	Dupilumab 300 mg q.2.w. N = 118	Placebo N = 115	Dupilumab 300 mg q.2.w. N = 115
Disease severity	**Moderate (IGA = 3)**		**Severe (IGA = 4)**		**Moderate (IGA = 3)**		**Severe (IGA = 4)**	
IGA score of 0 or 1 and reduction from baseline of ≥ 2 points								
N (%)	16 (14.2)	62 (53.4)	7 (6.4)	23 (21.3)	17 (14.0)	54 (45.8)	3 (2.6)	30 (26.1)
Difference, % (95% CI)[a]		39.3 (26.9 to 50.7)		14.9 (1.9 to 28.0)		31.7 (19.34 to 43.4)		23.5 (10.2 to 36.1)
EASI-75								
N (%)	24 (21.2)	77 (66.4)	9 (8.2)	38 (35.2)	20 (16.5)	61 (51.7)	8 (7.0)	42 (36.5)
Difference, % (95% CI)[a]		45.1 (33.1 to 56.3)		27.0 (14.0 to 39.4)		35.2 (22.8 to 46.6)		29.6 (16.5 to 41.9)
Peak daily pruritus NRS score reduction of ≥ 4								
N/N1 (%)	15/101 (14.9)	47/108 (43.5)	11/110 (10.0)	40/105 (38.1)	13/111 (11.7)	43/115 (37.4)	8/110 (7.3)	38/110 (34.5)
Difference, % (95% CI)[a]		28.7(15.3 to 41.3)		28.1(14.8 to 40.5)		25.7 (12.7 to 38.1)		27.3 (13.8 to 40.0)
Peak daily pruritus NRS score reduction of ≥ 3								
N/N1 (%)	24/110 (21.8)	57/114 (50.0)	14/110 (12.7)	46/106 (43.4)	18/114 (15.8)	62/118 (52.5)	11/112 (9.8)	55/113 (48.7)
Difference, % (95% CI)[a]		28.2(15.2 to 40.4)		30.7(17.5 to 43.1)		36.8 (24.2 to 48.2)		38.9 (26.6 to 50.6)

CI = confidence interval; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; IGA = Investigator's Global Assessment; N1 = number of patients with baseline score; NRS = numerical rating scale; q.2.w. = every 2 weeks.

[a] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.

Source: Clinical Study Reports for SOLO 1[4] and SOLO 2.[5]

Table 36: Key Efficacy End Points for LIBERTY AD CHRONOS by Disease Severity

	Follow-up to week 16				Follow-up to week 52			
	Placebo N = 168	Dupilumab 300 mg q.2.w. + TCS N = 53	Placebo N = 147	Dupilumab 300 mg q.2.w. + TCS N = 53	Placebo N = 144	Dupilumab 300 mg q.2.w. + TCS N = 44	Placebo N = 120	Dupilumab 300 mg q.2.w. + TCS N = 45
Disease severity	**Moderate (IGA = 3)**		**Severe (IGA = 4)**		**Moderate (IGA = 3)**		**Severe (IGA = 4)**	
IGA score of 0 or 1 and reduction from baseline of ≥ 2 points								
N (%)	31 (18.5)	26 (49.1)	8 (5.4)	15 (28.3)	27 (18.8)	19 (43.2)	6 (5.0)	13 (28.9)
Difference, % (95% CI)[a]		30.6 (15.3 to 45.1)		22.9 (7.2 to 37.9)		24.4 (7.6 to 40.5)		23.9 (6.7 to 40.2)
EASI-75								
N (%)	48 (28.6)	37 (69.8)	25 (17.0)	36 (67.9)	37 (25.7)	26 (59.1)	20 (16.7)	32 (71.1)

	Follow-up to week 16				Follow-up to week 52			
	Placebo N = 168	Dupilumab 300 mg q.2.w. + TCS N = 53	Placebo N = 147	Dupilumab 300 mg q.2.w. + TCS N = 53	Placebo N = 144	Dupilumab 300 mg q.2.w. + TCS N = 44	Placebo N = 120	Dupilumab 300 mg q.2.w. + TCS N = 45
Disease severity	**Moderate (IGA = 3)**		**Severe (IGA = 4)**		**Moderate (IGA = 3)**		**Severe (IGA = 4)**	
Difference, % (95% CI)[a]		41.2 (26.3 to 55.2)		50.9 (36.1 to 64.2)		33.4 (16.7 to 49.0)		54.4 (38.4 to 68.6)
Peak daily pruritus NRS score reduction of ≥ 4								
N/N1 (%)	25/157 (15.9)	22/51 (43.1)	24/142 (16.9)	16/51 (31.4)	17/133 (12.8)	21/43 (48.8)	15/116 (12.9)	23/43 (53.5)
Difference (%) (95% CI)[a]		27.2 (11.6 to 42.1)		14.5 (-1.5 to 30.0)		36.1 (19.3 to 51.9)		40.6 (23.6 to 56.2)
Peak daily pruritus NRS score reduction of ≥ 3								
N/N1 (%)	50/162 (30.9)	34/52 (65.4)	35/144 (24.3)	35/53 (66.0)	23/138 (16.7)	21/43 (48.8)	17/118 (14.4)	28/45 (62.2)
Difference (%) (95% CI)[a]		34.5 (19.1 to 49.0)		41.7 (26.5 to 55.8)		32.2 (15.2 to 48.2)		47.8 (31.5 to 62.5)

CI = confidence interval; EASI-75 = Eczema Area and Severity Index score improvement from baseline ≥ 75%; IGA = Investigator's Global Assessment; N1 = number of patients with baseline score; NRS = numerical rating scale; q.2.w. = every 2 weeks; TCS = topical corticosteroid.

[a] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.

Source: Clinical Study Report for LIBERTY AD CHRONOS.[6]

Table 37: Key Efficacy End Points for CAFÉ by Disease Severity

	Placebo + TCS N = 56	Dupilumab 300 mg q.2.w + TCS N = 57	Placebo + TCS N = 52	Dupilumab 300 mg q.2.w + TCS N = 50
Disease severity	**Moderate (IGA = 3)**		**Severe (IGA = 4)**	
EASI-75				
N (%)	26 (46.4)	40 (70.2)	6 (11.5)	27 (54.0)
Difference, % (95% CI)[a]		23.7 (4.7 to 41.0)		42.5 (23.5 to 58.5)
IGA score of 0 or 1 and reduction from baseline of ≥ 2 points				
N (%)	13 (23.2)	24 (42.1)	2 (3.8)	19 (38.0)
Difference, % (95% CI)[a]		18.9 (1.1 to 36.9)		34.2 (15.2 to 51.5)
Peak daily pruritus NRS score reduction of ≥ 4				
N/N1 (%)	8/44 (18.2)	23/49 (46.9)	5/47 (10.6)	20/45 (44.4)
Difference, % (95% CI)[a]		28.8 (8.5 to 47.4)		33.8 (13.5 to 51.8)
Peak daily pruritus NRS score reduction of ≥ 3				
N/N1 (%)	13/48 (27.1)	28/52 (53.8)	6/50 (12.0)	28/47 (59.6)
Difference, % (95% CI)[a]		26.8 (7.2 to 44.9)		47.6 (28.5 to 63.6)

CI = confidence interval; EASI-75 = Eczema Area and Severity Index score improvement from baseline greater than or equal to 75%; IGA = Investigator's Global Assessment; NRS = numerical rating scale; q.2.w. = every two weeks; TCS = topical corticosteroid.

[a] Difference is dupilumab minus placebo. Confidence interval calculated using exact method.

Source: Clinical Study Report for LIBERTY AD CAFÉ.[7]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and minimal important difference).

To summarize the validity of the end point measures:

- Eczema Area and Severity Index (EASI)
- Investigator's Global Assessment (IGA)
- Scoring Atopic Dermatitis (SCORAD)
- Patient Global Assessment of Disease Status (PGADS)
- Pruritus numerical rating score (NRS)
- Dermatology Life Quality Index (DLQI)
- Children's Dermatology Life Quality Index (CDLQI)
- EuroQol 5-Dimensions (EQ-5D)
- Hospital Anxiety and Depression Scale (HADS)
- Patient-Oriented Eczema Measure (POEM).

Table 38: Outcome Measures Included in Each Study

Outcome measure	SOLO 1 (Study 1334)	SOLO 2 (Study 1416)	LIBERTY AD CHRONOS (Study 1224)	LIBERTY AD CAFÉ (Study 1424)	SOLO CONTINUE (Study 1415)	Study 1526
EASI	Primary, other secondary		Primary, key secondary, other secondary, exploratory	Primary, secondary	Primary, other secondary	Primary, key secondary, other secondary
IGA	Primary, other		Primary, key secondary, exploratory	Secondary	Key secondary, other secondary	Primary, other
SCORAD	Other secondary			Secondary	Other secondary	Other secondary
PGADS	Other		Other exploratory	Other	NR	Other
Pruritus NRS	Key secondary, other secondary		Key secondary, other secondary, other exploratory	Secondary	Other secondary	Key secondary, other secondary
DLQI	Other secondary		Other secondary	Secondary	Other secondary	NR
CDLQI	NR					Other secondary
EQ-5D	Other		Other exploratory	Other	NR	NR
HADS	Other secondary			Secondary	Other secondary	Other secondary
POEM	Other secondary			Secondary	Other secondary	Other secondary

DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; HADS = Hospital Anxiety and Depression Scale; NR = not reported; NRS = numerical rating scale; PGADS = Patient Global Assessment of Disease Status; POEM = Patient-Oriented Eczema Measure; SCORAD = Scoring Atopic Dermatitis.

Note: An outcome measure (e.g., EASI) can be assessed in different ways and reported in different categories (e.g., EASI score ≥ 75 at week 16 was assessed as the primary outcome; EASI change from baseline at week 16 was assessed as other efficacy outcome).

Source: Clinical Study Reports.[9,15,22,23,38,42]

Findings

Table 39: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
EASI	A scale used in clinical trials to assess the severity and extent of AD	EASI is a validated scale and can be used reliably in the assessment of severity and extent of AD. The total EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD. EASI score of 75 indicates ≥ 75% improvement from baseline.	6.6 points
IGA	A scale that provides a global clinical assessment of AD by investigator	IGA is a 5-point scale that provides a global clinical assessment of AD severity (ranging from 0 to 4). "0" indicates clear, and "4" indicates severe AD. No information on the validity and MID of the IGA scale in patients with AD was identified.	Unknown
SCORAD	A tool used in clinical research to standardize the evaluation of the extent and severity of AD	SCORAD is a tool used in clinical research to assess the extent and severity of AD. The maximum possible total score of SCORAD is 103, with a higher score indicating a poorer or a more-severe condition. A difference of 8.7 points in SCORAD was estimated as the MID for the patients with atopic eczema (also known as AD).	8.7 points
PGADS	A scale used for global assessment of AD by patients	PGADS is a 5-point Likert scale. A higher score indicates a better overall condition. No information on the validity and MID of the PGADS in patients with AD was identified.	Unknown
Pruritus NRS	A tool for patients with AD used to report the intensity of their itch	Information provided by the sponsor reported the validity and reliability of the NRS based on three phase III and one phase IIb RCTs. The most appropriate definition of a responder on the pruritus NRS was considered to be a score of 3 to 4 points.	3 points
DLQI	A questionnaire used to assess six different aspects that may affect quality of life of patients in dermatology	The DLQI is a widely used 10-item dermatology-specific quality-of-life instrument that assesses six different aspects that may affect quality of life.[31,32] The overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30).[31,32] The higher the score, the more quality of life is impaired. The DLQI has shown good test-retest reliability, internal consistency reliability, construct validity, and responsiveness in patients with psoriasis. Estimates of the MID have ranged from 2.2 to 6.9.[26,31] However, no validity and MID information was found for the patients with AD.	2.2 to 6.9 unknown for AD
CDLQI	Self-explanatory and completed by the child alone and/or with help from the parents or guardian to measure the quality of life of children with skin conditions	CDLQI includes 10 questions covering six areas of daily activities, including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The total scores range from 0 to 30. A higher CDLQI score indicates a greater degree of quality-of-life impairment. The CDLQI is a widely used questionnaire to measure the quality of life of children with skin disease. There was evidence of	Unknown

Outcome measure	Type	Conclusions about measurement properties	MID
		high internal consistency, test-retest reliability, responsiveness to change, and significant correlation with other subjective and objective measures. No minimal clinically important difference was identified in the literature.	
EQ-5D	A generic quality-of-life instrument that has been applied to a wide range of health conditions and treatments	EQ-5D includes three parts. The first part is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The second part is a 20 cm visual analogue scale that has end points labelled 0 and 100. The third part is the EQ-5D index score, which is generated by applying a multi-attribute utility function to the descriptive system. The MID for the EQ-5D ranges from 0.033 to 0.074. No information was found in a literature search for EQ-5D in AD.	0.033 to 0.074, unknown for AD
HADS	A patient-reported questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions	The HADS questionnaire contains 14 items that assess symptoms experienced in the previous week. A patient can score between 0 and 21 for each subscale (anxiety and depression). A high score is indicative of a poor state. No additional validity and MID information regarding HADS was found from the literature search for AD.	Unknown
POEM	A questionnaire used in clinical trials to assess disease symptoms in children and adults with eczema	POEM is a 7-item questionnaire used in clinical trials to assess disease symptoms in children and adults. It was reported that the overall mean MID of the POEM was 3.4 points for adult patients, when an IGA was improving, with one point used as anchor. The MID for children was 3 to 4 points.	3.4 points in adults In children, 3.0 to 3.9 points indicates a probable MIC; 4 points indicates a very likely MIC

AD = atopic dermatitis; CDLQI = Children Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D = EuroQol 5-Dimensions; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; MIC = minimal important change; MID = minimal important difference; NRS = numerical rating score; PGADS = Patient Global Assessment of Disease Status; POEM = Patient-Oriented Eczema Measure; RCT = randomized controlled trial; SCORAD = Scoring Atopic Dermatitis.

Eczema Area and Severity Index

The EASI is a scale used in clinical trials to assess the severity and extent of atopic dermatitis (AD).[16-19] The EASI was recommended as the core outcome measure for the clinical signs of eczema.[46] In the EASI, four disease characteristics of AD (erythema, infiltration and/or papulation, excoriations, and lichenification) are assessed for severity by the investigator on a scale of "0" (absent) to "3" (severe). The scores are added up for each of the four body regions (head, arms, trunk, and legs). The assigned percentages of body surface area (BSA) for each section of the body are 10% for head, 20% for arms, 30% for trunk, and 40% for legs, respectively. Each subtotal score is multiplied by the BSA represented by that region. In addition, the affected area of AD assessed as a percentage by each body region is converted to a score of 0 to 6, where the area is expressed as 0 (none), 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). Each of the body area scores are multiplied by the area affected. Therefore, the total EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD.[17] It is suggested that the severity of AD based on EASI be categorized as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 2l.1 to 50.0 = severe; 50.1 to 72.0 = very severe.[20] EASI-75 indicates ≥ 75% improvement from baseline.[15] The validity and reliability of the EASI were examined

in several studies.[16-19,21] The correlation coefficients were estimated between EASI and SCORAD to assess validity.[18] A moderate-to-high correlation between the EASI and SCORAD (r = 0.84 to 0.93) was reported.[18] Intra- and inter-rater reliability was examined (r = 0.8 to 0.9).[18] The authors concluded that EASI is a validated scale and can be used reliably to assess severity and extent of AD.[17,47] One study[16] reported that the overall MID was 6.6 points when an IGA was improving, with one point used as anchor.

Investigator's Global Assessment

The IGA is a five-point scale that provides a global clinical assessment of AD severity (ranging from 0 to 4). A score of "0" indicates clear, and "4" indicates severe AD.[15] A decrease in score indicates an improvement in signs and symptoms. However, the IGA was designed and is commonly used for clinical trials and is rarely used in clinical practice.[47] The clinical expert consulted for this review explained that, in practice, a physician would assess a patient's AD more subjectively (evaluating inflammatory lesions or erythema) without using the IGA. It was reported that the intra-class correlation coefficient (ICC) (or intra-rater reliability by investigator) for the IGA was 0.54,[19] which appears to be below what would typically be considered acceptable (0.70). A literature review found no information on the validity of the IGA scale in patients with AD. Similarly, no information was found on what would constitute an MID in patients with AD.

Patient Global Assessment of Disease Status

The PGADS is a five-point Likert-scale tool. A higher score indicates a better overall condition. In the pivotal clinical studies,[15,22,23] patients rated their overall well-being based on a scale from poor to excellent. Patients were asked: "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices were: "Poor," "Fair," "Good," "Very Good," and "Excellent."[4] No information in the literature reviewed was found on the validity, reliability, or MID of PGADS in AD.

Scoring Atopic Dermatitis

The SCORAD is a tool used in clinical research that was developed to standardize the evaluation of the extent and severity of AD.[15,24] The SCORAD is considered a valid and reliable tool for the objective assessment of eczema clinical signs.[46] It assesses three components of AD: the affected BSA, severity of clinical signs, and symptoms. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas. The maximum score is 100%. The severity of six specific symptoms of AD (redness, swelling, oozing and/or crusting, excoriation, skin thickening and/or lichenification, dryness) is assessed using the four-point scale (i.e., none = 0, mild = 1, moderate = 2, and or severe = 3), with a maximum of 18 total points. The symptoms (itch and sleeplessness) are recorded by the patient or relative on a visual analogue scale (VAS), in which 0 is no symptom and 10 is the worst imaginable symptom, with a maximum possible score of 20. The SCORAD is calculated based on the three components of the AD. The maximum possible total score is 103, with a higher score indicating poorer or a more-severe condition.[15] The ICC was calculated to assess intra-rater reliability; the coefficient of variation was used to assess inter-rater variability.[19] It was reported that the ICC for the SCORAD was 0.66, indicating fair to good reliability in patients with AD.[19] Based on the analysis of the data from three randomized controlled trials (RCTs) in patients with atopic eczema, the MID was estimated using mean change in SCORAD scores of patients who showed a relevant improvement based on IGA, defined as an "improvement" or "decline" of ≥ 1 point in PGA and IGA. A difference of 8.7 points was the estimated MID for the patients with atopic eczema (also known as AD).[16]

Pruritus Numerical Rating Scale

The pruritus NRS is a tool that patients use to report the intensity of their itch during a daily recall period using an interactive voice response system (IVRS). Patients were asked to rate their overall (average) and maximum intensity of itch experienced during the past 24 hours based on a scale of 0 to 10 (0 = "no itch" and 10 = "worst itch imaginable").[15] The proportion of patients with improvement (reduction ≥ 3 or ≥ 4 points) in weekly average of peak daily pruritus NRS from baseline to week 16 was reported in the pivotal studies.[15] Additional information provided by the sponsor included the validity and reliability of the NRS based on three phase III and one phase IIb RCTs.[25,26] In these RCTs, the NRS item was completed daily from baseline through week 16 and weekly from week 17 to week 52.[25,26] Patient data from weeks 15 and 16 were used to examine test-retest reliability, and ICCs were computed. The pooled ICC from the three RCTs was 0.96, and the ICC from the phase IIb study ranged from 0.95 to 0.97.[25,26] The ICC values indicated that the NRS scores were stable over a period of time when the patients' disease was stable. To assess the validity of the NRS, a priori hypotheses were evaluated using correlational analyses and three known-groups analyses of variance models (an "absent/mild" group based on the pruritus categorical scale; a "poor" disease group based on the PGADS; and a "no impact" on skin-related quality-of-life group based on DLQI total scores). Results for all three known groups were in the anticipated direction and were statistically significant, and the effect sizes for the differences between the extreme categories for each known group were all above Cohen's threshold of 0.80 for large effect sizes (Cohen).[25,26] Based on the data from the phase IIb study, using EASI and IGA as anchors, the NRS responder reportedly ranged between 2.2 and 4.2, with the highest estimates based on the most stringent clinical criteria (EASI = 90-100 and IGA = 0 or 1). Using PCS as an anchor, the responder was estimated as 2.6 points. These analyses suggested that the most appropriate definition of a responder on the pruritus NRS is in the range of 3 to 4 points.[25,26]

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific quality-of-life instrument. It is a 10-item questionnaire that assesses six different aspects that can affect quality of life.[27,28,29] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[27,28] The maximum score per aspect is either 3 (with a single question) or 6 (with two questions), and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 ("not at all") to 3 ("very much") and the overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30).[27,28] The higher the score, the more quality of life is impaired. The meaning of the DLQI scores on a patient's life is as follows:[30]

- 0 to 1 = no effect
- 2 to 5 = small effect
- 6 to 10 = moderate effect
- 11 to 20 = very large effect
- 21 to 30 = extremely large effect.

The validity of the DLQI has been assessed in patients with eczema.[48-51] The DLQI has shown good test-retest reliability (correlation between overall DLQI scores was 0.99, $P < 0.0001$, and for individual question scores it was 0.95 to 0.98, $P < 0.001$),[28] internal consistency reliability (with Cronbach's alpha coefficients ranging from 0.75 to 0.92 when assessed in 12 international studies),[30] construct validity (37 separate studies have mentioned a significant correlation of the DLQI with either generic or dermatology-specific

and disease-specific measures),[30] and responsiveness (the DLQI was able to detect changes before and after treatment in patients with psoriasis in 17 different studies).[30,50,51]

Estimates of the MID ranged from 2.2 to 6.9.[27,30] Some of the anchors that were used to obtain the DLQI MID were not patient-based (e.g., Basra et al.[30] derived estimates from Psoriasis Area and Severity Index and physician global assessment anchors, as well as a distribution-based approach).

Limitations associated with the DLQI are as follows:

- Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their cross-cultural equivalence and age and gender; however, these concerns were only identified in two citations out of the 12 international studies identified.[30]
- The patient's emotional aspects may be underrepresented, and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures, such as the mental component of the Short-Form (36) Health Survey or HADS.[30]
- Benchmarks for the MID of DLQI scores in general dermatological conditions are not available, although there have been some attempts to determine these differences for specific conditions such as psoriasis.[30]
- The DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[52]
- No validity and MID information were found for the patients with AD.[53]

Children's Dermatology Life Quality Index

The CDLQI is a 10-item, widely used questionnaire in clinical practice and clinical trials to measure the impact of skin disease on the quality of life in children.[31,32] The CDLQI measures how much a patient's skin problems affect health-related quality of life. The CDLQI is completed by the child alone and/or with help from the parents or guardian.[31] It covers six areas of daily activities, including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The questions are answered using a four-point Likert scale (scored from 0 to 3 for each question) based on recall of the past week's experiences. Total scores range from 0 to 30, with higher scores indicating a greater degree of health-related quality-of-life impairment.[31] In 2013, Salek et al.[32] conducted a review to assess the clinical application of the CDLQI and its psychometric properties. It was found that a total of 102 studies used the CDLQI for 14 different skin conditions. The majority of the studies (N = 63) were conducted in patients with atopic eczema. Based on studies published between 1995 and 2012, it was reported that the CDLQI had been used internationally in clinical studies and was available in 44 languages. It had been used for many skin conditions and in the assessment of topical and systemic drugs as well as therapeutic interventions. The internal consistency of the CDLQI was good, with six studies reporting alpha values ranging from 0.82 to 0.92 (all greater than the minimum requirement of 0.70 for good internal consistency). Test-retest reliability was calculated in four studies, with Spearman's rank order correlation coefficients ranging from 0.74 to 0.97 ($P < 0.01$). An ICC of 0.80 was reported in one study. Responsiveness was examined in 26 studies, demonstrating the responsiveness to change of the CDLQI. Correlations of the CDLQI with other subjective or objective measures were described in 47 articles. No studies demonstrating content validity were identified. It was also reported that the CDLQI was correlated with the SCORAD in 10 studies. The correlation coefficient ranged from 0.18 to 0.70. Based on the Salek et al. review, it appears that there is evidence of high internal consistency, test-retest reliability, responsiveness to change, and significant correlation with

other subjective and objective measures with the CDLQI.[32] No MID was identified in the literature.

EuroQol 5-Dimensions

The EQ-5D is a generic quality-of-life instrument that has been applied to a wide range of health conditions and treatments, including AD.[54,55] The first part of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of five dimensions: mobility; self-care; usual activities; pain or discomfort; and anxiety or depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their own health state for each of the five dimensions. A scoring function (EQ-5D index score) can be used to assign a value to self-reported health states from a set of population-based preference weights.[54,55] The second part is a 20 cm VAS that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the VAS that best represents their health on that day. The third part is the EQ-5D index score, which is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The EQ-5D therefore produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions, represented by a five-digit descriptor, such as 11121 or 33211
- A population preference-weighted health index score based on the descriptive system
- A self-reported assessment of health status based on the VAS.

The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

The MID for the EQ-5D ranges from 0.033 to 0.074.[56] EQ-5D index utility scores and VAS scores were reported in the pivotal studies.[15,22,23] No additional validity and MID information was found from a literature search for EQ-5D in AD.

Hospital Anxiety and Depression Scale

The HADS is a widely used patient-reported questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions. Repeated administration also provides information about changes in a patient's emotional state.[33-35] The HADS questionnaire contains 14 items that assess symptoms experienced in the previous week, among which seven items are related to anxiety and seven are related to depression. Patients provided responses to each item based on a four-point Likert scale. Each item is scored from 0 (the best) to 3 (the worst); a person can therefore score between 0 and 21 for each subscale (anxiety and depression). A high score was indicative of a poor state. Scores of 11 or more on either subscale were considered to be a "definite case" of psychological morbidity, while scores of 8 to 10 represented "probable case" and 0 to 7 "not a case."[33] One study[57] indicated that HADS had good construct validity, with no overall floor or ceiling effects. HADS may be useful for the assessment of AD patients in clinical trials and practice. The author concluded that additional research is needed to confirm construct validity and to assess content validity and feasibility in research and

clinical practice.[57] No additional validity and MID information regarding HADS was found from a literature search for AD.

Patient-Oriented Eczema Measure

The POEM is a seven-item questionnaire used in clinical trials to assess disease symptoms in children and adults.[36] Based on frequency of occurrence during the past week, the seven items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) are assessed on a five-point scale. The possible scores for each question are: "0" for no days, "1" for one to two days, "2" for three to four days, "3" for five to six days, and "4" for every day. The maximum total score is 28; a high score is indicative of poor quality of life (0 to 2 indicates clear or almost clear, 3 to 7 mild eczema, 8 to 16 moderate eczema, 17 to 24 severe eczema; and 25 to 28 very severe eczema).[36] One study[16] reported that the overall mean MID of the POEM was 3.4 points (standard deviation [SD] = 4.8) when IGA was improving, with one point used as anchor.

In 2018, the minimally important change (MIC) of POEM in children (N = 300) with moderate-to-severe atopic eczema was calculated in one study.[37] Based on distribution-based methods, the estimated MICs were 1.07 (using an SD of 0.2 for baseline POEM scores) and 2.68 (using an SD of 0.5 for baseline POEM scores). The estimated MICs were 3.09 to 6.13 and 3.23 to 5.38 based on patient- or parent-reported anchor-based methods and investigator-reported anchor-based methods, respectively. The authors provided a recommended threshold to interpret changes in POEM scores in children: a score of 3 to 3.9 indicates a probably clinically important change; ≥ 4 indicates a very likely clinically important change.[37]

References

1. CADTH Common Drug Review. Clinical review report dupilumab (Dupixent — Sanofi-Aventis Canada Inc.). Ottawa (ON): CADTH; 2018.
2. NICE. Dupilumab for treating moderate to severe atopic dermatitis after topical treatments *(Technology appraisal guidance TA534)* 2018; https://www.nice.org.uk/guidance/indevelopment/gid-ta10218. Accessed 2018 Jun 7.
3. Ariens LFM, Gadkari A, van Os-Medendorp H, et al. Dupilumab versus cyclosporine for the treatment of moderate-to-severe atopic dermatitis in adults: indirect comparison using the eczema area and severity index. *Acta Derm Venereol.* 2019;99(10):851-857.
4. Alexander H, Patton T, Jabbar-Lopez ZK, Manca A, Flohr C. Novel systemic therapies in atopic dermatitis: What do we need to fulfil the promise of a treatment revolution? *F1000Res.* 2019;8(132).
5. Canadian Pharmacists Association. e-CPS. Ottawa (ON): Canadian Pharmacists Association; 2019: https://www.e-therapeutics.ca. Accessed 2019 Dec 31.
6. Drucker A, Thiruchelvam D, Redelmeier D. Eczema and subsequent suicide: a matched case-control study. *BMJ Open.* 2018;8(11):e023776.
7. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.
8. Grey matters: a practical tool for searching health-related grey literature. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/grey-matters. Accessed 2020 Jan 7.
9. Clinical Study Report: R668-AD-1526. A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥12 to <18 years of age, with moderate-to-severe atopic dermatitis [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2018 Feb 23.
10. Health Canada reviewer's report: Dupixent (dupilumab) [**CONFIDENTIAL** internal report]. Ottawa (ON): Therapeutics Products Directorate, Health Canada; 2019.
11. Center for Drug Evaluation Research. Medical review(s). *Dupixent (dupilumab) injection. Company: Regeneron Pharmaceuticals, Inc. Application No.:761055. Approval date: 03/28/2017 (FDA approval package)*. Rockville (MD): U. S. Food and Drug Administration (FDA); 2017: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761055Orig1s000MedR.pdf. Accessed 2019 Nov 7.
12. CDR submission: Dupixent (dupilumab), 300 mg & 200 mg injection [**CONFIDENTIAL** sponsor's submission]. Mississauga (ON): Sanofi Genzyme; 2019 Oct 22.
13. Worm M, Simpson EL, Thaci D, et al. Efficacy and safety of multiple dupilumab dose regimens after initial successful treatment in patients with atopic dermatitis: a randomized clinical trial. *JAMA Dermatol.* 2019.
14. Clinical Study Report: R668-AD-1225. An open-label study of dupilumab in patients with atopic dermatitis who participated in previous dupilumab clinical trials [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2016 Jul 20.
15. Clinical Study Report: R668-AD-1334. Phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate-to-severe atopic dermatitis [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2015 Feb 5.
16. Schram M, Spuls P, Leeflang M, Lindeboom R, Bos J, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference *Allergy.* 2012;67(1):99-106.
17. Hanifin J, Thurston M, Omoto M, Cherill R, Tofte S, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol.* 2001;10(1):11-18.
18. Schmitt J, Langan S, Deckert S, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation *J Allergy Clin Immunol.* 2013;132(6):1337-1347.
19. Badia-Tahull M, Cobo-Sacristan S, Leiva-Badosa E, et al. Use of Subjective Global Assessment, Patient-Generated Subjective Global Assessment and Nutritional Risk Screening 2002 to evaluate the nutritional status of non-critically ill patients on parenteral nutrition. *Nutr Hosp.* 2014;29(2):411-419.
20. Leshem Y, Hajar T, Hanifin J, Simpson E. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol.* 2015;172(5):1353-1357.
21. Barbier N, Paul C, Luger T, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *Br J Dermatol.* 2004;150(1):96-102.
22. Clinical Study Report: R668-AD-1224. A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis[**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2015 Oct 2.
23. Clinical Study Report: R668-AD-1416. A phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate-tosevere atopic dermatitis [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2015 Feb 5.

24. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. *Dermatology.* 1993;186(1):26-31.

25. Simpson E, Beck L, Gadkari A, Eckert L, Reaney M. Defining a responder on the Peak Pruritus Numerical Rating Scale (NRS) in patients with moderate-to-severe atopic dermatitis: detailed analysis from randomized trials of dupilumab *J Am Acad Dermatol.* 2017;76(6 Suppl 1):AB93.

26. Sanofi Genzyme response to March 2, 2018 CDR request for additional information regarding the Dupixent (dupilumab) CDR review: the clinically meaningful improvement of Peak Pruritus NRS [**CONFIDENTIAL** additional sponsor's information]. Mississauga (ON) Sanofi Genzyme; 2018 Mar 5.

27. Shikiar R, Harding G, Leahy M, Lennox R. Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. *Health Qual Life Outcomes.* 2005;3(36).

28. Finlay A, Khan G. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210-216.

29. Apfelbacher CJ, Ofenloch R. Good evidence on measurement properties of the Dermatology Life Quality Index, Itchy Quality of Life and 5-dimensions itch scales in atopic eczema, but problems with structural validity remain. *Br J Dermatol.* 2019;180(5):979-980.

30. Basra M, Salek M, Camilleri L, Sturkey R, Finlay A. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology.* 2015;230(1):27-33.

31. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol.* 1995;132(6):942-949.

32. Salek MS, Jung S, Brincat-Ruffini LA, et al. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-2012. *Br J Dermatol.* 2013;169(4):734-759.

33. Zigmond A, Snaith R. The hospital anxiety and depression scale *Acta Psychiatr Scand.* 1983;67(6):361-370.

34. Bjelland I, Dahl A, Haug T, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res.* 2002;52(2):69-77.

35. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res.* 1997;42(1):17-41.

36. Charman C, Venn A, Williams H. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. *Arch Dermatol.* 2004;140(12):1513-1519.

37. Howells L, Ratib S, Chalmers J, Bradshaw L, Thomas K, CLOTHES trial team. How should minimally important change scores for the Patient-Oriented Eczema Measure be interpreted? A validation using varied method. *Br J Dermatol.* 2018;178(5):1135-1142.

38. Clinical Study Report: R668-AD-1424. A phase 3 study investigating the efficacy, safety, and tolerability of dupilumab administered to adult patients with severe atopic dermatitis who are not adequately controlled with or are intolerant to oral cyclosporine a, or when this treatment is not medically advisable [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2017 May 11.

39. Clinical Study Report: R668-AD-1434. An open-label extension study to assess the long-term safety and efficacy of dupilumab in patients ≥6 months to <18 years of age with atopic dermatitis [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2018 Sep 7.

40. Clinical Study Report: R668-AD-1412. A phase 2A study investigating the safety, pharmacokinetics, immunogenicity, and exploratory efficacy of dupilumab [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2016 Oct 10.

41. Clinical Study Report: R668-AD-1607. An open-label, randomized, actual use study of dupilumab auto-injector device in patients with atopic dermatitis [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals; 2018.

42. Clinical Study Report: R668-AD-1415. A phase 3, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of multiple dupilumab dose regimens administered as monotherapy for maintaining treatment response in patients with atopic dermatitis [**CONFIDENTIAL** internal sponsor's report]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; .

43. Deleuran M, Thaçi D, Beck L, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol.* 2020;82(2):377-388.

44. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol.* 2019;181(3):459-473.

45. Marks DH, Mesinkovska N, Senna MM. Cause or cure? Review of dupilumab and alopecia areata. *J Am Acad Dermatol.* 2019.

46. Chalmers J, Schmitt J, Apfelbacher C, et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). *Br J Dermatol.* 2014;171:1318-1325.

47. Eichenfield L, Tom W, Chamlin S, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis *J Am Acad Dermatol.* 2014;70(2):338-351.

48. Rehal B, Armstrong A. Health outcome measures in atopic dermatitis: a systematic review of trends in disease severity and quality-of-life instruments 1985-2010. *PLoS One.* 2011;6(4):e17520.

49. Lewis V, Finlay A. 10 years experience of the Dermatology Life Quality Index (DLQI). *J Investig Dermatol Symp Proc.* 2004;9(2):169-180.

50. Reilly M, Lavin P, Kahler K, Pariser D. Validation of the Dermatology Life Quality Index and the Work Productivity and Activity Impairment-Chronic Hand Dermatitis questionnaire in chronic hand dermatitis. *J Am Acad Dermatol.* 2003;48(1):128-130.

51. Wallenhammar L, Nyfjall M, Lindberg M, Meding B. Health-related quality of life and hand eczema--a comparison of two instruments, including factor analysis. *J Invest Dermatol.* 2004;122(6):1381-1389.

52. Fernandez-Penas P, Jones-Caballero M, Espallardo O, Garcia-Diez A. Comparison of Skindex-29, Dermatology Life Quality Index, Psoriasis Disability Index and Medical Outcome Study Short Form 36 in patients with mild to severe psoriasis *Br J Dermatol.* 2012;166(4):884-887.

53. Heinl D, Prinsen C, Deckert S, et al. Measurement properties of adult quality-of-life measurement instruments for eczema: a systematic review. *Allergy.* 2016;71(3):358-370.

54. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.

55. Brooks R. EuroQol: the current state of play. *Health Policy.* 1996;37(1):53-72.

56. Sinnot P, Joyce V, Barnett P. Guidebook: preference measurement in economic analysis Menlo Park (CA): Health Economics Resource Center; 2007: https://www.herc.research.va.gov/files/BOOK_419.pdf. Accessed 2018 Jan 25.

57. Silverberg JI, Gelfand JM, Margolis DJ, et al. Measurement properties of the Hospital Anxiety and Depression Scale used in atopic dermatitis in adults. *J Invest Dermatol.* 2019;139(6):1388-1391.