CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

DUPILUMAB (DUPIXENT)

(Sanofi-Aventis Canada Inc.)

Indication: Moderate-to-severe atopic dermatitis (AD)

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AE	adverse event
AD	atopic dermatitis
BSA	body surface area
CI	confidence interval
CSA	cyclosporine A
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI-75	improvement of ≥ 75% in Eczema Area and Severity Index score from baseline
EQ-5D	EuroQol 5-Dimensions questionnaire
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale–Anxiety Subscale
HADS-D	Hospital Anxiety and Depression Scale–Depression Subscale
IGA	Investigator's Global Assessment
IL	interleukin
IVRS	interactive voice response system
IVWS	interactive Web response system
LS	least squares
NRS	Numerical Rating Scale
MCID	minimal clinically important difference
PGADS	Patient Global Assessment of Disease Status
POEM	Patient-Oriented Eczema Measure
RCT	randomized controlled trial
SAE	serious adverse event
SCORAD	Scoring Atopic Dermatitis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TCS	topical corticosteroids
TCI	topical calcineurin inhibitor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

Drug	Dupilumab (Dupixent)
Indication	For the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.
Reimbursement Request	As per indication
Dosage Form(s)	Solution for subcutaneous injection
NOC Date	30-11-17
Manufacturer	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 (folded skin 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 impacts 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 treatment with specific bathing, cleansing, and moisturizing practices. While there is no cure for AD, there are several therapeutic options available to patients to manage the condition. The majority of patients treat AD 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 corticosteroids (TCS) and topical calcineurin-inhibiting (TCI) compounds. AD is commonly associated with secondary skin infections and the anti-infective drugs commonly used to treat them. If the 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 (e.g., psoriasis).

Dupixent (dupilumab) is a fully human monoclonal antibody in solution that is administered via subcutaneous injection. Dupilumab inhibits interleukin (IL) 4 and IL-13 signalling by binding to the IL-4Rα subunit. IL-4 and IL-13 are important cytokines involved in the release of pro-inflammatory cytokines. Dupixent is indicated for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without TCS.

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

Results and Interpretation

Included Studies

Three phase III randomized controlled trials (RCTs) identified as pivotal trials by the manufacturer (SOLO 1,[4] SOLO 2,[5] and LIBERTY AD CHRONOS[6]) were included in this review. An additional RCT sponsored by the manufacturer also met the inclusion criteria for the review (LIBERTY AD CAFÉ).[7]

SOLO 1 and SOLO 2 were 16-week, randomized, double-blind, 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 dosage 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 with medium-potency TCS daily 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 the clinical study report was published, 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 where 325 patients were randomized to one of three groups with concomitant use of 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.

Generally, the studies were well designed with various measures in place to prevent biases. Internal validity was potentially compromised by missing data, where some of the secondary outcomes were missing over 50% of the data. In addition, several of the secondary outcomes did not have AD-specific minimal clinically important difference (MCID) values, limiting the ability to quantitatively make conclusions regarding clinical significance. External validity of the studies was limited by the use of placebo-controls; thus, no information on the relative efficacy of dupilumab to active comparators could be obtained from the trials. At the time of preparation of this review, none of the extended follow-up studies were available for assessment.

Efficacy

The severity of AD was assessed using the proportion of patients with 75% or greater improvement from baseline in the Eczema Area and Severity Index (EASI-75), the Investigator's Global Assessment (IGA) score, and the Scoring Atopic Dermatitis

(SCORAD) tool. The EASI-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 with the placebo group with a range in difference of proportion across trials from 32.3% (95% confidence interval [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 a reduction from baseline of two 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 with the placebo group, 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). Each trial yielded statistically significant findings ($P < 0.0001$). While no relevant MCID 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 percentage change in SCORAD from baseline to week 16 was a secondary end point across all four trials. The least squares (LS) percentage mean change from baseline was greater in the dupilumab group compared with the placebo group. Across trials, the LS mean difference in SCORAD score between the 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. Subgroup analysis for moderate AD and severe AD revealed greater efficacy in the dupilumab groups compared with placebo for both the EASI-75 and IGA end points.

Symptoms of AD were assessed using the Pruritus Numerical Rating Scale (NRS) and the Patient-Oriented Eczema Measure (POEM). The proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of four or more points from baseline to week 16 was one of the secondary end points in all of the studies. Compared with 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 for the proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of three 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 percentage change in POEM from baseline to week 16 was an additional secondary end point across all four trials. The LS mean change from baseline was greater in the dupilumab group compared with the placebo group. Across trials, the LS mean difference in POEM score between the 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 was statistically significant ($P < 0.0001$) and clinically significant (MCID = 3.4[8]) across all trials. Although the Pruritus NRS was statistically significant, no AD-specific validity or AD-specific MCID information was found in the literature search, but the clinical expert stated that the findings were clinically relevant.

Health-related quality of life was assessed as the secondary end point across all trials using the change from baseline to week 16 in the Dermatology Life Quality Index (DLQI) and the EuroQol 5-Dimensions questionnaire (EQ-5D). The LS mean change from baseline was greater in the dupilumab group compared with the placebo group. Across trials, the difference in the LS mean change from baseline in DLQI score between the 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 was both statistically significant ($P < 0.0001$) and potentially clinically relevant based on

an MCID 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 LS mean change from baseline was numerically greater in the dupilumab group compared with the placebo group in the SOLO trials and in LIBERTY AD CHRONOS. Across the three trials, the difference in LS mean change from baseline in the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) index utility score between the 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 LS mean difference was statistically significant ($P < 0.0001$) in SOLO 1 and SOLO 2 and, while no AD-specific MCID exists, the results in the trials are clinically relevant based on the general MCID for the EQ-5D, which ranged from 0.033 to 0.074. 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.

Harms

Adverse events (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 in the infections and infestations category, which 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 and affected 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. Serious AEs were reported in 1.7% to 4.7% of patients in the dupilumab group and 3.5% to 9.3% in the placebo group. [redacted]. 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. [redacted].

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

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 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 potent TCS. In LIBERTY AD CHRONOS and LIBERTY AD CAFÉ, 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 with the placebo group, 3.8% to 15.0% and 0.4% to 6.5%, respectively.

Potential Place in Therapy[1]

Dupilumab, an IL-4 and IL13 antagonist that limits type 2 T helper–driven inflammatory activity, is the first biologic drug approved for treatment of moderate and severe AD in Canada.

Dupilumab has, in phase III trials, demonstrated efficacy in AD through 52 weeks of treatment.[6] There is evidence that dupilumab is effective in patients who have failed cyclosporine.[7] Safety analyses through 52 weeks have not shown serious concerns.

Presently, patients achieving suboptimal disease control with appropriate disease-specific skin care measures (irritant avoidance, emollients, bleach baths, etc.), TCS and/or TCIs, and narrow-band ultraviolet B (NB-UVB) phototherapy are offered treatment with off-label immunosuppressive drugs. In Canada, the most commonly chosen immunosuppressive drug is methotrexate, followed by cyclosporine, azathioprine, and mycophenolate mofetil. Because of their potential toxicities, these drugs are generally prescribed as intermittent courses in AD. There are patients for whom some or all of these drugs are contraindicated or for whom toxicities limit their use. There are also patients who do not respond to these drugs.

In practice, dupilumab will likely offer a useful alternative for those patients who have contraindications to, experience adverse effects from, or are unresponsive to the immunosuppressive drugs. It will also be useful for the subset of patients who respond to immunosuppressive drugs but who require continuous long-term systemic therapy.

Conclusions

Four phase III, placebo-controlled RCTs were included in this review. 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 considered pivotal by the manufacturer and Health Canada.

Consistently across all trials, there was a statistically significantly ($P < 0.0001$) greater percentage of patients with improvements (reductions) in AD severity in the dupilumab group compared with the placebo group. The clinical expert consulted for this review indicated that the cut-offs for the primary efficacy end points (i.e., the proportion of patients with IGA 0 or 1 (on a five-point scale) and a reduction from baseline of two or more points at week 16, and the proportion of patients with EASI-75) used in the studies were clinically relevant. There were also statistically significant improvements ($P < 0.0001$) found for the secondary efficacy end points assessed (including AD symptoms reduction and quality of life) across all trials.

The most common AEs were in the infections and infestations category and similarly affected both the placebo and dupilumab groups. The prevalence of AD flares, worsening, or aggravation that required or prolonged hospitalization (reported as “dermatitis atopic”) was greater in the placebo group, where 14.8% to 35% of patients in the placebo group were affected compared with 7.5% to 14% of patients in the dupilumab group for SOLO 1, SOLO 2, and LIBERTY AD CAFÉ.[9,10] In LIBERTY AD CHRONOS at week 52, 46% of

[1] This information is based on information provided in draft form by the clinical expert consulted by the CDR reviewers for the purpose of this review.

patients in the placebo group and 18% of patients in the dupilumab group experienced AD flare–related AEs.[11] Trials without the concomitant use of TCS (SOLO 1 and SOLO 2) had [redacted]. Across all trials, patients in the dupilumab group had higher occurrences of eye disorders (including conjunctivitis), injection-site reactions, and herpes simplex infections compared with the placebo group.

There is an absence of evidence to assess the long-term effects of dupilumab as monotherapy and as a concomitant treatment with TCS beyond 16 weeks and 52 weeks of treatment, respectively. Additionally, there were no active comparator trials identified in the CADTH Common Drug Review (CDR) systematic review to assess the efficacy and safety of dupilumab versus drugs that are commonly used in clinical practice.

Table 1: Summary of Results

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
IGA score of 0 or 1 and reduction from baseline of ≥ 2 points										
N (%)	23 (10.3)	85 (37.9)	20 (8.5)	84 (36.1)	39 (12.4)	41 (38.7)	33 (12.5)	32 (36.0)	15 (13.9)	43 (40.2)
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 (%)	33 (14.7)	115 (51.3)	28 (11.9)	103 (44.2)	73 (23.2)	73 (68.9)	57 (21.6)	58 (65.2)	32 (29.6)	67 (62.6)
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
SCORAD										
Baseline mean (SD)	68.3 (13.9)	66.9 (13.9)	69.2 (14.8)	67.2 (13.4)	66.0 (13.5)	69.3 (15.2)	65.7(13.3)	69.9 (15.1)	67.0(12.2)	68.6 (11.9)
N observed / N imputed	97/127	172/52	105/131	193/40	188/127	92/14	101/163	71/18	89/19	103/4
LS mean change (SE)	−29.0 (3.2)	−57.7 (2.1)	−19.7 (2.5)	−51.1 (2.0)	−36.2 (1.7)	−63.9 (2.5)	−47.3 (2.2)	−69.7 (3.1)	−29.5 (2.6)	−62.4 (2.5)
LS mean 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)
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	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
peak daily Pruritus NRS score reduction of ≥ 4										
N/N1 (%)	26/212 (12.3)	87/213 (40.8)	21/221 (9.5)	81/225 (36.0)	59/299 (19.7)	60/102 (58.8)	32/249 (12.9)	44/86 (51.2)	13/91 (14.3)	43/94 (45.7)
Difference (%) (95% CI)[a]		28.6 (20.6 to 36.5)		26.5 (19.1 to 33.9)		39.1 (28.5 to 49.6)		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 (%)	38/221 (17.2)	103/220 (46.8)	29/226 (12.8)	117/231 (50.6)	85/306 (27.8)	69/105 (65.7)	40/256 (15.6)	49/88 (55.7)	20/98 (20.4)	57/99 (57.6)
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)	20.3 (5.89)	19.8 (6.37)	21.0 (5.94)	20.8 (5.49)	20.0 (5.98)	20.3 (5.68)	20.1 (6.03)	20.6 (5.66)	19.1 (5.96)	19.3 (6.21)
N observed / N imputed	96/128	173/51	104/132	196/37	187/128	92/14	99/165	71/18	88/20	103/4
LS mean change (SE)	−5.1 (0.7)	−11.6 (0.5)	−3.3 (0.6)	−10.2 (0.5)	−5.3 (0.41)	−12.7 (0.6)	−7.0 (0.57)	−14.2 (0.78)	−4.3 (0.62)	−11.9 (0.60)
LS mean difference (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
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)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
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N observed / N imputed	96/128	173/51	105/131	197/36	188/127	92/14	NR	NR	89/19	103/4
LS mean change (SE)[e]	0.1 (0.0)	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	NR	NR	−90.0 (79.0)	−8.2 (79.2)
P value[c, d]		< 0.0001		< 0.0001		0.0058		NR		0.4577
LS mean difference (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)	14.8 (7.21)	13.9 (7.37)	15.4 (7.69)	15.4 (7.07)	14.7 (7.37)	14.5 (7.31)	15.2 (7.35)	15.0 (7.32)	13.2 (7.60)	14.5 (7.63)
N observed / N imputed	97/127	173/51	105/131	197/36	187/128	92/14	101/163	71/18	89/19	103/4
LS mean change (SE)	−5.3 (0.5)	−9.3 (0.4)	−3.6 (0.5)	−9.3 (0.4)	−5.8 (0.3)	−10.0 (0.5)	−7.2 (0.4)	−11.4 (0.6)	−4.5 (0.5)	−9.5 (0.5)
LS mean difference (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 (%)	40 (17.9)	16 (7.1)	46 (19.5)	13 (5.6)			52 (16.5)	9 (8.5)	5 (4.6)	0
SAEs										
N (%)	11 (5.0)	7 (3.1)	17 (7.3)	4 (1.7)			11 (3.5)	4 (3.6)	10 (9.3)	5 (4.7)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
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WDAEs										
N (%)	2 (0.9)	4 (1.7)	5 (2.1)	2 (0.8)			15 (4.8)	1 (0.9)	1 (0.9)	0
Notable harms, N (%)										
Dermatitis atopic[f]	67 (30)	30 (13)	81 (35)	32 (14)	[redacted]	[redacted]	[redacted]	[redacted]	16 (14.8)	8 (7.5)
Rescue medication use										
N (%)	115 (51.8)	48 (21.0)	122 (52.1)	38 (16.1)			120 (38.1)	12 (10.9)	19 (17.6)	4 (3.7)

ANCOVA = analysis of covariance; CI = confidence interval; CSA = cyclosporine A; DLQI = Dermatology Life Quality Index; EASI-75 = improvement of ≥ 75% in Eczema Area and Severity Index (EASI) score from baseline; EQ-5D = EuroQol 5-Dimensions questionnaire; IGA = Investigator's Global Assessment; LS = least squares; NA = not applicable; NR = not recorded; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; q.2.w. = once every two weeks; SAE = serious adverse event; SCORAD = Scoring Atopic Dermatitis; SD = standard deviation; SE = standard error; TCS = topical corticosteroids; WDAE = withdrawal due to adverse event.

[a] Difference is dupilumab minus placebo. CI 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] The CI with *P* value is based on the treatment difference (dupilumab group versus placebo) of the LS mean change using ANCOVA model with baseline measurement as 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 percentage change/difference in LS mean in LIBERTY AD CAFÉ.

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

Source: Simpson, 2016;[9] Blauvelt, 2017;[11] De Bruin-Weller, 2017;[10] and clinical study reports for SOLO 1,[4] SOLO 2,[5] LIBERTY AD CHRONOS[6] and LIBERTY AD CAFÉ.[7]

Introduction

Disease Prevalence and Incidence

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 (rash). 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 (folded skin behind the knees) and the antecubital) folded skin 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.

AD is a hereditary form of eczema that generally presents in infancy with most cases beginning before the age of five.[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 there is evidence to suggest that 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 result in 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 patient experiences describe a physically and mentally exhausting condition that can result in anxiety, depression, and decrease in quality of life.

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

Standards of Therapy

General Skin Care

General skin care practices for patients with AD include irritant avoidance and managing dry skin. The symptoms of AD may be reduced or prevented through the avoidance of 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, has been recommended to 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 to 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. The use of moisturizers is important 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 act to soften the skin; reduce itching; and minimize cracking, fissuring, and lichenification.[3,14] Moisturizes 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, soy sterols) lubricate and soften the skin by smoothing out the surface of the skin by 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 when applied to open skin and are not useful in children with AD. Occlusive agents (e.g., petrolatum, dimethicone, 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 topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). TCS act as anti-inflammatory therapy and are considered to be the first-line treatment for AD.[2] There are over 30 different types of TCS, which can take the form of lotions, creams, oily creams, ointments, or gels and can be combined with other drugs, such as antibiotics.[15] TCS vary in potency. In Canada, hydrocortisone 1% (low potency) is the most commonly prescribed type of TCS for the face.[3] For the body, triamcinolone or betamethasone valerate (moderate potency) are most commonly prescribed. TCS are 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 of TCS 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] TCIs are steroid-free, anti-inflammatory, immunosuppressant drugs that can be used long-term. In Canada, the two second-line drugs available 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 is an ointment that can be used for short-term and intermittent long-term therapy of moderate-to-severe AD, and demonstrates rapid and sustained AD symptom control.[3,15] The most common AE associated with TCIs is application site–specific burning and irritation.[2,3]

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 antimicrobial, antihistamine, or immunomodulatory drugs.[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 drug depends upon the skin culture and sensitivity profile. Sedating antihistamines have been used in cases where patients are not achieving adequate sleep due to itching.[1,15] Immunomodulatory drugs, 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 commonly used off-label treatments are used in the lowest dose for the shortest duration possible due to side effects.[16,17]

Other Therapy

Phototherapy is another second-line therapy that is commonly used after failure of TCS and TCIs. 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 clinical expert consulted for this CADTH Common Drug Review (CDR), there have been cases where AD has been treated with off-label drugs including retinoids (e.g., acitretin, alitretinoin), biologics (e.g., ustekinumab), and small molecules (e.g., apremilast).

Drug

Dupixent (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-4Rα subunit. IL-4 and IL-13 are important cytokines involved in release of pro-inflammatory cytokines.

Dupilumab is indicated for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of dupilumab (Dupixent) for the treatment of patients with moderate-to-severe AD.

Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to CDR, as well as those meeting the selection criteria presented in Table 1.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients 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 to one or more systemic therapy
Intervention	Subcutaneous injections of dupilumab with an initial dose of 600 mg followed by 300 mg given every other week, alone or in combination with TCS.
Comparators	The following comparators used alone or in combination with topical therapy: • immune-modulating drugs[a] (e.g., methotrexate, cyclosporine A, azathioprine, mycophenolate mofetil • retinoids[a] (e.g., acitretin, alitretinoin[b]) • biologics[a] (e.g., ustekinumab) • small molecules[a] (e.g., ampremilast[c]) • placebo
Outcomes	**Key efficacy outcomes:** • Severity of AD and AD lesions (e.g., IGA score, EASI, SCORAD) • Symptom reduction (e.g., pruritus[d], pain, sleep disturbance[d]) • Health-related quality of life[d] (e.g., EQ-5D score, DLQI score) **Other efficacy outcomes:** • Mood (e.g., anxiety,[d] depression[d]) • Productivity (e.g., days of missed work/school) **Harms outcomes:** • AEs • SAEs • WDAEs • AEs of special interest (e.g., exacerbations/flares,[d] injection-site reaction, hypersensitivity, conjunctivitis)
Study Design	Published and unpublished phase III RCTs

AD = atopic dermatitis; AE = adverse event; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D = EuroQol 5-Dimensions questionnaire; IGA = Investigator's Global Assessment; RCT = randomized controlled trial; SAE = serious adverse event; SCORAD = Scoring Atopic Dermatitis; TCS = topical corticosteroids; q.2.w. = once every two weeks; WDAE = withdrawal due to adverse event.

[a] These drugs do not have a Health Canada–approved indication for the treatment of adult patients with AD; however their use is supported by clinical guidelines[16] or are commonly used in clinical practice, according to the clinical expert consulted for this review.

[b] Drug has Health Canada–approved indication for the treatment of adult patients with severe hand eczema.

[c] Drug has Health Canada–approved indication for the treatment of adult patients with moderate-to-severe plaque psoriasis and psoriatic arthritis.

[d] Outcomes identified as important from patient input.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Dupixent (dupilumab).

No methodological filters were applied to limit retrieval to study type. Retrieval was not limited by publication year 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 23, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on April 11, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Results

Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are presented in Table 3; excluded studies (with reasons) are presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

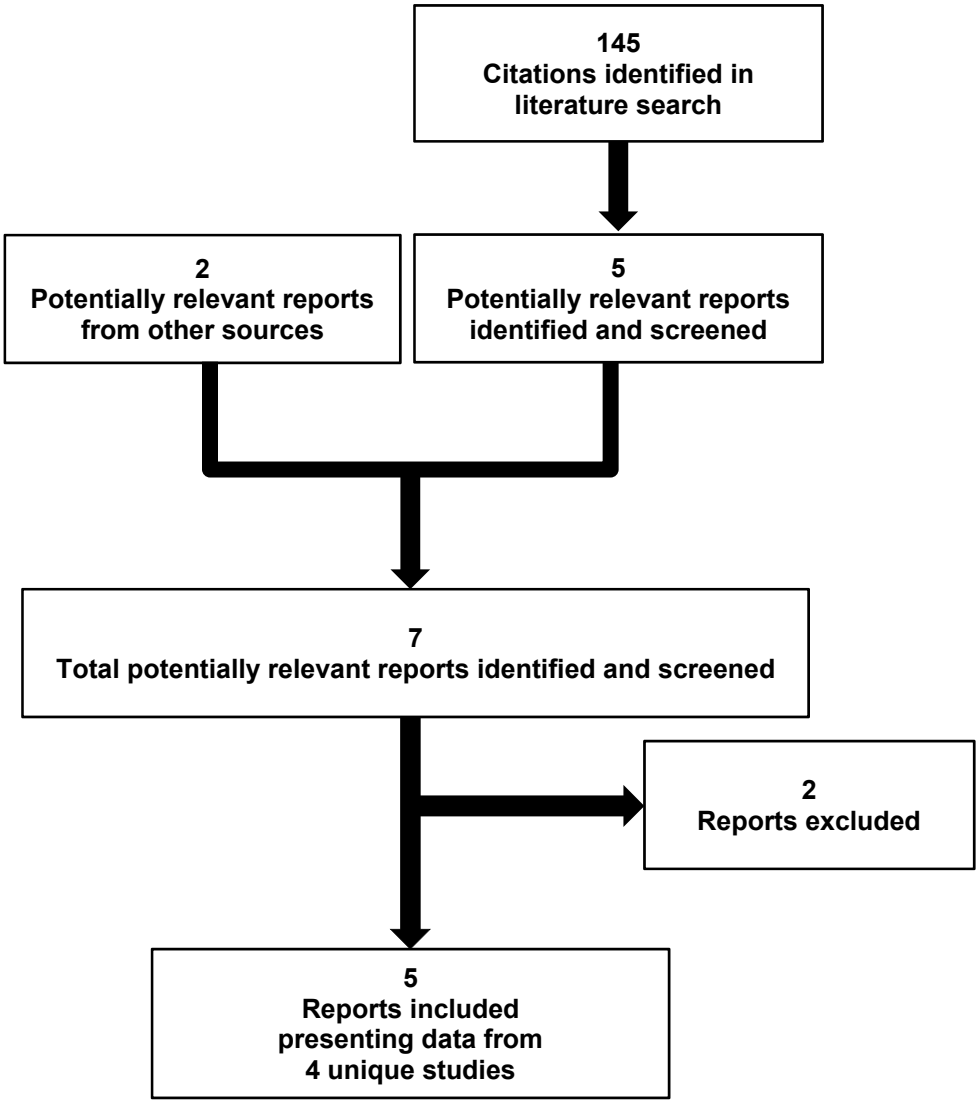


Table 3: Details of Included Studies

		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, and ≥ 10% BSA with AD, where topical treatment was inadvisable or provided inadequate treatment. Patients had to have had 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, and ≥ 10% BSA with AD, where topical treatment was inadvisable or provided inadequate treatment. Patients had to have had 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, and ≥ 10% BSA with AD, where topical treatment was provided inadequate treatment. Patients had to have had 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, and ≥ 10% BSA with AD, where treatment with potent TCS was indicated, but who had had inadequate response to TCS. History of: • prior CSA exposure and either inadequate response to CSA or intolerance and/or unacceptable toxicity or • no prior exposure (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 substance or excipients.
	Exclusion Criteria	Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, treatment with immunosuppressive or	Participation in prior dupilumab clinical study, treatment with investigational drug within 8 weeks, treatment with immunosuppressive 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 or intolerance to TCS, treatment with

		SOLO 1	SOLO 2	LIBERTY AD CHRONOS	LIBERTY AD CAFÉ
		immunomodulating drugs, or phototherapy within 4 weeks of baseline visit, treatment with TCS or TCI within 1 week before baseline visit, or treatment with biologics within 6 months of the baseline visit.	immunomodulating drugs, or phototherapy within 4 weeks of baseline visit, treatment with TCS or TCI within 1 week before baseline visit, or 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 medium or higher potency TCS. Treatment with TCS or TCI within 1 week before the baseline visit.	systemic CSA or systemic corticosteroids, or phototherapy within 4 weeks of screening, treatment with 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 of 0 or 1 and a reduction from baseline of ≥ 2 points at week 16. Proportion of patients with ≥ 75% improvement on the EASI-75 at week 16.	Proportion of patients with IGA of 0 or 1 and a reduction from baseline of ≥ 2 points at week 16. Proportion of patients with ≥ 75% improvement on the EASI-75 at week 16.	Proportion of patients with IGA of 0 or 1 and a reduction from baseline of ≥ 2 points at week 16. Proportion of patients with ≥ 75% improvement on the EASI-75 at week 16.	Proportion of patients with ≥ 75% improvement on the EASI-75 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 days / missed school days assessment	The change from baseline to week 16 in the SCORAD; DLQI; POEM; HADS; EQ-5D Sick-leave days / 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. Percentage change from baseline to week 16 in weekly average of peak daily Pruritus NRS. The change from baseline to weeks 16 and 52 in the SCORAD, DLQI, POEM, and HADS.	≥ 4 points) of weekly average of peak daily Pruritus NRS from baseline to week 16. The change from baseline to week 16 in the SCORAD, DLQI, POEM, and HADS.
NOTES	**Publications**	Simpson, 2016[9]	Simpson, 2016[9]	Blauvelt, 2017[11]	De Bruin-Weller, 2017[10]

AD = atopic dermatitis; BSA = body surface area; CSA = cyclosporine A; DB = double blind; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-75 = improvement of ≥ 75% in EASI score from baseline; EQ-5D = EuroQol 5-Dimensions questionnaire; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; q.2.w. = once every two weeks; q.w. = once weekly; RCT = randomized control trial; SC = subcutaneous; SCORAD = scoring atopic dermatitis; TCI = topical calcineurin; TCS = topical corticosteroids.

Note: Two additional reports were included (CADTH Common Drug Review submission[18] and Health Canada reviewers' report[19]).

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

Included Studies

Description of Studies

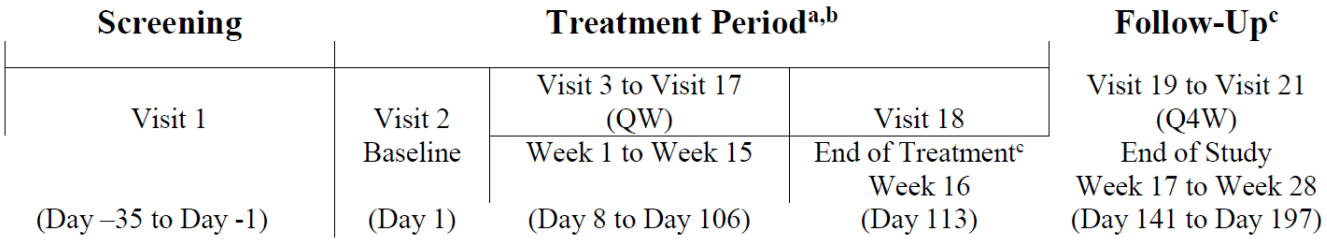
Four phase III randomized controlled trials (RCTs) were identified by the manufacturer. These included three 16-week trials (SOLO 1, SOLO 2, and LIBERTY AD CAFÉ) and one 52-week trial (LIBERTY AD CHRONOS).[4-7] SOLO 1, SOLO 2, and LIBERTY AD CHRONOS were classified as pivotal by the manufacturer and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

SOLO 1 and SOLO 2

The manufacturer sponsored two phase III trials of identical design. SOLO 1 and SOLO 2 were double-blind, placebo-controlled, parallel-group, randomized trials. Within the 35 days prior to randomization, patients were washed out if they had used other AD treatments. This included use of immunosuppressive or immunomodulating drugs and phototherapy, which could not be used within four weeks prior to baseline; treatment with TCS or TCIs within one week prior to baseline; and regular use (more than two uses per week) of a tanning bed 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). The dosing schedule for dupilumab once every other week was consistent with the Health Canada–recommended dosage and was the focus of this review. Patients were randomized using a central randomization scheme provided by an interactive voice response (IVRS) / interactive Web response system (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 [Investigator's Global Assessment [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 the individuals involved in the study. To ensure blinding, patients in the group being treated every two weeks received injections with placebo on the 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 an SAE. In these studies, patients and/or caregivers were provided with training on subcutaneous injection protocols for the initial four visits or until they were competent. Throughout the entire trial, the option for injections to be administered by clinical staff 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. Figure 2 shows a visual representation of the study design for SOLO 1 and SOLO 2.

Figure 2: Design of SOLO 1 and SOLO 2



[a] Patients received a loading dose of study drug on day 1 and then received dupilumab weekly or every 2 weeks or matching placebo during the subsequent 15 weeks. Patients in the Q2W group received matching placebo in the weeks when dupilumab was not administered.

[b] Patients remained at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug from day 1 through week 2.

[c] The follow-up period was for those patients who declined to enter the open-label extension or the maintenance study.

Q2W = once every two weeks; Q4W = once every four weeks; QW = once weekly.

Source: Clinical study reports for SOLO 1[4] and SOLO 2.[5]

LIBERTY AD CHRONOS

The LIBERTY AD CHRONOS trial was a long-term manufacturer-sponsored study. Similar to the SOLO trials, LIBERTY AD CHRONOS was a randomized, double-blind, placebo-controlled, parallel-group trial. Patients were randomized using IVRS/IWRS in a 3:1:3 ratio for treatment with the following: weekly subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day one, or treatment every other week with subcutaneous injections of 300 mg dupilumab (and treatment with placebo in between weeks) following a loading dose of 600 mg on day one (in accordance with the Health Canada–approved dosage), or weekly subcutaneous injections of placebo, respectively. Similar to the SOLO trials, randomization was stratified by baseline disease severity and geographic region, patients underwent a run-in period of up to 35 days to allow for washout of various alternative treatments for AD, patients were given the same subcutaneous injection training and the option of clinician-administered injections throughout the study, and blinding procedures were the same. Patients in all three groups were also treated with medium-potency TCS daily on areas of the skin with active lesions. Lesions under control (clear or almost clear) were treated with low-potency TCS for seven days. Patients could be treated with TCIs on problem areas that had not been treated concomitantly with TCS.

Patients in LIBERTY AD CHRONOS were enrolled from North America, Europe, and Asia from approximately 250 sites. For this trial, 740 patients were randomized; by the pre-specified cut-off date of April 27, 2016, 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. Figure 3 shows a visual representation of the study design for LIBERTY AD CHRONOS.

Figure 3: Design of LIBRETY AD CHRONOS

Screening	Treatment Period (Weeks, Days)[a,b]							Follow-Up
V1	V2	V3	V4	V5	V6	V7- V18 (QW)	V19-V27 (Q4W)	V28-V30 (Q4W)
(Day –35 to - 1)	Baseline (Day 1)	W1 Day 8	W2 Day 15	W3 Day 22	W4 Day 29	W5 W16 Day 36-113	W20-W52 End of Treatment Day 141-365	W56-W64 End of Study Day 393-449

a Patients received: 600 mg SC dupilumab loading dose on day 1 and then 300 mg dupilumab QW starting at day 8; 600 mg SC dupilumab loading dose on day 1 and then 300 mg Q2W starting at day 15; or matching placebo with a placebo "loading dose" on day 1.

b Patients remained at the study site for a minimum of 30 minutes after each of the first 3 doses of study drug on day 1, day 8, and day 15.

Q2W = once every two weeks, Q4W = once every four weeks; QW = once weekly; SC = subcutaneous; V = visit; W = week.

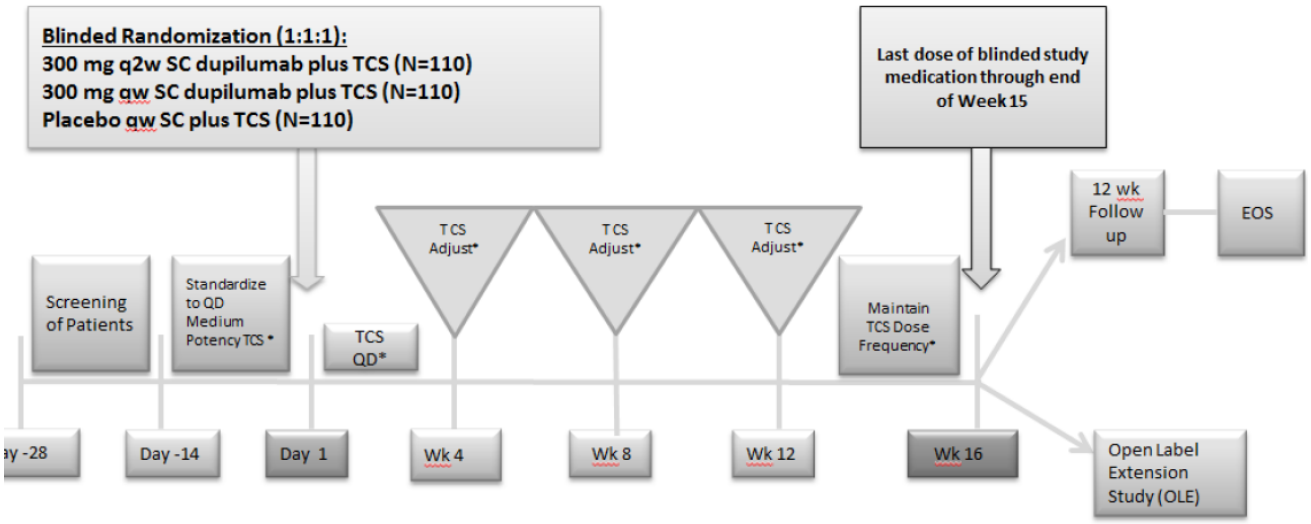
Source: Clinical study report for LIBERTY AD CHRONOS.[6]

LIBERTY AD CAFÉ

The LIBERTY AD CAFÉ trial was a 16-week manufacturer-sponsored study. Similar to the other trials, LIBERTY AD CAFÉ was a randomized, double-blind, placebo-controlled, parallel-group trial. Patients were randomized in a 1:1:1 ratio for treatment with the following: weekly subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day one, or treatment every other week with subcutaneous injections of 300 mg dupilumab (and treatment with placebo in between weeks) following a loading dose of 600 mg on day one (in accordance with the Health Canada–approved dosage), or weekly subcutaneous injections of placebo, respectively. For this trial, randomization was stratified by baseline disease severity and CSA history (no prior CSA exposure and not currently a candidate for cyclosporine A (CSA) treatment, or prior CSA exposure that should not have been continued or restarted). Patients underwent a run-in period of up to 28 days to allow for washout of various alternative treatments for AD. Consistent with the other studies, patients were given the same subcutaneous injection training and an option for clinician-administered injections throughout the study, and blinding procedures were the same. Consistent with LIBERTY AD CHRONOS, patients in all three groups were also treated with medium-potency TCS daily on areas of the skin with active lesions. Lesions under control (clear or almost clear) were treated with low-potency TCS for seven days. Patients could be treated with TCIs on problem areas that had not been treated concomitantly with TCS.

Patients in LIBERTY AD CAFÉ were enrolled from Europe and were planned to be enrolled from approximately 115 sites in countries where systemic CSA was approved for the treatment of AD. For this trial, 325 patients were randomized. Patients enrolled in the trial were treated over the course of 16 weeks and either followed up for an additional 12 weeks or transitioned to an open-label extension study. Figure 4 shows a visual representation of the study design for LIBERTY AD CAFÉ.

Figure 4: Study Design for LIBERTY AD CAFÉ



*A symptom-based (IGA) adjustment per protocol-specified TCS tapering algorithm.

EOS = end of study; IGA = Investigator's Global Assessment; q2w = once every two weeks; QD = once daily; qw = once weekly; SC = subcutaneous; TCS = topical corticosteroids; wk = week.

Source: Clinical study report for LIBERTY AD CAFÉ.[7]

Populations

Inclusion and Exclusion Criteria

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 (i.e., EASI score greater than or equal to 16, IGA score greater than or equal to 3). The main unique inclusion criteria for the SOLO trials required patients where topical treatment was inadvisable or provided inadequate treatment. This is contrary to the criteria in the LIBERTY AD CHRONOS trial that required only patients where topical treatment provided inadequate treatment and excluded patients that experienced important side effects to topical medications (e.g., intolerance, 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 the score of 16 or more required for the other three studies. The SOLO trials and LIBERTY AD CHRONOS excluded patients who received treatment with TCS or TCIs within one week prior to the baseline visit. Patients in LIBERTY AD CAFÉ were excluded if they received treatment with TCIs 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

The baseline characteristics were relatively balanced between groups for each study. Across studies, 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% not identifying as such. The majority of patients, ranging from 65.2% to 97.2%, identified their race as white, and male patients comprised 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. LIBERTY AD CAFÉ recruited patients from Europe, with approximately 62% originating from Western Europe, and over 96% identified 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 4 summarizes the baseline characteristics for each trial.

Table 4: Summary of Baseline Characteristics

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

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
Chronic AD diagnosis age, n (%)								
Before the age of 5	118 (52.7)	117 (52.2)	131 (55.5)	122 (52.4)	180 (57.1)	61 (57.5)	67 (62.0)	73 (68.2)
Between ages 5 and 9	37 (16.5)	30 (13.4)	30 (12.7)	31 (13.3)	45 (14.3)	9 (8.5)	9 (8.3)	5 (4.7)
Between ages 10 and 19	23 (10.3)	32 (14.3)	37 (15.7)	31 (13.3)	37 (11.7)	19 (17.9)	11 (10.2)	12 (11.2)
Between ages 20 and 29	16 (7.1)	14 (6.3)	12 (5.1)	24 (10.3)	20 (6.3)	7 (6.6)	7 (6.5)	6 (5.6)
Between ages 30 and 39	10 (4.5)	12 (5.4)	11 (4.7)	9 (3.9)	12 (3.8)	2 (1.9)	6 (5.6)	6 (5.6)
Aged 40 years and above	18 (8.0)	19 (8.5)	12 (5.1)	13 (5.6)	21 (6.7)	8 (7.5)	8 (7.4)	5 (4.7)
Unsure	1 (0.4)	0	3 (1.3)	3 (1.3)	0	0		
Missing	1 (0.4)	0						
Duration of AD, years mean (SD)	29.5 (14.5)	28.5 (16.1)	28.2 (14.4)	27.2 (14.2)	27.5 (14.3)	30.1 (15.5)	29.2 (14.7)	29.6 (15.6)
EASI score, mean (SD)	34.5 (14.5)	33.0 (13.6)	33.6 (14.3)	31.8 (13.1)	32.6 (12.9)	33.6 (13.3)	34.4 (10.1)	33.5 (10.5)
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)
Weekly average of peak daily Pruritus NRS,[a] mean (SD)	7.4 (1.8)	7.2 (1.9)	7.5 (1.8)	7.6 (1.60)	7.3 (1.8)	7.4 (1.7)	6.4 (2.2)	6.4 (2.2)
SCORAD score, mean (SD)	68.3 (14.0)	66.9 (14.0)	69.2 (14.9)	67.2 (13.5)	66.0 (13.5)	69.3 (15.2)	68.8 (11.1)	68.4 (10.5)
DLQI score, mean (SD)	14.8 (7.2)	13.9 (7.4)	15.4 (7.7)	15.4 (7.1)	14.7 (7.4)	14.5 (7.3)	13.0 (6.8)	13.3 (7.8)
PGAD, n (%)								
Poor (scale = 1)	109 (48.7)	87 (38.8)	111 (47.0)	95 (40.8)	139 (44.1)	49 (46.2)	21 (30.9)	15 (23.1)
Fair (scale = 2)	75 (33.5)	86 (38.4)	67 (28.4)	85 (36.5)	117 (37.1)	35 (33.0)	28 (41.2)	25 (38.5)
Good (scale = 3)	33 (14.7)	39 (17.4)	46 (19.5)	45 (19.3)	46 (14.6)	21 (19.8)	14 (20.6)	21 (32.3)
Very good (scale = 4)	6 (2.7)	11 (4.9)	9 (3.8)	8 (3.4)	12 (3.8)	1 (0.9)	5 (7.4)	3 (4.6)
Excellent (scale = 5)	0	1 (0.4)	3 (1.3)	0	1 (0.3)	0	0	1 (1.5)
Missing	1 (0.4)	0						
POEM, mean (SD)	20.3 (5.9)	19.8 (6.4)	21.0 (5.9)	20.8 (5.5)	20.0 (6.0)	20.3 (5.7)	19.5 (5.6)	18.7 (6.5)
EQ-5D visual analogue scale, mean (SD)	54.7 (24.8)	56.8 (23.3)	57.0 (24.4)	55.4 (23.0)	56.5 (23.7)	57.9 (22.6)	53.0 (22.3)	57.4 (21.7)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
EQ-5D utility, mean (SD)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.7(0.3)	0.7 (0.2)	0.8 (0.2)
Total HADS, mean (SD)	12.6 (8.3)	12.2 (7.3)	13.7 (8.3)	13.7 (7.5)	12.6 (8.1)	12.9 (7.7)	12.4 (7.2)	11.7 (8.5)
HADS-A, mean (SD)	7.0 (4.5)	7.0 (4.1)	7.8 (4.5)	7.5 (4.1)	7.0 (4.4)	7.4 (4.2)	6.8 (4.2)	6.4 (4.5)
HADS-D, mean (SD)	5.6 (4.7)	5.2 (3.9)	5.9 (4.5)	6.2 (4.2)	5.5 (4.3)	5.5 (4.3)	5.6 (3.9)	5.3 (4.8)

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

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

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

Interventions

In the SOLO trials, patients received treatment with subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day one. Patients received treatment with dupilumab weekly or once every two weeks. For patients in the group receiving treatment every two weeks, 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 the placebo given on day one to match the loading dose. Both SOLO 1 and SOLO 2 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. TCS or TCIs 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 had interventions similar to the SOLO trials with one major difference. In addition to treatment with dupilumab weekly or once every two weeks or treatment with placebo, patients were required to initiate treatment on day one with medium-potency TCS applied once daily to areas with active lesions. If the lesion was present on an area of thin skin (e.g., face, neck, intertriginous areas, genital areas, areas of skin atrophy) patients were required to use low-potency TCS instead of medium-potency TCS. Once lesions became clear or almost clear, treatment was switched from 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. Similar to 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 was 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. TCIs could be used for problem areas (e.g., face and 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. Similar to the 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 TCS on active lesions starting on day −14. The LIBERTY AD CAFÉ trial was 16 weeks in duration. Background treatment with moisturizers and prohibited and permitted concomitant medications remained consistent with the other trials, with the addition of the prohibition of phototherapy. Patients treated with rescue medications, systemic corticosteroids, and 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 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 IGA 0 or 1 (on a five-point scale) and a reduction from baseline of two or more points at week 16. For the European Union, the European Union reference market countries, and Japan, the co-primary end points were the proportion of patients with an improvement of 75% or more in Eczema Area and Severity Index (EASI) score from baseline (EASI-75) at week 16, and the proportion of patients with IGA 0 or 1 (on a five-point scale) and a reduction from baseline of two or more points at week 16. LIBERTY AD CAFÉ evaluated the proportion of patients with EASI-75 at week 16 as the primary efficacy end point. The EASI has been determined to be both reliable[8,20-22,22] and valid[12,20] for assessing the severity and extent of AD.[12,20] Validity was determined using the correlation coefficient between EASI and SCORAD where high correlation was found,[21] and reliability was assessed via intra- and inter-rater reliability. The minimal clinically important difference (MCID) for the EASI from one study was determined to be 6.6 points in patients with AD.[8] To determine the EASI score, four disease characteristics of AD (erythema, infiltration/papulation, excoriations, and lichenification) were assessed for severity by the investigator on a scale of 0 (absent) to 3 (severe) for each of four body regions (head, arms, trunk, and legs) and weighted by body surface area (BSA) for each region. The total EASI score ranged from 0 to 72 points, with higher scores indicating greater severity. The EASI-50 (50% or greater improvement from baseline) was included as a secondary end point in each trial. The reliability, validity, and MCID for the assessment of AD using the IGA were not identified in the literature search. The IGA is a five-point scale that provides a global clinical assessment of AD severity (ranging from 0 to 4, where 0 indicates clear, 2 is mild, 3 is moderate, and 4 indicates severe AD).[4]

The SOLO trials, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ included the SCORAD as a secondary end point. The SCORAD is a clinical research tool developed to standardize the evaluation of the extent and severity of AD.[4,23] It assesses three components of AD: the affected BSA, the severity of clinical signs, and the symptoms and results. The maximum score is 103, with a higher score indicating a more severe condition. The tool has been demonstrated to have fair-to-good intra-rater reliability based on the intra-class correlation coefficient,[22] and has a reported MCID of 8.7 points for patients with AD.[8]

Symptoms of AD were assessed using the Pruritus NRS and the Patient-Oriented Eczema Measure (POEM). Pruritus NRS was used for patients to report in a diary on a daily basis the overall and maximum intensity of their itch on a scale of 0 to 10.[4] No information on the validity and MCID was found from the literature search. The seven-item POEM was used to assess the frequency of occurrence during the past week of the following items using a five-

point scale: dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping.[24] Higher scores on a scale from 0 to 28 indicate poor quality of life and increasing severity of eczema. The MCID for the POEM was determined to be 3.4 points in patients with AD.[8]

The Patient Global Assessment of Disease Status (PGADS) assessed overall well-being based on a five-point Likert scale from poor to excellent.[4] No information in the literature reviewed was found on the validity, reliability, and MCID on the use of the PGADS in patients with AD.

Quality of life was assessed using the Dermatology Life Quality Index (DLQI) and the EuroQol 5-Dimensions questionnaire (EQ-5D). The DLQI assessed the impact of a (general) dermatological disease on a patient's quality of life over a one-week period by assessing the following six dimensions: symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment.[25] Scores range from 0 to 30, with higher scores indicating poorer quality of life.[4,26] The validity of the DLQI has been assessed in patients with eczema,[27-30] and the average MCID has been identified as 3.3 (range: 2.2 to 6.9) in a population of patients with a variety of dermatological conditions.[22,26,31,32] No validity and MCID information was found for the patients with AD.[33] The EQ-5D is a generic quality-of-life instrument that includes the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) was used to assess these dimensions across three levels of severity (no problem, some problems, severe problems). No studies specifically validating the EQ-5D-3L in patients with AD were identified. The MCID for the EQ-5D ranges from 0.033 to 0.074.[34]

The Hospital Anxiety and Depression Scale (HADS) uses 14 items to assess symptoms experienced in the previous week related to anxiety and depression. Patients provided responses to each item based on a four-point Likert scale, with higher scores indicative of a poor state.[35] Each item is scored from 0 (the best) to 3 (the worst); thus, a person can score between 0 and 21 for each subscale (anxiety and depression). 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 were considered "not a case." No validity and MCID information regarding HADS was found from the literature search for AD. All trials reported the AEs, SAEs, and withdrawal due to adverse events (WDAEs). AEs were defined as any untoward medical occurrence in a patient administered a study drug that may or may not have had a causal relationship with the study drug. This included any worsening of a pre-existing condition that was temporally associated with the use of the study drug. SAEs were defined as any untoward medical occurrence that, at any dose: resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, or was an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that did not result in hospitalization; or development of drug dependency or drug abuse).

Statistical Analysis

The four included trials (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 IGA 0 or 1 (on a

five-point scale) and a reduction from baseline of two or more points at week 16. For the European Union, the European Union reference market countries, and Japan, the co-primary end points were the proportion of patients with EASI-75 at week 16, and the proportion of patients with IGA 0 or 1 (on a five-point scale), and a reduction from baseline of two 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. Relevant to this review, secondary end points included the following:

- proportion of patients with an improvement (reduction) of ≥ 4 and ≥ 3 points from baseline to week 16 in the weekly average of the peak daily Pruritus NRS
- proportion of patients with EASI-50 (≥ 50% improvement in EASI from baseline) at week 16
- percentage change from baseline to week 16 in the SCORAD
- change from baseline to week 16 in the:
  - DLQI
  - POEM
  - HADS
  - EQ-5D.

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 the hierarchical testing procedure with a pre-specified order unique to each trial, as listed below.

SOLO 1 and SOLO 2:

- proportion of patients with EASI-75 at week 16
- proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of:
  - ≥ 4 from baseline to week 16
  - ≥ 3 from baseline to week 16
- percentage change from baseline to week 16 in the weekly average of peak daily Pruritus NRS
- proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of:
  - ≥ 4 from baseline to week 4
  - ≥ 4 from baseline to week 2
- change from baseline to week 16 in the weekly average of peak daily Pruritus NRS
- percentage change in EASI score from baseline to week 16
- proportion of patients with EASI-50 at week 16
- proportion of patients with EASI-90 (≥ 90% improvement in EASI from baseline) at week 16
- change from baseline to week 16 in percentage of BSA

- percentage change from baseline to week 16 in SCORAD
- change from baseline to week 16 in:
  - DLQI
  - POEM
  - HADS
- percentage change from baseline to:
  - week 16 in Global Individual Signs Score (GISS)
  - week 2 in the weekly average of peak daily Pruritus NRS
- incidence of:
- skin infection treatment-emergent adverse events (TEAEs) requiring systemic treatment from baseline through week 16
  - treatment-emergent serious adverse events (TESAEs) from baseline through week 16
  - TESAEs leading to treatment discontinuation from baseline through week 16.

LIBERTY AD CHRONOS:

- proportion of patients with an EASI-75 response (reduction of EASI score by ≥ 75% from baseline) at week 16
- proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of:
  - ≥ 4 from baseline to week 16
  - ≥ 3 from baseline to week 16
- proportion of patients with:
  - IGA 0 or 1 and a reduction from baseline of ≥ 2 points at week 52
  - an EASI-75 response at week 52
- percentage change from baseline to week 16 in the weekly average of peak daily Pruritus NRS
- proportion of patients with improvement (reduction) in the weekly average of peak daily Pruritus NRS of:
  - ≥ 4 from baseline to week 52
  - ≥ 3 from baseline to week 52
  - ≥ 4 from baseline to week 24
  - ≥ 4 from baseline to week 4
  - ≥ 4 from baseline to week 2
- change from baseline to week 16 in the weekly average of peak daily Pruritus NRS
- percentage change in EASI score from baseline to week 16
- change from baseline to week 16 in BSA percentage
- percentage change in SCORAD from baseline to week 16

- change from baseline to week 16 in:
  - DLQI
  - POEM
  - HADS
- percentage change in GISS from baseline to week 16
- proportion of topical AD medication–free days through week 52
- percentage change from baseline to week 2 in the weekly average of peak daily Pruritus NRS
- percentage change in EASI score from baseline to week 52
- change in BSA percentage from baseline to week 52
- percentage change in SCORAD from baseline to week 52
- percentage change in GISS from baseline to week 52
- change from baseline to week 52 in:
  - DLQI
  - POEM
- change in HADS from baseline to week 52
- number of events in flares through week 52
- change in Asthma Control Questionnaire 5 (ACQ-5) score from baseline to week 16
- change in Sino-Nasal Outcome Test 22 (SNOT-22) score from baseline to week 16
- incidence of TESAEs through week 52
- incidence of TESAEs leading to study drug discontinuation from baseline through week 52
- proportion of patients with skin infection TESAEs (excluding herpetic infections) from baseline through week 52
- incidence rate of skin infection TEAEs (excluding herpetic infections) from baseline through week 52
- proportion of patients with skin infection TEAEs (excluding herpetic infections) requiring systemic treatment from baseline through week 52
- incidence rate of skin infection TEAEs (excluding herpetic infections) requiring systemic treatment from baseline through week 52

LIBERTY AD CAFÉ:

- proportion of patients with EASI-75 at week 16 at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks
- percentage change in EASI score from baseline to week 16 at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks

- percentage change from baseline to week 16 in the weekly average of peak daily Pruritus NRS at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks
- percentage change from baseline to week 16 in SCORAD at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks
- proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of ≥ 4 from baseline to week 16 at a dosage of 300 mg once weekly
- change from baseline to week 16 in BSA percentage at a dosage of 300 mg once weekly
- proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of ≥ 4 from baseline to week 16 at a dosage of 300 mg once every two weeks
- change from baseline to week 16 in BSA percentage at a dosage of 300 mg once every two weeks
- proportion of patients with IGA 0 or 1 (on a five-point scale) and a reduction from baseline of ≥ 2 points at week 16 at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks
- change from baseline to week 16 in:
  - DLQI at a dosage of 300 mg once weekly
  - POEM at a dosage of 300 mg once weekly
- proportion of patients with prior CSA use with EASI-75 at week 16 at a dosage of 300 mg once weekly
- change from baseline to week 16 in:
  - DLQI at a dosage of 300 mg once every two weeks
  - POEM at a dosage of 300 mg once every two weeks
- proportion of patients with prior CSA use with EASI-75 at week 16 at a dosage of 300 mg once every two weeks
- mean weekly use of TCS during the treatment period at a dosage of:
  - 300 mg once every week
  - 300 mg once every two weeks
- change from baseline to week 16 in HADS at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks
- incidence of skin infection TEAE (excluding herpetic infections) from baseline through on-treatment period at a dosage of:
  - 300 mg once weekly
  - 300 mg once every two weeks
- incidence of TESAEs from baseline through on-treatment period at a dosage of 300 mg once weekly

- incidence of TEAEs leading to treatment discontinuation from baseline through on-treatment period at a dosage of 300 mg once weekly
- overall incidence of TEAEs through on-treatment period at a dosage of 300 mg once weekly
- incidence of TESAEs from baseline through on-treatment period at a dosage of 300 mg once every two weeks
- incidence of TEAEs leading to treatment discontinuation from baseline through on-treatment period at a dosage of 300 mg once every two weeks
- overall incidence of TEAEs through on-treatment period at a dosage of 300 mg once every two weeks.

The European Union, European Union 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 dose 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. If a patient had a missing value at week 16, they were counted as a nonresponder at week 16. Sensitivity analyses were included that utilized alternative methods to account for missing data (last observation carried forward), 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 analysis of covariance (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 dose regimen and placebo. Sensitivity analyses for secondary end points included analysis based on all observed data, regardless 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 method, the last observation carried forward 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 weekly and once every two weeks) while adjusting the significance level to account for multiplicity. In LIBERTY AD CHRONOS 300, 100, and 300 patients in the dupilumab 300 mg once weekly, in the dupilumab 300 mg once every two weeks, and in the 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 for the secondary end point for the proportion of patients with an improvement (reduction ≥ 4 points) in the 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

The four included studies included the following analysis populations:

The full analysis set / intention-to-treat (ITT) population included all patients who 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. Major efficacy-related protocol 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, which included all patients from the pharmacokinetic population with at least one non-missing functional dupilumab concentration following the first dose of study drug and at least one non-missing IGA, EASI, or Pruritus NRS value.
- The neutralizing anti-drug antibody population, which 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.

Patient Disposition

The proportion of patients who discontinued from each study 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, withdrawals by patient) were cited as the main reasons for discontinuation.

Table 5: Patient Disposition for SOLO 1 and SOLO 2

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

q.2.w. = once every two weeks; q.w. = once weekly.

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[9] and clinical study reports for SOLO 1[4] and SOLO 2.[5]

Table 6: Patient Disposition for LIBERTY AD CHRONOS and LIBERTY AD CAFÉ

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

TCS = topical corticosteroids; q.w. = once weekly; q.2.w. = once every two weeks.

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

[a] There were four patients randomized to dupilumab 300 mg q.w. plus TCS who received ≥ three fewer injections than planned through week 16. These four patients were counted in the dupilumab 300 mg q.2.w. plus TCS group for the Safety Analysis Set.

Source: Blauvelt, 2017;[11] De Bruin-Weller, 2017;[10] and clinical study reports for LIBERTY AD CHRONOS[6] and LIBERTY AD CAFÉ.[7]

Exposure to Study Treatments

The mean injection compliance ([number of injections during the exposure period] ÷ [number of planned injections during the exposure period] × 100%) was similar across treatment groups and trials, with 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, LIBERTY AD CAFÉ) with a range from 70.1% to 88.9%. LIBERTY AD CHRONOS had a background treatment compliance rate 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.

Critical Appraisal

Internal Validity

SOLO 1, SOLO 2, LIBERTY AD CHRONOS, and LIBERTY AD CAFÉ were randomized, double-blind, placebo-controlled, parallel-group trials. Each trial was clearly described with specific objectives, end points, and interventions. Each trial clearly described the random component in sequence generation. 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 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 for the dupilumab once-every-two-weeks group, and blinding of end point assessors.

The patient disposition for each trial was clearly presented. The greatest proportions of patients who discontinued were within the placebo groups in all trials. This presents the potential for bias toward inflated efficacy of dupilumab, as non-response imputation is used to account for missing data.

The primary outcomes assessed in the trial were based on the IGA and EASI score. The EASI has been determined to be both reliable[8,20-22,22] and valid[12,20] for the assessment of the 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 MCID for the EASI was 6.6 points.[8] Reliability, validity, and MCID for the assessment of AD using the IGA were not identified in the literature search. A lack of MCID restricts the ability to determine clinical relevance of the IGA outcome for disease severity.

Several subgroup (e.g., age, sex, ethnicity, race, duration of AD, geographic region, baseline disease severity) analyses were specified a priori and conducted across the four trials. 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.

Power calculations were provided for sample sizes, yielding 99% power in each trial for both the IGA and EASI end points for SOLO 1, SOLO 2, and LIBERTY AD CHRONOS, and for the EASI and the improvement (reduction ≥ 4 points) in the weekly average of peak daily Pruritus NRS end point for LIBERTY AD CAFÉ. These calculations were all based on estimates of efficacy from phase II studies on dupilumab (R668-AD-1117, R668-AD-1021) for the placebo and treatment groups; while these values were considered reasonable, SOLO 2 was based on estimates that overestimated the therapeutic effect in both the placebo and dupilumab groups, while the therapeutic effect was underestimated in the placebo group for the LIBERTY AD CHRONOS trial. The estimated percentage difference between dupilumab and placebo that was used in the power calculations was similar to the actual experimentally obtained values across trials.

The main analysis was conducted on all randomized patients based on the treatment allocated at the time of randomization for each trial. This intention-to-treat analysis was appropriate, as it preserved statistical power and better reflects 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, prior CSA use). For comparative purposes, the trials also included an analysis set based on per-protocol. The studies all used multiple imputation using the Markov-chain Monte Carlo algorithm and ANCOVA to account for missing data for continuous end points. All primary efficacy end points across the four trials had less than 10% missing data, with the majority missing less than 5%. [redacted]

[redacted]. Sensitivity analyses were included that utilized alternative methods to account for missing data (last observation carried forward) and to assess all patient data, regardless of use of rescue medication with and without imputation.

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 the hierarchical testing procedure with a pre-specified order (see statistical analysis). The European Union, European Union 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 dose regimen, an intersection-union method was applied to the co-primary end points, which required the 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. Based on the pre-specified hierarchies, all secondary end points were accounted for, with the exception of the PGADS and the EQ-5D.

External Validity

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 in this review suggested that the study population was generally representative of the Canadian adult patients seen in clinical practice. All patients in LIBERTY AD CAFÉ were recruited from Europe, and over 96% of patients identified their race as white. Across studies, a common inclusion criterion was for patients to be 18 years of age or older; thus, the data are not generalizable to the pediatric population.

The inclusion and exclusion criteria for each study were clearly described and differed slightly between studies. Among other criteria, the SOLO studies required patients where topical treatment was inadvisable or provided inadequate treatment, while the LIBERTY AD CHRONOS trial only required patients where topical treatment provided inadequate treatment, and excluded patients who experienced important side effects to topical medications (e.g., intolerance, 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 TCS or TCIs 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. These inclusion criteria among others relating to AD therapies used within specific timeframes, create a study population that may be inconsistent with the Canadian population and may have contributed to the approximately [redacted]% of patients who failed screening.

The treatment groups with dupilumab were compared with a placebo group in each of the four trials; no head-to-head comparative data were available to compare dupilumab with other active treatments.

It should be noted that while the IGA and EASI are not currently used in clinical practice, no tool has been recommended to assess disease severity for patients with AD. Severity of AD is typically assessed long-term at the physician's discretion. The manufacturer consulted with different health authorities who requested the use of the IGA and EASI. Additional scales (i.e., SCORAD) were used to assess disease severity.

The majority of trials (SOLO 1, SOLO 2, and LIBERTY AD CAFÉ) were 16 weeks in duration. The clinical expert consulted for this review indicated that this time frame is sufficient to determine the efficacy of treatment with dupilumab. While one trial (LIBERTY AD CHRONOS) was 52 weeks in duration, the long-term effects of dupilumab in patients where treatment with TCS was inadvisable, or in patients who were not eligible for treatment with CSA or who 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.

Efficacy

Only those efficacy end points identified in the review protocol are reported below (Table 7). Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to CDR as well as those meeting the selection criteria presented in Table 1. See Appendix 4 for detailed efficacy data.

Severity of Atopic Dermatitis

Severity of AD was measured using the IGA, the EASI, and the SCORAD tool.

The proportion of patients with an IGA score of 0 or 1 and reduction from baseline of two 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 (Table 7). This proportion was consistently greater in the dupilumab group (36.1% to 40.2%) compared with 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 a reduction from baseline of two 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 with the SOLO trials.

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 7). This proportion was consistently greater in the dupilumab group (44.2% to 68.9%) compared with 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 in both the placebo and dupilumab groups in the LIBERTY trials compared with the SOLO trials. As a secondary end point, the proportion of patients who achieved 50% improvement from baseline in the EASI was also statistically significant ($P < 0.0001$) across all trials with a trend similar to the EASI-75 efficacy results.

The percentage change in SCORAD from baseline to week 16 was a secondary end point across all four trials (Table 7). The least squares (LS) mean percentage change from baseline was greater in the dupilumab group (51.1% to 63.9% reduction) compared with the placebo group (19.7% to 36.2% reduction). Across trials, the LS mean percentage difference in SCORAD score between the 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.

Consistently across all trials, the severity of AD showed a statistically significant ($P < 0.0001$) decrease in the dupilumab group compared with placebo group, regardless of which measure was used (Table 7). 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 the use of rescue treatment. If a patient had a missing value at week 16, they were counted as a nonresponder at week 16. Sensitivity analyses were included that utilized alternative methods to account for missing data (i.e., last observation carried forward, no multiple imputation), and to assess all patient data regardless of use of rescue medication, with and without imputation (via multiple-imputation methodology). Across all sensitivity analyses, statistical significance remained consistent. 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 with placebo (Appendix 4).

Symptom Reduction

AD symptom reduction was assessed using the Pruritus NRS and the POEM.

The proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of four or more points from baseline to week 16 was one of the secondary end points in all of the studies (Table 7). Compared with 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 for the proportion of patients with an improvement (reduction) in the weekly average of peak daily Pruritus NRS of three 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 percentage change in POEM from baseline to week 16 was an additional secondary end point across all four trials (Table 7). The LS mean change from baseline was greater in the dupilumab group (reduction of 10.2 to 12.7 points) compared with the placebo group (3.3- to 5.3-point reduction). Across trials, the LS mean difference in POEM score between the 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 was statistically significant ($P < 0.0001$) and clinically significant (MCID = 3.4[8]) across all trials.

Health-Related Quality of Life

Health-related quality of life was assessed using the DLQI and EQ-5D-3L.

The change in DLQI from baseline to week 16 was a secondary end point across all four trials (Table 7). The LS mean change from baseline was greater in the dupilumab group (reduction of 9.3 to 10.0 points) compared with the placebo group (reduction of 5.8 to 7.2

points). Across trials, the LS mean difference in DLQI score between the 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 was statistically significant ($P < 0.0001$) but not clinically significant (MCID of 2.2 to 6.9. points) across all trials. 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.

The change in EQ-5D index utility score from baseline to week 16 was a secondary end point across all four trials (Table 7). The LS mean change from baseline was numerically greater in the dupilumab group (0.22 to 0.24) compared with the placebo group (0.06 to 0.16) in the SOLO trials and LIBERTY AD CHRONOS. Across the three trials, the LS mean difference in EQ-5D index utility score between the 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 MCID exists, the results in the trials are clinically relevant using the general MCID for the EQ-5D, which ranges from 0.033 to 0.074 The LS mean difference was statistically significant ($P < 0.0001$) in SOLO 1 and SOLO 2. The change in EQ-5D visual analogue scale (EQ-VAS) score from baseline to week 16 was statistically significant ($P < 0.0001$) in SOLO 1, SOLO 2, and LIBERTY AD CHRONOS.

Other Efficacy End Points

The HADS and its subscales for anxiety and depression were used to assess mood at week 16 (Table 7). For the total HADS score, statistical significance ($P < 0.0001$) was found for the LS mean difference between dupilumab and placebo in SOLO 2 and LIBERTY AD CAFÉ. SOLO 1 had a $P = 0.0006$, and LIBERTY AD CHRONOS had $P = 0.1596$ and $P = 0.0337$ at week 16 and week 52, respectively.

Productivity was assessed though the measurement of days missed from school or days of sick leave from work. Patients in the placebo group missed 1.8 to 6.2 days of school/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 7).

Overall well-being was assessed using the PGADS (Table 7). The proportion of patients who responded with “very good” or “excellent” at week 16 was greater for the patients in the dupilumab group compared with the placebo group. The findings were statistically significant ($P < 0.0001$) across all trials at week 16; however, these results were not adjusted for multiplicity.

Table 7: Key Efficacy End Points

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
IGA Score of 0 or 1 and reduction from baseline of ≥ 2 points										
N (%)	23 (10.3)	85 (37.9)	20 (8.5)	84 (36.1)	39 (12.4)	41 (38.7)	33 (12.5)	32 (36.0)	15 (13.9)	43 (40.2)
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 (%)	33 (14.7)	115 (51.3)	28 (11.9)	103 (44.2)	73 (23.2)	73 (68.9)	57 (21.6)	58 (65.2)	32 (29.6)	67 (62.6)
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	19 (26.4)	40 (58.0)
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 (%)	55 (24.6)	154 (68.8)	52 (22.0)	152 (65.2)	118 (37.5)	85 (80.2)	79 (29.9)	70 (78.7)	47 (43.5)	91 (85.0)
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)	68.3 (13.9)	66.94 (13.9)	69.2 (14.8)	67.2 (13.4)	66.0 (13.5)	69.3 (15.2)	65.7 (13.3)	69.9 (15.1)	67.0 (12.196)	68.6 (11.9)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
N observed / N imputed	97/127	172/52	105/131	193/40	188/127	92/14	101/163	71/18	89/19	103/4
LS mean % change (SE)	−29.0 (3.2)	−57.7 (2.1)	−19.7 (2.5)	−51.1 (2.0)	−36.2 (1.7)	−63.9 (2.5)	−47.3 (2.2)	−69.7 (3.1)	−29.5 (2.6)	−62.4 (2.5)
LS mean % 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)
***P* value[c]**		< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001
peak daily Pruritus NRS score reduction of ≥ 4										
N/N1 (%)	26/212 (12.3)	87/213 (40.8)	21/221 (9.5)	81/225 (36.0)	59/299 (19.7)	60/102 (58.8)	32/249 (12.9)	44/86 (51.2)	13/91 (14.3)	43/94 (45.7)
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 (%)	38/221 (17.2)	103/220 (46.8)	29/226 (12.8)	117/231 (50.6)	85/306 (27.8)	69/105 (65.7)	40/256 (15.6)	49/88 (55.7)	20/98 (20.4)	57/99 (57.6)
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)	20.3 (5.9)	19.8 (6.4)	21.0 (5.9)	20.8 (5.5)	20.0 (6.0)	20.3 (5.7)	20.1 (6.0)	20.6 (5.7)	19.1 (6.0)	19.3 (6.2)
N observed / N imputed	96/128	173/51	104/132	196/37	187/128	92/14	99/165	71/18	88/20	103/4

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
LS mean change (SE)	−5.1 (0.7)	−11.6 (0.5)	−3.3 (0.6)	−10.2 (0.5)	−5.3 (0.4)	−12.7 (0.6)	−7.0 (0.6)	−14.2 (0.8)	−4.3 (0.6)	−11.9 (0.6)
LS mean difference (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)	14.8 (7.2)	13.9 (7.4)	15.4 (7.7)	15.4 (7.1)	14.7 (7.4)	14.5 (7.3)	15.2 (7.4)	15.0 (7.3)	13.2 (7.6)	14.5 (7.6)
N observed / N imputed	97/127	173/51	105/131	197/36	187/128	92/14	101/163	71/18	89/19	103/4
LS mean change (SE)	−5.3 (0.5)	−9.3 (0.4)	−3.6 (0.5)	−9.3 (0.4)	−5.8 (0.3)	−10.0 (0.5)	−7.2 (0.4)	−11.4 (0.6)	−4.5 (0.5)	−9.5 (0.5)
LS mean difference (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
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 / N imputed	96/128	173/51	105/131	197/36	188/127	92/14	NR	NR	89/19	103/4
LS mean change (SE)[e]	0.1 (0.0)	0.2 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	NR	NR	−90.0 (79.0)	−8.2 (79.2)
LS mean difference (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

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
EQ-5D Index VAS Score										
Baseline mean (SD)	54.6 (24.8)	56.8 (23.4)	56.9 (24.3)	55.4 (23.0)	56.5 (23.7)	57.8 (22.5)	NA	NA	53.4 (24.5)	55.5 (22.8)
N observed / N imputed	97/127	173/51	105/131	196/37	188/127	91/15	NR	NR	89/19	103/4
LS mean change (SE)[e]	7.1 (1.8)	19.5 (1.5)	3.9 (1.7)	14.9 (1.4)	9.5 (1.2)	20.4 (1.7)	NR	NR	58.9 (23.2)	111.7 (23.1)
LS mean difference (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 (%)	25 (11.2)	85 (37.9)	28 (11.9)	89 (38.2)	49 (15.6)	53 (50.0)	NR	NR	17 (15.7)	55 (51.4)
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)	12.4 (8.01)	12.0 (7.03)	13.7 (8.23)	13.7 (7.43)	12.6 (8.06)	12.9 (7.73)	13.1 (8.05)	13.5 (7.74)	13.0 (7.85)	12.8 (8.01)
N observed / N imputed	82/142	159/65	103/133	191/42	188/127	92/14	101/163	71/18	89/19	103/4
LS mean change (SE)	−3.0 (0.65)	−5.2 (0.54)	−0.8 (0.44)	−5.1 (0.39)	−4.0 (0.37)	−4.9 (0.58)	−3.8 (0.47)	−5.5 (0.71)	−2.3 (0.56)	−6.1 (0.54)

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
LS mean difference (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)	6.9 (4.32)	7.0 (3.98)	7.8 (4.46)	7.5 (4.09)	7.0 (4.40)	7.4 (4.23)	7.5 (4.42)	7.7 (4.12)	7.3 (4.54)	7.0 (4.33)
N observed / N imputed	82/142	159/65	103/133	191/42	188/127	92/14	101/163	71/18	89/19	103/4
LS mean change (SE)	−2.2 (0.37)	−2.9 (0.31)	−0.8 (0.26)	−2.8 (0.22)	−2.3 (0.22)	−2.8 (0.32)	−2.3 (0.30)	−3.2 (0.40)	−1.5 (0.31)	−3.4 (0.31)
LS mean difference (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)	5.4 (4.50)	5.1 (3.78)	5.9 (4.42)	6.2 (4.14)	5.5 (4.29)	5.5 (4.33)	5.7 (4.24)	5.8 (4.39)	5.7 (4.09)	5.8 (4.37)
N observed / N imputed	82/142	159/65	103/133	191/42	188/127	92/14	101/163	71/18	89/19	103/4
LS mean change (SE)	−1.0 (0.32)	−2.4 (0.28)	−0.1 (0.25)	−2.2 (0.22)	−1.7 (0.20)	−2.1 (0.31)	−1.5 (0.27)	−2.4 (0.36)	−0.8 (0.29)	−2.8 (0.28)
LS mean difference (95% CI)[c]		−1.4 (−2.03 −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 Days / Missed School Days — Full-Time Status										
N	151	167	168	165	NR	NR	263	87	85	83

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS (Follow-Up at Week 16)		LIBERTY AD CHRONOS (Follow-Up at Week 52)		LIBERTY AD CAFÉ	
	Placebo N = 224	Dupilumab 300 mg q.2.w. N = 224	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo N = 315	Dupilumab 300 mg q.2.w. + TCS N = 106	Placebo N = 264	Dupilumab 300 mg q.2.w. + TCS N = 89	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
Mean days missed (SD)	1.8 (6.9)	0.5 (1.9)	2.6 (7.4)	1.2 (6.4)	NR	NR	2.3 (9.7)	0.43 (2.5)	6.16 (21.3)	0.14 (0.5)
Patients with any day missed, N (%)	31 (20.5)	26 (15.6)	54 (32.1)	27 (16.4)	NR	NR	72 (27.4)	8 (9.2)	14 (16.5)	7 (8.4)
Sick-Leave Days / Missed School Days — Part-Time Status										
N	37	35	34	45	NR	NR	61	21	9	12
Mean days missed (SD)	4.9 (18.2)	0.1 (0.6)	4.3 (8.0)	0.5 (1.6)	NR	NR	2.4 (6.8)	1.0 (2.9)	1.1 (3.3)	0.4 (1.2)
Patients with any day missed, N (%)	10 (27.0)	2 (5.7)	14 (41.2)	6 (13.3)	NR	NR	13 (21.3)	3 (14.3)	1 (11.1)	2 (16.7)

ANCOVA = analysis of covariance; CI = confidence interval; CSA = cyclosporine A; DLQI = Dermatology Life Quality Index; EASI-75 = improvement of ≥ 75% in Eczema Area and Severity Index score from baseline; EQ-5D = EuroQol 5-Dimensions questionnaire; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D = Hospital Anxiety and Depression Scale–Depression Subscale; IGA = Investigator's Global Assessment; LS = least squares; 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. = once every two weeks; SCORAD = Scoring Atopic Dermatitis; SD= standard deviation; SE = standard error; TCS = topical corticosteroids; 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] The confidence interval with *P* value is based on the treatment difference (dupilumab group versus placebo) of the LS mean change using an ANCOVA model with baseline measurement as 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 percentage change/difference in LS mean 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 subsequently.

Adverse Events

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 AEs was in the infections and infestations category and 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 and affected 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 8.

Serious Adverse Events

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. Regardless of treatment group, patients in LIBERTY AD CAFÉ had the highest frequency of SAEs. [redacted]

Withdrawals Due to Adverse Events

WDAEs 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 across all trials at week 16. The greatest number of WDAEs was found in LIBERTY AD CHRONOS, where 4.8% of patients in the placebo group and 0.9% of patients in the dupilumab group withdrew by week 16.

Mortality

Two deaths occurred in the dupilumab groups in SOLO 2 (one each in the weekly and every other week dupilumab groups); one death occurred in LIBERTY AD CHRONOS (in the dupilumab every other week group). It was reported that the deaths were unrelated to the study drug.

Notable Harms

The prevalence of AD flares, worsening, or aggravation that required or prolonged hospitalization (reported as “dermatitis atopic”) was greater in the placebo group, where 14.8% to 35% of patients were affected compared with 7.5% to 14% of patients in the dupilumab group for SOLO 1, SOLO 2, and LIBERTY AD CAFÉ.[9,10] In LIBERTY AD CHRONOS at week 52, 46% of patients in the placebo group and 18% of patients in the dupilumab group experienced AD flare–related AEs.[11] Trials without use of TCS (SOLO 1 and SOLO 2) [redacted]. Consistently across trials, conjunctivitis (and general eye disorders) affected more patients in the dupilumab group

(conjunctivitis: 3.8% to 15.0%) compared with the placebo group (conjunctivitis: 0.4% to 6.5%).

Rescue Medication Use

Rescue medication was used in 21.0% and 16.1% of patients in the dupilumab groups, and in 51.8% and 52.1% of patients in the placebo groups 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 groups, and 34.6% and 14.8% of patients in the placebo groups, respectively. Across all trials, the most common form of rescue medication was potent (group III) TCS. In the SOLO trials, 8.5% and 13.1% of patients in the dupilumab groups, and 29.1% and 34.2% of patients in the placebo groups used potent TCS. In LIBERTY AD CHRONOS and LIBERTY AD CAFÉ, potent TCS was used in 8.2% and 2.8% of patients in the dupilumab groups, and 28.3% and 10.2% of patients in the placebo groups for each trial, respectively. Data on rescue medication use across trials are presented in Table 9.

Table 8: Harms at Week 16

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 234	Dupilumab 300 mg q.2.w. N = 236	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 110	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
AEs								
Subjects with > 0 AEs, N (%)	145 (65.3)	167 (72.9)	168 (71.8)	154 (65.3)	214 (67.9%)	81 (73.6%)	75 (69.4%)	77 (72.0%)
Most common AEs[a]								
Infections and infestations	63 (28.4)	80 (34.9)	76 (32.5)	65 (27.5)	111 (35.2)	39 (35.5)	44 (40.7)	49 (45.8)
Nasopharyngitis	17 (7.7)	22 (9.6)	22 (9.4)	20 (8.5)	33 (10.5)	15 (13.6)	18 (16.7)	22 (20.6)
Conjunctivitis	2 (0.9)	11 (4.8)	1 (0.4)	9 (3.8)				
Upper respiratory tract infection	5 (2.3)	6 (2.6)	5 (2.1)	7 (3.0)	20 (6.3)	7 (6.4)		
Oral herpes	4 (1.8)	9 (3.9)	4 (1.7)	8 (3.4)			3 (2.8)	1 (0.9)
Herpes simplex	3 (1.4)	7 (3.1)			5 (1.6)	3 (2.7)	0	3 (2.8)
Sinusitis	NA	NA	NA	NA	3 (1.0)	0	NA	NA
Viral upper respiratory tract infection	NA	NA	NA	NA	4 (1.3)	2 (1.8)	NA	NA
Skin infection	NA	NA	NA	NA	7 (2.2)	0	NA	NA
Gastroenteritis	NA	NA	NA	NA	NA	NA	1 (0.9)	2 (1.9)
Pharyngitis	NA	NA	NA	NA	NA	NA	3 (2.8)	1 (0.9)
General disorders and administration conditions	20 (9.0)	39 (17.0)	32 (13.7)	41 (17.4)	32 (10.2)	20 (18.2)	12 (11.1)	9 (8.4)
Injection-site reaction	13 (5.9)	19 (8.3)	15 (6.4)	32 (13.6)	18 (5.7)	11 (10.0)	NA	NA
Fatigue	1 (0.5)	5 (2.2)	3 (1.3)	6 (2.5)	7 (2.2)	1 (0.9)	1 (0.9)	4 (3.7)
Skin and subcutaneous tissue disorders	78 (35.1)	47 (20.5)	93 (39.7)	49 (20.8)	110 (34.9)	20 (18.2)	21 (19.4)	22 (20.6)
Dermatitis atopic[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 234	Dupilumab 300 mg q.2.w. N = 236	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 110	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
Pruritus	5 (2.3)	0	5 (2.1)	1 (0.4)	NA	NA	NA	NA
Alopecia	NA	NA	3 (1.3)	1 (0.4)	NA	NA	NA	NA
Urticaria	NA	NA	NA	NA	8 (2.5)	1 (0.9)	NA	NA
Nervous system disorders	20 (9.0)	30 (13.1)	23 (9.8)	29 (12.3)	27 (8.6)	9 (8.2)	12 (11.1)	14 (13.1)
Headache	13 (5.9)	21 (9.2)	11 (4.7)	19 (8.1)	15 (4.8)	4 (3.6)	9 (8.3)	10 (9.3)
Dizziness	NA	NA	6 (2.6)	3 (1.3)	NA	NA	NA	NA
Eye disorders	4 (1.8)	18 (7.9)	NA	NA	19 (6.0)	23 (20.9)	15 (13.9)	21 (19.6)
Conjunctivitis allergic	2 (0.9)	12 (5.2)	NA	NA	10 (3.2)	7 (6.4)	7 (6.5)	16 (15.0)
Blepharitis	NA	NA	NA	NA	2 (0.6)	5 (4.5)	NA	NA
Eye pruritus	NA	NA	NA	NA	2 (0.6)	2 (1.8)	NA	NA
Gastrointestinal disorders	9 (4.1)	21 (9.2)	18 (7.7)	22 (9.3)	33 (10.5)	11 (10.0)	16 (14.8)	9 (8.4)
Diarrhea	4 (1.8)	7 (3.1)	3 (1.3)	9 (3.8)	7 (2.2)	0	2 (1.9)	3 (2.8)
Nausea	1 (0.5)	5 (2.2)	3 (1.3)	5 (2.1)	7 (2.2)	2 (1.8)	NA	NA
Abdominal pain	NA	NA	NA	NA	NA	NA	4 (3.7)	0
Musculoskeletal and connective tissue	13 (5.9)	19 (8.3)	15 (6.4)	27 (11.4)	27 (8.6)	10 (9.1)	12 (11.1)	4 (3.7)
Arthralgia	3 (1.4)	6 (2.6)	6 (2.6)	6 (2.5)	8 (2.5)	2 (1.8)	3 (2.8)	1 (0.9)
Back pain	4 (1.8)	2 (0.9)	5 (2.1)	7 (3.0)	NA	NA	NA	NA
Investigations	9 (4.1)	13 (5.7)	NA	NA	26 (8.3)	8 (7.3)	NA	NA
Blood creatine phosphokinase increased	4 (1.8)	5 (2.2)	NA	NA	6 (1.9)	1 (0.9)	NA	NA
Blood lactate dehydrogenase increased	NA	NA	NA	NA	4 (1.3)	4 (3.6)	NA	NA
Respiratory, thoracic, and mediastinal disorders	NA	NA	16 (6.8)	17 (7.2)	33 (10.5)	8 (7.3)	14 (13.0)	14 (13.1)
Oropharyngeal pain	NA	NA	4 (1.7)	5 (2.1)	7 (2.2)	1 (0.9)	2 (1.9)	3 (2.8)
Asthma	NA	NA	NA	NA	11 (3.5)	3 (2.7)	3 (2.8)	1 (0.9)
Rhinitis allergic	NA	NA	NA	NA	NA	NA	1 (0.9)	7 (6.5)
Cough	NA	NA	NA	NA	NA	NA	1 (0.9)	4 (3.7)
Rhinorrhea	NA	NA	NA	NA	NA	NA	3 (2.8)	0
Vascular disorders	NA	NA	NA	NA	NA	NA	1 (0.9)	4 (3.7)
Blood and lymphatic system disorders	NA	NA	NA	NA	NA	NA	4 (3.7)	4 (3.7)
Lymphadenopathy	NA	NA	NA	NA	NA	NA	4 (3.7)	2 (1.9)
Psychiatric disorders	NA	NA	17 (7.3)	6 (2.5)	NA	NA	NA	NA
Depression	NA	NA	5 (2.1)	0	NA	NA	NA	NA
Vascular disorders	NA	NA	6 (2.6)	7 (3.0)	NA	NA	NA	NA
Hypertension	NA	NA	4 (1.7)	5 (2.1)	NA	NA	NA	NA

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 234	Dupilumab 300 mg q.2.w. N = 236	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 110	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
SAEs								
Subjects with > 0 SAEs, N (%)	11 (5.0)	7 (3.1)	17 (7.3)	4 (1.7)	11 (3.5)	4 (3.6)	10 (9.3)	5 (4.7)
Most common reasons	11 (5.0)	7 (3.1)	17 (7.3)	4 (1.7)	11 (3.5)	4 (3.6)	10 (9.3)	5 (4.7)
Skin and subcutaneous tissue disorders	3 (1.4)	2 (0.9)	12 (5.1)	2 (0.8)	5 (1.6)	2 (1.8)	8 (7.4)	2 (1.9)
Dermatitis atopic[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	3 (1.4)	0	NA	NA	NA	NA	NA	NA
Infections and infestations	NA	NA	4 (1.7)	1 (0.4)	NA	NA	NA	NA
WDAEs								
WDAEs, N (%)	2 (0.9)	4 (1.7)	5 (2.1)	2 (0.8)	15 (4.8)	1 (0.9)	1 (0.9)	0
Most common reasons	NA	NA	NA	NA			NA	NA
Skin and subcutaneous tissue disorders	NA	NA	NA	NA	10 (3.2)	1 (0.9)	NA	NA
Dermatitis atopic[b]	NA	NA	NA	NA	8 (2.5)	0	NA	NA
Deaths								
Deaths, N (%)	0	0	0	1 (0.4)	0	0	0	0

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

[a] Frequency ≥ 2% during 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]

Table 9: Rescue Medication Use During 16-Week Period

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 110	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
Subjects with > 0 rescue medication, N (%)	115 (51.8)	48 (21.0)	122 (52.1)	38 (16.1)	120 (38.1)	12 (10.9)	19 (17.6)	4 (3.7)
Corticosteroids, dermatological preparations	109 (49.1)	42 (18.3)	106 (45.3)	35 (14.8)	109 (34.6)	10 (9.1)	16 (14.8)	3 (2.8)
Corticosteroids, potent (group III)	76 (34.2)	30 (13.1)	68 (29.1)	20 (8.5)	89 (28.3)	9 (8.2)	11 (10.2)	3 (2.8)
Corticosteroids, moderately potent (group II)	55 (24.8)	19 (8.3)	50 (21.4)	15 (6.4)	1 (0.3)	0		
Corticosteroids, very potent (group IV)	18 (8.1)	5 (2.2)	24 (10.3)	2 (0.8)	40 (12.7)	3 (2.7)	7 (6.5)	0
Corticosteroids, potent, combinations with antibiotics	11 (5.0)	3 (1.3)	1 (0.4)	0	NA	NA	NA	NA
Corticosteroids, weak (group I)	10 (4.5)	5 (2.2)	5 (2.1)	3 (1.3)	NA	NA	NA	NA
Corticosteroids, moderately potent, combinations with antiseptics	1 (0.5)	0	1 (0.4)	0	NA	NA	NA	NA
Corticosteroids, potent, combinations with antiseptics	0	0	1 (0.4)	0	NA	NA	NA	NA
Corticosteroids, weak, combinations with antibiotics	1 (0.5)	0	0	1 (0.4)	NA	NA	NA	NA
Corticosteroids, potent, other combinations	1 (0.5)	0	1 (0.4)	0	NA	NA	NA	NA
Corticosteroids, weak, combinations with antiseptics	1 (0.5)	0	1 (0.4)	0	NA	NA	NA	NA
Other dermatological preparations	17 (7.7)	9 (3.9)	24 (10.3)	4 (1.7)	NA	NA	NA	NA
Agents for dermatitis, excluding corticosteroids	17 (7.7)	9 (3.9)	24 (10.3)	4 (1.7)	NA	NA	NA	NA
Corticosteroids for systemic use	17 (7.7)	3 (1.3)	30 (12.8)	4 (1.7)	17 (5.4)	5 (4.5)	2 (1.9)	0
Glucocorticoids	17 (7.7)	3 (1.3)	30 (12.8)	4 (1.7)	17 (5.4)	5 (4.5)	2 (1.9)	0

	SOLO 1		SOLO 2		LIBERTY AD CHRONOS		LIBERTY AD CAFÉ	
	Placebo N = 222	Dupilumab 300 mg q.2.w. N = 229	Placebo N = 236	Dupilumab 300 mg q.2.w. N = 233	Placebo + TCS N = 315	Dupilumab 300 mg q.2.w. + TCS N = 110	Placebo + TCS N = 108	Dupilumab 300 mg q.2.w. + TCS N = 107
Glucocorticoids for systemic use, combinations	NA	NA	NA	NA	1 (0.3)	0		
Immunosuppressants	5 (2.3)	3 (1.3)	16 (6.8)	1 (0.4)	11 (3.5)	1 (0.9)	3 (2.8)	0
Calcineurin inhibitors	4 (1.8)	2 (0.9)	13 (5.6)	1 (0.4)	6 (1.9)	0	3 (2.8)	0
Selective immunosuppressants	0	1 (0.4)	NA	NA	3 (1.0)	0	NA	NA
Other immunosuppressants	1 (0.5)	0	4 (1.7)	0	2 (0.6)	1 (0.9)	0	0

NA = not applicable; q.2.w. = once every two weeks; TCS = topical corticosteroids.

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

Discussion

Summary of Available Evidence

The evidence presented in this review was acquired from four manufacturer-sponsored phase III RCTs. In each trial, patients were randomized to receive treatment with weekly subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day one, treatment every other week with subcutaneous injections of 300 mg dupilumab following a loading dose of 600 mg on day one, 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 excluded patients who experienced important side effects to topical medications (e.g., intolerance, hypersensitivity). The inclusion and exclusion criteria in LIBERTY AD CHRONOS were also reflected in the 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 medium-potency TCS on active lesions. In the SOLO trials, use of any TCS was classified as use of rescue medication.

Across all studies, the proportion of patients with EASI-75 at week 16 was the primary efficacy end point. The proportion of patients with IGA 0 or 1 (on a five-point scale) and a reduction from baseline of two 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. The primary efficacy analysis used intention-to-treat methodology. Patients were classified as nonresponders for the time points following study withdrawal or use of rescue treatment. If a patient had a missing value at week 16, they were counted as a nonresponder at week 16. Hierarchical testing was applied to the primary and secondary

end points at a two-sided significance level of 0.025 for the comparison between each dupilumab dose regimen and placebo. The trials also included the same primary efficacy analysis using per-protocol methodology. Sensitivity analyses were included that utilized alternative methods to account for missing data (last observation carried forward), and to assess all patient data, regardless of use of rescue medication with and without imputation (via multiple-imputation methodology). An AD-specific MCID was found for the EASI but not for the IGA although, according to the clinical expert consulted for this review, AD severity and response to therapy is typically assessed on a continuous basis at the discretion of the patient's physician and not by using a tool such as the EASI or IGA.

Secondary end points assessing AD severity (i.e., SCORAD), AD symptoms (i.e., Pruritus NRS, POEM), and health-related quality of life (i.e., DLQI, EQ-5D) were consistent across all trials. Continuous end points 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 dose regimen and placebo. Sensitivity analyses for secondary end points included analysis based on all observed data, regardless whether rescue treatment was used or if data were collected after withdrawal using the multiple-imputation method and 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 method, the last observation carried forward method, and no imputation.

Across the trials, the baseline characteristics and baseline disease severity were similar across treatment groups. One inclusion criteria in the LIBERTY AD CAFÉ trial required patients to have a baseline EASI of 20 or greater, while the other studies required a baseline EASI of 16 or greater. This specific inclusion criterion did not appear to select a more severe set of patients, as the mean EASI score for LIBERTY AD CAFÉ (mean = 33.5) was similar to that of the other studies (mean range = 32.6 to 34.4). Over the course of the studies, the greatest proportions of patients who discontinued the trial were most commonly from the placebo groups. AEs, including those related to the disease itself (i.e., AD flares), were cited as the main cause of discontinuation. While no major safety issues were noted in the trials, more patients in the dupilumab groups experienced AEs relating to eye disorders than those in the placebo group.

Interpretation of Results

Efficacy

Across the studies, the same tools were used to assess AD severity. These tools included the EASI, the IGA, and the SCORAD.

Consistency in results between the primary end points (using the EASI and IGA) and the secondary end point (using the SCORAD) was seen. Regardless which measure was used, the severity of AD showed a statistically significant ($P < 0.0001$) decrease in the dupilumab group compared with the placebo group at week 16. LIBERTY AD CHRONOS showed a consistent statistically significant ($P < 0.0001$) decrease in disease severity for all three

end points at week 52. Sensitivity analyses showed minor numerical differences, but statistical significance remained consistent.

Secondary efficacy end points that assessed the symptoms of AD (Pruritus NRS and POEM) provided efficacy results similar to those of the AD severity end points. Regardless which measure was used, the intensity of AD symptoms showed a statistically significant ($P < 0.0001$) decrease in the dupilumab group compared with the placebo group at week 16 across studies. Patients were most concerned about symptoms such as pruritus. Additionally, patients were concerned about health-related quality of life. Regardless which quality-of-life tool was used (DLQI or EQ-5D-3L), the improvement in quality of life was statistically significant ($P < 0.0001$). [redacted]. In both the EASI and IGA efficacy end points, greater efficacy was seen in the LIBERTY trials' placebo groups compared with the placebo groups in the SOLO trials. This was expected due to concomitant treatment with medium-potency TCS in the LIBERTY trials. This difference in treatment highlights the issue with comparing the trials but is important, as dupilumab is indicated for use with or without TCS. Subgroup data for some of the efficacy end points by geographic region were included and showed numerically variable results by region. With the data distributed between four regions (North and South America, Asia Pacific, Western Europe, Eastern Europe) sample sizes for each treatment group were small (N < 30) in some groups and the CIs were large; this precludes the ability to make specific quantitative conclusions about the treatment effect according to geographic region.

[redacted]. Each of the four trials evaluated in this review were placebo-controlled; therefore, there is no evidence to assess the efficacy of dupilumab compared with other drugs. However, the availability of Health Canada–approved products to treat AD in patients who are suboptimally controlled on disease-specific skin care measures (irritant avoidance, emollients, bleach baths, etc.), TCS, and/or TCIs is lacking.

A matching-adjusted indirect comparison (MAIC) was identified in the company evidence submission template for the single technology appraisal of dupilumab by NICE.[36] The company indicated that a MAIC was performed for the comparison between dupilumab and ciclosporin (the only EMA licensed immunosuppressant therapy available for patients with AD) due to the lack of active comparator trials and the lack of common comparators to enable an indirect treatment comparison of dupilumab versus ciclosporin. In the MAIC, the company included patient-level data from the CHRONOS trial to inform the efficacy and safety of dupilumab, and used aggregate-level data from two trials (Haeck, 2011 and Jin, 2015) to inform the efficacy and safety of ciclosporin. Improvements in absolute SCORAD values (after weighting) were significantly higher for dupilumab in comparison to ciclosporin suggesting that dupilumab + TCS has superior efficacy compared to low-dose cyclosporine

and high-dose ciclosporin initiation followed by low-dose maintenance ciclosporin. However, the Evidence Review Group (ERG) indicated that the results of the MAIC were limited by small sample sizes, heterogeneity, and limited prognostic factors and agreed with the submitting company's decision "not to place much emphasis on the result of the MAIC and would recommend interpreting the results with caution."[36]

Harms

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. Regardless of treatment group, patients in LIBERTY AD CAFÉ had the highest frequency of SAEs. [redacted]. The greater number of SAEs present in the placebo group were not unexpected, as they relate to the condition itself. Two deaths occurred in SOLO 2 and one death occurred in LIBERTY AD CHRONOS. It was reported that the deaths were unrelated to the study drug. Consistently across trials, conjunctivitis (and general eye disorders) affected more patients in the dupilumab group compared with the placebo group. This may relate to the mechanism of action, as dupilumab binds specifically to the IL-4Rα subunit of the IL-4 and IL-13 receptor complex and inhibits the signalling related to the immune response. Although there are some harms associated with dupilumab, patients indicated the desire to try alternative medications, as many of them stated that none of the currently available treatments work. Current second-line treatment for moderate-to-severe AD includes off-label therapies such as methotrexate, cyclosporine, azathioprine, and mycophenolate mofetil. These therapies are generally used for a short duration, as they are associated with negative side effects and highlight the need for novel second-line therapies.

Potential Place in Therapy[2]

Dupilumab, an IL-4 and IL-13 antagonist that limits type 2 T helper–driven inflammatory activity, is the first biologic drug approved for treatment of moderate and severe AD in Canada.

Dupilumab has, in phase III trials, demonstrated efficacy in AD through 52 weeks of treatment.[6] There is evidence that dupilumab is effective in patients who have failed.[7] Safety analyses through 52 weeks have not shown serious concerns.

Presently, patients achieving suboptimal disease control with appropriate disease-specific skin care measures (irritant avoidance, emollients, bleach baths, etc.), TCS and/or TCIs, and narrow-band ultraviolet B (NB-UVB) phototherapy are offered treatment with off-label immunosuppressive drugs. In Canada, the most commonly chosen immunosuppressive drug is methotrexate followed by cyclosporine, azathioprine, and mycophenolate mofetil. Because of their potential toxicities, these drugs are generally prescribed as intermittent courses in AD. There are patients for whom some or all of these drugs are contraindicated or for whom toxicities limit their use. There are also patients who do not respond to these drugs.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

In practice, dupilumab will likely offer a useful alternative for those patients who have contraindications to, experience adverse effects from, or are nonresponsive to immunosuppressive drugs. It will also be useful to that subset of patients who respond to immunosuppressive drugs, but who require continuous long-term systemic therapy.

Conclusions

Four phase III, placebo-controlled RCTs were included in this review. 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 considered pivotal by the manufacturer and Health Canada.

Consistently across all trials, there was a statistically significantly ($P < 0.0001$) greater percentage of patients with improvements in AD severity in the dupilumab group compared with the placebo group. The clinical expert consulted for this review indicated that the cut-offs for the primary efficacy end points (i.e., the proportion of patients with IGA 0 or 1 [on a five-point scale] and a reduction from baseline of two or more points at week 16, and the proportion of patients with EASI-75) used in the studies were clinically relevant. There were also statistically significant improvements ($P < 0.0001$) found for the secondary efficacy end points assessed (including AD symptoms reduction and quality of life) across all trials.

The most common AEs were in the infections and infestations category and similarly affected both the placebo and dupilumab groups. The prevalence of AD flares, worsening, or aggravation that required or prolonged hospitalization (reported as “dermatitis atopic”) was greater in the placebo group, where 14.8% to 35% of patients in the placebo group were affected compared with 7.5% to 14% of patients in the dupilumab group for SOLO 1, SOLO 2, and LIBERTY AD CAFÉ.[9,10] In LIBERTY AD CHRONOS at week 52, 46% of patients in the placebo group and 18% of patients in the dupilumab group experienced AD flare–related AEs.[11] Trials without the concomitant 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. Across all trials, patients in the dupilumab group had higher occurrences of eye disorders (including conjunctivitis), injection-site reactions, and herpes simplex infections compared with the placebo group.

There is an absence of evidence to assess the long-term effects of dupilumab as monotherapy and as a concomitant treatment with TCS beyond 16 weeks and 52 weeks of treatment, respectively. Additionally, there were no active comparator trials identified in the CDR systematic review to assess the efficacy and safety of dupilumab versus the drugs that are commonly used in clinical practice.

Appendix 1: Patient Input Summary

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

1. Brief Description of Patient Groups Supplying Input

The Eczema Society of Canada (ESC) provided input for the CADTH Common Drug Review (CDR) submission for dupilumab. The ESC is a registered Canadian charity dedicated to improving the lives of Canadians living with eczema. With the help of dedicated physicians and contributors, the ESC delivers evidence-based, up-to-date disease and treatment information to Canadians living with eczema and to caregivers and health care providers.

ESC receives funding from private citizen donations, funds and foundations (including Canada Helps, FedEx Cares Employee Community Fund, Fondation Pierre Fabre, United Way) and corporate sponsors including Actelion Pharmaceuticals, Astellas Pharma Canada, Beiersdorf Canada, Blistex, Galderma Canada, GlaxoSmithKline Canada, Johnson & Johnson, L'Oreal Canada, Paladin Labs, Pediapharm, Pierre Fabre Dermo-Cosmétique Canada, Sanofi Canada, Sanofi Genzyme Canada, Shoppers Drug Mart, Skinfix, Unilever, Valeant Canada, and Wellspring Pharmaceutical. However, ESC declared no conflicts of interest with respect to this submission.

2. Condition-Related Information

This information was collected through an online survey. In total, 377 Canadian adults with atopic dermatitis (AD) and their caregivers responded to the online survey. A number of one-on-one interviews took place with individuals across Canada, as well. Out of the total respondents, 88% suffer from moderate or severe AD. The focus of this survey and interview questions was moderate and severe AD, for which dupilumab is indicated. For the purpose of the survey and discussion herein, AD severity was defined as the following: moderate (AD with areas of dry skin, frequent itching, and redness with or without broken or localized skin thickening) and severe (AD with widespread areas of dry skin, incessant itching, and redness with or without broken skin, and extensive skin thickening, bleeding, oozing, and cracking).

AD, commonly known as eczema, is an inflammatory skin condition characterized by intense itching which manifests with a red, raised rash that can ooze, crust, and bleed. Patients may experience mild eczema with few lesions, and the spectrum continues to severe, recalcitrant AD where patients could have entire body involvement. Patients report that this intense itch can persist all day and often worsens at night, thereby affecting sleep. Living with chronic itch, pain, and chronic cycles of flares (acute worsening of the disease) takes a significant toll on quality of life. Of those who responded to the survey, 87% stated that the negative effects of AD on their day-to-day life (quality of life) include interrupted and/or loss of sleep, anxiety, depression, social isolation, unwanted career change, poor self-esteem, and suicidal thoughts.

The following quotations provide some insight into the day-to-day challenges for 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."

3. Current Therapy-Related Information

ESC indicated that the current therapies for AD include topical corticosteroids (e.g., hydrocortisone, betamethasone, and clobetasol; 98% of respondents), bathing and moisturizing techniques (89%), oral antihistamines (e.g., Benadryl and Atarax; 69%), topical calcineurin inhibitors (e.g., tacrolimus and pimecrolimus; 51%), and phototherapy (30%). Among those respondents, 91% reported that their AD is not well controlled. A total of 41% reported they have treatment needs that are not being met by existing therapies, and 25% reported that they have lived 10 years or more without adequate treatment.

Patients provided the following statements to illustrate their experience with various treatments for their severe AD.

"I have lived with atopic dermatitis since childhood and I've tried every treatment you can imagine. Nothing works (on) my eczema, including prednisone. My doctor said it will destroy my health if I keep using it, but nothing else works."

"The creams and ointments all help in the short term, but the eczema comes right back. When I apply the medicines, the stinging and burning from the medicine, and the itch the creams cause, are almost worse than the eczema itself."

When asked about their overall experience with eczema treatments, respondents noted the following: difficulty dressing after applying treatments (52% of respondents); uncomfortable (49%); difficulty finding time during the day to apply the medications (44%); difficulty adhering to a topical treatment plan (38%); interference with work and/or day-to-day life caused by topical medications (38%); and physical pain when applying treatments (32%). However, 37% of respondents indicated that their current therapy is effective for managing their eczema. For patients with recalcitrant AD, off-label systemic therapies are sometimes used. AD is a chronic condition requiring lifelong therapy. However, these systemic therapies are not suitable for long-term use. In the survey, 63% of respondents who have tried off-label systemic therapies reported that they did not work well to manage their AD.

Caregivers reported feelings of helplessness and frustration while the patient is suffering with a condition that cannot be controlled and continues to flare. The caregivers indicated they also experienced sleep loss, along with anxiety and depression.

4. Expectations About the Drug Being Reviewed

The information provided in this section was obtained through one-on-one interviews and written questionnaires.

Based on patients' experiences with the new drug as part of a clinical trial, ESC has learned 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. Patients with AD in Canada expect that access to dupilumab will effectively treat moderate-to-severe AD and address gaps in the current treatment options. While current therapies are able to treat inflammation and rash with varying success, patient are seeking a treatment that will break the cycle of flares and manage the itch. Patients also expect the new medication to improve their quality of life.

Patient quotations about their experience with dupilumab treatment follow:

"Dupilumab has had a tremendously positive impact on my condition and my life, but the most significant change has been to my sleep. I get 7 to 8 hours of sleep every night. Before starting dupilumab, I never had a good night's sleep for as long as I can remember — maybe never."

"The most significant change from this drug to the other treatments I have tried is that it worked, but also it seems like a cure — the eczema is gone. The itch is gone."

"Skin outbreaks are gone and the itching is significantly reduced. This drug is the first treatment to actually manage the disease, and it actually feels like this drug prevents the flares from occurring.

"I no longer rip apart my skin from itching and inflammation."

"I want to reiterate that there has been no real therapy or drug that manages severe AD presently available. This is the first drug in my entire life that I have used that actually manages and makes the AD almost a non-issue."

"Over the last three to four years on the dupilumab drug trial, my severe eczema was under control for the first time in my life; I was able to work productively, focus on building my business, and enjoy the outdoors with my family and friends."

"I have experienced no adverse effects and I've been on the drug for almost three years."

"The once-weekly injection of dupilumab is much less frequent than other treatments for eczema, and this is much more convenient… It impacts my quality of life positively in that I no longer need to be constantly laundering clothes and bed sheets from the transfer of creams and ointments."

"There was a period of time where I didn't want to have kids because I was worried I would pass this condition on to my child. Now I feel better that there is hope that, even if my child did have eczema, they could get treatment."

"The drug is life-changing. I used to have an invisible ceiling hanging over my life that is no longer there."

5. Additional Information

Based on patients' experiences involved in the clinical trial, patients with AD have learned that dupilumab is a life-altering medication. Patients believe that it should be publicly available for Canadian patients for whom it is indicated. Once available, patients think dupilumab will significantly improve the quality of life for patients living with recalcitrant

moderate-to-severe AD. The following comments from the survey show that patients have concerns over their treatment when the dupilumab clinical trial is over:

“The trials are now finished and I have had no access to dupilumab since then. I am very worried about what will happen to my condition when I can longer get this drug.”

"Now (that the trial is over), I am experiencing a severe eczema outbreak because I no longer have access to dupilumab… it's mentally draining. I have spent the last three weeks confined to my bed and apartment… and I am trying to understand how to move forward with life and work due to a lack of effective treatments for severe eczema."

Appendix 2: Literature Search Strategy

Overview	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	November 23, 2017
Alerts:	Bi-weekly search updates until April 11, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-Database Strategy	
1	1190264-60-8.rn,nm.
2	(dupilumab* or dupixent* or REGN668 or REGN 668 or SAR231893 or SAR 231893 or 420K487FSG).ti,ab,kf,ot,hw,rn, nm.
3	or/1-2
4	3 use medall
5	*dupilumab/
6	(dupilumab* or dupixent* or REGN668 or REGN 668 or SAR231893 or SAR 231893).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	8 not conference abstract.pt.
10	4 or 9
11	remove duplicates from 10

Other Databases	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 2017
Keywords:	Dupixent (dupilumab), atopic dermatitis
Limits:	No date or language limits used

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 Trials
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Simpson, 2017[37]	Study type not applicable
Beck, 2014[38]	Phase II trial

Appendix 4: Detailed Outcome Data

Table 10: Key Efficacy End Points for SOLO 1 and SOLO 2 by [redacted]

	SOLO 1				SOLO 2			
	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]
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[redacted]

q.2.w. = once every two weeks.
Source: Clinical study reports for SOLO 1[4] and SOLO 2.[5]

Table 11: Key Efficacy End Points for LIBERTY AD CHRONOS by [redacted]

	Follow-Up to Week 16				Follow-Up to Week 52			
	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]

[redacted]

q.2.w. = once every two weeks; TCS = topical corticosteroids.

Source: Clinical study report for LIBERTY AD CHRONOS.[6]

Table 12: Key Efficacy End Points for CAFÉ by [redacted]

	Placebo + TCS N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]	Placebo + TCS N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]
[redacted]	[redacted]		[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]

	Placebo + TCS N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]	Placebo + TCS N = [redacted]	Dupilumab 300 mg q.2.w. + TCS N = [redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]

[redacted]

q.2.w. = once every two weeks; TCS = topical corticosteroids.
Source: Clinical study report for LIBERTY AD CAFÉ.[7]

Table 13: Key Efficacy End Points for SOLO 1 by [redacted]

	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]
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[redacted]

q.2.w. = once every two weeks.
Source: Clinical study report for SOLO 1.[4]

Table 14: Key Efficacy End Points for SOLO 2 by [redacted]

	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]		[redacted]		[redacted]		[redacted]

[redacted]

q.2.w. = once every two weeks.

Source: Clinical study report for SOLO 2.[5]

Table 15: Key Efficacy End Points for LIBERTY AD CHRONOS by [redacted]

	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]								
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]
[redacted]								
[redacted]								
[redacted]								
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[redacted]

q.2.w. = once every two weeks.
Source: Clinical study report for LIBERTY AD CHRONOS.[6]

Table 16: Key Efficacy End Points for LIBERTY AD CAFÉ by [redacted]

	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]	Placebo N = [redacted]	Dupilumab 300 mg q.2.w. N = [redacted]
[redacted]				
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[redacted]				
[redacted]				

[redacted]

q.2.w. = once every two weeks.
Source: Clinical study report for LIBERTY AD CAFÉ.[7]

Appendix 5: Validity of Outcomes Measures

Aim

To summarize the validity of the following end point measures:

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

Findings

Table 17: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
EASI	A scale used in clinical trials to assess the severity and extent of AD	Yes	6.6 points	8
IGA	A scale that provides a global clinical assessment of AD by investigators	Yes	Unknown	12,22
SCORAD	A tool used in clinical research to standardize the evaluation of the extent and severity of AD	Yes	8.7 points	8
PGADS	A scale used for global assessment of AD by patients	unknown	Unknown	4
Pruritus NRS	A tool for patients with AD to report the intensity of their itch	Yes	3 points[a]	4 39,40
DLQI	A questionnaire used to assess six different aspects that may affect quality of life	Yes	2.2 to 6.9	31,32
EQ-5D	A generic QoL instrument that has been applied to a wide range of health conditions and treatments	Yes	Unknown for AD	4,5,34,41-43
HADS	A patient-reported questionnaire designed to identify anxiety disorders and depression in patients at non-psychiatric medical institutions	Unknown	Unknown	35,44,45
POEM	A questionnaire used in clinical trials to assess disease symptoms in children and adults with eczema	Yes	3.4 points	8

AD = atopic dermatitis; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D = EuroQol 5-Dimensions questionnaire; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; MCID = minimal clinically important difference; NRS = Numerical Rating Scale; PGADS = Patient Global Assessment of Disease Status; POEM = Patient-Oriented Eczema Measure; QoL = quality of life; SCORAD = Scoring Atopic Dermatitis.

[a] A reduction of three points in Pruritus NRS was considered a clinical meaningful improvement.[39,40]

Eczema Area and Severity Index

The EASI is a scale used in clinical trials to assess the severity and extent of atopic dermatitis (AD).[8,20-22] In EASI, four disease characteristics of AD (erythema, infiltration/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, an area score of 0 to 6 is assigned for each body region, depending on the percentage of AD-affected skin in that area: 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 resulting EASI score ranges from 0 to 72 points, with the highest score indicating worse severity of AD.[20] It has been suggested that the severity of AD based on EASI score should 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.[46] EASI-75 indicates ≥ 75% improvement from baseline.[4]

The validity and reliability of the EASI was examined in several studies.[8,20-22,22] The correlation coefficients were estimated between EASI and SCORAD to assess the validity.[21] A moderate to high correlation between the EASI and SCORAD (r = 0.84 to 0.93) was reported.[21] intra- and inter-rater reliability was examined (r = 0.8 to 0.9).[21] The authors concluded that EASI is a validated scale and can be used reliably in the assessment of severity and extent of AD.[12,20] In one study,[8] it was reported that the overall minimal clinically important difference (MCID) was 6.6 points when IGA improving by one point was used as anchor. However, the reported MCID was not relevant for interpreting the EASI data (such as EASI-75) reported in the pivotal studies.

Investigator's Global Assessment Scale

The IGA is a five-point scale that provides a global clinical assessment of AD severity ranging from 0 to 4, where 0 indicates clear, 2 is mild, 3 is moderate, and 4 indicates severe AD.[4] A decrease in score relates to an improvement in signs and symptoms. However, it was indicated that IGA was designed for and is commonly used for clinical trials and rarely used in clinical practice.[12] 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 (intra-rater reliability by investigator) for the IGA (0.54)[22] is below what would typically be considered acceptable (0.70). A review of the literature found no information on the validity of the IGA scale in patients with AD. Similarly, no information was found on what would constitute an MCID in patients with AD.

Patient Global Assessment of Disease Status

PGADS is measured using a five-point Likert scale. Higher score indicates a better overall condition. In the pivotal clinical studies,[4-6] patients rated their overall well-being based on five response choices ranging 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 MCID 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.[4,23] 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/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using a four-point scale (i.e., none = 0, mild = 1, moderate = 2, severe = 3) with a maximum possible total of 18 points. The symptoms (itch and sleeplessness) are recorded by the patient or caregiver on a visual analogue scale, where 0 is no symptoms 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 discussed previously. The maximum possible SCORAD score is 103; higher scores indicate poorer or more severe condition.[4] The intra-class correlation coefficient (ICC) was calculated to assess intra-rater reliability; the coefficient of variation was used to assess inter-rater variability.[22] It was reported that the ICC for SCORAD was 0.66, indicating fair-to-good reliability in patients with AD.[22] Based on the analysis of the data from three randomized controlled trials (RCTs) with patients with atopic eczema, the MCID was estimated using the mean change in SCORAD scores among patients who showed a relevant improvement based on IGA, defined as an "improvement" or "decline" of ≥ 1 point in Physician's Global Assessment and IGA. A difference of 8.7 points in SCORAD was estimated as the MCID for the patients with atopic eczema (also known as AD).[8]

Pruritus Numerical Rating Scale

The Pruritus NRS is a tool that patients used to report the intensity of their itch during a daily recall period using an interactive voice response system. Patients were asked to rate their overall (average) and maximum intensity of itch experienced during the past 24 hours on a scale from 0 to 10 (0 = no itch and 10 = worst itch imaginable).[4] The proportion of patients with improvement (reduction ≥ 3 or ≥ 4 points) in the weekly average of the peak daily Pruritus NRS from baseline to week 16 was reported in the pivotal studies.[4] Additional information provided by the manufacturer reported the validity and reliability of the Pruritus NRS based on three phase III and one phase IIb RCTs.[39,40] In the aforementioned RCTs, the Pruritus NRS was completed daily from baseline through week 16, and weekly from week 17 to week 52. [39,40] Patient data from weeks 15 and 16 were used to examine the 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. [39,40] The ICC values indicated that the Pruritus NRS scores were stable over a period of time when the patients' disease was stable. To assess the validity of the Pruritus NRS, a priori hypotheses were evaluated using correlational analyses and three known-groups analysis of variance (ANOVA) models ("absent/mild" group based on the Pruritus Categorical Scale [PCS]; "poor" disease group based on the PGADS, and "no impact" on the skin-related quality-of-life group based on DLQI total score). 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, 1998).[39,40] Based on the data from the phase IIb study, using EASI, IGA as anchors, 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.[39,40]

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 may affect quality of life.[31,32] These aspects are symptoms and feelings, daily activities, leisure, work and school performance, personal relationships, and treatment.[31,32] 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).[31,32] 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:[26]

- 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 DLQI has shown good test–retest reliability (correlation between overall DLQI scores was 0.99 [$P < 0.0001$], and for individual question scores was 0.95 to 0.98 [$P < 0.001$]),[32] internal consistency reliability (with Cronbach's alpha coefficients ranging from 0.75 to 0.92 when assessed in 12 international studies),[26] construct validity (37 separate studies have mentioned a significant correlation between the DLQI and either generic or dermatology-specific and disease-specific measures),[26] and responsiveness (the DLQI being able to detect changes before and after treatment in patients with psoriasis in 17 different studies).[26]

Estimates of the minimal important difference (the smallest difference a patient would regard as beneficial) have ranged from 2.2 to 6.9.[26,31] It should be noted that some of the anchors that were used to obtain the DLQI MCID were not patient-based (i.e., Basra et al.[26] derived estimates from the Psoriasis Area and Severity Index and Physician's Global Assessment anchors, as well as a distribution-based approach).

Limitations associated with the DLQI are as follows:

- Concerns have been identified regarding its 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 identified in only two citations out of the 12 international studies identified.[26]
- The patient's emotional responses to their disease 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 (SF-36) or HADS.[26]
- There are no available benchmarks for the MCID in DLQI scores in general dermatological conditions, although there have been some attempts to determine these differences for specific conditions, such as psoriasis.[26]
- The DLQI may lack sensitivity in detecting change from mild to severe psoriasis.[47]

No validity information or MCID information was found for the patients with AD.

EuroQol 5-Dimensions Questionnaire

The EQ-5D[41,42] is a generic quality-of-life instrument that has been applied to a wide range of health conditions and treatments, including AD. The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged 12 years or older) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/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 one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[41,42] The second part is a 20 cm visual analogue scale (EQ-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 EQ-VAS that best represents their own health on that day. Hence, the EQ-5D 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 EQ-VAS.

The EQ-5D index score 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 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 lower than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1 are assigned to the health states "dead" and "perfect health," respectively.

The MCID for the EQ-5D ranges from 0.033 to 0.074.[34] The EQ-5D index utility score and EQ-VAS score were reported in the pivotal studies.[4-6] No additional validity information or MCID information for the EQ-5D in AD was found from literature search.

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.[35,44,45] The HADS questionnaire contains 14 items that assess symptoms experienced in the previous week; among these, seven items are related to anxiety and seven are related to depression. Patients provide responses to each item based on a four-point Likert scale. Each item is scored from 0 (the best) to 3 (the worst); thus, a person can 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 are considered to be a "definite case" of psychological morbidity, while scores of 8 to 10 represent "probable case" and 0 to 7 "not a case."[35] No additional information about the validity of or MCID for the HADS in AD was found from the literature search.

Patient-Oriented Eczema Measure

The POEM is a seven-item, questionnaire used in clinical trials to assess disease symptoms in children and adults.[24] Based on frequency of occurrence during the past week, the seven items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) are assessed using a five-point scale. The possible scores for each question are: 0 (no days), 1 (1 to 2 days), 2 (3 to 4 days), 3 (5 to 6 days), and 4 (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 skin, 3 to 7 indicates mild eczema, 8 to 16 indicates moderate eczema, 17 to 24 indicates severe eczema, and 25 to 28 indicates very severe eczema).[24] In one study,[8] it was reported that the overall mean MCID of the POEM was 3.4 points (standard deviation = 4.8) when IGA improving by one point was used as anchor.

Conclusions

The IGA, EASI, and SCORAD are the most commonly used tools in clinical trials to evaluate disease severity in patients with AD. Among them, the IGA is widely accepted and considered a “validated” scale. The MCID for EASI, SCORAD, and POEM was estimated to be 6.6, 8.7, and 3.4 points, respectively, for the patients with AD. Additional information provided by the manufacturer suggested that a reduction of 3 to 4 points in the Pruritus NRS was a reasonable threshold for treatment response. Although the PGADS and HADS are commonly used in clinical practice to assess AD, no validity information and no MCID information were found for AD. The DLQI and EQ-5D (3-Levels questionnaire) are commonly used tools to assess health-related quality of life in patients with AD; however, no information about the validity of or MCID for the EQ-5D and DLQI in AD was found from the literature search.

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