Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende upadacitinib til behandling af moderat til svær atopisk eksem hos unge og voksne (≥ 12 år)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. upadacitinib
2. Forhandlingsnotat fra Amgros vedr. upadacitinib
3. Ansøgers endelige ansøgning vedr. upadacitinib

2022 12 23

Høringssvar til udkast til Medicinrådets vurderingsrapport vedrørende upadacitinib til behandling af atopisk eksem

Kære Medicinråd,

Vi har den 12 december modtaget udkast til Medicinrådets vurderingsrapport vedrørende upadacitinib til behandling af atopisk eksem.

AbbVie vil gerne komplimentere Medicinrådet for et grundigt og gennemarbejdet dokument, og har ingen yderligere kommentarer.

Med venlig hilsen,

Jeanette Lagerlund

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DATO 20.12.2022

DBS, SNI

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.01.2023
Leverandør	Abbvie
Lægemiddel	Rinvoq (upadacitinib)
Ansøgt indikation	Moderat til svær atopisk eksem hos unge og voksne (> 12 år)

Forhandlingsresultat

Amgros har en aftale om følgende pris på Rinvoq (upadacitinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Nuværende pris SAIP	Rabatprocent ift. AIP
Rinvoq (upadacitinib)	15 mg depottabletter	28 stk.	6.313,52	[redacted]	[redacted]
Rinvoq (upadacitinib)	30 mg depottabletter	28 stk.	12.627,05	[redacted]	[redacted]

[redacted]

Konkurrencesituationen og relation til behandlingsvejledning

Der er flere lægemidler, som har godkendt indikation til moderat til svær atopisk dermatitis, som også indgår i andre terapiområder.:

[redacted]

Der er allerede konkurrence på terapiområdet moderat til svær atopisk dermatitis.

[redacted]

Tabel 2: Sammenligning af lægemiddeludgift

Lægemiddel	Dosering	Styrke og pakningsstørrelse	Pakningspris, SAIP	Antal pakninger pr. år	Lægemiddeludgifter, SAIP pr. år
Rinvoq (upadacitinib)*	15 mg dagligt	15 mg, 28 stk.	[redacted]	13	[redacted]
Rinvoq (upadacitinib)*	30 mg dagligt	30 mg, 28 stk.	[redacted]	13	[redacted]
Dupixent (dupilumab)	Startdosis på 600 mg efterfulgt af 300 mg hver 2 uge	300 mg, 2 stk.	[redacted]	14	[redacted]

*Rinvoq (upadacitinib): 70 % af patienterne får en daglig dosis på 15 mg og 30 % får en daglig dosis på 30 mg.
Den gennemsnitlige lægemiddeludgift i SAIP er [redacted] kr.

Status fra andre lande

Norge: Anbefalet[1]

England: Anbefalet[2]

Konklusion

[redacted]

Rinvoq(upadacitinib) [redacted]

[1] https://nyemetoder.no/metoder/upadacitinib-rinvoq-indikasjon-iv-
[2] https://www.nice.org.uk/guidance/ta814

Application for the assessment of Rinvoq (upadacitinib) for moderate to severe Atopic Dermatitis

Version 1.0

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Rinvoq
Generic name	Upadacitinib
Marketing authorization holder in Denmark	AbbVie Deutschland GmbH & Co. KG
ATC code	L04AA44
Pharmacotherapeutic group	Janus kinase inhibitor (JAK)
Active substance(s)	Upadacitinib

Overview of the pharmaceutical	
Pharmaceutical form(s)	Prolonged-release tablet
Mechanism of action	Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2
Dosage regimen	The recommended dose of upadacitinib is 15 mg once daily
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	RINVOQ is indicated to treatment of moderate to severe atopic dermatitis for patient > 12 years
Other approved therapeutic indications	RA
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Monotherapy or in combination with TCS
Packaging – types, sizes/number of units, and concentrations	Each pack contains 28, 15mg or 30 mg prolonged-release tablets
Orphan drug designation	No

2. Abbreviations

AD: Atopic dermatitis
AE: Adverse Event
AIP: Pharmaceutical paying price
BARI: Baricitinib
BSA: Body surface area
BSC: Best supportive care
CUA: Cost utility analysis
EASI: Eczema Area Severity Index
EASI-50, -75, -90: 50, 75, 90 percent decrease in EASI from baseline respectively
EMA: European Medicines Agency
EOW: Every Other Week
DDS: Dansk Dermatologisk Selskab
DLQI: Dermatology Life Quality Index
DSA: Deterministic sensitivity analysis
DUP: Dupilumab
IGA: Investigator's Global Assessment
ICER: Incremental cost-effectiveness ratio
IV: Intravenously
JAK: Januse kinase

JAKi: Januse kinase inhibitor
MACE: Major adverse cardiac events
MR: Medicinraadet
NMSC: Nonmelanoma skin cancer
NSAID: Non-steroidal anti-inflammatory drug
QALY: Quality-adjusted life year
QoL: Quality of Life
RTI: Respiratory tract infection
SC: Subcutaneously
SE: Standard error
SF-36: Short Form 36
SmPC: Summary of product Characteristics
TCI: Topical calcineurin inhibitor
TCS: Topical corticosteroid(s)
TNF: Tumor Necrosis Factor
UPA: upadacitinib
VTE: venous thrombosis event
PSA: Probabilistic sensitivity analysis

3. Tables and Figures

4. Summary

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin condition characterized by eczematous skin lesions with uncontrolled debilitating intense itch, pain, and episodes of flares. The constant, unpredictable, and disruptive nature of symptoms alongside the frequent and episodic exacerbations in disease, can severely impact quality of life (QoL) through sleep problems, depression, and suicidal ideation, contributing to reduced work productivity. The prevalence of AD has increased in industrial countries the past decades, estimated prevalence for children in industrial countries is 15-30% and approximately 2-10 % in adults. The disease often presents in early childhood, and about one third are affected into adulthood. Considering the high prevalence of AD and its chronic and troubling symptoms, the economic burden associated with AD is substantial. The economic burden associated with AD includes direct costs and indirect costs through missed days of work or lost productivity at work or school, career modification or impact on career attainment.

The Danish dermatology association recommends a treatment sequence of emollients, moderate to potent TCS, followed by systemic treatment. If patients are suboptimal treated with topical therapy, systemic therapy should be initiated in patients with moderate to severe disease. Conventional systemic treatments are not suitable for long-term use and are associated with a wide range of side-effects. The currently approved advanced systemic treatments for AD are dupilumab, a human anti-IL-4Rα inhibitor and baricitinib, an oral JAK-1/2 inhibitor. Dupilumab is recommended by the dermatology association for use in Denmark for patients fulfilling one or several of the following criteria: EASI>16, BSA>10%, POEM>16, DLQI>10, who have tried and not reached treatment goals or have contraindications to convential systemic treatments. Baricitinib has recently been approved by the Medicines Council, but is not yet included in the recommendation.

Despite advances, an unmet medical need remains for patients with moderate-severe AD. Current conventional and advanced systemic treatments in AD deliver limited efficacy and are associated with relatively poor slide-effect profiles. New, effective therapies with more favorable side-effect profiles that can be administered in a convenient way, and with the prospect of not having to rely on concomitant TCS to achieve treatment targets, are urgently needed for patients with severe as well as moderate AD who are candidates for systemic treatment.

Upadacitinib is a selective and reversible JAK inhibitor. In human cellular assays, upadacitinib preferentially inhibits signaling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Upadacitinib delivers a well-characterized benefit: risk profile in several inflammatory diseases and provides significant improvement in patient's quality of life and clinical outcomes and offers dosing flexibility based on patient's need, is administered orally once daily, and can be given as monotherapy or in combination with topical corticosteroids.

The marketing authorization for Rinvoq received Aug 23rd is for the treatment of people aged 12 years or over with moderate-to-severe AD who are candidates for systemic therapy. While this population includes patients, who are eligible for conventional systemic therapies (i.e., immunosuppressant therapies), it is anticipated that upadacitinib will be positioned to patients who are contraindicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. This population aligns with the population in the upadacitinib clinical trials and the population for which dupilumab is recommended in Denmark. The most relevant choice of comparator, based on section 2.4 of the Medicine Councils guideline, is dupilumab. Upadacitinib is an oral tablet available in two doses. Most patients will be treated with the lower dose, considering the dosage in the SPC which states that 15 mg should be starting and maintenance dose, and the only dose for patients aged 12 to 17 and >65 years of age. Patients with high disease burden might during a period be treated with 30 mg, but the lowest possible dose should be used for maintenance treatment. Results from the market authorization

studies show that most patients treated with 15 mg in monotherapy will reach the treatment goals used in Danish clinical practice (EASI 75 or EASI 50 + ≥ 4 point improvement in DLQI). Based on Danish registry data more patients in Danish clinical practice are treated with systemic treatments alone than treated in combination with TCS. Most patients also have an infrequent use of TCS, and overall TCS use has been shown to be lower after hospital referral where treatment with systemics will be initiated and continues to decrease over the years thereafter in patients treated with systemic treatment. Combined with the fact that a high proportion of patients reach the defined outcomes for sufficient treatment response defined by the Danish specialists association, EASI 75 or EASI 50 + ≥ 4 point improvement in DLQI, in the pivotal clinical trials, it seems likely that upadacitinib will be used predominantly in monotherapy in clinical practice.

Based on the proportion of patients in the clinical trials reaching the treatment goals defined by the Danish specialist's association, AbbVie predict that 70 % of the patients will use 15 mg in clinical practice. To evaluate the in-label use of upadacitinib this proportion of patients using 15 mg is used in the health economic model and the remaining 30 % of patients will be treated with 30 mg in the model.

Upadacitinib has demonstrated significantly better efficacy compared with dupilumab for EASI 75 and EASI 90 in a head-to head trial. In addition, two network metanalyses (NMA) have been performed to evaluate the relative efficacy of upadacitinib compared to dupilumab with or without concomitant TCS use. The monotherapy network including studies where TCS could be used as a rescue therapy, is the network AbbVie considers reflects both how upadacitinib will be used in clinical praxis and how TCS is used in clinical praxis based on Danish registry data. Results from this network is the available evidence that best mimic the relative efficacy in clinical practice.

In an analysis based on the expected dosing from the label described above, and evaluating the clinically relevant endpoint EASI-75, upadacitinib was significantly more effective than dupilumab [redacted]
This analysis evaluated the efficacy of the expected in label use of upadacitinib as compared to the most relevant comparator dupilumab in Denmark. In the upadacitinib pivotal trials no new safety risks were observed compared to the safety profile of upadacitinib in the previously approved indications rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. At week 16, incidence of serious adverse events was similar across the pivotal trials ranging from 1.8-2.3 % in the upadacitinib 15 mg arm, 1.3-2.8 % in the upadacitinib 30 mg arm and 2.8-3.0 % in the placebo arm. The most common TEAE reported included were acne, upper respiratory tract infection and nasopharyngitis. As upadacitinib, dupilumab has not shown any increased serious adverse events compared with placebo. In all pivotal trials, conjunctivitis and injection-site reactions were significantly higher with dupilumab compared to placebo. These adverse events are not seen with upadacitinib, due to different mode of administration and mechanism of action.

To evaluate the cost-effectiveness of upadacitinib compared with dupilumab a cost-utility analysis (CUA) has been performed, where results are presented per patient. In the cost-utility model patients starts in a decision tree representing the first 16 weeks of treatment. According to response, patients are then transitioned into a Markov model with a lifetime horizon. Evaluation of efficacy after 16 weeks is used both in clinical trials of upadacitinib and dupilumab and in clinical practice in Denmark making the model structure suitable. As described above the clinical evidence most appropriate is the results from the network meta-analysis comparing upadacitinib and dupilumab in monotherapy, where TCS is used as rescue by patients not achieving sufficient response in monotherapy. Health utility data comes from the pivotal trials, using the Danish value set for EQ-5D-5L and are age-adjusted according to relevant guidelines.

The model includes costs for active treatment (upadacitinib or dupilumab), administration, adverse events, patient costs, as well as treatment-related costs and monitoring. Base-line patient characteristics are derived from the pivotal

clinical trials. The model also has a budget impact module including the same costs, except for patient-costs. In the base case analysis, treatment with UPA is dominant, resulting in cost savings and substantial QALY gains (0.362) per patient. A scenario analysis using a full societal perspective, i.e., including also cost for productivity losses were performed. The results showed that the cost savings per patient more than doubled when a wider perspective, taking the full effect of AD into account, was used.

The results are robust through all sensitivity analyses demonstrating that UPA constitutes a cost effective and valuable treatment options for patients with moderate to severe AD in Denmark. An integrated budget impact model was developed and resulted in a net/cumulative cost saving of 2,3 million DKK. Including productivity losses would lead to substantially higher cost savings also in the budget impact calculations as the cost saving per patient more than doubled in the cost effectiveness analysis when including productivity losses.

Overall, the analyses demonstrate that UPA is a cost-effective treatment option for patients with moderate to severe AD that are candidate for systemic treatment, while at the same constituting an attractive treatment option from a health care budget perspective. In conclusion, introducing upadacitinib for treatment of moderate to severe atopic dermatitis would benefit both patients, by increasing the number of QALYs generated, and society, by reducing the cost of treatment.

5. The patient population, the intervention and choice of comparator(s)

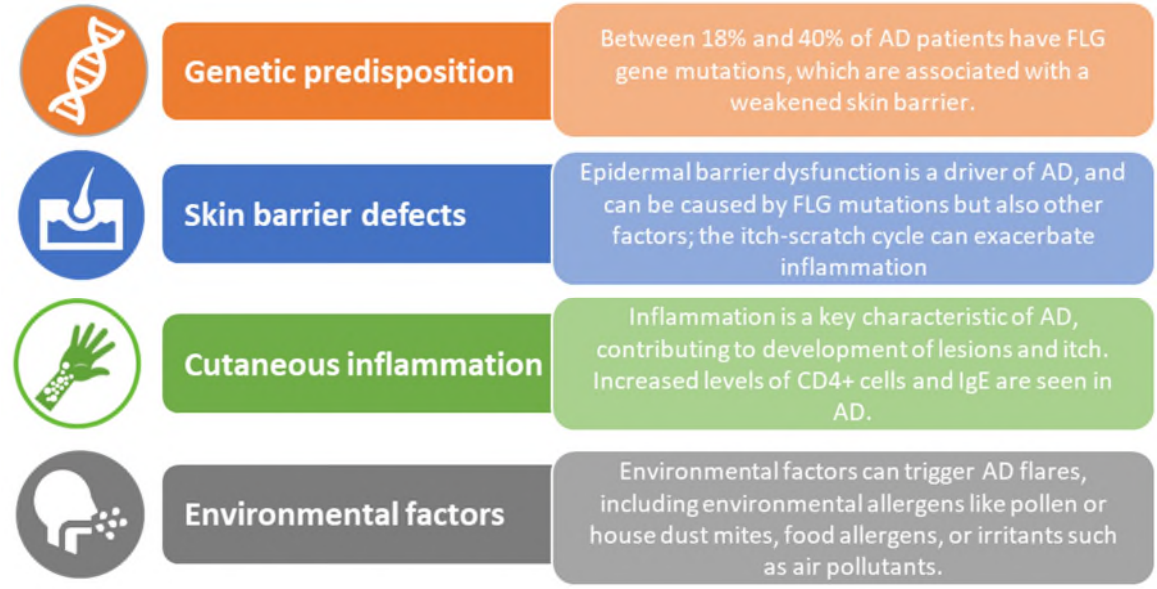
5.1 The medical condition and patient population

Atopic dermatitis (AD) also known as atopic eczema is a chronic, relapsing systemic inflammatory disease and the most common form of eczema(1). The disease usually starts in early infancy. In infants, AD often presents as tiny bumps on the cheeks, however in older children and adults the disease usually presents as patches of red or brown skin, intense itching of the skin and/or dry, cracked, scaly skin, in the folds of the joints, back of the hands or on the scalp (2). Childhood onset of AD is often associated with allergic disease later in life (3).

Intense itch is the major disease characteristic specific to AD, as well as the most prevalent and debilitating symptom, disrupting sleep and driving impairment of patient QoL.(4) Patients can suffer itch to such an extent that they scratch to the point of bleeding, worsening AD-associated lesions and causing further inflammation. The constant, unpredictable, and disruptive nature of the disease symptoms, frequent and episodic exacerbations in disease, as well as social stigma related to itching, scratching and visible skin disease, have a large impact on patients' quality of life and patients with AD suffer from high rates of anxiety, depression, and difficulties with concentrating.

The pathogenesis of AD is complex and involves a variety of potential underlying causes. Firstly, a genetic state of atopy, or tendency towards allergic disease, can contribute to an increased epidermal inflammatory response.(1) Triggers of AD include genetic and environmental factors (Figure 1). Additionally, immunoglobin E (IgE) inflammatory response can be triggered by hypersensitivity to allergens such as dust mites, food, mould, pollen, or animal dander.(1, 5, 6). In genetically susceptible individuals, both gene–gene and gene–environment effects contribute to the underlying pathological mechanisms of epidermal barrier abnormalities and T cell-driven skin inflammation (7-10). AD involves a complex interplay between the defective skin barrier, and a dysregulated immune response (11).

Figure 1. Triggers of Atopic Dermatitis



Genetic susceptibility

The strongest risk factor for AD is a positive family history of atopic diseases, especially AD itself, supported by both cross-sectional studies and genome wide association studies.(12, 13) There are several genetic mutations associated with AD, with mutations in the FLG gene the most common.(14) Between 18% and 40% of those with AD carry FLG null mutations. The FLG gene encodes the epidermal protein filaggrin and null mutations in FLG lead to a reduction in filaggrin expression. Filaggrin is vital for the normal functioning of the skin barrier. The skin barrier is formed by the terminal differentiation of keratinocytes, which create a tough insoluble layer known as the cornified envelope (CE). Filaggrin reinforces the CE, allowing it to carry out its normal functions such as the prevention of water loss and pathogenic invasion through the skin (14, 15). Therefore, the absence of filaggrin causes the skin barrier to be weakened, which increases the likelihood of AD development. However, over 50% of individuals carrying FLG mutations fail to develop atopic disease, highlighting that there are additional factors other than FLG mutations needed to drive full AD manifestation (14).

Defective skin barrier

One of the strongest genetically determined causes of AD is a defective skin barrier, also known as epidermal barrier dysfunction (15). A defective skin barrier results in reduced expression of structural proteins or lipids and can be worsened by itching and scratching. Epidermal changes related to reduced barrier function, such as reduced pH, reduced water retention, increased irritation and increased susceptibility to infection have been observed in the skin of AD patients (1, 5, 6). The underlying defective skin barrier seen in AD is aggravated by the itch-scratch cycle and inflammation, contributing to the burdensome symptoms seen in AD.

Inflammation

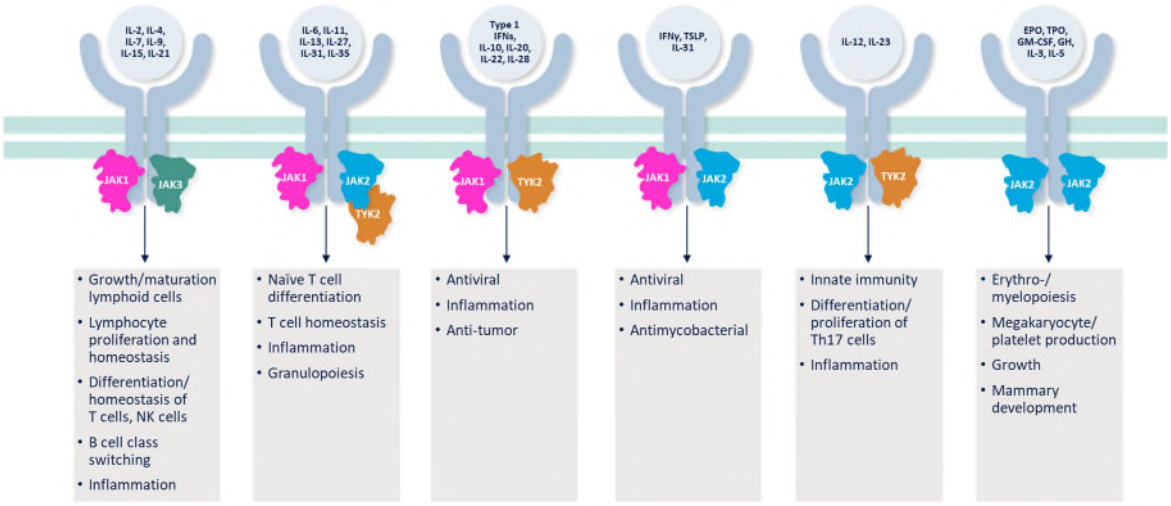
The immunopathology of AD is highly complex and involves a broad array of inflammatory pathways, many of which signal via the JAK1 pathway (6, 15, 16). Inflammation is a key characteristic of AD, and cutaneous inflammation contributes to the formation of lesions as well as the presence of itch and other symptoms in AD (15). There is an increased inflammatory response in AD patients, with a higher level of inflammatory cells present compared to healthy skin. The inflammatory infiltrate is predominantly composed of CD4+ cells, which are key drivers of inflammation (17).

Patients with AD commonly exhibit blood markers for increased inflammation as well (6, 16). Serum cytokines (IL-4, IL-5, IL-13, IL-19, IL-22, IL-31, TSLP, and IFNγ) are known to be increased in AD, with further activation of multiple inflammatory pathways in some patients. In AD, a number of these cytokines then transmit pro-inflammatory signals through the JAK-STAT pathway (IL-4, IL-13, IL-31 and TSLP). Targeting specific immunological mechanisms and pathways suggests a promising option by treating the underlying drivers of disease.(16) Due to the complex nature of AD, optimal treatment should target the broad range of immune markers which are known to drive the disease.

The role of the JAK pathway in the development of AD

Many key cytokines involved in the pathogenesis of AD signal via the JAK-STAT pathway, leading to upregulation of the inflammatory process characteristic of AD (18). The JAK family of enzymes (JAK1, JAK2, JAK3 and tyrosine kinase 2 [TYK2]) are important signaling molecules involved in a diverse range of biological functions (18, 19). JAKs transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function, as seen in Figure 2. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. The JAK/ STAT signaling axis is known to play a critical role in the dysregulation of immune responses in AD, involving amplification of Th2 cell response, instigation of eosinophils, and suppression of regulatory T cells (20). Inhibitors of the JAK/STAT signaling axis are categorized as small molecules blocking intracellular targets, as opposed to anti-cytokine or anti-receptor agents (20). Inhibiting various JAKs will consequently have downstream effect on different physiological responses. It is of the essence to target the JAKs mediating the downstream signaling from the cytokines involved in AD and spare other JAKs.

Figure 2. JAK-STAT signaling and the physiological responses



EPO, erythropoietin; GH; growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; NK, natural killer; Th, T-helper; TPO, thrombopoietin; TSLP, thymic stromal lymphopoietin; TYK, tyrosine kinase

AD pathogenesis and chronicity are driven by Th1 and Th2 cytokines, many of which signal through JAK1 (15, 18). JAK1 activation allows transduction of cellular signals leading to changes in cellular and immune function, including, but not limited to, keratinocyte proliferation, Th2 differentiation of T cells, IgE class switching of B cells and nerve mediated itching, all of which are key characteristics of AD. Indeed, recent evidence demonstrates that JAK1 signaling mediates itch signals in sensory neurons specifically, linking JAK1 to AD directly (21). JAK-STAT activation of Th2 differentiation

also leads to activation of the Th2 immune response.(18) Activation of the Th2 immune response leads to further production of inflammatory cytokines, resulting in inflammation and loss of skin barrier function (18). JAK1 specifically facilitates the signaling of key cytokines involved in the pathogenesis of AD (eg, IL-4, IL-13, IL-22, IL-31, TSLP, IFNγ), suggesting that JAK1 plays an important role in the development and chronicity of AD, inflammation, barrier dysfunction and itch (15, 18). This suggests that JAK1 is an important therapeutic target in this disease.

Clinical presentation

AD is a heterogenous disease with complex pathogenesis, which manifests with severe pruritus and painful eruptions. The eruptions are due to itch and are characterized by eczematous (wet), erythematous (red) patches, papules and plaques with excoriations, crusts, and serous exudate, most commonly on flexural areas and the face (2). Unlike psoriasis where new lesions are similar to chronic lesions, AD has acute and chronic stages. The acute stage is characterized by patches with diffuse redness and papules which develops into blisters. Upon scratching the blisters break and exude, this in turn leads to crust formation and in some cases even secondary infections. In the subacute stage, the lesions are still red but have dried up and have a scalier feature. As the disease progresses and become chronic the affected skin is characterized with patches and plaques with excoriation (wounds due to itching) and lichenification (thickening and hardening of the skin) (22).

The lesions can appear on any part of the body but usually show a morphology and distribution related to age. In infants the lesions are often acute and appears mainly on the face and on the extensor surface of the limbs. In toddlers and preschoolers, the lesions have a varied morphology and appear mainly in the flexural folds of the limbs. Adolescents and adults often have lichenified areas and excoriated plaques, usually present in flexural folds, hands, wrists, ankles, eyelids (head and neck type), upper trunk and shoulders. There could also be involvement of the scalp (22).
Patients with AD are more likely to suffer from one or more comorbidities compared to the general population, such as atopic comorbidities, asthma, rhinitis, and food allergies (23). These include other forms of allergic disease, infections, autoimmune disease, and psychiatric disease (24-26). The high number and severity of these comorbidities contribute to the high patient burden in AD, and often the debilitating symptoms exacerbate or make the comorbidities worse, especially in the psychiatric comorbidities such as anxiety and depression.

Itching

Itching is the hallmark and most debilitating symptom of AD, leading to direct and secondary consequences of AD and contributing to a high patient burden of the disease.(23) . Furthermore, over half of patients describe their itch as unbearable or severe(23).(27) In a large multinational Phase IIb clinical trial, which collected patient reported outcomes (PROs) from 380 patients with AD, the majority (85.8%) of patients reported experiencing itch every day, with 41.5% reported itching 18 hours a day or more.(23) The overwhelming burden of this is highlighted when considering that 59% have had AD for 25 years or more.(28) Additionally, more than 60% of patients reported that their itch was unbearable or severe (Figure 3). Similarly, in a recent online survey of 304 individuals in AD, 91% reported daily itching with the majority experiencing itch more frequently at night.(23, 29)

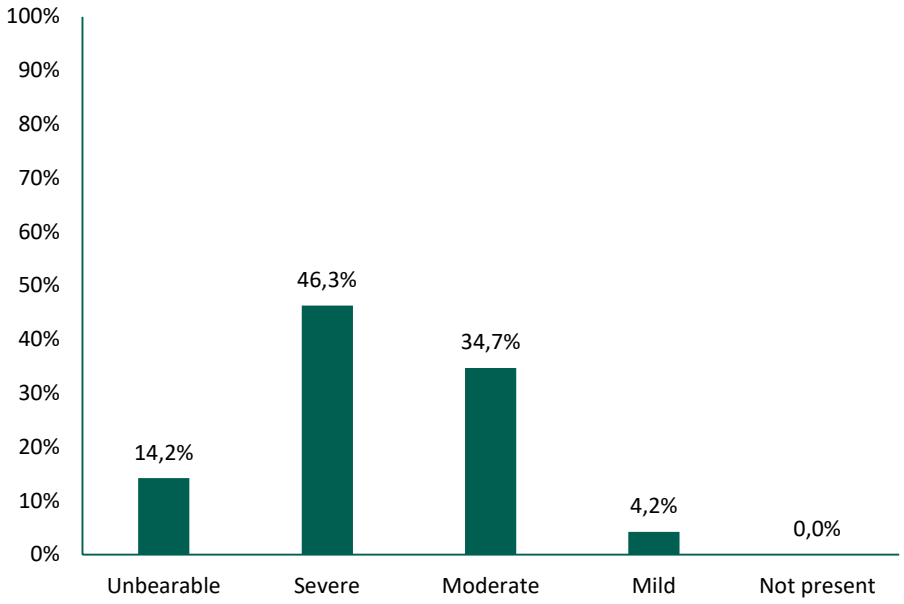


Figure 3. The severity of itch reported by patients in the multinational REGN668 trial(23)

Itch is extremely bothersome to patients, and it impacts a wide range of daily activities and in all areas of life, in particular sleep. In the above-mentioned study 68.2 % of patients reported that itch had a severe impact on sleep.

Flare

Disease flares are commonly reported in patients with AD, indicating the highly fluctuating nature of AD. In a Danish cross-sectional study containing 3348 and 3834 adults with dermatologist verified psoriasis and AD respectively and 2946 adults from the general population, patients with psoriasis and AD reported frequent flares, which increased with diseases severity. As shown in Figure 4 the AD population reported more flares compared to the psoriasis population. They also reported a severe impact of QoL reflected in DLQI (30).

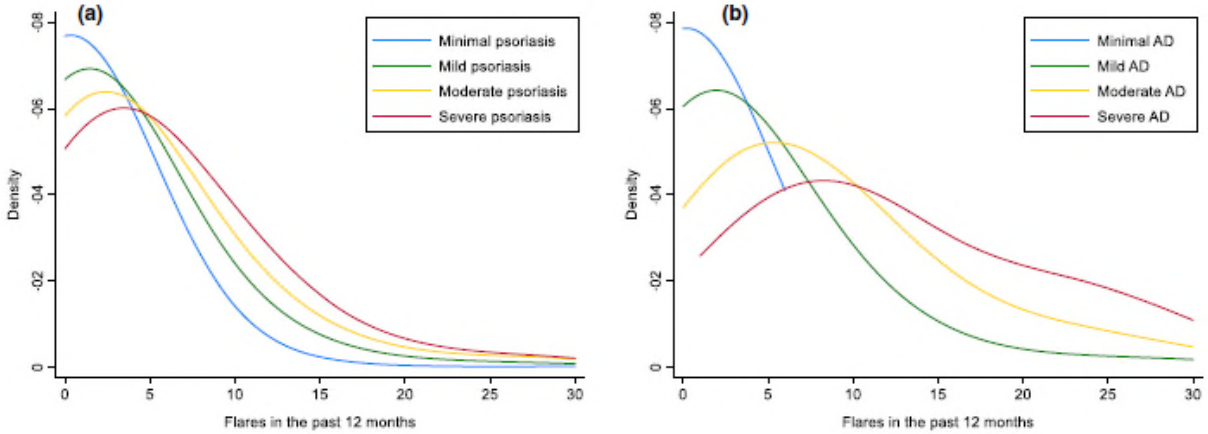


Figure 4. Density of flares in psoriasis and AD patients(30)

There are many triggers for disease flares, including environmental factors such as food, inhaled allergens, and stress.(3, 31) The incidence of flares is extremely high, with the majority of patients experiencing flares. In the International Study of Life with Atopic Eczema (ISOLTE) trial, patients with moderate to severe AD (n=2,000) reported an average of 9 flares per year, with each flare lasting approximately 15 days. Consequently, patients may spend as much as 1 in every 3 days in a state of disease flare, demonstrating the poor level of control in moderate to severe

AD.(31) Despite the high incidence of flares, there is currently no consensus on the most appropriate measure or definition of flares. Current definitions include a sudden worsening or exacerbation of symptoms, the use of topical anti-inflammatory medications and the escalation of treatment that require physician consultations or application of prescription medication.(31) This variability in flare definitions results in varied reports of flare incidence and so the true burden of flares is unknown, although is likely to be substantial.

Current treatment options fail to achieve long-term disease control, with flares persisting. Consequently, AD treatment is often reactive, aiming to relieve symptoms of pain and itch and lengthening the time between flares as opposed to preventing them.(31, 32)

Consequences of AD clinical presentation on patient and caregiver

Sleep problems

Sleep problems are one of the most frequently reported consequences of AD symptoms and are thought to be driven primarily by itch(23). Loss of sleep and difficulty getting to sleep negatively impact the daily lives of patients as they contribute to daytime sleepiness and fatigue, further reducing functional activities and adversely affecting mood, HRQoL and mental health.

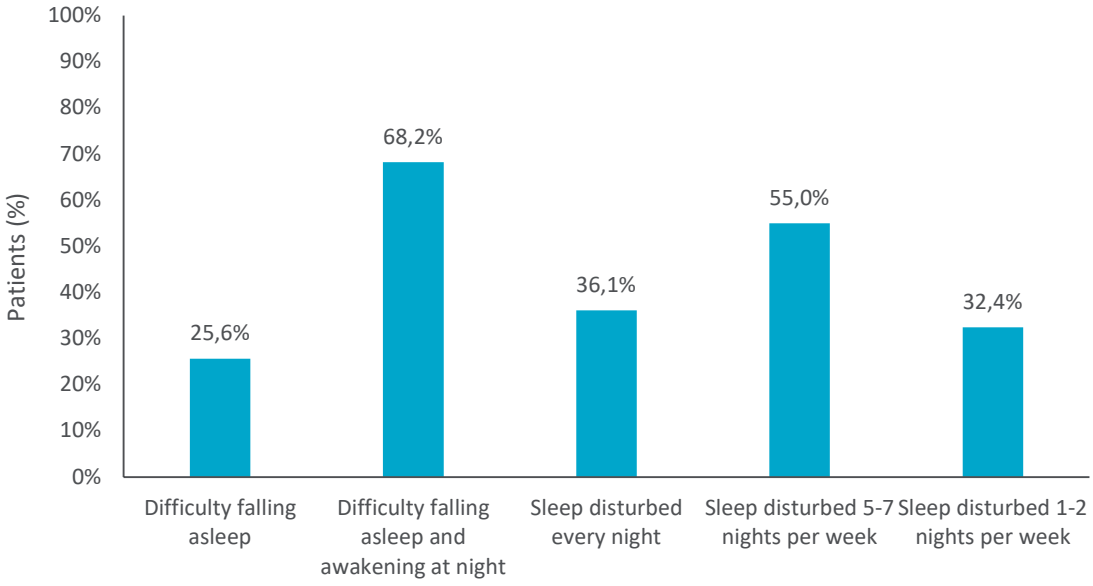


Figure 5. Sleep problems associated with AD

Sleeping problems related to AD was recently confirmed in, the earlier mentioned, Swedish population-based, cross-sectional questionnaire study performed among 34,313 Swedish adults in 2017. As seen in Table 1, the relative risk ratio (RRR) of severe sleeping problems and severe tiredness were increased in adults with AD compared with adults without AD. Adults with severe AD had those conditions in an even higher proportion.

Table 1. AD and sleep in a cross-sectional random sample of adults in Sweden in unadjusted and adjusted analyses (33)

Outcome variable	Category	Mild AD[a] RRR (95% CI)	Severe AD[a] RRR (95% CI)	Mild AD[a] aRRR[b] (95% CI)	Severe AD[a] aRRR[b] (95% CI)
Sleeping problems	Mild	1.24 (1.15–1.34)	1.71 (1.49–1.94)	1.27 (1.17–1.36)	1.72 (1.50–1.96)
	Severe	1.76 (1.39–2.22)	7.90 (6.17–10.11)	1.82 (1.44–2.30)	7.44 (5.76–9.59)
Tiredness	Mild	1.44 (1.33–1.56)	1.93 (1.68–2.21)	1.47 (1.35–1.59)	1.97 (1.71–2.60)
	Severe	2.62 (1.93–3.53)	10.18 (7.30–14.20)	2.61 (1.93–3.52)	9.80 (6.99–13.73)

[a]No AD as reference. [b]Adjustments were made for sex, age group (defined as 18–29, 30–69, 70 years and older), highest achieved education.
aRRR: adjusted relative risk ratio.

Psychological conditions

The discomfort, embarrassment, social stigma and stress associated with AD and its visible and burdensome skin symptoms leads to a significant psychological impact in many patients.(23) There are several psychiatric comorbidities associated with AD, in particular anxiety, depression, suicidal ideation and sleep disorders. Patients also frequently report social issues associated with AD, such as isolation, bullying, teasing, embarrassment, and self-consciousness. These psychiatric comorbidities are actually observed in higher rates than other skin diseases, highlighting the uniquely high mental health burden of AD, linked to the severe and ever-present signs and symptoms.(17)
In a survey of 1,863 adults with AD in France, Germany, Italy, Spain and the UK, anxiety was reported in 31%, 32% and 36% of patients with mild, moderate and severe self-rated AD respectively.(34) Depression and sleep disorders were reported in similarly high rates, with the highest rates seen in patients with severe AD (36% and 27%, respectively) (Figure 6)

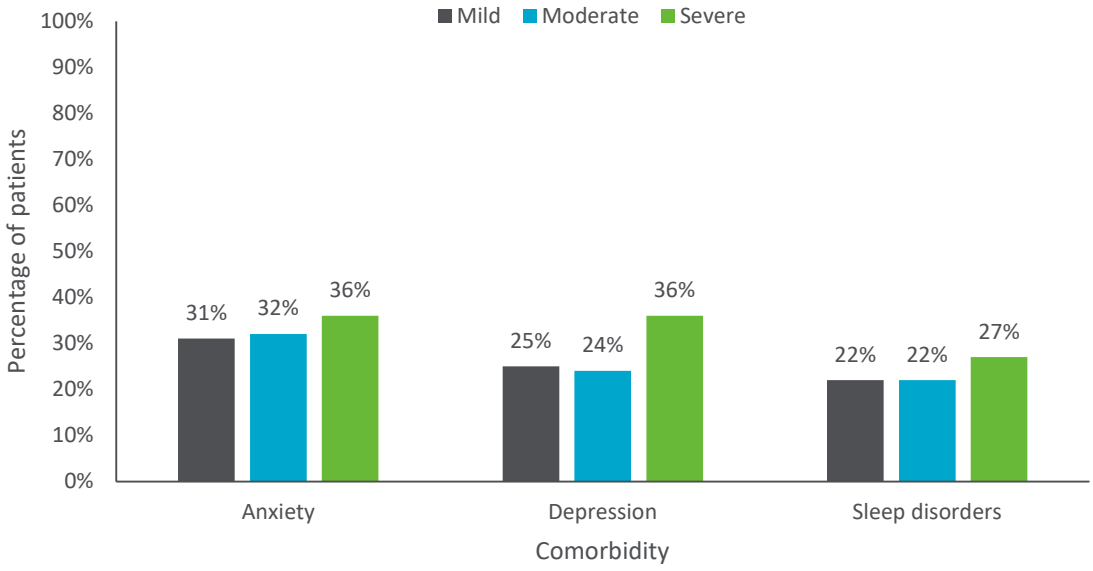


Figure 6. Percentage of mild, moderate and severe self-rated AD patients with anxiety, depression and sleep disorders in France, Germany, Italy, Spain and the UK (34)

In a multinational meta-analysis consisting of 13 studies and 48,626 patients, a positive association was found between adult AD and anxiety, supporting the anxiety burden in AD across a high number of patients.(35) One study included in the meta-analysis used the Danish health registry records of 1,044 patients with AD, and showed a particularly strong link between AD and anxiety (Figure 7).(35)

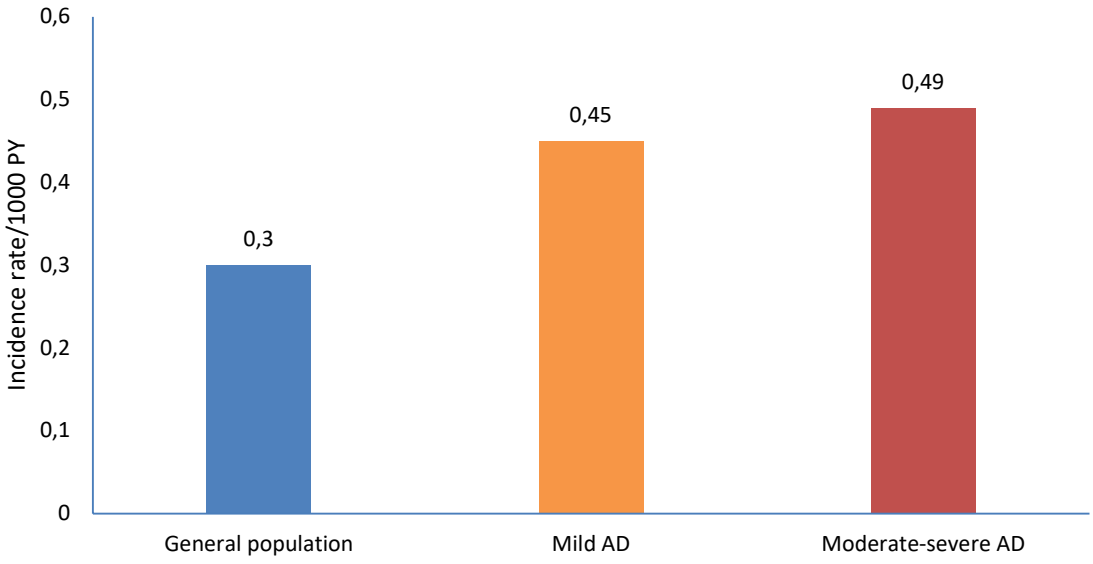


Figure 7. Incidence of anxiety in the general Danish population and those with mild and moderate-severe AD (35)

The high rates of depression and anxiety in patients with AD may reflect the psychological distress produced by both the stigma associated with visible AD skin lesions and the unpredictability of disease flares.(23) This may be manifested by the high proportion of patients (61.6%) who report being embarrassed by or self-conscious of AD. This psychological burden can further negatively impact mood and HRQoL. In the population-based, cross-sectional questionnaire study earlier described, performed among 34,313 Swedish adults with AD, 30% decreased odds of higher mental wellbeing in analyses adjusted for education, sex and age (OR 0.67 for mild AD and OR 0.30 for those with severe AD). All mental health symptoms and conditions increased in severe AD, see Table 2 (33). The association between AD and mental health is shown in Table 3.

Table 2. Risk of depression and anxiety among adults with atopic dermatitis, presented as relative risk ratios in a sample from mid-Sweden in crude and adjusted analyses (33)

Symptom of mental health	Category	Mild AD[a] RRR (95% CI)	Severe AD[a] RRR (95% CI)	Mild AD[a] aRRR[b] (95% CI)	Severe AD[a] aRRR[b] (95% CI)
Anxiety[c]	Mild	1.49 (1.38–1.61)	2.02 (1.24–2.35)	1.46 (1.35–1.58)	2.48 (1.99– 3.11)
	Severe	2.75 (2.21–3.42)	8.79 (6.65–11.62)	1.97 (1.69–2.30)	6.22 (4.60–8.42)
Depressive symptoms[c]	Mild	1.46 (1.35–1.58)	1.85 (1.56–2.18)	1.44 (1.33–1.55)	2.39 (1.92–2.98)
	Severe	2.64 (2.13–3.28)	8.03 (5.95–10.81)	1.78 (1.50– 2.12)	5.62 (4.10– 7.71)

[a]No AD as reference. [b]Adjustments were made for sex, age group (defined as 18–29, 30–69, 70 years and older), highest achieved education (defined as compulsory, post-compulsory, university). [c]No as base outcome.
aRRR: adjusted relative risk ratio.

Table 3 Association of atopic dermatitis (AD) and mental health in a cross-sectional random sample of adults in mid-Sweden (33).

Outcome	Category	Mild AD[a] OR (95% CI)	Severe AD[a] OR (95% CI)	Mild AD[a] aORb (95% CI)	Severe AD[a] aORb (95% CI)
Self-reported diagnose of depression[c]	Yes	1.53 (1.37–1.72)	3.44 (2.70–4.40)	1.49 (1.33–1.68)	2.84 (2.20–3.66)
Long-term sick-leave due to any mental health condition[c]	Yes	1.30 (1.01–1.67)	2.30 (1.18–4.45)	1.29 (1.01–1.66)	2.16 (1.10–4.20)

[a]No AD as reference. [b]Adjustments were made for sex, age group (defined as 18–29, 30–69, 70 years and older), highest achieved education (defined as compulsory, post-compulsory, university). [c]No as base outcome.
aOR: adjusted odds ratio.

Additionally, suicidal ideation is also associated with AD.(35) In a 2018 meta-analysis including 6 studies (n=13,011), a positive association was found between adult AD and suicidal ideation. The reason for increased suicidal ideation is unclear, however it has been suggested that the negative effects on mental health due to itch, disrupted sleep and social isolation may contribute to the increased association with suicide.(35)

In the study using the Danish health registry records described above, suicide ideation was rare but increased in AD patients in comparison with the general population.(35) There were 3.4 incidents of suicide ideation in the AD population compared to 1.7 incidents in the general population, per 1,000 person-years. In a separate Danish study, which skin disease patients responded to a questionnaire package including the QLQI, Beck's Depression Inventory (BDI) and Brief Symptom Inventory (BSI), a significantly higher proportion of patients with AD had thoughts about suicide in the past 2 weeks compared to healthy controls (18.9% versus 6.8%, $P<0.01$). These rates were also higher than other eczema patients (5.8%) and urticaria patients (6.3%) and similar to psoriasis patients (21.2%).(36)

Social impact and impact on daily life

AD affects patient engagement with life on a daily basis, is associated with impaired social interactions, and impaired sexual relationships, all which can result in reduced patient QoL.(37)

Visible signs of the disease can cause social stigma for those who suffer from AD. In children this can lead to embarrassment, as well as lower participation in sports and recreational activities.(38) Visible signs of disease can also result in bullying, teasing and long-term self-esteem problems. Psychosocial deficits are also seen in children affected by AD, due to the disease often occurring at various early stages of development.(39, 40) Social isolation is an issue for AD patients from a very young age, with parents of children with AD reported to avoid social interactions between their children and friends and family, in order to avoid the possibility of discussion of their condition.(38)

In adults, the high symptom burden of AD, particularly the constant and burdensome itch, causes a huge impact on daily life, career opportunities and relationships.(23) In the recent multinational REGN668 Phase IIb clinical trial, 27% of AD patients reported problems in their relationships and 44% reported an impact on their social activities. Most patients reported that their condition affected their social life or leisure time, their sports participation, their work or study and their relationships. (Figure 8). Additionally, most of these patients reported that they had itchy, painful, stinging skin for 'a lot of the time' (87.6%). The negative effects of AD extend to patients' daily lives. Among adults with moderate-to-severe AD, 75% reported that their AD interferes with their jobs and house chores, 71% reported interference with participation in sports and hobbies, and nearly 50% reported interference with their social lives and intimacy. Nearly two thirds of these patients reported feeling less healthy because of their AD. Furthermore, AD is responsible for a substantial negative impact on social behavior and feelings in adults. In the same study as above, 61.6% of AD patients reported feelings of embarrassment or self-consciousness, and 57.9% of patients reported that their AD impacted the clothes they wore.

Figure 8. Social and day to day impact of AD(23)

QoL impact

Regardless of which PRO instrument is used, AD has a detrimental effect on QoL (40, 41). In a cross-sectional survey conducted in the UK, Germany and France (n=1,974) from the 2014 Adelphi AD Disease Specific Program, where the DLQI instrument was used to analyze QoL scores in AD, a similarly large impact was reported (41). In this study, 73.9%, 32.2% and 27.3% of UK patients with severe, moderate, and mild uncontrolled AD were recorded as having a DLQI of less than 10, which indicates a large effect on QoL. In Germany and France, the proportion of patients with severe, moderate, and mild uncontrolled AD who had DLQI score of less than 10 followed the same trend.

Diagnostics

AD can be challenging to diagnose due to its heterogenous nature, furthermore there are no examinations or clinical markers to ensure diagnosis. Diagnosis relies on clinical features, and due to this various diagnose criteria has been created to facilitate diagnosis. In randomized controlled trials (RCTs) the most used diagnose criteria is the Hanifin-Rajka (Table 4). To achieve an AD diagnose using these criteria, patients must have three of four major criteria and three of 19 minor criteria. The Hanifin-Rajka criteria has been refined in the UK Working Party diagnostic criteria, also shown in Table 4, to be easier to use and address population-based studies. The UK Working Party are also referred to as Williams criteria. (42).

Hanifin-Rajka Criteria		UK Working Party Criteria
Must have 3 or more basic features:		**Must have:**
Pruritus		An itchy skin condition (or parental report of scratching or rubbing in a child)
Typical morphology and distribution: Flexural lichenification or linearity in adults Facial and extensor involvement in infants/ children		
Chronic or chronically-relapsing dermatitis		
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermtitis)		
Plus 3 or more minor features:		**Plus 3 or more of the following**
Xerosis	Ichthyosis/palmar linearity/keratosis pilaris	History of involvement of the skin creases such as folds of elbows, behind the knee, front of ankles or around the neck (including cheeks in children under 10).
Immediate (type I) skin test reactivity	Elevated serum IgE	
Early age of onset	Tendency toward cutaneous infections	A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4).
Tendency toward non-specific hand or foot dermtitis	Nipple eczema	
Cheilitis	Recurrent conjunctivitis	A history of a general dry skin in the last year.
Dennie-Morgan infraorbital fold	Keratoconus	
Anterior subcapsular cataracts	Orbital darkening	Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4).
Facial pallor/facial erythema	Pityriasis alba	
Anterior neck folds	Itch when sweating	Onset under the age of 2 (not used if child is under 4).
Intolerance to wool and lipid solvents	Perifollicular accentuation	
Food intolerance	Course influenced by environmental/emotional factors	
White demographism/ delayed blanch		

Table 4. Hanifin-Rajka and UK working party diagnose criteria (42)

Scoring systems

More than 60 different measures have been used to assess the symptoms and severity of AD. These assessments vary considerably with respect to content, scale, instructions, validity, and concordance, and assess criteria such as intensity of lesions, and/or extent, symptoms, disease course, and epidermal function.(43) There is no golden standard in AD as in psoriasis were PASI is used. The scoring systems used in all clinical trials conducted on new systemic immunotherapy as well as new biologics are predominantly with regards to physician assessment of disease severity, EASI followed by IGA and BSA. For PROs the most commonly used scoring tools are DLQI and POEM, also pruritus is measured by an 11 grade NRS scale. (44-49). The different instruments are described in Table 5.

Table 5 Scoring instruments used in Atopic Dermatitis

Instrument	Concepts measured	Items/domains	Scoring	MCID*
Peak pruritis NRS(50)	Intensity of worst itch in previous 24 hours	1 item and 1 domain: intensity of itch (indicated on scale)	From 0 (no itch) to 10 (worst imaginable itch)	≥ 2-4
EASI(51, 52)	Assess the severity and extent of AD	Four disease characteristics (erytema, thickness, scratching, lichenifcation). Assessed for severity 0 (absent) to 3 (severe). Extent score 0 to 6.	0 (best) to 72 (worst)	
IGA(43, 51)	Assess overall disease severity at one given time point	6-point severity scale clinical characteristics erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment.	(0 = clear, 1 = almost clear, 2 = mild disease, 3 = moderate disease, 4 = severe disease and 5 = very severe disease).	
POEM(52)	Frequency of symptoms	A measure which involves self-reporting by patients of the frequency of 1) oozing/crusting, 2) weeping/ exudation dryness cracking/ fissuring, 3) flaking and 4) bleeding	0 (best) to 28 (worst).	3.4, and approximately 3 in young children
DLQI(53)	Dermatology specific QoL	10 items; 5 domains: skin clinical manifestations, feelings of embarrassment, day-to-day activities, working, and social life	0 (best) to 30 (worst) 0 to 1 - no effect 2 to 5 - small effect 6 to 10 - moderate 11 to 20 - very large 21 to 30 - extremely large effect	Estimates range from 2.2 to 6.9, but in general thought to be 464

The scoring systems are also used in Danish clinical practice to evaluate a patient´s need for treatment and to evaluate if a patient has responded to treatment. According to the DDS guidelines a patient is a candidate for advanced systemic treatment if one or more of the following is fulfilled: EASI>16, BSA >10%, DLQI>10 and POEM >16. The patient is considered a responder if the change from treatment initiation is at least 75 % reduction in EASI score

(EASI75) and a partial response who should continue treatment if the reduction of EASI is at least 50 % (EASI50) and the patient show at least 4-point-reduction in DLQI (54).

In Europe, EASI is used to evaluate the effect of treatment over time. Despite some limitations, relative EASI (relative improvement from a baseline value) is today an established tool and used for assessing the treatment effect in AD. The measure EASI 90 is often an ambition, which refers to a 90% improvement in AD according to the EASI scale. In the past, EASI 50 and EASI 75 have also been used to evaluate treatment effect. As new treatment options have been introduced, EASI 90 has lately become an ambition of a new therapeutic target value (55).

Economic burden of disease

Given the prevalence of AD and its chronic and troubling symptoms, the economic burden associated with AD is substantial. The high costs of AD are due to direct costs, which include prescription medicines, visits to health care providers, hospitalizations, travel to and from appointments, as well as indirect costs through missed days of work or lost productivity at work or school, career modification or impact on career attainment. Out-of-pocket and prescription costs can also be substantial for patients themselves. The cost associated with caring for young patients with AD also contributes significantly to the overall economic impact of the disease, which is particularly significant given the prevalence of AD in children. Additional detriment to career progression for both caregivers and patients is also likely to contribute to the high indirect costs, but to date is not well characterized.(59)

The total cost per patient with AD is also high compared to other chronic conditions, as demonstrated in a recent study of 1,189 patients across nine European countries including Sweden. 5 Telephone interviews were used to investigate the total annual costs associated with AD and compared with previously published costs for psoriasis and rheumatoid arthritis.(60, 61) Total direct costs were estimated at €2,229 per patient per year for AD, indirect costs at €4,257 and out-of-pocket costs at €927. Of note, out-of-pocket costs were substantially higher for patients with AD compared to patients with psoriasis and rheumatoid arthritis (62). Understanding the economic impact of AD is important to contextualize the burden of AD in society, but also to highlight how new treatments can reduce both direct and indirect costs, reducing the high economic impact of the disease for patients, payers and society (63).

Direct costs of AD

The substantial direct costs of AD are driven by the chronic inflammatory nature of the disease, with patients continuously accruing costs over their lifetime.(63) Direct costs of AD include visits to health care providers, hospitalizations, travel to and from appointments, as well as costs associated with prescription medicine, and significant out-of-pocket costs (63). A survey of patients with moderate-to-severe AD (n=90) in the Netherlands estimated that total annual direct costs due to AD were €5,191 (range: €4,382–6,019) per patient per year (64).

Emergency department visits for patients with AD also constitute a significant use of healthcare resources, which has increased substantially over time. These visits primarily occur due to severe intermittent flares, rash, persistent disease, acute non-specific skin eruption, viral infection, or bacterial infection in cracked, inflamed and broken skin (65). Although AD is not commonly considered a major reason for hospitalization, the inpatient financial burden of AD represents a substantial proportion of the total direct cost. Hospitalization in AD is driven by severe intermittent flares or persistent disease refractory to outpatient treatment, sometimes in association with a psychiatric comorbidity or inability to properly self-care (66).

The out-of-pocket costs associated with AD place a considerable economic burden on patients and their families. Patients with AD require a high volume of emollients, moisturizers and other specialist personal hygiene and cleaning products, regardless of the severity of their disease.

The out-of-pocket costs associated with AD were estimated in the European study described earlier, where telephone interviews were conducted with 1,189 patients with AD across nine European countries. This study found that out-of-pocket costs were incurred due to AD patients having to buy everyday items such as emollients, moisturizers and bandages, as shown in Figure 9. Out-of-pocket spending was found to be on average €927 per patient year, and 95% of AD patients reported out-of-pocket expenses.(62)

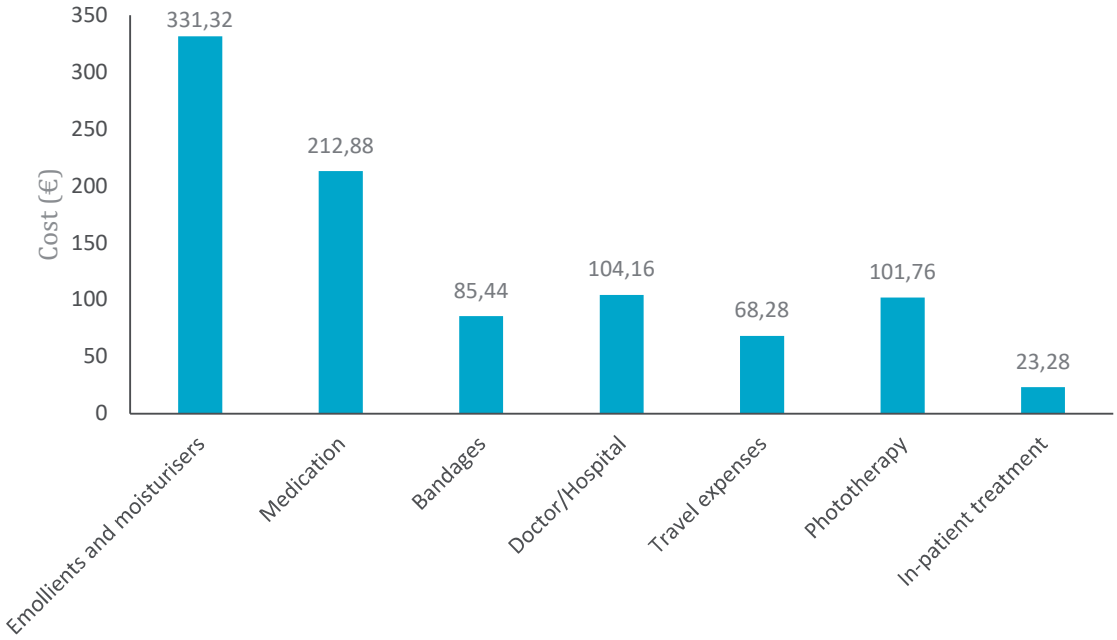


Figure 9. Average out-of-pocket cost per year for patients with AD from 9 European countries (€)(62)

The study also reported extra out-of-pocket expenses on non-medical items for AD patients, compared to those without AD, results are shown in Figure 10. Personal hygiene items represented the most significant extra spend, at 18% more than for patients without AD. Clothing, washing powder, foods, cleaning products, bedding and gloves also incurred extra expense at 7% to 9% higher for patients with AD.(62) Finally, AD has been shown to limit career choices and is associated with early retirement and reduced earnings. Therefore, the impact of these out-of-pocket expenses are likely to be higher in patients with AD compared to healthy counterparts.(67)

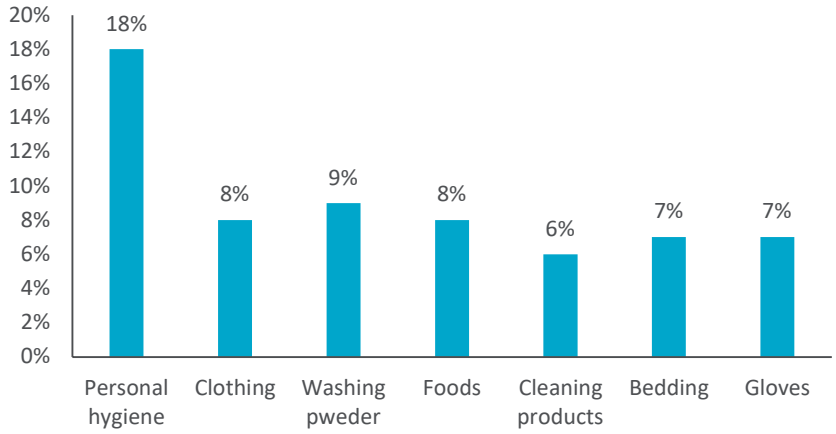


Figure 10 . Extra spending on everyday items for patients with AD compared to patients without AD [59]

Economic burden by disease severity and disease control

Like out-of-pocket costs, total direct costs associated with AD also increase with severity and lack of disease control.(63). In a Netherlands survey of patients with moderate-to-severe AD (n=90), the direct costs per patient per year were also reported to be associated with disease control. Total direct costs per patient per year were significantly higher for patients with uncontrolled AD (€6 993, range €5 552–€8 406) compared to patients with controlled AD (€4 401, range €3 695–€5 215) (p=0.014).(64)

A recent study in UK, presented in October 2020, analyzed healthcare resource use of patients (n=252 589) with AD by severity of disease.(68) Data from the CPRD database (covering primary care) were collected, analyzed, and linked with data from the HES database (covering secondary care). The study reported that primary care was the most attended healthcare setting, with GP and physician appointments common and increasing with AD severity. The cost of secondary care per patient per year (PPPY) (including both inpatient care (£442) and outpatient care (£151)) outweighed the cost of primary care (£463).(68) The median cost PPPY increased with severity in all healthcare settings. The overall cost per patient within both the primary and secondary setting was £10 468. The overall costs were found to increase with AD severity, (£8 758 per patient with mild AD, £11 091 per patient with moderate AD, and £11 600 per patient with severe AD) demonstrating the substantial economic burden associated with increased AD severity.(68)

Indirect costs of AD

The indirect cost impact of AD is far reaching. Initial presentation is in childhood or adolescence long before career or education choices are made, and the high indirect costs are driven by the significant impact of AD on QoL, work productivity, and school attendance (11, 15, 16). Indirect costs are not included in the base case analysis of cost-utility analysis per the Medicines Council Methods Guidance. However, the effect of adopting a full societal perspective is analyzed in a scenario analysis where costs for productivity losses, i.e., indirect costs are included (see section 8.7.2). In this scenario, the economic benefit of more effective AD treatment is further underlined.

It is estimated that 85% of patients develop the disease before 5 years of age, and those who develop moderate-to-severe disease in childhood are of particular risk of disease persisting into adolescence and adulthood (as described in section 1.1). Therefore, the presence of moderate-to-severe AD in adolescence and early adulthood can have profound impact on the careers of patients, at a time when their academic and work performance is crucial to future success.(69) In particular, AD-related mental health issues are known to affect adolescents severely.(70, 71) These may limit academic performance, with a subsequent impact on careers and earning potential. In particular, some careers, such as those involving contact with potential irritants, may be ruled out entirely.(69) As AD is also highly prevalent in childhood, the indirect costs to caregivers can also be substantial.(59)

Impact of AD on work and activity

Work productivity impairment is high for people with AD. One study examined work productivity impairment using data from the 2013 National Health and Wellness Survey of the US population with self-questionnaires of 428 AD patients and 74,572 people without AD.(40) This study demonstrated that those with AD were more severely impacted in terms of absenteeism, presenteeism, overall work impairment and activity impairment in the week preceding the study, Figure 11(40) Impairment of the work and activities of patients can have a significant financial impact due to the knock-on effects in earnings, career progression and subsequent loss of income due to social and psychological difficulties limiting job choices. The study also indicated a correlation between increased disease severity and increased work and activity impairment in the week preceding the study, Figure 12.(40)

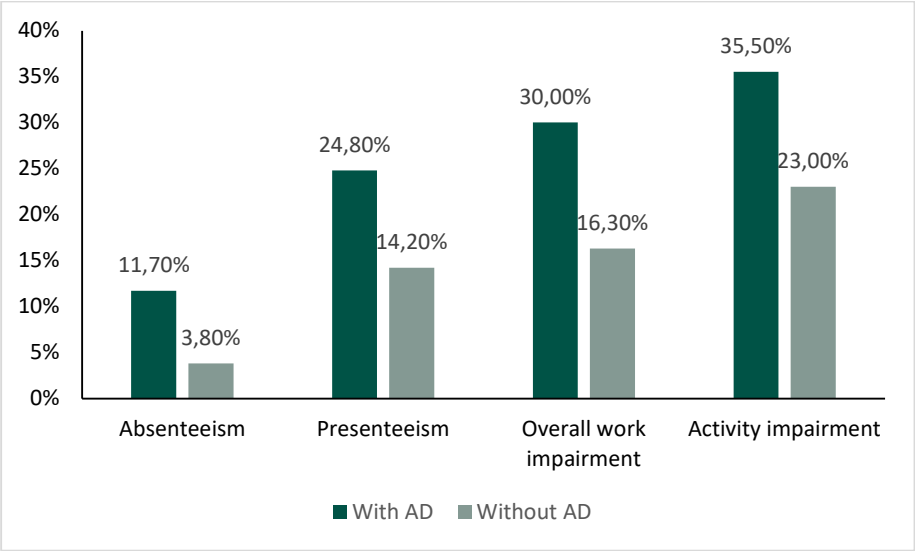


Figure 11. Work productivity and impairment and activity impairment in those with AD and without AD(40)

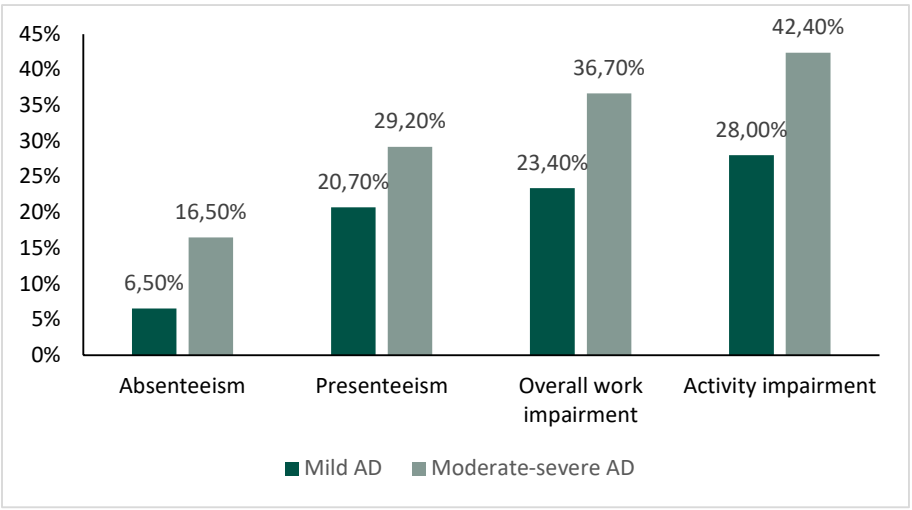


Figure 12. Differences in work productivity impairment in patients with mild AD and moderate-severe AD(40)

Similar results were demonstrated in the population-based, cross-sectional questionnaire study performed among 34,313 Swedish adults earlier described. Individuals with severe AD, were less likely to have a university degree or higher, and had a lower income, compared with persons without AD and with mild to moderate AD. Adults with AD were more often unemployed, and the RRR increased with severe AD. Adults with severe AD were more often on sick leave and more often had a blue-collar occupation. Individuals with AD were more often working fewer hours and were more likely to be on sick leave for mental health conditions as well as for stress/burnout. Adults with AD were more often on sick leave for more than 29 days, long-term sick leave/on “activity stimulation” and taking an early pension due to disease, compared with adults without AD.

In a registry-based cohort study on 28 156 Danish citizens and a 20-fold control, sick leave and disability pension was examined. Patients with AD was found to be associated with increased risk of receiving paid sick leave or disability pension compared to the control. The risk was most pronounced for younger patients with severe AD. The use of disability pension was increased for all groups of patients, but most pronounced for older patients, compared to controls (72).

In addition, a survey of patients with moderate-to-severe AD (n=90) in the Netherlands reported that reduced work capacity was associated with disease control. (64) Compared with patients with controlled AD, patients with uncontrolled AD reported higher absenteeism (11.1% vs. 0.6%, p=0.020), presenteeism (32.1% vs. 14.6%, p=0.015), overall work impairment (33.5% vs. 15.8%, p=0.024) and activity impairment (38.8% vs. 22.4%, p=0.006).
A cross sectional study, which investigated 253 Dutch employees with AD who took sick leave, identified a link between symptom interference and the number of sick days taken.(73) The effect of AD symptom interference, was defined as the influence of severity of complaints on work performance, need of rest, perceived threshold for return to work. In the study, 12% of patients had taken sick leave due to AD in the two weeks preceding the study, with 42% taking sick leave due to AD within the past year. Symptom interference was found to be directly correlated with the number of sick days, with an odds ratio of 1.6 demonstrating a likely correlation. Therefore, those patients who feel restricted by their AD at work are more likely to take sick leave than those who are not restricted.(73) Increased sick leave can have a detrimental effect on patient career progression, as can the visible signs and stigma of the disease. Fourteen percent of patients with AD reported that their career progression was slower because of AD, and 11% believed that they had been discriminated against in the workplace due to AD.(63)

The earlier described cross-sectional study of 1189 patients with AD in 9 European countries also studied missed workdays due to AD. As shown in Figure 13, 57% of patients had missed at least 1 day (1–5 days) and 26% at least 1 week (6–10 days) at work due to AD within the previous year, and 13% missed 11 days or more. Most missed workdays were reported by patients who had been recently diagnosed with AD, individuals receiving systemic treatment, those who were less satisfied with their treatment, and those with current moderate or severe AE.

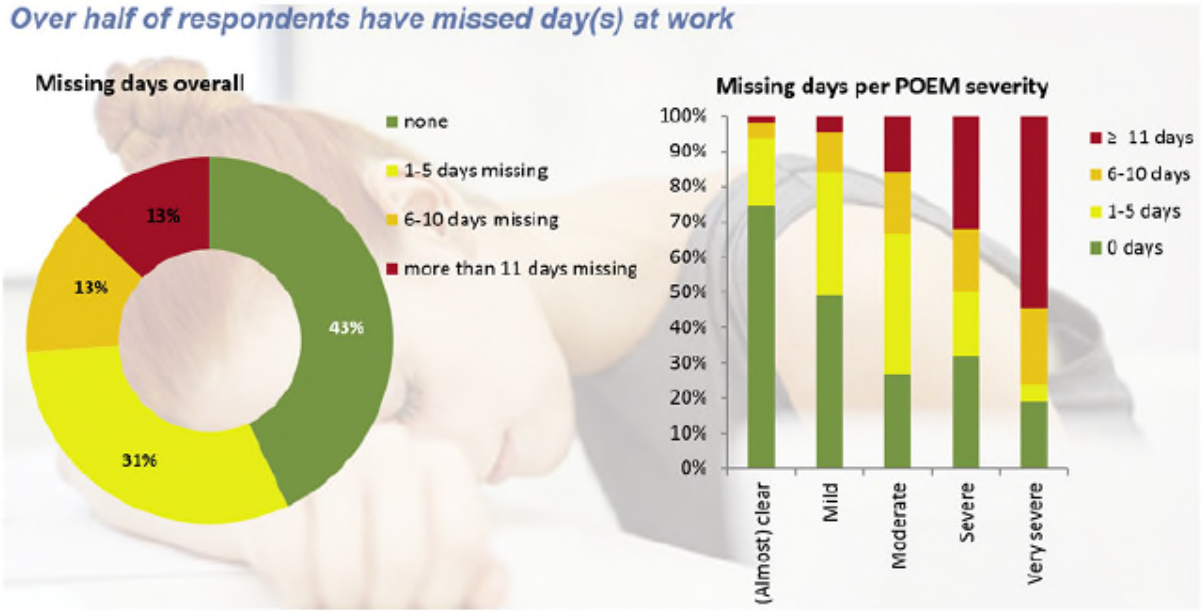


Figure 13. Number of workdays missed due to AD within the last 12 months. POEM: Patient Oriented Eczema Measure

Impact of AD on the lives of caregivers (caregiver burden)

As well as patient burden, AD has a high burden on caregivers.(74) There is a particularly high psychological impact on caregivers for children with AD, where caregivers have many worries and concerns about the social impact of AD on their children, as well as on their children's future.

The International Study of Life with Atopic Eczema (ISOLATE) was a large-scale study in 2006 using telephone interviews that assessed the effect of AD on the lives of patients, caregivers and society across 8 countries (n=2,002).(74) In this, caregivers reported that they had concerns over what their child can wear (71%), worried about

the way their child looked (63%), feelings of being out of control (52%), and also anxiety about what the future will hold (46%). In addition, significantly more caregivers looking after younger children (62%) and those with severe disease (65%) were worried about AD flares compared with the total sample ($p<0.05$). Caregiver concerns also extended to the treatment of AD. Up to 64% of caregivers were worried about the side effects of the treatment their child receives for their AD. Of those respondents who expressed concern about the use of topical corticosteroids, 89% of the caregivers were either very or fairly concerned regarding their use. The impact of AD on their own life, impact on their children, as well as their concerns about current treatments in AD, clearly take an emotional toll on AD caregivers, which is particularly potent as they are often the parents of patients with AD.

The particularly high emotional burden of AD in caregivers can also be captured in specific caregiver burden instruments.(75) For example, a study published in 2016 identified factors associated with caregiver suffering, using the Caregiver Pictorial Representation of Illness and Self-Measure (Caregiver-PRISM), a tool designed to measure the suffering that caregivers experience in association with their child's. The Caregiver-PRISM was administered to 45 parents of patients with AD from an outpatient service in Italy. The mean Caregiver-PRISM score was higher for patients with moderate-to-severe disease severity and associated with higher suffering in parents, indicating that high severity AD has a negative impact beyond the patients themselves.

Prevalence of AD

AD is more common in children, where 85 % debut in early childhood before the age of 5 (37). The symptoms of early onset usually wane in adolescence, but 33% have persistent symptoms into adulthood. The prevalence of AD has increased in industrial countries the past decades, estimated prevalence for children in industrial countries is 15-30% and approximately 2-10 % in adults (6). Estimating prevalence is difficult, and it varies from country to country. In an international, cross-sectional, web-based survey conducted in 2016 data was collected from several countries including the EU (56). In these countries, the survey used pre-specified criteria for diagnosis of AD and was based on questions from the International Study of Asthma and Allergies in Childhood (ISAAC) and the UK Working Party criteria modified for self-completion. The overall prevalence of AD in this study ranged from 2.1% to 8.1%. The Medicine Council (DMC) commented in the evaluation of dupilumab that there is a lack of data on the prevalence and incidence on severity of disease with the population with AD in Denmark. The estimated prevalence of AD, regardless of severity, in the adult population was estimated to be 14% in Denmark (57).

Although many AD patients suffer from mild disease; a substantial proportion of patients suffer from moderate-to-severe disease (Figure 14).(56) In the prevalence study described above collecting data through a web-based survey, disease severity was assessed using 3 validated patient-reported outcome (PRO) measures including the Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD), the Patient-Orientated Eczema Measure (POEM), and the Patient Global Assessment (PGA). Using the PO-SCORAD measure, between 26% and 41% of patients reported mild disease and 59% to 74% reported moderate-to-severe disease.

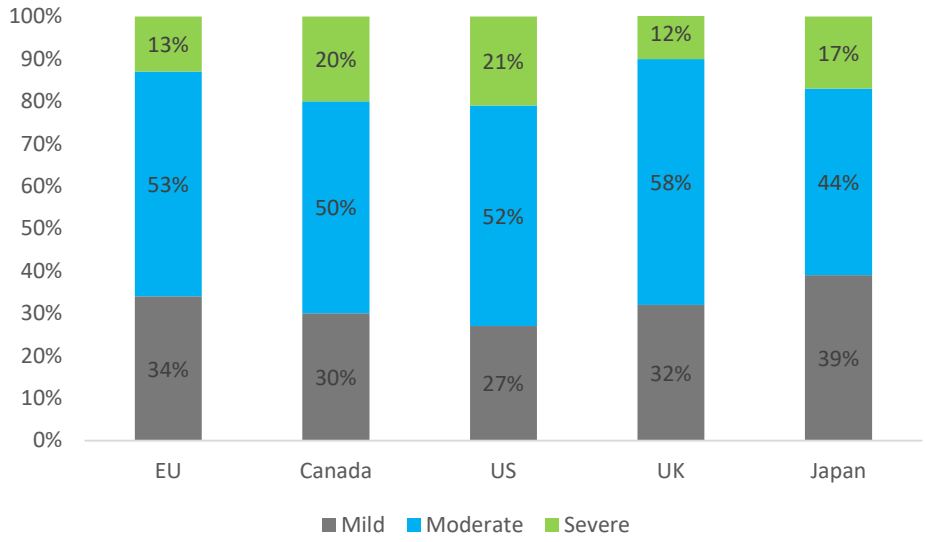


Figure 14. Prevalence of AD by severity in various countries(56)

Source: Barbarot, 2018; Severity according to the PO-SCORAD index of severity, based on a mild, moderate and severe score of 0-24, 25-45 and more than 50 respectively. ***EU: European Union; UK: United Kingdom; US: United States.***

In a recently published study based on the Danish Skin Cohort 34 % of the 3834 patients included had moderate AD and 4 % had severe AD, based on PO-SCORAD. Most patients had mild disease (55%) and a small proportion (7%) of patients were in remission (58). Both moderate and severe disease are associated with poor HRQoL outcomes and higher rates of mental health issues (56).

5.1.1 Patient populations relevant for this application

Rinvoq is indicated for treatment of moderate to severe atopic dermatitis for patients > 12 years, and this is also the population relevant for this application. Following the Danish treatment guidelines, described further down in the document, advanced systemic treatments such as Rinvoq will be given to patients having tried and failed all other treatment option.

The assumption of the patient number is estimated based on previous assessment reports of AD from the DMC. In the assessment report for baricitinib the expert committee estimated the patient population already treated with dupilumab and candidates for baricitinib (prevalence) to be 225 patients and 30 new patient per year (incidence) (27).

For the patient population 12-17 years old (adolescents) 50 patients are candidates for treatment, and with an incidence of 13-16 new patients per year based on the assumptions made by the expert committee in the evaluation of dupilumab (57). For adolescents patients treated with dupilumab is 11, and new patient per year (incidence) is expected to be 13-16. The resulting patient numbers are summarized in Table 6.

Table 6. Prevalence and incidence of patients with moderate to severe AD eligible for treatment with upadacitinib in Denmark

	Adults	Adolescents	Total
Prevalence, n	225	11	236
Incidence, n	30	16	46

For both adults and adolescents, a market uptake of 30 % year 1, 40 % year 2, 50 % year 3, 75 % year 4 and 80 % in year 5 is assumed for upadacitinib. The resulting patient numbers are shown in Table 7.

Table 7: Number of patients expected to be treated if UPA is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
UPA	85	103	126	161	197
DUPI	197	225	248	260	269
Total patient number	**282**	**328**	**374**	**420**	**466**

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

AD is characterized by anomalies of the skin barrier, which in turn facilitate penetration of allergens into the skin. This increases irritation and further subcutaneous inflammation. Treatment of AD is focused on repairing and improving skin barrier function and pruritus as well as avoiding trigger factors to prevent flares (acute exacerbations). Several factors can exacerbate the disease such as allergies and microbial colonization which can induce superinfections. AD is a chronic disease and treatment must be considered in a long-term perspective, although management of acute flares is therapeutically challenging. It requires efficient short-term control of acute symptoms, without affecting the overall management plan for long-term stabilization (76, 77)

Dansk Dermatologisk Selskab (DDS) have published a guideline for diagnosing and treating atopic dermatitis, including a treatment algorithm describing different treatments depending on severity of disease, see Figure 15 (54). The treatments included in the treatment algorithm are described in the following sections.

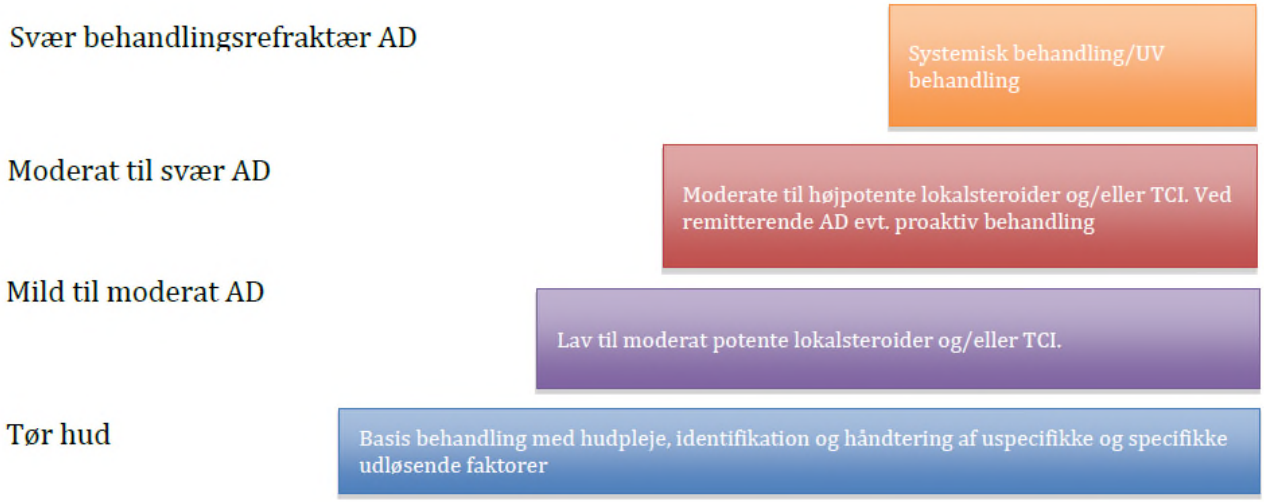


Figure 15. Danish treatment guidelines for atopic dermatitis.

Local pharmacological therapies

The mainstay in AD treatment includes local topical treatment such as moisturizers and topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), topical antihistamines and antipruritics. Topical pharmacological therapy is usually a reactive treatment of visible lesion. Additionally, antimicrobials can be added if secondary complications arise with skin infections (78). According to the DDS guidelines, although TCS is an important mainstay in the treatment of AD as shown in Figure 15, long term use of potent topical corticosteroids should be avoided due to the risk for skin atrophy, and long-term use of corticosteroids might lead to lowered sensitivity to the corticosteroid used (54). In line with the treatment guidelines infrequent use of topical corticosteroids is more common than continuous use in Denmark. In a study based on the Danish Skin Cohort 10 % of patients were frequent users of TCS (defined as having filled a

prescription at least once every 90 days during 12 months) while 90% were infrequent users of topical corticosteroids (defined as having filled a prescription for TCS within the past 12 months but not at least one prescription every 90 days) (58).

Topical therapies for AD (TCS and TCI) offer limited efficacy in moderate-to-severe AD, and their application is time consuming and inconvenient (79-82). Further, due to this it is not uncommon that patients do not follow the treatment recommendations (83). In an open labelled 8-week study investigating adherence in patients treated with TCS, the adherence rate was 32 % (84). In clinical practice these numbers are more likely to be even lower, since they are not monitored as in clinical trials thus do not have the same incentive to apply their topical treatment (83). There are several side-effects correlated to use of TCS, particular to higher potency agents and long-term use.(85, 86). Skin related side-effects include spontaneous scars, purpura (discolored spots), telangiectasia (red lines or patterns on the skin), striae (stretch marks), focal hypertrichosis (excessive hair growth), and acne or rosacea like eruptions.(85, 86) Skin atrophy (the thinning on the skin) is also a common side-effect of topical corticosteroid use.(86) Due to this it is important to evaluate the topical treatment and move forward to more advanced treatments in time. Furthermore, having advanced treatments not relying on TCS or TCS would be beneficial for the patients, to minimize the burden of treatment regimen and adverse events.

Phototherapy

Phototherapy involves the use of UV light waves as a medical therapy. Originally used to treat psoriasis, this therapy is based on the observation that sunny climates are beneficial to patients with AD.(87) In general, the effects of UV on the skin can be anti-inflammatory as well as anti-pruritic (88-90). Several different light sources and treatment regimens are used in phototherapy, but generally medium-dose UVA1 and narrowband UVB are recommended for the treatment of AD in adult patients (85, 90).

The patient must travel between 3 and 5 times per week and for 6 to 12 weeks to a site that offers this therapy (85, 90). Furthermore, UV light cannot effectively treat areas of the skin with hair, as well as scalp and skin folds. In practice, phototherapy is usually part of a wider treatment plan, e.g. as a second-line treatment, and is generally used in adults rather than in younger patients. All UV treatments may pose a long-term risk of skin ageing and developing skin cancer

Conventional systemic therapies

Escalation to conventional systemic therapy, sometimes referred to as traditional systemic immunomodulators (cyclosporine, methotrexate, azathioprine, mycophenolate, corticosteroids) is currently recommended following the failure of topical regimens and/or phototherapy to adequately control the signs and symptoms of disease, or in patients with severe or persistent AD.

AD is a chronic disease that requires continuous treatment and the conventional systemic treatment most used in treating AD show moderate effect, several are not recommended for long-term use and only a few are approved for use in AD. Further, the evidence for using conventional systemic treatment is limited and often based on expert opinion (91).

Currently there are no conventional systemic treatments that are approved for moderate AD, although it has been identified that moderate AD patients could benefit of conventional systemic treatment (76) Furthermore, there are several conditions where these are not appropriate such as newly diagnosed cancer and alcoholism which are contraindicated to use due to the malignancy risk in ciclosporin, azathioprine and mycophenolate, and in methotrexate due to the risk of liver disease (92). Of the approved systemic treatments for AD, none is recommended

for long-term use. As highlighted in the above publication from the IEC, systemic CS should only be used short-term under certain circumstances (93), furthermore according to the European guidelines, CSA should only be used for a maximum of two years, if tolerated for such long time(87)

Conventional systemic treatments are not suitable for long-term use and associated with a wide range of side-effects, including nephrotoxicity, hypertension, gastrointestinal and liver toxicity, myelosuppression, and leukopenia. Therefore, many patients with moderate-to-severe AD have very few treatment options available to them and remain under-treated due to a lack of systemic therapies with a favorable benefit/risk profiles suitable for long-term use (85-87).

Advanced systemic therapies
The approved advanced systemic treatments for AD are dupilumab, a human anti-IL-4Rα inhibitor, and baricitinib a selective oral JAK 1/2 inhibitor. **Baricitinib** is further described in this section. **Dupilumab** is the relevant comparator to upadacitinib and will as such be described in more detail, please refer to sections 5.2.3 and 7.

Baricitinib modulates the pro-inflammatory cytokine signaling and is approved by EMA for adult patients with moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy (94). The phase III program for baricitinib comes from two monotherapy studies, BREEZE-AD1 and BREEZE-AD2. The BREEZE-AD3 study is an open label extension of BREEZE-AD1 and BREEZE-AD2. Two studies the BREEZE-AD4 and BREEZE-AD7 are combination studies with TCS. Patients with inadequately response to cyclosporine were investigated in the BREEZE-AD5 study. An open label extension study of BREEZE-AD5 is the BREEZE-AD6 study. In BREEZE-AD1 and BREEZE-AD2, 16.8% and 13.8% of patients receiving the approved dose 4 mg achieved vIGA-AD 0/1 (clear or almost clear skin). For the other approved dose 2 mg, 11.4% and 10.6% achieved IGA 0/1 at week 16. The proportion of patients achieving EASI75 in BREEZE-AD1 and BREEZE-AD2 for the 4 mg and 2 mg dose was 24.8%, 21,1% and 18.7%, 17.9% respectively. The placebo response in the BREEZE-AD1 and BREEZE-AD2 was for vIGA-AD and EASI75, 4.8%, 4.5% and 8.8%, 6.1% respectively. In the combination studies BREEZE-AD4 and BREEZE-AD7, treatment responses were higher indicating a beneficial effect of concomitant use with TCS. In BREEZE-AD4 the vIGA 0/1 was 21.7% for the 4 mg dose and 15.1% for the 2 mg dose, the corresponding placebo response was 9.7%. The EASI75 response was for the 4 and 2 mg dose, 31.5% and 27.6% respectively and the placebo response was 17.2%. In the BREEZE-AD7 study, only the 4 mg dose achieved primary endpoint, with vIGA-AD response of 31% and EASI75 response of 48%, the placebo response was 15% and 23% respectively. The most common adverse events are nasopharyngitis, headaches, influenza, diarrhea, folliculitis and oral herpes. Serious adverse events (SAE) were between 0.8-4% in the 4 mg arm, 0-2,4% in the 2 mg arm, 0.7-7.3% in the 1 mg arm. One case of pulmonary embolism has been reported in the 4 mg arm in phase III studies of baricitinib. More patients discontinued in the 4 mg treatment arm. (95-104)

Baricitinib was recently approved by the MR for patients with moderate to severe AD but it is yet to be seen how baricitinib will be used in clinical practice in Denmark. Although a promising MoA, there is still a high unmet need as a high proportion of patients treated with baricitinib does not reach treatment goals set up by the DDS, for example EASI 75.

Treatment of moderate to severe AD in Denmark
Several studies report on treatment patterns in Danish clinical practice, and to be relevant for this submission the studies should also report treatment related to severity of disease.

In a study on 3834 adult patients from the Danish Skin Cohort reporting treatment of AD per degree of severity. (58) A summary of different treatments is shown in Table 8. As expected, the proportion of patients using each treatment

increases with increasing disease severity in most cases. The study does not report on amount of drugs used but did examine whether patients were infrequent users of TCS, defined as “patients filling at least one prescription of TCS within the past 12 months but not at least one prescription every 90 days prior to index” or frequent users of TCS, defined as “patients that filled a prescription for a topical corticosteroid at least once every 90 days during the 12 months prior to index”.

Of the patients on systemic treatment, 83 % of the patients were not frequent users of TCS. Patients with many flares, had a higher degree of TCS use. These studies on use of TCS in Danish patients with AD suggests that though TCS is widely used, the use is intermittent, and associated with flares.

Table 8 . AD treatment for patients with varying degree of severity (58)

	Remission	Mild	Moderate	Severe
	n = 261	n = 2126	n = 1304	n = 143
	(PO-SCORAD = 0)	(PO-SCORAD < 25)	(PO-SCORAD 25–50)	(PO-SCORAD > 50)
Topical corticosteroids[a], n (%)				
Mild	3 (1.2)	39 (1.8)	67 (5.1)	12 (8.4)
Moderate	17 (6.5)	224 (10.5)	318 (24.4)	39 (27.3)
Potent	31 (11.9)	374 (17.6)	540 (41.4)	69 (48.3)
Very potent	5 (1.9)	126 (5.9)	162 (12.4)	35 (24.5)
Topical calcineurin inhibitors, n (%)				
Topical tacrolimus	0 (0.0)	78 (3.7)	143 (11.0)	18 (12.6)
Topical pimecrolimus	<3 (NS)	43 (2.0)	58 (4.5)	8 (5.6)
Topical antibiotic treatment, n (%)				
Without topical corticosteroids	<3 (NS)	76 (3.6)	72 (5.5)	13 (9.1)
Combined with topical corticosteroids	11 (4.2)	75 (3.5)	83 (6.4)	12 (8.4)
Topical antiviral treatment, n (%)				
Aciclovir	0 (0.0)	7 (0.3)	8 (0.6)	<3 (NS)
Systemic antibiotic treatment				
Dicloxacillin	5 (1.9)	108 (5.1)	89 (6.8)	19 (13.3)
Systemic antiviral treatment				
Aciclovir	8 (3.1)	81 (3.8)	68 (5.2)	6 (4.2)
Valaciclovir	<3 (NS)	24 (1.1)	22 (1.7)	3 (2.1)
Oral corticosteroids, n (%)				
All patients	11 (4.2)	106 (5.0)	108 (8.3)	17 (11.9)
Patients without asthma	9 (4.4)	52 (3.6)	48 (7.3)	6 (10.3)
Methotrexate, n (%)	6 (2.3)	40 (1.9)	57 (4.4)	3 (2.1)
Azathioprine, n (%)	<3 (NS)	28 (1.3)	37 (2.8)	4 (2.8)
Cyclosporine, n (%)	0 (0.0)	5 (0.2)	3 (0.2)	<3 (NS)
Mycophenolate, n (%)	3 (1.2)	6 (0.3)	9 (0.7)	4 (2.8)

Abbreviation: NS, not shown due to data security requirements.
[a]Excludes combination products (topical corticosteroids + antibiotics).

In another study report from the Danish Skin Cohort, ordered by Abbvie, again treatment stratified by AD severity was investigated. Based on this data on adult patients with active disease within the least 12 months the most common prescribed therapy for both patients with moderate and severe disease was topical therapy alone. As shown in Table 9, 146 (11%) of patients with moderate to severe disease had systemic treatment alone and 99 (7%) patients had systemic treatment with concomitant TCS (105).

Table 9. AD patient characteristics and treatment stratified by AD severity (105).

	All (n=2341)	**Asymptomatic** (n=11) (PO-SCORAD=0)	**Mild** (n=952) (PO-SCORAD <25)	**Moderate** (n=1238) (PO-SCORAD 25-50)	**Severe** (n=140) (PO-SCORAD >50)
Age (years), median (IQR)	45.1 (35.6; 55.2)	48.4 (38.3; 61.2)	44.8 (36.7; 54.8)	45.2 (34.9; 55.0)	46.2 (33.8; 58.6)
Sex, n (%)					
Women	1647 (70.4)	8 (72.7)	699 (73.4)	844 (68.2)	96 (68.6)
Men	694 (29.6))	3 (27.3)	253 (26.6)	394 (31.8)	44 (31.4)
Age of AD onset (years), median (IQR)	3.0 (1.0; 10.0)	12.5 (6.5; 30.5)	4.0 (1.0; 15.0)	2.0 (1.0; 7.0)	1.0 (0.0; 5.0)
Duration of AD (years), mean (SD)	38.3 (26.4; 48.6)	30.3 (14.6; 43.3)	36.8 (24.5; 45.2)	39.6 (28.2; 49.9)	39.1 (27.1; 50.9)
Body Surface Area (%), median (IQR)	5.0 (2.0; 15.0)	0.0 (0.0; 0.0)	2.0 (1.0; 5.0)	7.0 (3.0; 20.0)	30.0 (19.0; 70.0)
Current no prescrition therapy, n (%)	1529 (65.3)	7 (63.4)	705 (74.1)	752 (60.7)	65 (46.4)
Current topical therapy alone, n (%)	NS	≤3	139 (14.6)	272 (22.0)	44 (31.4)
Current systemic therapy alone, n (%)	NS	≤3	75 (7.9)	133 (10.7)	13 (9.3)
Current topical + systemic therapy, n (%)	132 (5.6)	0	33 (3.5)	81 (6.5)	18 (12.9)
Asthma, n (%)	1054 (45.0)	4 (36.4)	346 (36.3)	621 (50.2)	83 (59.3)
Allergic rhinitis, n (%)	1332 (56.9)	5 (45.5)	475 (49.9)	763 (61.6)	89 (63.6)
Body mass index, n (%)					
Underweight (BMI <18.5)	44 (1.9)	0	21 (2.2)	19 (1.5)	4 (2.9
Normal weight (BMI 18.5-25)	1144 (48.9)	5 (45.5)	495 (52.0)	582 (47.0)	62 (44.3)
Overweight (BMI 25-30)	749 (32.0)	3 (27.3)	290 (30.5)	418 (33.8)	38 (27.1)
Moderately obese (BMI 30-35)	249 (10.6)	3 (27.3)	89 (9.4)	133 (10.7)	24 (17.1)
Severely obese (BMI 35-40)	85 (3.6)	0	27 (2.8)	52 (4.2)	6 (4.3)
Very severely/morbidly obese (BMI >40)	NS	0	18 (1.9)	26 (2.1)	NS
Unknown	NS	0	12 (1.3)	8 (0.7)	<3

AD, atopic dermatitis; BMI, body mass index; IQR, interquartile range; NS, not shown; SD, standard deviation; TCS, topical corticosteroids
*Current therapy = filled prescription within last 12 months

Treatment patterns in Denmark before and after hospital referral has been investigated in a registry-based longitudinal drug utilization study among 8213 Danish patients of all ages (106). The study, though recently published, was done before advanced systemic treatments entered the market. The study included all grades of severity. 20 % of the patients were treated with systemic treatments, and was by the authors of the study therefore considered to have severe AD. As shown in Figure 16. Use of systemic treatments before and after hospital referral (year 0) in Denmark the use of systemic treatment increased in the year leading up to hospital referral and declined thereafter.

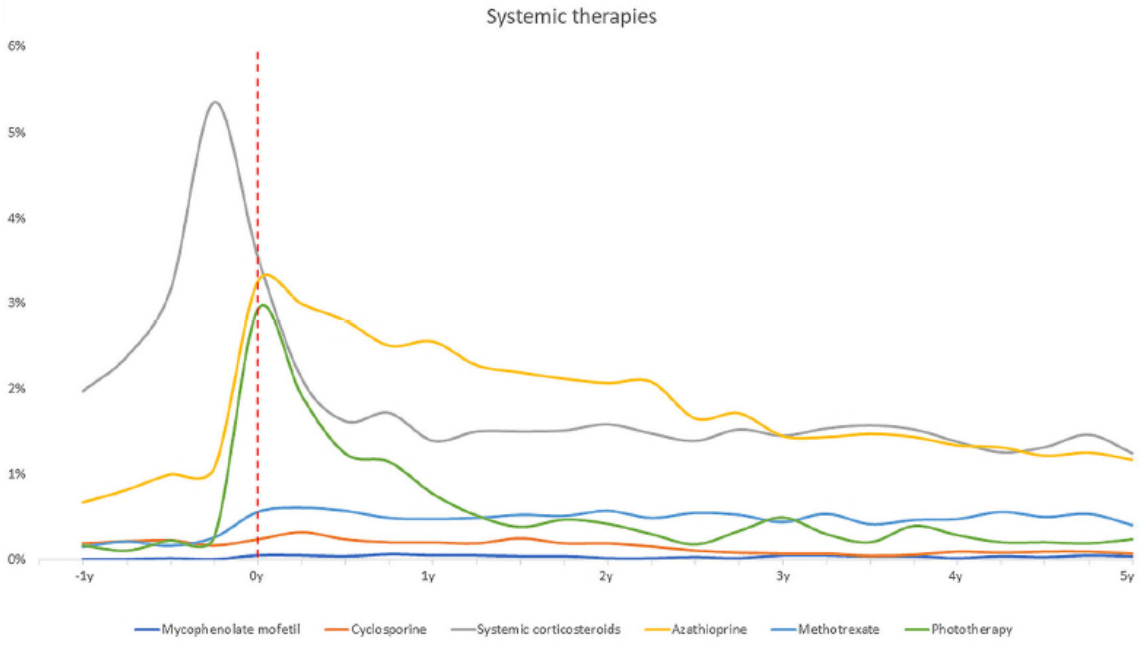


Figure 16. Use of systemic treatments before and after hospital referral (year 0) in Denmark (106)

TCS use also decreased significantly after hospital referral and continued to decrease over the years thereafter in patients treated with systemic treatment (and thereby defined as having severe disease in the study). As shown in

Figure 17, after 1 year less than 10 % of patients were treated with potent TCS, 5% with moderately potent TCS, about 2,5 % with very potent TCS and TSC with antibiotics respectively, and finally 2% with mild TCS.

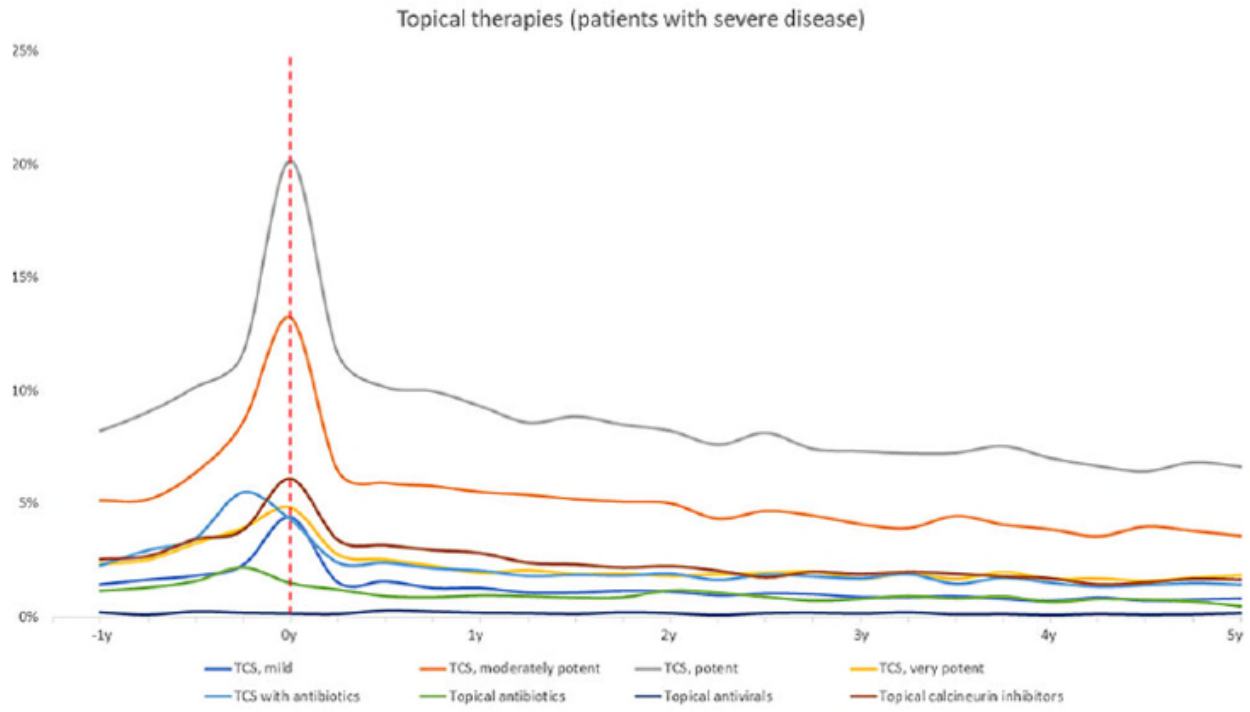


Figure 17. TCS use in patients Treated with systemic treatment (106)

5.2.2 Choice of comparator(s)

The anticipated marketing authorization for upadacitinib is for the treatment of people aged 12 years or over with moderate-to-severe AD who are candidates for systemic therapy. While this population includes patients, who are eligible for conventional systemic therapies (i.e., immunosuppressant therapies), it is anticipated that upadacitinib will be positioned to patients who are contraindicated to, intolerant of, had an inadequate response to or for whom it is otherwise medically inadvisable to receive treatment with a systemic immunosuppressant. This population aligns with the population in the upadacitinib clinical trials and the population for which dupilumab is recommended in Denmark (107). Dupilumab is in the DDS guidelines recommended for patients with moderate to severe AD, defined as EASI>16, BSA>10, DLQI>10 and POEM>16, who do not respond adequately to relevant local treatment with corticosteroids or calcineurin inhibitor and other systemic treatment, or when such treatment is not suitable.

Dupilumab is the relevant comparator to upadacitinib as it is the advanced systemic treatment used in clinical practice in Denmark, though baricitinib recently was recommended for use by the Medicines council, and dupilumab comply with the recommendations about choice of comparator in section 2.4 of the guideline. Contrary to baricitinib which only has indication for adults, upadacitinib and dupilumab can be used from 12 years of age. Upadacitinib has also been compared with dupilumab in a randomized controlled trial.

5.2.3 Description of the comparator(s)

Dupilumab is AN IL-4 receptor inhibitor given as an injection every other week. Patients administer dupilumab at home, after being instructed on how to handle the injection. Basic information about dupilumab is summarized in Table 10.

Table 10. Basic information about dupilumab (108)

<table>
<tr><td>Generic name(s) (ATC-code)</td><td>Dupilumab (D11AH05)</td></tr>
<tr><td>Mode of action</td><td>IL-4 receptor inhibitor (monoclonal antibody)</td></tr>
<tr><td>Pharmaceutical form</td><td>Solution for injection in prefilled syringe or prefilled pen</td></tr>
<tr><td>Posology</td><td>200 mg
300 mg</td></tr>
<tr><td>Method of administration</td><td>Subcutaneous injection</td></tr>
<tr><td>Dosing</td><td>The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week administered as subcutaneous injection. The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in the table below:
<table>
<tr><th>Body Weight of Patient</th><th>Initial Dose</th><th>Subsequent Doses (every other week)</th></tr>
<tr><td>less than 60 kg</td><td>400 mg (two 200 mg injections)</td><td>200 mg</td></tr>
<tr><td>60 kg or more</td><td>600 mg (two 300 mg injections)</td><td>300 mg</td></tr>
</table></td></tr>
<tr><td>Should the pharmaceutical be administered with other medicines?</td><td>Dupilumab can be used with or without TCS and/or TCI.</td></tr>
<tr><td>Treatment duration/criteria for end of treatment</td><td>Efficacy is measured at 16 weeks. Patients without sufficient response should be considered discontinuing treatment. (DDS: EASI 75 or EASI50 and DLQI 4)</td></tr>
<tr><td>Necessary monitoring, both during administration and during the treatment period</td><td>None</td></tr>
<tr><td>Need for diagnostics or other tests (i.e. companion diagnostics)</td><td>None</td></tr>
<tr><td>Packaging</td><td>Dupixent 200 mg, solution for injection in pre-filled syringe, 2 syringes
Dupixent 200 mg, solution for injection in pre-filled pen, 2 pens
Dupixent 300 mg, solution for injection in pre-filled syringe, 2 syringes
Dupixent 300 mg, solution for injection in pre-filled pen, 2 pens</td></tr>
</table>

5.3 The intervention

Upadacitinib (RINVOQ®) is a small molecule, a reversible JAK inhibitor. In engineered cellular assays upadacitinib has demonstrated relative nM potency for JAK1 with ~40-fold greater selectivity over JAK2, ~130-fold over JAK3 and ~190-fold over TYK2.(109) It is an oral extended-release tablet administered as a once daily, 15 mg or 30 mg dose to patients with moderate to severe AD. Bodyweight is not correlated with upadacitinib clearance, therefore adjustments in dose according to weight is not necessary. Upadacitinib can be given as monotherapy or in combination with TCS. Basic information about upadacitinib is available in Table 11.

The recommended starting and maintenance dose for all patients will be 15 mg per the SPC, and 15 mg will also be the only dose recommended for patients aged 12 – 18 and over 65 years of age. The use of the 30 mg dose will be limited to patients with a very high disease burden, and the dose should be lowered to 15 mg whenever possible.

Table 11 Basic information about upadacitinib.

Generic name(s) (ATC-code)	Upadacitinib (L0AA44)
Mode of action	Reversible janus kinase (JAK) inhibitor
Pharmaceutical form	Depot tablet
Posology	15 mg 30 mg
Method of administration	Per oral administration
Dosing	<u>Adults</u> The recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation. • A dose of 30 mg once daily may be appropriate for patients with high disease burden. • A dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily. • The lowest effective dose for maintenance should be considered. For patients ≥ 65 years of age, the recommended dose is 15 mg once daily. <u>Adolescents (from 12 to 17 years of age)</u> The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.
Should the pharmaceutical be administered with other medicines?	Upadacitinib can be used with or without TCS and/or TCI
Treatment duration/criteria for end of treatment	Efficacy is measured at 16 weeks. Patients without sufficient response should be considered discontinuing treatment. (DDS: EASI 75 or EASI50 and DLQI 4)

Necessary monitoring, both during administration and during the treatment period	Laboratory monitoring for Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC), Hemoglobin (Hb), Hepatic transaminases and Lipids. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib Patients should be monitored for the development of signs and symptoms of TB (tuberculosis), including patients who tested negative for latent TB infection prior to initiating therapy. Screening for viral hepatitis and monitoring for reactivation should be performed before starting and during therapy with upadacitinib.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Packaging	28 tablets

Upadacitinib 15 mg is currently approved for three adult rheumatic indications in Denmark (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis). EMA approval for upadacitinib 15 mg and 30 mg for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy was approved August 23rd, 2021 (positive opinion June 24th, 2021). Upadacitinib is also being investigated for a range of other immunology indications including Ulcerative Colitis, Crohn´s Disease, and Giant cell arteritis.(110-113).

Upadacitinib is expected to be used primarily in monotherapy, with no or little use of concomitant administration of TCS. This is a clinical advantage since long-term steroid use increases the risk of adverse events. Tolerance to TCS, resulting in increases in dose or potency of steroids over time must be considered (54). It is also of advantage to patients since administration of topical treatments is inconvenient and time consuming (79-83).

Upadacitinib is expected to be used in the same position in the treatment sequence as dupilumab and the recently approved baricitinib, for patients with moderate to severe AD who does not achieve adequate efficacy with conventional systemic treatments or when conventional therapy is not suitable. In the treatment algorithm from DDS, see Figure 15, upadacitinib will be placed with other systemic treatment, as the final step in the treatment algorithm. Upadacitinib is expected to be a treatment alternative for patients that would otherwise be treated with dupilumab or baricitinib.

The results of Measure-Up 1, Measure-UP 2 and Ad-UP were recently published (114, 115). In a comment to the published clinical studies in the same issue by Thyssen and Thomsen the efficacy of upadacitinib is compared to dupilumab and baricitinib and the authors conclude (116):

"The efficacy of upadacitinib suggests that clinicians might soon be able to offer patients with atopic dermatitis an oral treatment solution with little or no need for concomitant administration of topical corticosteroids."

The changes to clinical practice are expected to be small. However, due to the proportion of patients reaching the treatment goals used in Danish clinical practice described above, Rinvoq is assumed to lessen the need for concomitant TCS administration.

5.3.1 Administration and dosing

Upadacitinib is administered as a once daily, oral dose, 15 mg/30 mg dose, and is indicated for moderate to severe AD for adolescents and adults 12 years and older who are candidates for systemic therapy. Upadacitinib 15 mg is the standard starting and maintenance dose based on the proposed EMA labelling. The recommended dose for upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation:

- The lowest effective dose for maintenance should be considered.
- A dose of 30 mg once daily may be appropriate in patients with an inadequate response to 15 mg once daily.
- A starting dose of 30 mg once daily may be appropriate for patients with high disease burden.
- For patients ≥ 65 years of age, the recommended dose is 15 mg once daily.
- The recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.
- In AD, upadacitinib can be given as monotherapy or in combination with TCS.

Treatment response have been defined as reaching EASI 75 or the composite endpoint of EASI 50 and at least 4 point reduction of DLQI, and/or at least a 4 point reduction in POEM, in accordance with the DDS-guideline (54). Using this definition of response, the majority, about 70%, of patients in the clinical trials had a clinically relevant response with upadacitinib 15 mg (see section 7.1 for more information about efficacy outcomes). In addition, patients aged 12 to 17 and older than 65 should always use 15 mg only. Based on this information an assumption is made that 70% of patients will be treated with 15 mg, and 30 % with 30 mg. This estimate of the proportion patients treated with 15 mg is likely to be conservative as in addition all patients aged 12 to 17 years and 65 years or older should be treated with 15 mg only according to the SmPC. Data from the Swedish prescription registry also supports the assumptions of the dose split. After the reimbursement decision in the end of January 2022, the proportion between the strengths, prescribed by dermatologists (which is seen as a proxy for patients with AD) is [redacted] for February and March. (AbbVie Data on File).

Metabolism and excretion
Upadacitinib is metabolized hepatically, via the cytochromes P450s (CYPs) and is mainly eliminated via CYP3A mediated metabolism.

Inhibition of IL-6 induced STAT3 and IL-7 induced STAT5 phosphorylation
Upadacitinib results in a dose and concentration-dependent inhibition of IL-6 (JAK1/JAK2) -induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation in whole blood. The maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval.

Pharmacokinetics
Upadacitinib plasma exposures are proportional to dose over the therapeutic dose range. Steady state plasma concentrations are achieved within 4 days with minimal accumulation after multiple once daily administrations.

Absorption
Following oral administration of upadacitinib extended-release formulation, upadacitinib is absorbed with a median time to maximum (Tmax) of 2 to 4 hours. Co-administration of upadacitinib with a high-fat/high-calorie meal had no clinically relevant effect on upadacitinib exposures (increased AUC (area under the curve) by 29% and Cmax (maximum concentration achieved) by 39%). In clinical trials, upadacitinib was administered without regard to meals. Distribution Upadacitinib is 52% bound to plasma proteins. Upadacitinib partitions similarly between plasma and blood cellular components with a blood to plasma ratio of 1.0.

Metabolism
Upadacitinib metabolism is mediated by mainly Cytochrome P450 3A4 (CYP3A4) with a potential minor contribution from Cytochrome P450 2D6 (CYP2D6). The pharmacologic activity of upadacitinib is attributed to the parent molecule. In a human radio-labeled study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma while the main metabolite detected (product of mono-oxidation followed by glucuronidation) accounted for 13% of the total plasma radioactivity. No active metabolites have been identified for upadacitinib.

Elimination
Following single dose administration of upadacitinib immediate-release solution, upadacitinib was eliminated predominantly as the unchanged parent substance in urine (24%) and feces (38%). Approximately 34% of upadacitinib dose was excreted as metabolites. Upadacitinib mean terminal elimination half-life ranged from 8 to 14 hours.

Specific Populations
Body weight, gender, race, age, and ethnicity did not have a clinically meaningful effect on upadacitinib exposure.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A comprehensive literature search was performed using a very broad set of inclusion criteria, by Abbvie's global team. This search was intended to identify all relevant literature in adults and adolescents (≥12 years) with active moderate to severe AD. The PICO for this search is described in Appendix A, and was considered to identify all studies relevant for this application. The searches were conducted following guidance from NICE and the Canadian Agency for Drugs and Technologies in Health (CADTH) Grey Matters report for searching health-related grey literature.(117, 118) The search strategy for identification of efficacy and safety studies was:*((search terms and synonyms for Atopic dermatitis or Eczema) AND (search terms, synonyms, and serial/chemical abstract numbers for interventions) AND (search filters for: randomised or controlled studies))* The Cochrane Collaboration's Highly Sensitive Search Strategy (HSSS) merged with the Cooper et al. P3 filter was used.(119, 120)

The search would however also identify studies that included interventions that were not of interest for the Danish context, the search resulted in 179 records representing 50 different studies. Of the 179 publications included in the clinical SLR, 45 were primary publications, 132 were associated publications, and two were clinical trial registries for UPA, representing 50 unique studies. The discrepancy between the number of primary publications (n=45) and number of unique studies (n=50) is because 5 publications each published the findings from 2 unique studies. All primary publications and associated publications were included for data extraction.
The 50 unique studies evaluated:

- Upadacitinib (UPA): 5 trials in 24 publications, and 2 trial registries
- Abrocitinib (ABR): 6 trials in 30 publications
- Azathioprine (AZA): 1 trial in 1 publication
- Baricitinib (BAR): 7 trials in 20 publications
- Ciclosporin (CsA): 5 trials in 5 publications
- Dupilumab (DUP): 13 trials in 67 publications
- Methotrexate (MTX): 2 trials in 5 publications
- Mycophenolate mofetil: 1 trial in 1 publication
- Phototherapy: 2 trials in 2 publications
- Prednisolone (PRED): 3 trials in 3 publications

- Tralokinumab (TRA): 5 trials in 19 publications

In order to do the comparison between upadacitinib and dupilumab relevant for the Danish context and to do an indirect treatment comparison, a narrower set of criteria was imposed on the 179 records that was the results of the SLR. The criteria differ on intervention (including only upadacitinib and dupilumab, with or without addition of TCS) and study design (excluding phase II-trials). Studies fully based in Asia were also excluded. The full set of criteria used in the indirect treatment comparison are shown in Table 12.

Table 12. Eligibility criteria used in the indirect treatment comparison.

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adults and adolescents (≥12 years) AND • Patients with moderate to severe AD*	• Children (<12 years) • Patients with other active skin diseases or infections requiring systemic treatment, or those that would interfere with assessment of AD lesions
Intervention	Any formulation of the following (without or without combination corticosteroids; concomitant therapies [e.g., emollients]; rescue therapy and/or retreatment): • UPA • DUPI	Studies only containing: • Systemic immunosuppressants • Topical retinoids • Phototherapy • Prednisolone
Comparators	• Placebo • Active intervention (i.e., head-to-head trials)	Studies only containing: • TCS • Systemic immunosuppressants • Topical retinoids • Phototherapy • Prednisolone
Outcomes	Efficacy • EASI	Studies only containing: • SCORAD • BSA • POEM • DLQI or CDLQI for adolescents† • HADS • EQ-5D overall, or any of 5 domains, or EQVAS, or EQ-5D-Y • SF-36 • IGA • Pruritus NRS‡ • Safety analyses
Study design	• RCTs (phase III, IV) • Randomized crossover/cluster trials, provided randomized phase is at least 12 weeks	• RCTs (phases I, II) • Long-term follow-up studies (e.g., open-label [OLE] follow-up studies with continuation of treatment) • Dose-ranging RCTs (that include a control arm) • Trial registries
Limits / language restriction	• English language¶ • Conference presentations published in 2018 or later	• Studies based in Asia

CDLQI, Children's Dermatology Life Quality Index; EQ-5D, European Quality of Life-5 Dimensions; ED-5D-Y, EQ-5D - youth; EQVAS, EQ-5D visual analogue scale; HADS, Hospital Anxiety and Depression Scale;; IL-4, interleukin-4; IL-13, interleukin-13; JAK, Janus kinase; NRS, numerical rating scale; OLE, open-label extension; SF-36, Short Form-36 Health Survey; VAS, visual analogue scale.

*Moderate to severe disease was defined according to thresholds for EASI, IGA, BSA, and pruritus as reported in each study.
†The CDLQI tool is validated for patients 4–16 years of age. The clinical SLR identified studies reporting results for adolescents 12–16 years of age.

‡May include alternative names for outcome, such as peak pruritus NRS, worst pruritus NRS, itch NRS.

Of the in total 18 studies identified for upadacitinib and dupilumab, 10 were excluded based on the criteria in Table 12. The studies and reason for exclusion are listed in Table 13. The remaining 8 studies are listed in Table 14. The ninth study, JADE COMPARE is included as it includes both dupilumab and placebo arms, though the main intervention is abrocitinib.

Table 13. Studies excluded from the systemic literature review.

Study-name	NTC-number	Reason for exclusion
M16-048	NCT02925117	Phase 2
Study M12	NCT01548404	Phase 2
Study C4	NCT01639040	Phase 2
LIBERTY AD SOLO-CONTINUE	NCT02395133	Open label extension of LIBERTY AD SOLO
R668-AD-1021	NCT01859988	Phase 2 study
LIBERTY AD OLE	NCT01949311	Open label extension of LIBERTY AD
LIBERTY AD EVALUATE	NCT02210780	Phase 2 study
LIBERTY AD ADOL	NCT03054428	Phase 2 study
LIBERTY AD PED-OLE	NCT02612454	Open label, non/randomized study
Zhao 2021	NCT03912259	Chinese population only

6.2 List of relevant studies

A list of relevant studies identified in the systematic literature review and with the inclusion and exclusion criteria in Table 12, are shown in Table 14 below. A more detailed description of the clinical studies is available in section 7.1, and in Appendix B, C, D, and E. These studies also form the evidence base for the indirect treatment comparison described in section 7.2.

Table 14. Studies identified for the comparison between upadacitinib and dupilumab

Reference	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Guttman-Yassky et al, 2021 (114)	Measure-Up 1	NCT03569293	2018-08-13 – 2025-10-09	Rinvoq vs dupilumab in moderate to severe AD
Guttman-Yassky et al, 2021 (114)	Measure-Up 2	NCT03607422	2018-07-27- 2025-12-03	Rinvoq vs dupilumab in moderate to severe AD
Reich et al, 2021 (115)	Ad-Up	NCT03568318	2018-08-09- 2025-11-16	Rinvoq vs dupilumab in moderate to severe AD
Blauvelt et al, 2021 (121)	Heads-Up	NCT03738397	2019-02-21- 2020-12-09	Rinvoq vs dupilumab in moderate to severe AD
Simpson et al, 2016(45)	LIBERTY AD SOLO1	NCT02277743	October 2014- February 2016	Rinvoq vs dupilumab in moderate to severe AD
Simpson et al, 2016 (45)	LIBERTY AD SOLO2	NCT02277769	2014-11-30 - 2016-01-31	Rinvoq vs dupilumab in moderate to severe AD
Blauvelt et al, 2017 (122)	LIBERTY AD CHRONOS	NCT02260986	September 2014 - October 2016	Rinvoq vs dupilumab in moderate to severe AD
De Bruin-Weller et al, 2018 (123)	LIBERTY AD CAFÉ	NCT02755649	2016-01-31 – 2017-03-31	Rinvoq vs dupilumab in moderate to severe AD
Bieber et al, 2021 (124)	JADE COMPARE	NCT03720470	2018-10-29 – 2020-03 – 06	Rinvoq vs dupilumab in moderate to severe AD

For detailed information about included studies, please refer to appendix B.

Several studies that were identified in the literature search have ongoing open label extension studies. These studies are listed in Table 15. together with other ongoing studies including upadacitinib.

Table 15. Ongoing studies for upadacitinib

Trial name	NCT number	Expected completion date	Comment
Measure-Up 1	NCT03738397	2018-08-13 – 2025-10-09	Open Label Extension (5 years follow-up)
Measure-Up 2	NCT03607422	2018-07-27- 2025-12-03	Open Label Extension (5 years follow-up)
Ad-Up	NCT03568318	2018-08-09- 2025-11-16	Open Label Extension (5 years follow-up)
HEADS-UP	NCT04195698	March 2023	52 week extension for Upadacitinib arm
AD-VISE	NCT05029895	2021-09-29- 2026-03-31	A post-marketing observational study to evaluate safety and effectiveness of upadacitinib in adolescent patients ages 12 to <18 years old diagnosed with Atopic Dermatitis (AD)
UP-TAINED	NCT05139836	2021-12-13 - 2025-06-03	Non-interventional, prospective observational cohort study to investigate the effectiveness and sustained disease control of an upadacitinib therapy in moderate to severe Atopic Dermatitis patients over two years
M16-049	NCT03646604	2019-01-31 - 2024-06-22	Open-label multiple dose study to evaluate the pharmacokinetics, safety and tolerability of upadacitinib in pediatric subjects with severe Atopic Dermatitis (Phase I)

7. Efficacy and safety

7.1 Efficacy and safety of Rinvoq compared to dupilumab for adolescent and adult patients with moderate to severe Atopic Dermatitis

7.1.1 Relevant studies

The efficacy and safety of **upadacitinib** compared to placebo was previously evaluated in one multicenter, double-blind, placebo-controlled Phase II trial. The trial included topical emollients as the only background therapy. Dose range investigations at week 2, week 16 and week 32 were also undertaken in this study.(125) Findings from the Phase II clinical trial program indicated that once daily upadacitinib was effective in rapid skin clearance and itch reduction in AD patients.(126) In particular, statistically significant differences in EASI score and pruritus NRS were observed by the first follow up visit (week 2), and more than half of the subjects in the upadacitinib 15 mg or 30 mg arms achieved meaningful improvements in skin clearance (EASI-75) and itch (pruritus NRS improvement ≥ 4) at week 16. All interim analysis undertaken during the trial at 16 and 32 weeks indicated a significant improvement in EASI score, and improvement in patient-reported pruritus NRS ratings.

The successful completion of the Phase II trial led to the commencement of the Phase III trial program, which includes 5 trials conducted in patients with moderate to severe AD, four of these are global studies and will be described in the

dossier. The fifth study is a Japanese study, where approximately 600 adults and adolescents were included. This study was excluded in the systemic literature search due to insufficient data. Due to this and the specific population, this study will not be included in the dossier, although data can be found at www.clinicaltrials.gov (NCT03661138).

The phase III pivotal trials consisted of MEASURE-Up1, MEASURE-Up2 and AD-Up. MEASURE-Up 1 and MEASURE-Up 2 are Phase III clinical trials that are investigating the safety and efficacy of upadacitinib as a monotherapy versus placebo in adolescents & adults with moderate to severe AD who are candidates for systemic therapy.
The clinical evidence for **dupilumab** comes from four Phase III clinical trials: two investigating dupilumab monotherapy compared to placebo (SOLO-1 and SOLO-2) and two investigating dupilumab combined with topical corticosteroids compared to topical corticosteroids alone (LIBERTY AD CAFÉ and LIBERTY AD CHRONOS).(45, 122, 123). In addition, clinical evidence for dupilumab is available from the study JADE compare (124).

The studies are described briefly in the sections below. Detailed information is available in the Appendices:

1. Inclusion and exclusion-criteria, primary and secondary outcomes, Appendix B
2. Baseline patient characteristics are presented in Appendix C
3. Outcomes are presented in Appendix D
4. Safety data is presented in Appendix E

In the upadacitinib pivotal trials no new safety risks were observed compared to the safety profile of upadacitinib in the previously approved indications rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. At week 16, incidence of serious adverse events was similar across the pivotal trials ranging from 1.8-2.3 % in the upadacitinib 15 mg arm, 1.3-2.8 % in the upadacitinib 30 mg arm and 2.8-3.0 % in the placebo arm. The most common TEAE reported included were acne, upper respiratory tract infection and nasopharyngitis. As upadacitinib, dupilumab has not shown any increased serious adverse events compared with placebo. In all pivotal trials, conjunctivitis and injection-site reactions were significantly higher with dupilumab compared to placebo. These adverse events are not seen with upadacitinib, due to different mode of administration and mechanism of action.

As described further in section 0 inhibiting various JAKs will consequently have downstream effect on different physiological responses. It is of the essence to target the JAKs mediating the signaling from the cytokines involved in AD and spare other JAKs. Upadacitinib has the highest affinity for JAK1 and JAK3, which are involved in the pathogenesis of AD, but have lower affinity for other JAKs. The differences in affinity to the different JAK /JAK pars will lead to differences in clinical effect and safety profiles between the JAK -inhibitors. Upadacitinib has demonstrated a positive benefit and risk balance which the European Commission, summarized in the assessment report as: “A clearly clinically relevant effect of upadacitinib has been demonstrated in AD combined with an overall acceptable safety profile, which did not qualitatively differ from that observed in other indications. The observed gain in efficacy of the 30 mg dose over the 15 mg dose is, in patients < 65 years, considered to outweigh the increased risk of AEs at the 30 mg dose.”

MEASURE-Up 1 and MEASURE-UP-2

MEASURE-Up 1 and 2 are ongoing Phase III placebo-controlled, multicenter (up to 185 sites), randomized, double-blind, placebo-controlled studies. The aim of these studies is to assess the efficacy and safety of upadacitinib for the treatment of adolescent and adult subjects with moderate to severe AD who are candidates for systemic therapy.

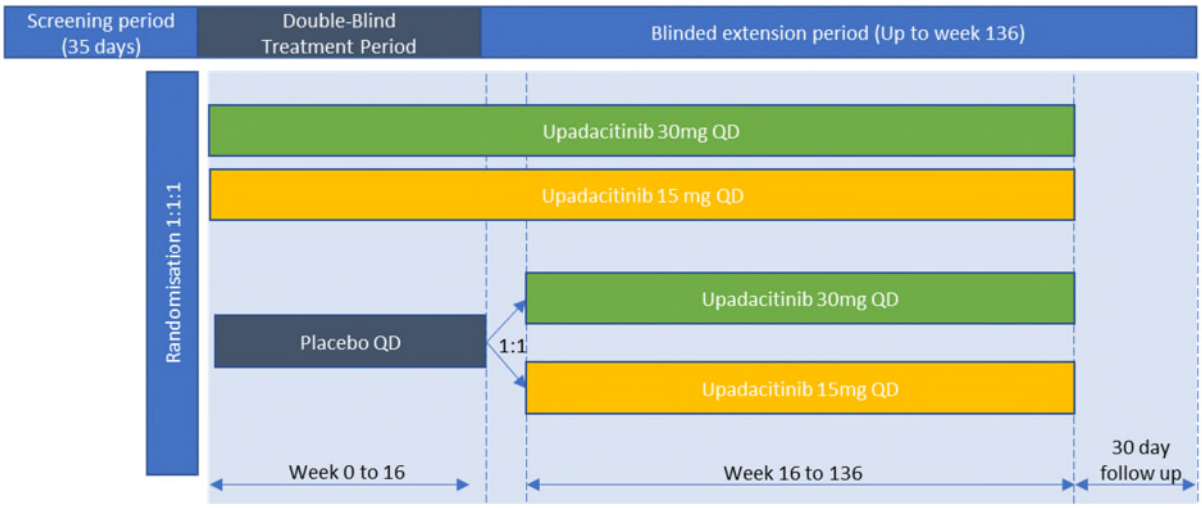


Figure 18. MEASURE-Up 1 and MEASURE-Up 2 trial design (49)

MEASURE-Up 1 and 2 enrolled 912 and 916 adolescent and adult subjects, respectively. Patients were randomized 1:1:1 to receive oral doses of upadacitinib 15 mg, upadacitinib 30 mg or placebo and stratified according to geographic region. The placebo-controlled period of the study ran for 16 weeks, after which patients treated with placebo were randomized 1:1 to upadacitinib 15 mg or upadacitinib 30 mg. The study design for both trials is described in Figure 18. All treatment arms in both studies were able to receive rescue therapy where the first step was topical corticosteroid therapy. Patients receiving topical or oral corticosteroids could continue study drug, and this use of corticosteroids based on patients´ need is likely to reflect how TCS will be used in clinical practice

Ad-UP

AD-Up is an ongoing placebo-controlled, international study that aims to assess the efficacy and safety of upadacitinib in conjunction with TCS for the treatment of adolescent and adult subjects with moderate to severe AD.
The trial enrolled 969 adolescent and adult subjects. Patients were randomized 1:1: to receive oral doses of upadacitinib 15 mg, upadacitinib 30 mg, or placebo alongside TCS treatment. The study design is shown in Figure 19. Prior to entering the study, patients had a wash-out period of seven days for topical treatment. Patients were then initiated on medium-potency TCS treatment once daily for three consecutive weeks or until the lesions are clear or almost clear, whichever was shortest. Following this the TCS treatment was tapered to low-potency TCS once daily on visible lesions for seven days. If lesions were no longer active the TCS treatment was stopped.

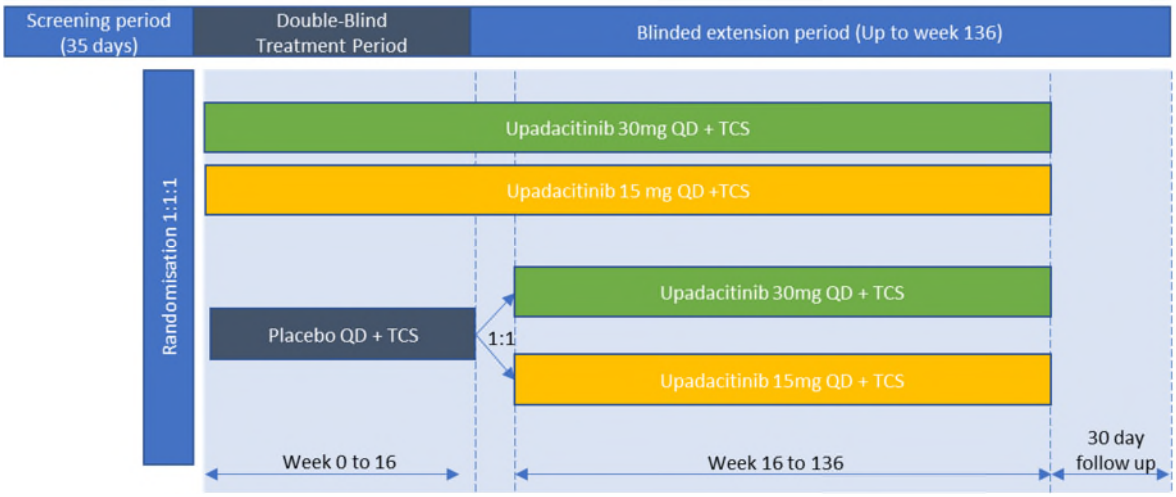


Figure 19: AD-Up study design (115)

This regime for TCS is not identical to the TCS regimes in the CHRONOS and CAFÉ- studies described below. Especially the CAFÉ-study differs in that patient starts TCS treatment 14 days prior to the dupilumab/placebo- start and do not completely discontinue TCS regardless of response. At the end of the 16-week double-blind treatment period, subjects in the placebo group were re-randomized in a 1:1 ratio to receive daily oral doses of upadacitinib 15 mg or 30 mg for up to 136 weeks.(127, 128). The co-primary endpoints of the study are the proportion of subjects receiving at least a 75% reduction in the EASI index from baseline at week 16 and the proportion of subjects achieving IGA1/2 with at least two grades of reduction from baseline.

HEADS-Up

HEADS-Up is an active comparator-controlled, double-dummy, double-blind, multicentre, international trial. The study aims to compare the efficacy and safety of upadacitinib with dupilumab for the treatment of adult subjects with Moderate to severe AD. The study is not part of the pivotal study-program for upadacitinib but is of importance since it is a direct comparison with a relevant comparator.

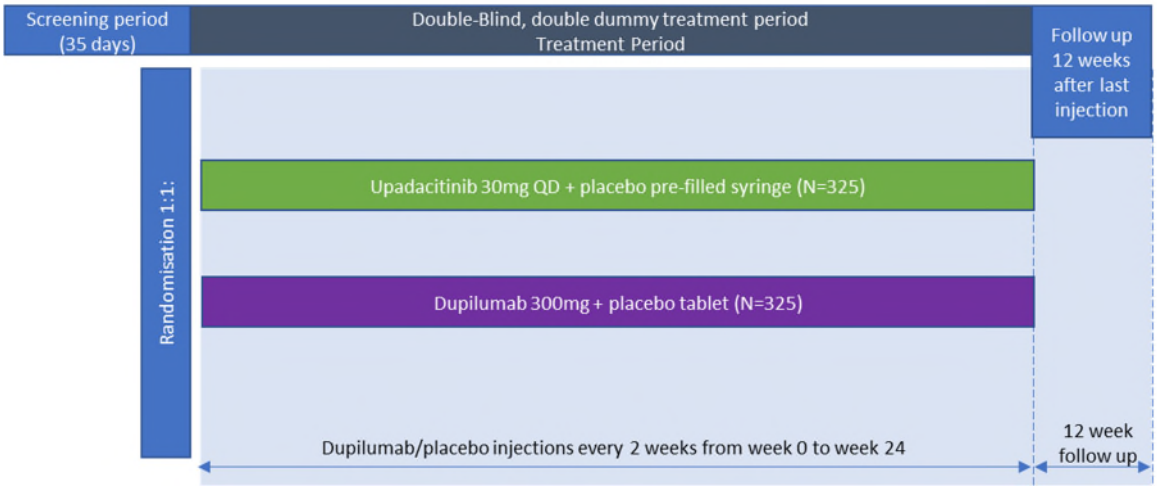


Figure 20: Study design for HEADS-Up [126, 134]

In the HEADS-Up study 692 adult subjects with moderate to severe AD who were candidates for systemic therapy were enrolled. Patients were randomized 1:1: to receive daily oral doses of upadacitinib 30 mg (n=348) or subcutaneous injections of dupilumab 300 mg (n=344) as shown in Figure 20. Patients received daily tablets and injections at the same frequency, in order to control for responses related to the method of administration (112).

One notable difference in HEADS-Up trial compared to the dupilumab trials SOLO-1 and SOLO-2, is that all patients in the HEADS-Up had the injections administered by trained professionals at hospital throughout the trial, while in the SOLO-1 and SOLO-2, patients had the option to self- or caregiver-administer the injections (129). The administration in SOLO-1 and SOLO-2 is likely to reflect the administration of dupilumab in clinical practice. The relative efficacy seen for upadacitinib compared to upadacitinib in Heads-UP is likely a conservative result. The primary endpoint of the study was the proportion of subjects receiving at least a 75% reduction in the EASI index from baseline at week 16. The secondary endpoints were pruritus NRS, EASI90, and EASI100. (112, 130)

SOLO-1 and SOLO-2 - monotherapy

SOLO 1 and 2 are Phase III placebo-controlled, multicenter, randomized, double-blind, placebo-controlled studies. The aim of these studies was to assess the efficacy and safety of dupilumab for the treatment of **adolescent and adult** subjects with **moderate to severe AD** who are candidate for systemic therapy. SOLO 1 enrolled 671 patients (224 to placebo, 224 to dupilumab 300 mg every second week, and 223 to dupilumab 300 mg every week). SOLO 2 enrolled 708 patients (236 to placebo, 233 to dupilumab 300 mg every second week, and 239 to dupilumab 300 mg every week). Both studies had a treatment period of 16 weeks. All patients started with an initial dose of 600 mg, or matching placebo.

If needed to control intolerable symptoms of atopic dermatitis, patients were permitted to receive rescue treatment (which included higher potency topical steroids or systemic immunosuppressants) at the discretion of the investigator. Patients who received rescue treatment were considered non-responders. To evaluate maintenance and durability of response, subjects treated with dupilumab for 16 weeks in SOLO 1 and SOLO 2 studies who achieved IGA 0 or 1 or EASI-75 were re-randomized in SOLO CONTINUE study to an additional 36-week treatment of dupilumab or placebo, for a cumulative 52- week study treatment. Endpoints were assessed at weeks 51 or 52**.**

LIBERTY AD CHRONOS – combination with TCS

The primary objective of the CHRONOS study was to demonstrate the efficacy of dupilumab administered concomitantly with topical corticosteroid (TCS) through week 16 in adult participants with **moderate-to-severe atopic** dermatitis (AD) compared to placebo administered concomitantly with TCS. Patients were to have prior inadequate response to topical treatments to be eligible for study inclusion.

CHRONOS was a randomized, double-blind, placebo-controlled study comparing dupilumab 300 mg weekly (n= 319) and dupilumab 300 mg every second week (n=106) to placebo (n=315). All participants were required to treatment with a (TCS) using a standardized regimen. Efficacy was evaluated at week 16, and patients were followed until week 52. After randomization and screening patients started with a loading dose of 600 mg dupilumab and placebo and started the TCS treatment. TCS treatment was carried out until disease was controlled (clear or almost clear) and after that was tapered and then stopped, to be repeated if lesions returned. The two coprimary endpoints were the proportion of patients with both IGA 0/1 (clear/almost clear; 0–4 scale) and 2-point or higher reduction from baseline at week 16, and the proportion of patients achieving 75% improvement in EASI (EASI-75) from baseline to week 16. (122) After completing the trial patients were eligible to enter the open-label extension, LIBERTY AD OLE NCT01949311.

LIBERTY AD CAFÈ – combination with TCS

The objectives of the CAFÈ study were to evaluate the efficacy, safety and tolerability of 2 dose regimens of dupilumab compared to placebo, administered with concomitant topical corticosteroids (TCS), in adult patients with **severe AD** who are not adequately controlled with, or are intolerant to, oral cyclosporine A (CSA), or when this treatment is currently not medically advisable.

The study is randomized, double-blind, placebo-controlled comparing dupilumab 300 mg weekly (n= 110) and dupilumab 300 mg every second week (n=107) to placebo (n=108). All participants were required to treat with a TCS using a standardized regimen. Efficacy was evaluated at week 16, and patients were followed until week 52. After randomization and screening patients started with a loading dose of 600 mg dupilumab and placebo. TCS treatment differ in CAFÉ compared to CHRONOS as well as AD-UP in that TCS treatment was started 14 days prior to dupilumab and was to be continued throughout the study. Patients with adverse reactions could stop, and patients reaching an IGA of 0 by weeks 4, 8 and 12 could taper TCS to every other day. The primary end point was the proportion of patients with≥ 75% improvement from baseline in EASI score (EASI-75) at Week 16. (123)

JADE-COMPARE

Data on efficacy for dupilumab and placebo are also available in the trial JADE-COMPARE. JADE-COMPARE was designed to assess the efficacy and safety of abrocitinib 200 mg + TCS (n=226) and abrocitinib 100 mg + TCS (n=238) versus dupilumab 300 mg + TCS (n=242) and placebo + TCS (n=133). The study is a phase III, randomized, double-blind and placebo controlled. Medium potency TCS was applied to active lesions until lesions were under control (clear or almost clear), and then once daily for a further 7 days, then stopped. Returning lesions could be treated again with this approach until lesion resolution. (124) Though abrocitinib is not relevant as a comparator, efficacy data on EASI50, EASI75 and EASI90 at 16 weeks from the dupilumab and placebo arms in JADE-COMPARE is relevant for the comparison between upadacitinib and dupilumab, and the study is included in the network meta-analysis.

7.1.2 Efficacy and safety – results per study

MEASURE-Up 1, MEASURE-UP-2, Ad-UP and Heads-UP

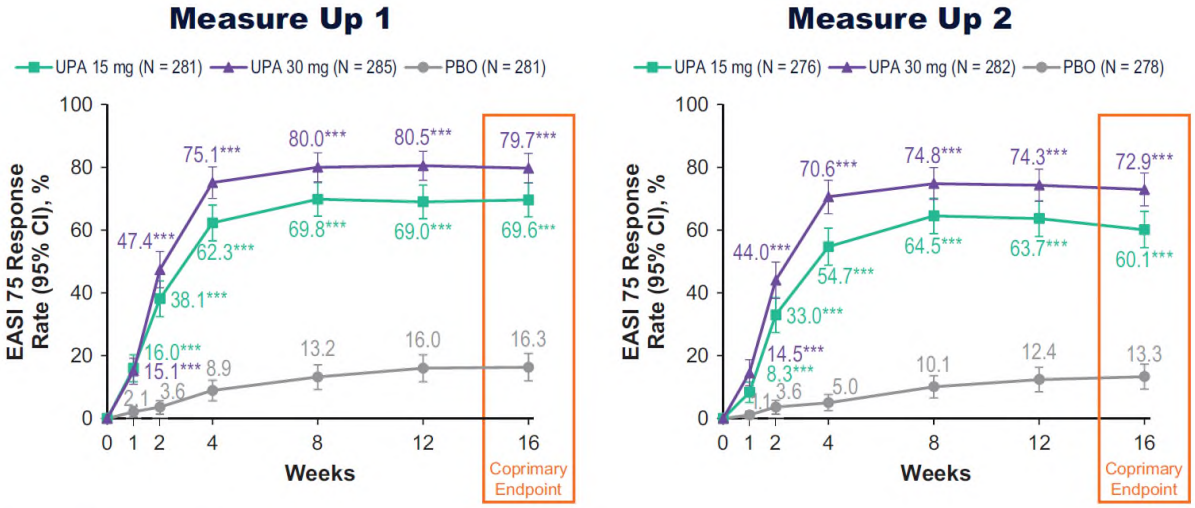
Throughout the pivotal trials the co-primary endpoints were EASI75 (at least 75% improvement in EASI-score from baseline) and vIGA-AD 0/1 (clear or almost clear) at week 16. The primary endpoint in the Heads-Up study was EASI75 at week 16. In Table 16 key efficacy data is compiled from the four studies which shows a significant higher efficacy results compared to placebo and dupilumab.

Table 16. Summary of efficacy outcome measures in the pivotal upadacitinib trials.

	MEASURE-Up 1			MEASURE-Up 2			AD-Up			HEADS-Up	
	Week 16			Week 16			Week 16			Week 16	
	UPA 15 mg (n=281)	UPA 30 mg (n=285)	PBO (n=281)	UPA 15 mg (n=276)	UPA 30 mg (n=282)	PBO (n=278)	UPA 15 mg + TCS (n=300)	UPA 30 mg + TCS (n=297)	PBO + TCS (n=304)	DUPI 300 mg Q2W	UPA 30 mg
Co-primary endpoints										Primary endpoint	
EASI-75	70%***	80%***	16%	60%***	73%***	13%	65%***	77%***	26%	61%	71%**
vIGA-AD 0/1	48%***	62%***	8%	39%***	52%***	5%	40%***	59%***	11%	Secondary endpoints	
Secondary endpoints											
Improvement in worst pruritus NRS≥4	52%***	60%***	12%	42%***	60%***	9%	52%***	64%***	15%	36%	55%***
EASI 90	53%***	66%***	8%	42%***	59%***	5%	43%***	63%***	13%	39%	61%***
EASI 100	17%***	27%***	2%	14%***	19%***	1%	12%***	23%***	1%***	7.6%	28%***
POEM improvement ≥4	75%***	81%***	23%	71%***	84%***	29%	NP	NP	NP	NR	NR
DLQI improvement ≥4	75%***	82%***	29%	72%***	78%***	28%	NP	NP	NP	NR	NR
DLQI 0 or 1	30%***	42%***	4%	24%***	38%***	5%	NP	NP	NP	NR	NR

Source: AbbVie, 2020; Guttman-Yassky et al, 2021, AbbVie, 2020; Clinicaltrials.gov; 2018, Reich et al, 2021, AbbVie 2020 data on file
***p<0.001 versus placebo, multiplicity controlled. ** p=0.006; UPA vs DUPI
DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; NRS: numerical rating scale; PBO, placebo;
POEM, Patient Oriented Eczema Measure; UPA, upadacitinib; vIGA: validated Investigator's Global Assessment

The EASI75 response was between 71-80% in patients treated with upadacitinib 30 mg and between 60-70% in patients treated with upadacitinib 15 mg at week 16. Similarly, vIGA-AD responses were between 52-62% in patients treated with the higher 30 mg upadacitinib dose, for the lower 15 mg dose the vIGA-AD response was between 42-53%.



Based on ITT Population, NRI-C.
***$P \leq .001$ vs PBO; P values are multiplicity controlled only at weeks 2 and 16; P values are nominal at all other time points.
COVID-19, coronavirus disease 2019; EASI 75, ≥ 75% reduction in Eczema Area and Severity Index; ITT, intent-to-treat for the main study; NRI-C, nonresponder imputation incorporating Multiple Imputation to handle missing data due to COVID-19; PBO, placebo; UPA, upadacitinib.

Figure 21. Kinetic of EASI75 response, MEASURE-Up 1 and MEASURE-Up 2

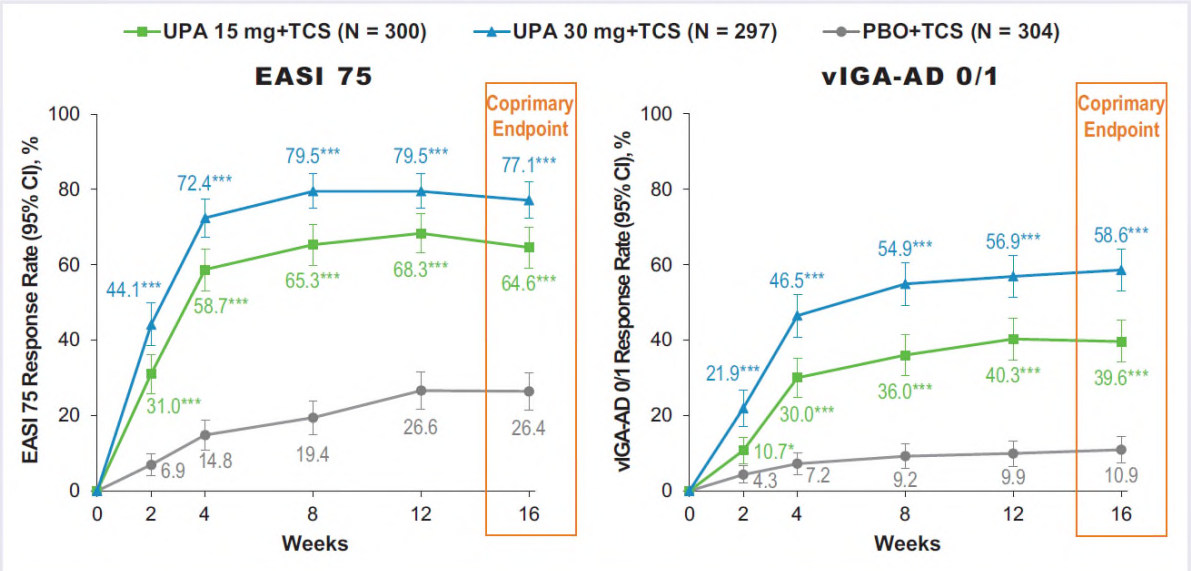


Figure 22. Kinetic co-primary endpoints EASI75 and vIGA-AD 0/1, AD-Up study

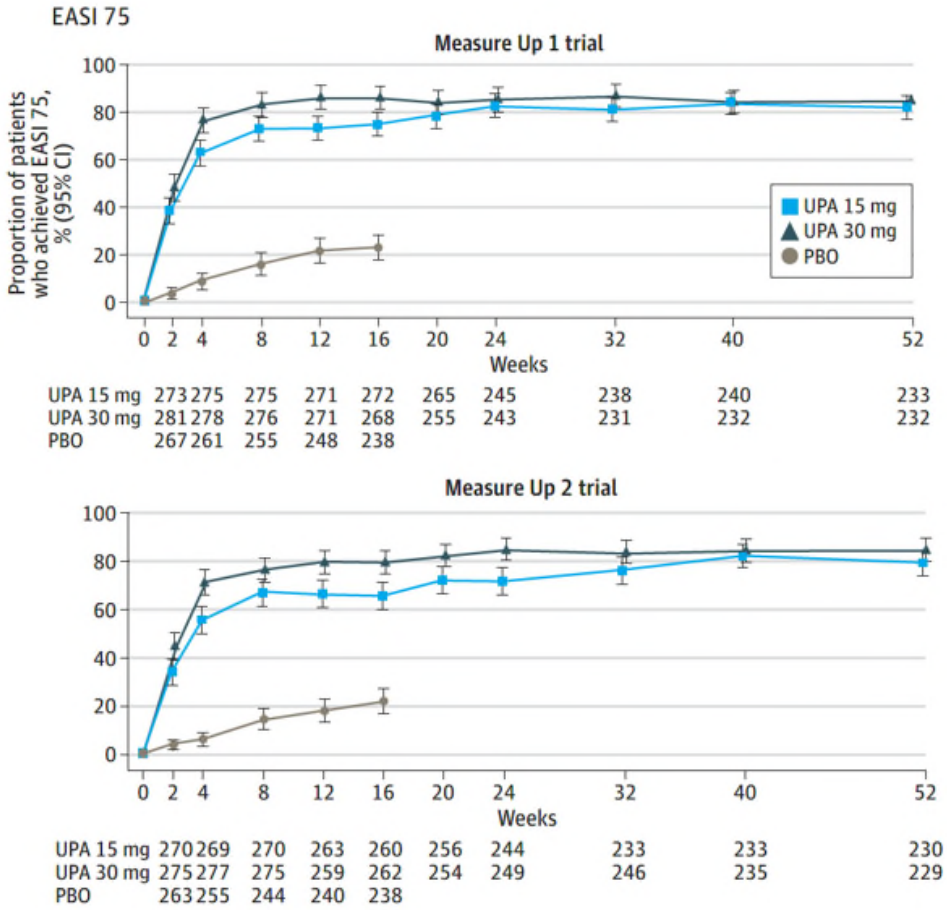
The data supports a rapid onset of effect, already significantly higher compared to placebo at week 1, and is fully achieved at week 8 to week 12. The effect is maintained through week 16 (Figure 21 and Figure 22).

The filed indication for upadacitinib is moderate to severe AD patients who are eligible for systemic treatment. In a subgroup analysis EASI75 response was assessed in patients with moderate disease defined as vIGA-AD <3 and patients with severe disease defined as vIGA-AD >4 at week 16. Regardless of disease severity the EASI75 response was similar between patients with moderate and severe disease, as shown in Figure 23.

Figure 23. EASI75 response in patients with moderate (left panel) and severe (right panel) AD. p <0.0001 for all comparisons versus placebo.

As shown in Figure 24 patients treated with active upadacitinib treatment, 15 mg and 30 mg, in the placebo period maintained the efficacy until week 52. For patients initially treated with placebo and then re-randomized to either 15 mg or 30 mg, patients reached the similar efficacy as the patients treated continuously with upadacitinib within a few weeks and maintained this efficacy until week 52 (131).

Figure 24. EASI75 response in pivotal studies at week 52, upper graph Measure Up 1, and bottom graph Measure Up 2 Up.



Results after 24 weeks in the Heads-UP study are show in the table below. As in the placebo-controlled studies, the effect is maintained through week 24. Dupilumab performs better in the Heads-UP trial compared to the placebo-controlled studies. One possible explanation is the difference in administration of dupilumab in the Heads-UP trial where dupilumab was administered in hospital by health care professionals. (130) The placebo-controlled studies likely give a better approximation of the efficacy in clinical practice.

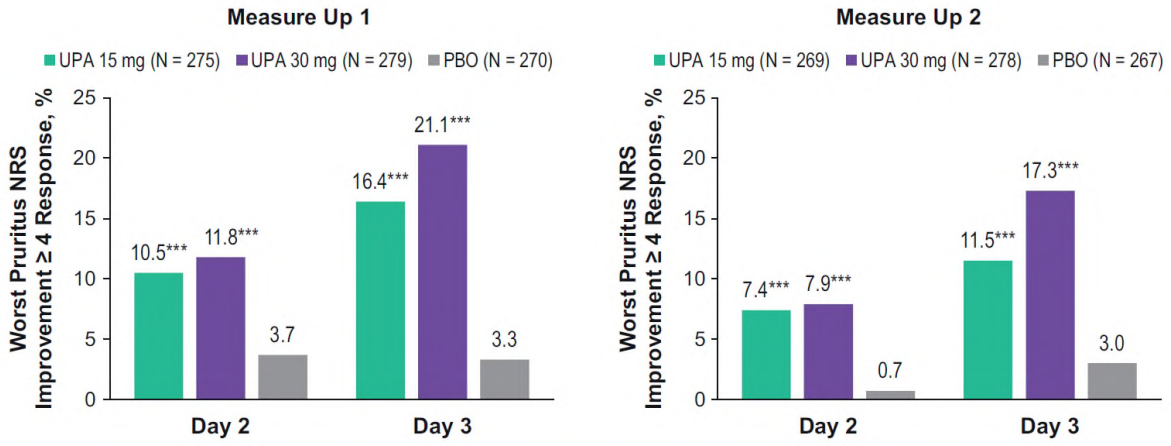
Table 17. Efficacy at week 24 in the Heads-Up study (Unranked) (130)

Endpoint	DUPI 300 mg (N = 344)	UPA 30 mg (N = 348)	Difference (*P* value)
Proportion of patients achieving EASI75 (%) [95% CI]	59.5 [54.4, 64.7]	64.2 [59.1, 69.2]	4.6 (0.211)
Proportion of patients achieving EASI90 (%) [95% CI]	47.6 [42.3, 52.9]	55.6 [50.4, 60.8]	8.0 (0.036*)
Proportion of patients achieving EASI100 (%) [95% CI]	13.1 [9.5, 16.6]	27.3 [22.6, 32.0]	14.8 (<0.001***)
Proportion of patients with Worst Pruritus NRS improvement ≥4[a] [95% CI]	41.9 [36.6, 47.1]	50.2 [44.8, 55.5]	8.3 (0.030*)

DUPI, dupilumab; UPA, upadacitinib; EASI, Eczema Area and Severity Index; NRS, numerical rating scale
[a]Analyzed for patients with Worst Pruritus NRS ≥4 at baseline, n=336 [DUPI] and n = 340 [UPA]
*: $P < 0.05$, ***: $P < 0.001$, UPA vs DUPI without multiplicity-control.

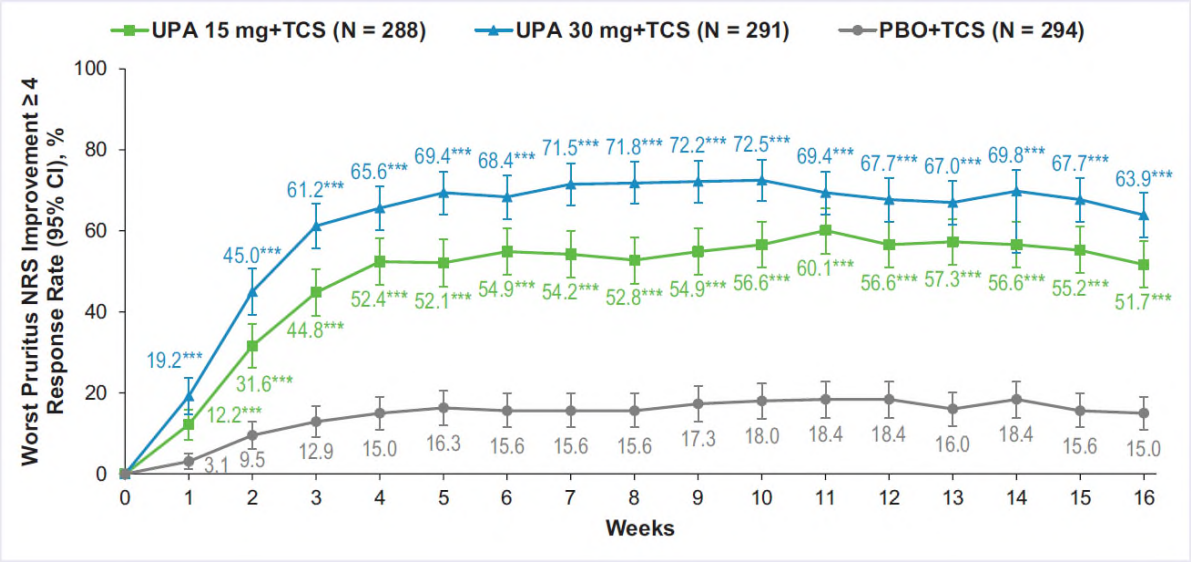
According to the patients the itch is the worst aspect of the disease.(132) Below is itch related PRO highlighted from the pivotal trials. In Figure 25 the improvement measured by a four-point reduction in worst skin itch is shown, which is deemed as clinical meaningful response. Twenty-four hours after the first dose patients treated with 30 mg upadacitinib, 8-12% had achieved improvement in worst pruritus NRS ≥ 4 and at 48 hours the patients treated with 30 mg upadacitinib 17-21% had achieved improvement in worst pruritus NRS ≥ 4. The corresponding numbers for the lower 15 mg dose was 7-11% and 12-16% respectively. In Figure 26 the kinetic for improvement in worst pruritus NRS ≥ 4 in the study AD-Up is shown. Already at week one upadacitinib shows significantly greater improvement compared to placebo, this increases until week 4 where it remains stable during the double blinded phase.

Figure 25 Kinetic of response MEASURE-Up 1 and MEASURE-Up 2, early improvement in worst pruritus NRS ≥ 4.



Based on ITT Population, NRI-C. Among patients with Worst Pruritus NRS ≥ 4 at baseline. Missing due to COVID-19, which were imputed by MI: 7 in Measure Up 1, 5 in Measure Up 2.
***$P \leq .001$ vs PBO; P values are multiplicity controlled only at day 2 for UPA 30 mg and only at day 3 for UPA 15 mg.
COVID-19, coronavirus disease 2019; ITT, intent-to-treat for the main study; MI, multiple imputation; NRI-C, nonresponder imputation incorporating MI to handle missing data due to COVID-19; NRS, Numerical Rating Scale; PBO, placebo; UPA, upadacitinib.

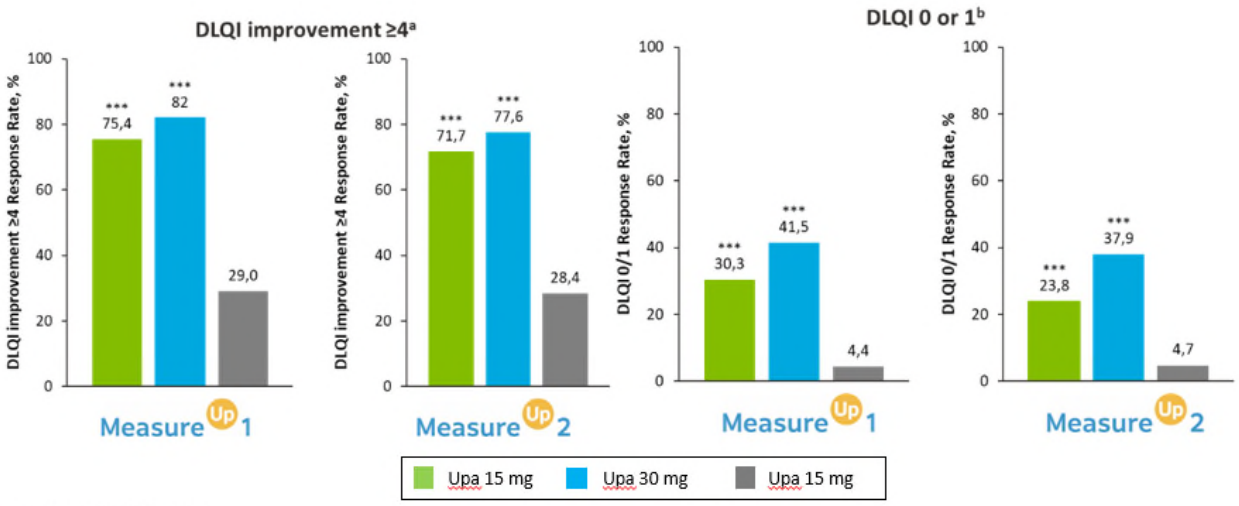
Figure 26. Kinetic of worst pruritus NRS improvement ≥ 4, AD-Up study



Based on weekly average. Among patients with Worst Pruritus NRS ≥4 at baseline. No data for Worst Pruritus NRS reduction ≥4 required imputation because of COVID 19.
***$P < .001$ vs PBO+TCS; P values were multiplicity controlled only for Weeks 1, 4, and 16; P values were nominal at all other time points.
ITT, intent-to-treat for the main study; NRI-C, nonresponder imputation incorporating multiple imputation to handle missing data because of coronavirus 2019; NRS, Numerical Rating Scale; PBO, placebo; TCS, topical corticosteroids; UPA, upadacitinib.

Overall, due to this unpredictable disease with amongst others intense pruritus, skin pain and sleep impairment the patient's quality of life is affected. Below, in Figure 27 are DLQI response at week 16 shown from the Measure-Up 1 and Measure-Up 2 studies. After 16 weeks of treatment clinical meaningful effect (DLQI improvement ≥4 from baseline) was achieved in 71,7-75,4 % of the patients receiving 15 mg upadacitinib and 77,6-82 % in the patients receiving upadacitinib 30 mg. Furthermore, for patients achieving DLQI 0/1, meaning no impact or little impact of their QoL, 37,9-41,5 % of patients receiving the upadacitinib 30 mg dose did achieve this, for the 15 mg upadacitinib dose this was achieved by 23,8-30,3 % of the patients.

Figure 27. DLQI response at week 16 shown from the Measure-Up 1 and Measure-Up 2(133)



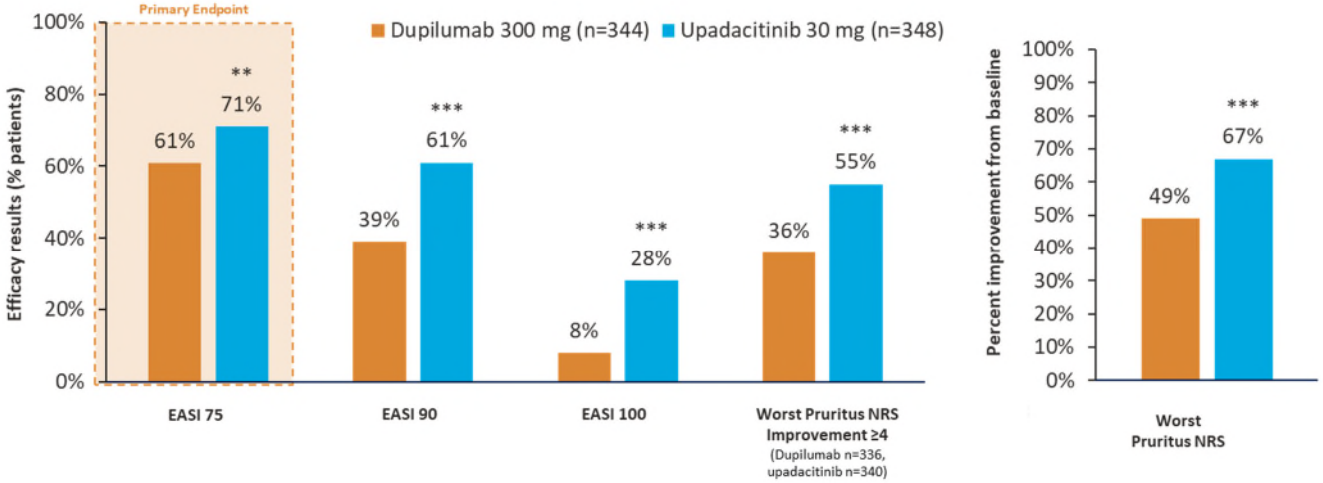
Based on ITT Population, NRI-C.

***P ≤ .001 vs placebo (multiplicity controlled)

[a]Among patients ≥ 16 years with DLQI ≥ 4 at baseline. Among patients ≥ 16 years with DLQI > 1 at baseline. COVID-19, coronavirus disease 2019; DLQI, Dermatology Life Quality Index; ITT, intent-to-treat for the main study; NRI-C, nonresponder imputation incorporating Multiple Imputation to handle missing data due to COVID-19

Upadacitinib has demonstrated statistically significant superior results in a direct comparison with dupilumab, in the Heads-Up study. The results for the primary and secondary outcomes are shown in Figure 28. Upadacitinib show significantly better results for EASI 75, and the difference between treatments is more pronounced for EASI 90 and EASI 100.

Figure 28. Primary and secondary endpoints in HEADS-Up



** *P* ≤ 0.01, *** *P* ≤ 0.001 vs dupilumab

EASI 75/90/100 is defined as at least a 75/90/100 percent reduction in Eczema Area and Severity Index.

Worst Pruritus NRS is defined as percent change from baseline in Worst Pruritus Numerical Rating Scale [NRS]

Worst Pruritus NRS improvement ≥4 is defined as an improvement (reduction) in Worst Pruritus NRS ≥4.

The endpoint was analyzed for participants with pruritus NRS ≥4 at baseline

1. https://news.abbvie.com/news/press-releases/rinvoq-upadacitinib-achieved-superiority-versus-dupixent-dupilumab-for-primary-and-all-ranked-secondary-endpoints-in-phase-3b-head-to-head-study-in-adults-with-atopic-dermatitis

Baseline patient characteristics in upadacitinib trials

The main inclusion and exclusion criteria for the pivotal studies were similar, and the patient characteristics are hence similar across trials as shown in Table 18 . To assess if the patient populations in the upadacitinib trials are relevant for the Danish clinical practice, a comparison has been done with the criteria used to decide if treatment with dupilumab should be initiated as recommended by DDS (please also refer to section 5). To start treatment patients should have tried and failed at least one systemic treatment and meet at least one of the following criteria of severity (DDS guideline):

- EASI > 16
- BSA > 10%
- and POEM > 16
- and DLQI > 10

The baseline characteristics of patients in Table 18 show that the mean severity-scores for patients in the upadacitinib trials are well above the criteria for severity to initiate advanced systemic treatment in Denmark. In addition to the characteristics shown in the table, about 50% of the patients in the pivotal studies had previously been treated with systemic treatment.(114, 115)

Table 18. Baseline patient characteristics in upadacitinib trials

	Measure Up 1			Measure Up 2			AD Up				Heads Up	
	PBO n= 281	UPA 15 mg, n=281	UPA 30 mg, n=285	PBO n=278	UPA 15 mg, n=276	UPA 30 mg, n=282	PBO + TCS n=304	UPA 15 mg + TCS n=300	UPA 30 mg + TCS n=297		DUPI 300 mg Q2W n=344	UPA 30 mg, n=348
Female, n (%)	137 (48.8)	124 (44.1)	130 (45.6)	124 (44.6)	121 (43.8)	120 (42.6)	126 (41.4)	121 (40.3)	107 (36.0)	**Female**, n (%)	150 (43.6)	165 (47.4)
Age, years, **mean** (range)	34.4 (12–75)	34.1 (12–74)	33.6 (12–75)	33.4 (13–71)	33.3 (12–74)	34.1 (12–75)	34.3 (12–75)	32.5 (13–74)	35.5 (12–72)	**Age**, years, **mean** (range)	36.9 (18–76)	36.6 (18–76)
Age group, n (%)										**Age group**, n (%)		
<18 years	40 (14.2)	42 (14.9)	42 (14.7)	36 (12.9)	33 (12.0)	35 (12.4)	40 (13.2)	39 (13.0)	37 (12.5)	<40 years	226 (65.7)	228 (65.5)
≥ 18 years	241 (85.8)	239 (85.1)	243 (85.3)	242 (87.1)	243 (88.0)	247 (87.6)	264 (86.8)	261 (87.0)	260 (87.5)	≥ 40- <65 years	101 (29.4)	102 (29.3)
										≥ 65	17 (4.9)	18 (5.2)
BMI, kg/m², **mean** (SD)	26.7 (6.3)	25.8 (6.1)	25.6 (5.9)	26.3 (5.7)	25.8 (5.6)	25.9 (5.8)	25.9 (5.7)	25.8 (6.2)	25.7 (5.4)	**BMI**, kg/m², **mean** (SD)	25.99 (5.7)	26.99 (6.5)
BSA affected, %, mean (SD)	45.7 (21.6)	48.5 (22.2)	47.0 (22.0)	47.6 (22.7)	45.1 (22.4)	47.0 (23.2)	48.6 (23.1)	46.7 (21.6)	48.5 (23.0)	**BSA affected**, %, mean (SD)	44.4 (22.8)	48.2 (24.0)
EASI, mean (SD)	28.8 (12.6)	30.6 (12.8)	29.0 (11.1)	29.1 (12.1)	28.6 (11.7)	29.7 (12.2)	30.3 (13.0)	29.2 (11.8)	29.7 (11.8)	**EASI**, mean (SD)	28.8 (11.5)	30.8 (12.5)
vIGA-AD, n (%)										**vIGA-AD**, n (%)		
Moderate (3)	156 (55.5)	154 (54.8)	154 (54.0)	125 (45.0)	126 (45.7)	126 (44.7)	141 (46.4)	143 (47.7)	140 (47.1)	Moderate (3)	171 (49.7)	174 (50.0)
Severe (4)	125 (44.5)	127 (45.2)	131 (46.0)	153 (55.0)	150 (54.3)	156 (55.3)	163 (53.6)	157 (52.3)	157 (52.9)	Severe (4)	173 (50.3)	174 (50.0)
Worst Pruritus NRS[a], mean (SD)	7.3 (1.7)	7.2 (1.6)	7.3 (1.5)	7.3 (1.6)	7.2 (1.6)	7.3 (1.6)	7.1 (1.6)	7.1 (1.8)	7.4 (1.6)	**Worst Pruritus NRS**[a], mean (SD)	7.5 (1.7)	7.4 (1.6)
DLQI, mean (SD)	17.0 (6.9)	16.2 (7.0)	16.4 (7.0)	17.1 (7.2)	16.9 (7.0)	16.7 (6.9)	16.3 (7.0)[b]	16.4 (7.2)[b]	17.1 (7.0)[b]	**DLQI**, mean (SD)	NR	NR
POEM, mean (SD)	21.5 (5.4)	21.2 (4.8)	21.4 (5.1)	21.9 (5.2)	21.2 (5.1)	21.8 (4.8)	21.1 (5.1)	21.0 (5.0)	21.5 (5.3)	**POEM**, mean (SD)	NR	NR

Proportion of patients reaching treatment goals as defined in Danish clinical practice.

The efficacy should be evaluated at 16 weeks after initiation of treatment. The criteria reaching treatment goals are (DDS):

- EASI 75 **or**
- At least 50% reduction of EASI compared to when treatment was initiated and at least 4-point reduction of DLQI

As discussed previously, most patients will have a sufficient response in monotherapy. The proportion of patients reaching **EASI 75** was 69.9 % (62.2 – 75.0) and 60.1 % (54.4 – 65.9) in patients treated with upadacitinib 15 mg, and 79.9 % (75.0-84.4) and 72.9 % (67.7 – 78.2) in patients treated with 30 mg in Measure-UP 1 and 2, respectively.(114) When pooling data from the two studies [redacted] of patients treated with 15 mg, and [redacted] in patients treated with 30 mg reached EASI 75. In Ad-Up 64,4 % (59,1 – 70,0) of patients treated with 15 mg and 77,1 % (72,3 – 81,9) of patients treated with 30 mg reached EASI 75. (115)

The proportion of patients on 15 mg upadacitinib reaching the composite endpoint of **EASI50 + ≤4-point reduction of DLQI** was [redacted] and [redacted] in Measure-UP 1 and 2, respectively. When pooling the data from two studies, about [redacted] of patients reached the treatment goals on 15 mg upadacitinib in monotherapy. The proportion is higher for 30 mg, [redacted] respective [redacted] in the two studies. Ad-UP show a higher proportion of patients reaching EASI50 + ≤4-point reduction of DLQI, [redacted] for 15 mg + TCS and [redacted] for 30 mg + TCS. (Abbvie Confidential Data)

These results show that most patients will reach the treatment goals used in Danish clinical practice treated with 15 mg upadacitinib in monotherapy. Patients not reaching the treatment goals can either add TCS to the treatment or increase the dose to 30 mg, which will increase the proportion of patients reaching treatment goals. Based on these data, an assumption is made that at least 70 % of patients will be treated with 15 mg in monotherapy when upadacitinib is used to treat AD in Denmark. Note that this is likely a conservative assumption, as in addition to the proportion reaching treatment goals, all patients aged 12 to 17 years and 65 years and older should be treated with 15 mg. Data from the Swedish prescription registry also supports the assumptions of the dose split. After the reimbursement decision in the end of January 2022, the proportion between the strengths, prescribed by dermatologists (which is seen as a proxy for patients with AD) is 82% 15 mg and 18% 30 mg for February and March. (Abbvie data on file)

Safety and tolerability

In the pivotal trials no new major safety risks were observed compared to the safety profile of upadacitinib in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Comprehensive data from each study is available in Appendix F.

At week 16, incidence of serious adverse events was similar across the pivotal trials ranging from 1.8-2.3 in the upadacitinib 15 mg arm, 1.3-2.8 in the upadacitinib 30 mg arm and 2.8-3.0 in the placebo arm. The most common TEAE reported included were acne, upper respiratory tract infection and nasopharyngitis. Acne was observed in the range of 6.8-12.7%, 13.8-17.2% and 2.0-2.2% in patients receiving upadacitinib 15 mg, upadacitinib 30 mg and placebo. The acne cases were mostly mild to moderate, often with a history of acne. There were few cases of eczema herpeticum, in the range of 0-1.0 in the upadacitinib 15 mg arm, 0-1.3 in the upadacitinib 30 mg arm and 0-1.4 in the placebo arm. Serious infections were reported by 0.4-1.0%, 0-0.7% and 0-1.0% in patients receiving upadacitinib 15 mg, upadacitinib 30 mg and placebo. There were no deaths or MACE reported in the pivotal trials. There was one case of VTE in placebo arm in the MEASURE-Up 2 study. (127, 128, 134-138).

In the HEADS-Up study, the safety profile of upadacitinib 30 mg was consistent with that previously reported in MEASURE-Up 1, MEASURE-Up 2 and AD-Up. Common AEs included acne and conjunctivitis for the upadacitinib and dupilumab group, respectively. Serious AEs were rare, occurring in 2.9% and 1.2% of patients receiving upadacitinib 30 mg and dupilumab 300 mg, respectively. Serious infections were again reported infrequently in both treatment groups, occurring in 1.1% and 0.6% of patients receiving upadacitinib and dupilumab. One treatment-emergent death due to bronchopneumonia was reported in upadacitinib while one non-melanoma skin cancer (NMSC) was reported in

the dupilumab treatment group. No malignancies were reported in patients receiving upadacitinib. No MACE or VTEs were reported in either treatment group.(139)

SOLO-1 and SOLO-2, Liberty AD CHRONOS and LIBERTY AD CAFÉ

Efficacy

From baseline to week 16, a significantly greater proportion of patients randomized to dupilumab achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of > 4 points on the pruritus NRS compared to placebo in all clinical studies, as summarized in Table 19 (108). Efficacy data is also available in Appendix D.

Table 19. Efficacy outcomes for dupilumab

Trial name	Treatment	4-point improvement in pruritis NRS	EASI-75	IGA 0/1
SOLO-1, wk 16	Dupilumab 300 mg Q2W	41%	51%	38%
	Dupilumab 300 mg QW	40%	52%	37%
	Placebo	12%	15%	10%
SOLO-2, wk 16	Dupilumab 300 mg Q2W	36%	44%	36%
	Dupilumab 300 mg QW	39%	48%	36%
	Placebo	10%	12%	9%
SOLO-CONTINUE, week 36	Dupilumab 300 mg Q8W	56%†	55%	33%
	Dupilumab 300 mg Q4W	49%†	58%	44%
	Dupilumab 300 mg Q2W	34%†	72%	54%
	Placebo	70%†	30%	14%
LIBERTY AD CHRONOS week 16/52	Dupilumab 300mg + TCS Q2W	59%/51%	69%/65%	39%/36%
	Dupilumab 300mg + TCS QW	51%/39%	64%/64%	39%/40%
	Placebo	19,7%/12,9%	23,2%/21,6%	12,4%/12,5%
LIBERTY AD CAFÉ Week 16	Dupilumab 300 mg Q2W + TCS	46%	63%	40%
	Dupilumab 300mg + TCS QW	40%	59%	39%
	Placebo	25%	30%	
LIBERTY AD OLE Week 52/76	Dupilumab 300 mg Q2W	65%/64%	87%/88%	56%/58%

QW: once every week; Q2W: once every two weeks; Q4W: once every four weeks; Q8W: once every eight weeks.
†Improvement in worst pruritus NRS≥3.

Safety and tolerability

In the clinical trials described above, there was no increase in infections or serious AEs (SAEs) compared with placebo.(123),(45, 122) In all the trials, conjunctivitis and injection-site reactions were significantly higher compared to placebo. In LIBERTY AD CAFÉ, conjunctivitis-related AEs were reported in 16% and 28% of patients for the 2 dupilumab plus topical corticosteroid treatment groups, compared to 11% of patients treated with just TCS.(123) In LIBERTY AD CHRONOS the incidence of conjunctivitis was 17.9% with dupilumab and topical corticosteroids treatment compared to 7.9% with topical corticosteroids and placebo, at week 52. In the SOLO trials, significantly higher rates of conjunctivitis were also observed with dupilumab monotherapy compared to placebo.

The safety profile of dupilumab has been established in long-term studies, with commonly reported treatment AEs including conjunctivitis, nasopharyngitis and injection site reactions. (122, 123, 140) SAE rates for dupilumab were low, and many of the reported SAE were related to disease flares (LIBERTY AD CHRONOS, Week 16 and 52). Comprehensive safety data from each study is available in Appendix F.

7.2 Comparative analyses of efficacy and safety

7.2.1 Method of synthesis

A network meta-analysis (NMA) is needed for the economic model assessing the value of upadacitinib for treating patients with moderate-to-severe AD. A clinical systematic literature review (SLR) was conducted that provide a published randomized clinical trials evidence base to assess the value of AbbVie's upadacitinib relative to dupilumab as treatment for adults with AD, please refer to section 6 for further information about the SLR and study selection. Details and results of this assessment using the SLR-produced evidence base via Bayesian network meta-analysis (NMA) are described here.

The primary study objective was to conduct an NMA to determine the comparative effectiveness of upadacitinib relative to dupilumab in patients with moderate to severe AD in the monotherapy setting. Analysis was also carried out for the comparative effectiveness of upadacitinib relative to dupilumab when combined with TCS. Published data from RCTs that were identified and extracted as part of a complete clinical SLR described in section 6 were utilized in the NMA. Data from eligible RCTs were collected using an Excel-based data extraction form. In addition to the outcomes of interest, study design and patient baseline characteristics were extracted to assess the comparability of studies and identify the presence of heterogeneity.

Phase 3 trials data were used for UPA and DUPI, with or without TCS. As described in section 6 data were identified in a SLR focused on published RCTs evaluating the efficacy and safety of competing interventions used for the treatment of moderate-to-severe AD and data extracted from UPA clinical trials. The full set of inclusion and exclusion criteria are available in Table 12. In studies, other that the upadacitinib pivotal trials, that assessed both licensed and unlicensed doses, unlicensed dose arms were excluded. Dose arms included in the NMA are shown in Table 20.

Table 20. Interventions and doses included in the NMA.

Treatment (Brand)	Admin	EMA-licensed dose(s) *unless otherwise indicated	Treatment dose(s) studied in RCTs	Code for treatment dose(s)
Upadacitinib (Rinvoq®)	Oral	15 mg QD (dose in trial)*	15 mg QD	UPA15
		30 mg QD (dose in trial)*	30 mg QD	UPA30
Dupilumab (Dupixent®)	SC injection	300 mg Q2W	300 mg Q2W	DUPI

Abbreviations: EMA=European Medicines Agency; QD=once daily; Q2W=every 2 weeks.

The common primary endpoint in the clinical trials were the percentage of patients reaching EASI75, and the clinical studies were powered to measure EASI75 versus placebo at week 16. EASI75 was therefore used as the primary endpoint also in the NMA. In addition, EASI50 and EASI90 were analyzed as part of the NMA. Outcomes were assessed at Week 16, defined as the primary endpoint timepoint in all studies. An intent-to-treat perspective was used so that the sample at randomization was used as the denominator in all analyses. All NMAs were conducted utilizing RCTs for AD where patients received upadacitinib, dupilumab or placebo (in monotherapy or in combination with TSC).

The NMA was developed based on methods considered valid by National Institute for Health and Care Excellence (NICE). (141-149)

7.2.2 Data imputation and assumptions

To prepare the extracted RCT data for NMA, the following data imputation and assumptions were made as needed per the Cochrane Handbook for Systematic Reviews of Interventions (150):

- If mean is missing and median is available: Assuming normality, the median was treated as mean.
- If standard error (SE) is missing and standard deviation (SD) is available: SE was obtained from the SD of a mean by dividing by the square root of the sample size (N).
- If SE and SD are missing and 95% confidence interval (CI) is available: SE was obtained from the 95% CI by dividing the width of the interval (upper limit to lower limit) by 3.92.
- If SE, SD, and 95% CI are missing and the interquartile range (IQR) is available: Assuming normality, SD was obtained from IQR using the following formula, where Q1 is the lower quartile and Q3 the upper quartile and σ is the SD:
- $\sigma = \frac{Q3-Q1}{2\times 0.6745}$
- If SE, SD, 95% CI and IQR are all missing: The highest SE from the other trials was used as a conservative estimate.
- If the "number of responders (n)" binary outcome is missing, but the proportion with response (%) and total sample size (N) are available: The n was imputed by multiplying % and N and rounding to the nearest integer.
- If outcomes plotted but no data values were published: Data values were extracted from graphs using the DigitizeIt digitizer software. (151)

All data imputation and assumptions were made prior to assessing the NMA feasibility.

7.2.3 Feasibility assessment

The feasibility of the NMAs based on the included RCTs was assessed as described in Cope et al. (2014).(152) First, the network connectivity of all included RCTs was checked and illustrated using a network plot, where each node represented a treatment regimen included in the network and lines represented direct comparisons between nodes. The networks are shown in Figure 29.

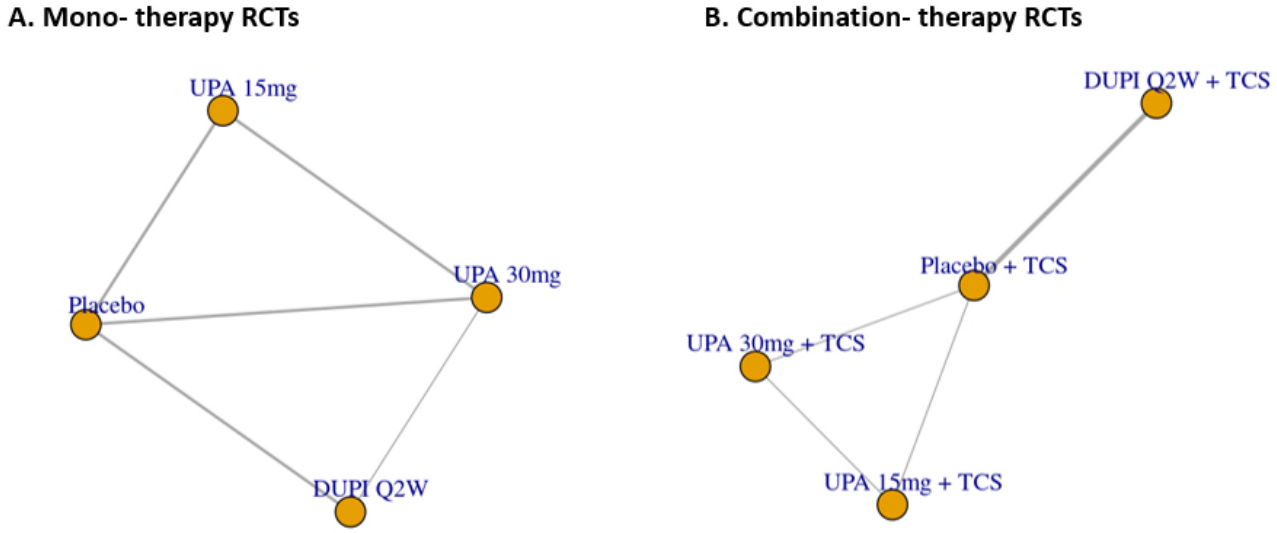


Figure 29. Network plots of monotherapy (a) and combination therapy (b), for all endpoints.

Then, relevant study and patient characteristics were considered and reviewed across the included RCTs to get a sense of their comparability and identify potential sources of cross-study heterogeneity. The following baseline

characteristics were identified a priori from published clinical research[1] (153-155) to be potential treatment effect modifiers:

- Age
- Gender
- Duration of disease
- Baseline severity (i.e., baseline EASI, baseline IGA, baseline Pruritus NRS)

Key baseline demographic and disease characteristics are provided in Appendix C and was used to perform a feasibility assessment. In the monotherapy network in the primary analysis of indirect treatment comparison the feasibility assessment found that age was similar between MEASURE UP1, MEASURE UP 2, HEADS UP, and SOLO 2 trials, whereas SOLO 1 included a slightly older population in the monotherapy network. Differences in age are not expected to impact results. The distribution of gender was comparable across trials. Disease duration across trials ranged from 18.8 to 28.0 years. Differences in disease duration remained small and are therefore not expected to impact results. Severity at baseline in respect key disease characteristics including EASI, IGA, PRS, and DLQI scores were similar across trials within the network.

For the additional analysis of the combination therapy average age was similar across trials, although the CHRONOS DUPI arm included a slightly older population. Differences in age are not expected to impact results. The distribution of gender was comparable across trials. All trials had a higher proportion of males compared to females with the proportion of males ranging from 59% to 64%. Disease duration was comparable across trials and ranged from 21.4 to 29.0 years. Studies with older patients also had higher reported disease duration. Differences in disease duration remained small and are therefore not expected to impact results. Severity at baseline in respect key disease characteristics including EASI, PRS, and DLQI scores were similar across trials within the network. There was a small proportion of patients with severe IGA in JADE-COMPARE, reflected by randomization criteria used in the trial. However, considering all other severity measures were comparable to remaining trials, differences in IGA alone would not be expected to impact results.

In summary, there appeared to be minimal cross-study heterogeneity with respect to baseline patient characteristics in the networks and it was not considered necessary to adjust for these characteristics in the analysis

7.2.4 Baseline risk adjustment

Baseline risk-adjusted sensitivity analysis was conducted that adjusted for differences in mean placebo effect across studies using code provided in NICE DSU TSD 3.(142) This adjustment captures many characteristics that are thought to modify the treatment effect, including those unmeasured or unknown, within a single measure. This is further described in Appendices K and L (section 3.3.5 in respective document).

[1] Gender, years since diagnosis and measures of severity including EASI, IGA, pruritus NRS have been identified as potential treatment effect modifiers in targeted literature review, including in: Chou JS, LeBovidge J, Timmons K, Elverson W, Morrill J, Schneider LC. Predictors of clinical success in a multidisciplinary model of atopic dermatitis treatment. Allergy & Asthma Proceedings 2011 Sep 1 (Vol. 32, No. 5); Bosma AL, Spuls PI, Garcia-Doval I, Naldi L, Prieto-Merino D, Tesch F, Apfelbacher CJ, Arents BW, Barbarot S, Baselga E, Deleuran M. TREatment of ATopic eczema (TREAT) Registry Taskforce: protocol for a European safety study of dupilumab and other systemic therapies in patients with atopic eczema. British Journal of Dermatology. 2020 Jun;182(6):1423-9; and Bosma AL, de Wijs LE, Hof MH, van Nieuwenhuizen BR, Gerbens LA, Middelkamp-Hup MA, Hijnen D, Spuls PI. Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry. Journal of the American Academy of Dermatology. 2020 May 30. Age is also tested as a potential treatment effect modifier given it is a key demographic.

7.2.5 Prior distributions

Per NICE DSU TSD2, vague or flat prior distributions were given to the parameters to be estimated by default.i For parameters assumed to be specified on a continuous scale, namely the relative treatment effects d, trial-specific baselines μ, and baseline adjustment regression term B (for models with baseline risk adjustment), a normal (0, 1002) prior distribution was used. For the between-study standard deviation σ (for RE models), a uniform (0, 5) prior distribution was used.

Posterior distributions were visually inspected for spikes and unwanted peculiarities. For the between-study standard deviation σ, posterior distributions were inspected for adequate posterior updating. In cases where the posterior distribution of σ appeared to include implausibly high values, likely when the number of units contributing to its estimation is small, a gamma (0.001, 0.001) prior distribution on the precision that gives a low prior weight to unfeasibly large σ on the logit scale was tested.

Uninformative priors were used in all NMA analyses for treatment effects [normal(0, precision=0.0001) and between-study heterogeneity, where applicable (uniform [0,5]).

7.2.6 Results from the comparative analysis

Separate results are presented for monotherapy and for treatment in combination with TCS. For each network, two models were investigated: fixed effects (FE), and random effects (RE). The FE model was selected in all analyses, which is further described in Appendices K and L (section 4.2 in respective document). As described in section 5.3.1, it is expected that 70% of the patient population will be treated with the lower dose of 15 mg, while 30% will use the higher dose of 30 mg. To reflect this distribution also in the efficacy analysis and to assess the relative effect of per label use of upadacitinib versus dupilumab, a weighted analysis was performed. For this analysis, the clinically relevant endpoint EASI-75 was used, and the appropriate odds ratios were derived from the standalone NMA analyses. The weighted analysis was performed using the Bucher method with bootstrapping to estimate weighted OR and SE, respectively.

Upadacitinib compared to dupilumab in monotherapy

The analysis evaluates treatment efficacy based on the expected dosing from the upadacitinib label compared to dupilumab. Building on the ORs from the NMA (given in Table 22 below) on the clinically relevant endpoint EASI-75, and using in label dosing, the OR (95% CI) was 1.42 (1.01, 1.99), demonstrating significantly superior efficacy of upadacitinib in an expected label dosing, when compared to dupilumab (Table 21).

Table 21. Odds ratio against dupi, EASI-75, monotherapy, FE model

	Odds Ratio (95% CI)	p-value
Weighted analyze per in label use (70% use of 15 mg and 30% of 30 mg)	[redacted]	[redacted]

Detailed results from the NMA in monotherapy are shown in the odds ratio league table in Table 22. Each cell presents the comparisons between the treatment presented in the relevant column versus the treatment specified in the row label. The odds ratio (OR) and 95% credible interval (CrI) comparison for each treatment versus all other treatments included are presented.

Table 22. Odds ratio league table, all endpoints, monotherapy, FE model.

EASI 75				
Odds Ratio (95% CrI)	**Placebo**	**DUPI Q2W**	**UPA 15mg**	**UPA 30mg**
Placebo				
DUPI Q2W				
UPA 15mg				
UPA 30mg				
EASI 90				
Odds Ratio (95% CrI)	**Placebo**	**DUPI Q2W**	**UPA 15mg**	**UPA 30mg**
Placebo				
DUPI Q2W				
UPA 15mg				
UPA 30mg				
EASI 50				
Odds Ratio (95% CrI)	**Placebo**	**DUPI Q2W**	**UPA 15mg**	**UPA 30mg**
Placebo				
DUPI Q2W				
UPA 15mg				
UPA 30mg				

Absolute response rates calculated in the NMA model using the estimated pooled placebo rate across all trials is presented in Table 23. The response rates for UPA 30mg was the highest at 72%, 60%, and 81% for EASI 75, EASI 90, and EASI 50, respectively. UPA 15mg had the second highest absolute rates of response, followed by DUPI. The response rates for EASI75 and EASI90 are used in the health economic analysis, see section 0.

Table 23. Percentage responding: all endpoints,monotherapy therapy, FE model

Treatment	EASI 75	EASI 90	EASI 50
Placebo			
DUPI Q2W			
UPA 15mg			
UPA 30mg			

Upadacitinib compared to dupilumab in combination with TCS

The analysis evaluates treatment efficacy based on the expected dosing from the upadacitinib label compared to DUPI in combination therapy. Building on the ORs from the combination NMA (given in Table 25 below) on the clinically relevant endpoint EASI-75, and using in label dosing, the OR (95% CI) was 1.22 (0.82, 1.81), demonstrating that upadacitinib in an expected label dosing, is as least equally effective as dupilumab (Table 24).

Table 24. Odds ratio against dupi, EASI-75, combination therapy, FE model

	Odds Ratio (95% CI)	p-value
Weighted analyze per in label use (70% use of 15 mg and 30% of 30 mg)		

Detailed results from the NMA including TCS are shown in the odds ratio league table in Table 25. Each cell presents the comparisons between the treatment presented in the relevant column versus the treatment specified in the row. The odds ratio (OR) and 95% credible interval (CrI) comparison for each treatment versus all other treatments included are presented in Table 25. Each cell presents the comparisons between the treatment presented in the relevant column label versus the treatment specified in the row label.

Table 25. Odds ratio league table, all endpoints, combination therapy., FE model

EASI 75				
Odds Ratio (95% CrI)	**Placebo + TCS**	**DUPI Q2W + TCS**	**UPA 15mg + TCS**	**UPA 30mg + TCS**
Placebo + TCS				
DUPI Q2W + TCS				
UPA 15mg + TCS				
UPA 30mg + TCS				
EASI 90				
Odds Ratio (95% CrI)	**Placebo + TCS**	**DUPI Q2W + TCS**	**UPA 15mg + TCS**	**UPA 30mg + TCS**
Placebo + TCS				
DUPI Q2W + TCS				
UPA 15mg + TCS				
UPA 30mg + TCS				
EASI 75				
Odds Ratio (95% CrI)	**Placebo + TCS**	**DUPI Q2W + TCS**	**UPA 15mg + TCS**	**UPA 30mg + TCS**
Placebo + TCS				
DUPI Q2W + TCS				
UPA 15mg + TCS				
UPA 30mg + TCS				

Absolute response rates calculated in the NMA model using the estimated pooled placebo rate across all trials are presented in Table 26. The response rates for UPA 30mg + TCS was the highest at 77%, 61%, and 89% for EASI 75, EASI 90, and EASI 50, respectively.

Table 26. Percentage responding: all endpoints, combination therapy, FE model.

	EASI 75	EASI 90	EASI 50
Placebo + TCS, % (95% CrI)	[redacted]	[redacted]	[redacted]
DUPI Q2W + TCS (95% CrI)	[redacted]	[redacted]	[redacted]
UPA 15mg + TCS (95% CrI)	[redacted]	[redacted]	[redacted]
UPA 30mg + TCS(95% CrI)	[redacted]	[redacted]	[redacted]

7.2.7 Relative efficacy of upadacitinib and dupilumab on POEM, DLQI and NRS.

In addition to EASI75, which measures the spread and severity of AD on the body, patient-reported outcomes such as POEM, DLQI and NRS are important to consider when comparing different treatments in AD. AD has a significant negative impact on the patient's quality of life. In the Danish treatment guidelines, patients who do not reach EASI 75 at evaluation after 16 weeks can stay on treatment if they reach the composite endpoint of EASI 50 and at least 4 point reduction of DLQI.

The change from baseline of Worst Pruritus NRS was measured in the direct comparison in the Heads-Up study. Upadacitinib shows statistically significant better efficacy compared to dupilumab, -66,88 vs -49,04, difference -17,84 (-23,17 to -12,50, P<0.001).

These outcomes has also been compared in naïve comparisons between dupilumab and upadacitinib are presented in Table 27 and Table 28 for monotherapy and combination therapy with TCS respectively. The comparison is carried out where possible, that is when the results from clinical trials are available for both upadacitinib and dupilumab.

For Worst Pruritus NRS the indirect comparison supports the findings in the direct comparison. The placebo adjusted response is – 24,3 and -29,1 for dupilumab in SOLO1 and SOLO2, versus -36,7 and - 34,2 for upadacitinib 15 mg and -45,9 and -49,4 for upadacitinib 30 mg in Measure UP 1&2. In combination with TCS the placebo adjusted response is -24,3 and -29,1 for dupilumab versus -34,2 and - 49,4 for upadacitinib 15 mg and 30 mg respectively in the AD-Up study. Regardless of dose or combination with TCS, upadacitinib performs better for change from baseline for Worst Pruritis NRS compared to dupilumab.

The placebo adjusted proportion of patients who had a ≥4-point improvement of DLQI from baseline to week 16 was 33 and 45 percentage points for dupilumab in SOLO1 and SOLO2 compared with 52,2 and 42,2 percentage points for upadacitinib 15 mg and 58, 6 and 54,8 percentage points for upadacitinib 30 mg in Measure UP 1&2. The placebo adjusted proportion of patients who had a ≥4-point improvement of POEM from baseline to week 16 was 41 and 48 percentage points for dupilumab in SOLO1 and SOLO2compared with 46,4 and 43,3 percentage points for upadacitinib 15mg and 53 and 49,2 percentage points for upadacitinib 30 mg in Measure UP 1&2. Apart from upadacitinib 15 mg in the Measure-UP 2 study and dupilumab in the SOLO 2 study (42,2 pp versus 45 pp) a higher proportion of patients reached a ≥4-point improvement of DLQI or POEM when treated with upadacitinib in the clinical studies.

Table 27. DLQI, POEM and NRS for upadacitinib and dupilumab when used in monotherapy.

	SOLO 1		SOLO 2		Measure Up 1			Measure Up 2			Heads-UP	
End Point	**Placebo**	**Dupi 300 mg**	**Placebo**	**Dupi 300 mg**	**Upa 15mg**	**Upa 30mg**	**Placebo**	**Upa 15mg**	**Upa 30mg**	**Placebo**	**Dupi 300mg**	**Upa 30mg**
DLQI score. ≥4-point improvement from baseline to week 16 — (%)	31%	64%	28%	73%	75.4 (70.1 – 80)	82.0% (77.3 – 86.7)	29.0 % (23.3 – 34.7)	71.7 % (66.1 – 77.39	77.6 % (72.5 – 82.5)	28.4 % (22.8 – 34)	-	-
Absolute responder rate vs placebo (percentage points)		33pp		45pp	46.4pp	53pp		43.3pp	49.2pp		-	-
POEM score. ≥4-point improvement from baseline to week 16 — (%)	27 %	68 %	24 %	72 %	75 % (69.9 – 80.1)	81.4% (79.6 – 86)	22.8% (17.8- 27.8)	70.9% (65.5 – 76.3)	83.5%. (79.1 – 88)	28.7 % (23.3% - 34.1)	-	-
Absolute responder rate vs placebo (percentage points)		41pp		48pp	52.2 pp	58.6 pp		42.2pp	54.8pp			
WP-NRS Change from baseline	-26.8	-51.1	-18.1	-47.2	-62.8 (-71.6 to -54.0)	-72.0 (-80.7 to-63.4)	-26.1 (-36.7 -15.5)	-51. (-55.8 to -46.6)	-66.49 (-71.0 to -62.0)	-17.04 (-22.4 to -11.7)	-49.04	-66.88
Absolute response vs placebo		-24.3		-29.1	-36.7	-45.9		-34.2	-49.4		-	-

Table 28. DLQI. POEM and NRS for upadacitinib and dupilumab when used in combination with TCS.

	CAFE		CHRONOS		Ad-UP		
End Point	**Placebo + TCS**	**Dupi 300 mg + TCS**	**Placebo + TCS**	**Dupi 300 mg+ TCS**	**Upa 15mg + TCS**	**Upa 30mg + TCS**	**Placebo+ TCS**
WP-NRS Change from baseline	-26.8	-53.9	-30.3	-56.6	-58.1 (-52.1 to -64.2)	-66.9 (-60.7 to -73.0)	-25.1 (-18.5 to -31.6)
Absolute response vs placebo		-28.5		-26.3	-33	-41.8	

7.2.8 Safety and adverse events comparison between upadacitinib and dupilumab.

Upadacitinib and dupilumab have different modes of actions and therefore different safety profiles. The safety profile for each treatment is described in section 7.1.2, and safety data from the clinical trials are available in Appendix F. To compare safety and adverse events profiles of upadacitinib, a comparison of the number of adverse events, serious adverse events, deaths and adverse events leading to treatment discontinuation is presented in Table 29 and Table 30 for both treatments in monotherapy and in combination with TSC. Both upadacitinib and dupilumab have similar rates of adverse and serious adverse events to placebo. Upadacitinib 30 mg have a slightly higher rate for any adverse event compared to placebo, but no difference for serious adverse events or events leading to discontinuation of study drug.

Table 29. Safety data for upadacitinib and dupilumab in monotherapy

Treatment	Study	Any adverse event	Serious adverse events	Adverse events leading to discontinuation of study drug	Deaths
Upadacitinib 15 mg	Measure Up 1	63%	2%	1%	0%
	Measure Up 2	60%	2%	4%	0%
Upadacitinib 30 mg	Measure Up 1	73%	3%	4%	0%
	Measure Up 2	61%	3%	3%	0%
Placebo	Measure Up 1	59%	3%	4%	0%
	Measure Up 2	53%	3%	4%	0%
Dupilumab 300mg	SOLO1	73%	3%	2%	0%
	SOLO2	65%	2%	1%	<1%
Placebo	SOLO1	65%	5%	1%	0%
	SOLO2	72%	6%	2%	0%

Table 30. Safety data for upadacitinib and dupilumab in combination with TCS

Treatment	Study	Any adverse event	Serious adverse events	Adverse events leading to discontinuation of study drug	Deaths
Placebo +TCS	Ad-UP	63%	3%	2%	0%
Upa 15 mg + TCS	Ad-UP	67%	2%	1%	0%
Upa 30 mg + TCS	Ad-UP	72%	1%	1%	0%
Placebo + TCS	Cafe	69%	2%	1%	0%
	Chronos	84%	5%	8%	0%
Dupilumab 300 mg +TCS	Café	72%	2%	0%	0%
	Chronos	88%	4%	2%	0%

Safety data was also collected in the Heads-UP trial and these observations were consistent with the known safety profile of each drug. The overall safety and most common adverse events (reported by ≥5% in either treatment group) is presented in Table 31. The rates of conjunctivitis, headache, nasopharyngitis were higher with dupilumab, while rates of acne, upper respiratory tract infection, and laboratory- test–related AEs were numerically higher with upadacitinib.

Table 31. Safety data from the Heads-UP trial

Patients, No. (%)	Dupilumab, 300 mg (n = 344)	Upadacitinib, 30 mg (n = 348)
AE	216 (62.8)	249 (71.6)
AE with reasonable possibility of being drug-related	122 (35.5)	153 (44.0)
Severe AE	14 (4.1)	25 (7.2)
SAE	4 (1.2)	10 (2.9)
SAE with reasonable possibility of being drug related	2 (0.6)	4 (1.1)
AE leading to discontinuation of study drug	4 (1.2)	7 (2.0)
AE leading to death	0	1 (0.3)
TEAEs reported by ≥5% in either treatment group		
Acne	9 (2.6)	55 (15.8)
Dermatitis atopic	29 (8.4)	24 (6.9)
Upper respiratory tract infection	13 (3.8)	22 (6.3)
Blood CPK level increased	10 (2.9)	23 (6.6)
Nasopharyngitis	22 (6.4)	20 (5.7)
Headache	21 (6.1)	14 (4.0)
Conjunctivitis	29 (8.4)	5 (1.4)

8. Health economic analysis

A cost-utility analysis (CUA) has been performed comparing the cost and QALY for treatment with upadacitinib and dupilumab for an average patient with moderate to severe AD.

Treatment attributes including efficacy for the patients with moderate and severe atopic dermatitis, and rate of adverse events (AEs) were derived from four pivotal clinical trials (Measure-Up 1 and 2 and SOLO-1 and 2). Efficacy from the head-to-head trial Heads-UP comparing upadacitinib and dupilumab was also included. For this population, the most relevant comparator is dupilumab, as dupilumab is recommended as standard treatment in Denmark.

Efficacy values at Week 16 for the moderate and severe patients were obtained from the clinical trials using the primary endpoint of the trials (EASI-75, a reduction of Eczema Area Severity Index by at least 75%). Also, efficacy values using EASI-90 was included to reflect the patients receiving better response.

Utility data for the model health states were derived from pooled data of all upadacitinib pivotal trials (Measure Up 1, Measure Up 2 and AD UP. Starting patient age in the model were based on the analysis of the pivotal clinical trials (Measure Up 1 and 2). A key aspect of the model is response status of the patient. This will influence continued treatment as well as have implications on the consumption of health care resources as well as on the patient health related quality of life. Although EASI-75 is the threshold for response and continued treatment, additional QALY gains for the proportion of patients reaching EASI-90 is also included.

Model results include direct medical costs, quality-adjusted life years (QALYs), incremental costs and QALY gains, and incremental cost-effectiveness ratios (ICER).

8.1 Model

A systematic literature review for non-clinical evidence was carried out and identified models evaluating the cost-effectiveness of treating patients with moderate to severe AD with advanced systemic treatment that had been accepted by reimbursement agencies. In addition, manual searches of the HTA-agencies in Denmark, Norway and Sweden were carried out to identify any additional relevant information. The model structure was selected following this systematic literature review of economic models in AD, and also to align with previous evaluations of AD (27, 57, 156, 157)

A combined decision tree and Markov model was determined to be the most appropriate modelling approach. A one-year decision tree capturing short-term treatment decisions and initial response to treatment is used in combination with a multi-responder Markov model reflecting the long-term course of AD with treatment response states starting from Year 2. After the first-year decision tree, the Markov cycles are one-year long, over a lifetime horizon defined as patients reaching 100 years of age as atopic dermatitis is a lifelong disease. A schematic of the model is provided in Figure 30 and Figure 31.

Efficacy values at Week 16 were derived from a NMA on the primary endpoint (EASI-75) of the pivotal clinical trials. Since upadacitinib will be available in two doses, efficacy for upadacitinib was weighted according to the expected use in clinical practice with has been derived using the results from clinical trials. The proportion (70%) of patients reaching the definition of response used in Danish clinical practice with 15 mg upadacitinib in monotherapy will receive 15 mg in the model and accruing health benefit and costs based on data for 15 mg from the clinical studies. The remaining 30 % of patients will be treated with 30 mg upadacitinib in the model. Other parameters such as health care resource use for controlled and uncontrolled AD were derived from the Swedish clinical inputs and validated by a

Danish clinician(157). Data on treatment specific discontinuation was obtained from the NICE assessment of dupilumab (156).

As depicted in Figure 30, patients with moderate to severe AD who are candidates for systemic treatment enter the model where they may either be treated with UPA or DUPI. At week 16, a clinical assessment is undertaken to dichotomize patients by response status. The criterion for response in the model is based on a reduction of at least 75% in Eczema Area Severity Index (EASI) score from baseline. This is a suitable modelling approach in relation to Danish clinical practice, where EASI 75 is used to define response to treatment at the latest at 16 weeks after treatment initiation (54).

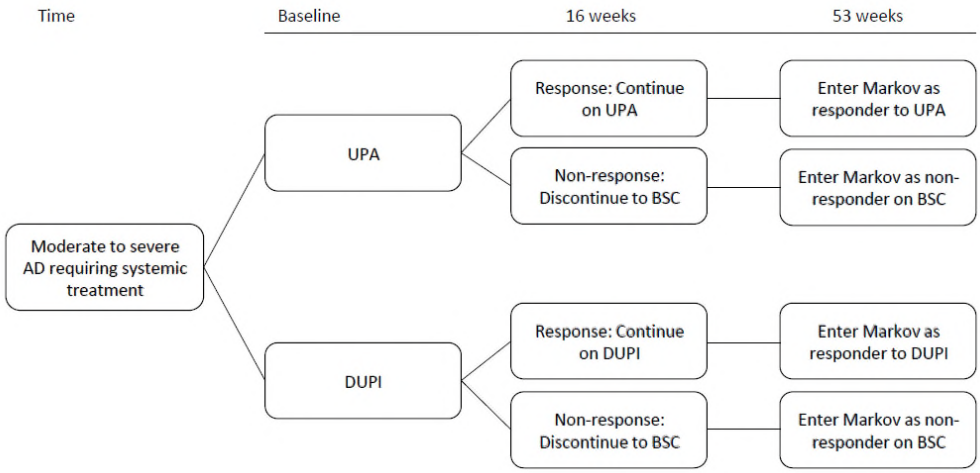


Figure 30. Short-term decision tree

AD, atopic dermatitis; BSC, best supportive care; UPA, Upadacitinib, DUPI, Dupilumab.

Responders are further categorized in EASI-75 and EASI-90. Responders (EASI-75 and EASI-90) will continue with active treatment (upadacitinib or dupilumab). Non-responder will discontinue treatment with upadacitinib or dupilumab and receive best supportive care (BSC). Responders to UPA or DUPI continue treatment for the remainder of the year and remain in the "EASI-75 health state". Non-responders discontinue to BSC and are assumed to be BSC non-responders in line with the NICE assessment of dupilumab (156)

Despite the first decision node being at Week 16, clinical trials often collect efficacy data at various timepoints, to demonstrate that patients exhibit response sooner. As such, for each comparator, the benefits of response start once half (50%) of the EASI-75 response at Week 16 is reached. In line with results from the pivotal trials, patients treated with UPA show an early response at 2 weeks (Measure Up 1 and 2) while the corresponding number for DUPI is four weeks (SOLO-1 and 2). Finally, a background mortality rate is assumed to occur at 6 months (not shown in Figure 30 for simplicity).

Based on 16-week data, responders enter the Markov part of the model designated as responders on either UPA or DUPI. If response is lost, patients enter the Markov model in the "non-responders" state. Within the Markov model (see Figure 31), at the end of each year-long cycle, patients can remain responders, discontinue treatment (from UPA or DUPI) and move to BSC, or die. Once a patient has entered BSC, no return to active treatment is possible. Death is an absorbing health state that is accessible from any model state.

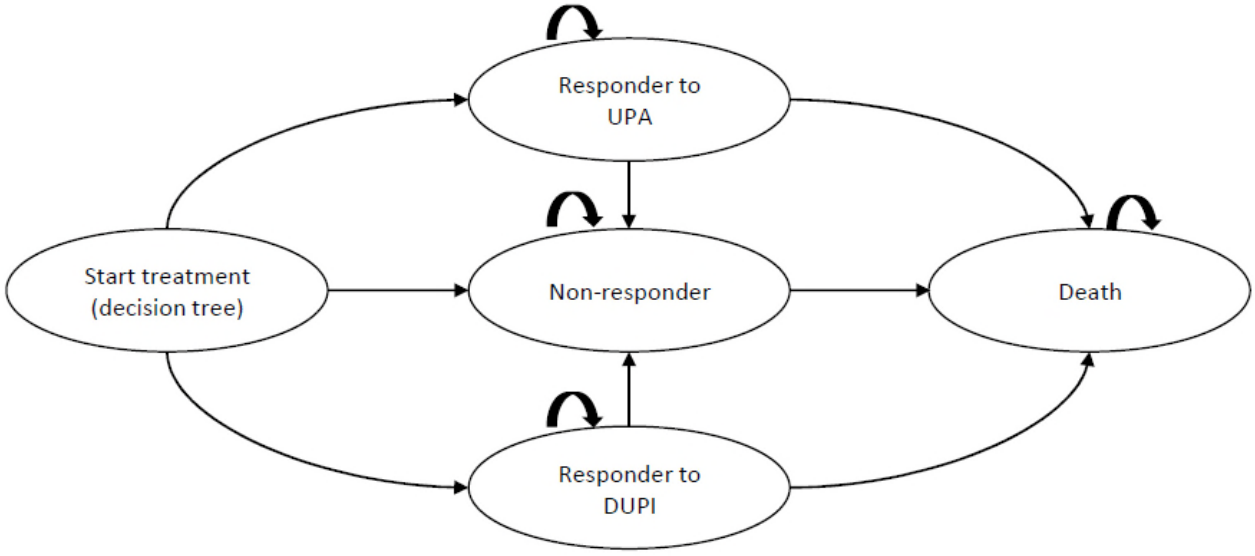


Figure 31 Long-term Markov model

BSC, best supportive care; UPA, Upadacitinib; DUPI, Dupilumab

For patients who initiated on UPA or DUPI and who were initial responders, discontinuation may occur for a variety of reasons: lack of long-term efficacy, adverse events (AEs), patient preference, or physician preference. Upon discontinuation, patients move to BSC and are categorized as non-responders, accruing the utility of a non-responder.

There is no discontinuation from BSC but in subsequent years, a waning effect for BSC dictates a return to baseline utility level. To avoid double counting, no waning is included for UPA or DUPI. Instead, discontinuation is assumed to also cover loss of efficacy.

The modelling was based on the Danish health care system. The base case was analysed from the limited societal perspective, including travel costs and patient costs but without costs for productivity loss. The effect of including cost for productivity losses were investigated in a scenario analysis. The model allocates costs for active treatment (upadacitinib or dupilumab), administration, adverse events, patient costs, as well as treatment-related costs and monitoring. Separate costs are included for controlled (responders) and uncontrolled (non-responders) patients. Adverse events do not accrue disutilities in this model as utilities are trial-based, and thus, adding additional disutilities for the AEs risks double counting. As dupilumab is an injection treatment, the model includes a treatment-related disutility for dupilumab.

Finally, general population mortality adjusted by age and gender is applied in the model with no adjustment for AD response or treatment. Death is the absorbing health state in the model. Patients may transition to death from any of the a forementioned states. All-cause mortality risk is derived from Danish life tables and is assumed to be unaffected by the choice of treatment for AD or by the condition itself.

Costs and QALYs accrued after the first year are discounted at an annual rate of 3.5% and 2.5% after 35 years. The model estimates total lifetime costs and total lifetime QALY gains for each treatment arm.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Clinical inputs to the model included data on treatment efficacy, adverse events, discontinuations, and population demographics. Data on treatment efficacy, and adverse events were obtained from the clinical trials Measure Up 1 and 2 and SOLO-1 and SOLO-2 and an indirect comparison (NMA) was used. Data on patient age were sourced from the Measure Up 1 and 2 trials while an equal gender distribution was assumed to adhere closely to the relevant situation in Denmark.

Both upadacitinib and dupilumab can be used with or without concomitant use of TCS. For the cost-utility analysis to show outcomes most likely to reflect use in clinical practice in Denmark, the real-world use of TCS in Danish clinical practice was investigated, as described in Current treatment options and choice of comparator(s). The results indicate that even though TCS use is common, most patients are infrequent users of TCS. For patients with moderate to severe disease who are treated with systemic treatments it is more common to be treated in monotherapy than with in combination with TCS. TCS use also decrease after patients are referred to hospitals – where treatment with upadacitinib and dupilumab are to be initiated. In summary, use of TCS in clinical practice in Denmark is intermittent rather than prespecified, to be less for patients with systemic treatment compared with systemic treatment alone and to decrease after hospital referral. The need for TCS use together with systemic treatment is assumed to be decreasing with the advanced systemic treatments, compared to the conventional systemic treatments. In addition, adherence to topical treatments have been shown to be poor in clinical practice compared to the clinical trial setting.

Because of this, the available evidence most likely to reflect the difference between upadacitinib and dupilumab when used in clinical practice in Denmark is the NMA carried out with studies of upadacitinib and dupilumab in monotherapy. The use of TCS as a rescue treatment in these monotherapy studies reflect use in clinical practice better than the TCS use by a predefined treatment schedule as in the combination studies.

Week 16 treatment efficacy

The proportion of patients achieving response at Week 16 used in the health economic model is obtained from evidence synthesized via a network meta-analysis (NMA), described in section 7.2 above. The relevant clinical trials are listed in Table 14 in section 6.2. and further described in section 7.1 and in Appendices.

The results of the NMA are shown in Table 32 which present the proportions of patients achieving EASI-75 and -90 used in the Cost utility model.

Table 32. EASI response at Week 16 in the base case.

Treatment	Percentage of patients achieving EASI response (%, [95% CrI])	
	EASI-75	EASI-90
UPA 15 mg	61.3 (53.5, 68.7)	46.5 (36.9, 56.6)
UPA 30 mg	71.8 (65.3, 77.6)	60.4 (51.1, 69.1)
DUP	56.3 (48.4, 64.1)	36.0 (27.5, 45.6)

CrI, credible interval; DUP, dupilumab; EASI, Eczema Area Severity Index; UPA, upadacitinib.

Discontinuation

Starting from the second year of the model, the model includes an annual rate at which responder patients discontinue treatment (except BSC, which is continued throughout the lifetime) due to various reasons (e.g., lack of

long-term efficacy, AE, patient preference, physician preference). This rate of discontinuation is applied to patients in the "Responder" health state of the Markov model. Patients who discontinue treatment enter the "Non-responders utility" health state. While it is possible that discontinuation rates may differ according to the choice of treatment, there are currently insufficient data to account for treatment-specific discontinuation rates. In fact, discontinuation data of the treatments included in our model are primarily available from their respective randomized clinical trials, most of which are 16-week studies. As such, the same annual discontinuation rates across all monotherapy treatments are based on the NICE evaluation on dupilumab (TA534) and is 6.3 % per year of all treatments.

Waning

Treatment discontinuation (see section 7.2.2) accounts for loss of efficacy for UPA and DUPI but no discontinuation occurs for BSC in the model. Instead, BSC efficacy is assumed to wane over time. A significant proportion of patients on BSC in the placebo arms of the Measure Up 1 and 2 trials achieved treatment response (EASI-75). This is likely a protocol driven effect related to improved adherence to topical treatments, which would not be observed outside the trial setting. As such, these benefits are assumed to diminish ove6
r time as and the cumulative proportion of patients losing response is shown in Table 33.

Table 33: Waning of BSC efficacy

Year	Cumulative proportion	Reference
Year 2	83.6%	(156)
Year 3	88.8%	
Year 4	92.5%	
Year 5	93.8%	
Year 6	96.5%	
Year 7+	96.5%	

BSC, best supportive care; EASI, Eczema Area Severity Index; UPA, upadacitinib

Flares

Due to a lack of data from a Danish setting, annualized event rates for flares were obtained from the NICE assessment of dupilumab and was estimated to 0.18 for patients on UPA and DUPI and 0.78 for patients on BSC, respectively (156) The rate used were identical to that used for dupilumab.

Adverse events

The AEs considered in the model are extracted from Measure Up 1 and 2 and SOLO-1 and SOLO-2. Table 34 present AE data applied in the model for UPA 15, UPA 30, DUPI and BSC, respectively.

Table 34: Adverse event rates

Adverse event	UPA 15	UPA 30	DUPI	BSC
Allergic conjunctivitis	0.36%	0.35%	3.01%	0.79%
Injection site reaction	0.00%	0.00%	10.97%	0.00%
Infectious conjunctivitis	0.54%	0.88%	4.30%	0.99%
Oral herpes	2.15%	4.23%	3.66%	1.18%
Herpes zoster	1.97%	1.59%	0.22%	0.39%
Adjudicated MACE	0.00%	0.00%	0.00%	0.00%
Adjudicated VTE	0.00%	0.00%	0.00%	0.10%

Malignancies excl. NMSC	0.00%	0.53%	0.00%	0.00%
Acne	9.69%	15.87%	0.00%	1.18%
Nasopharyngitis	6.82%	8.99%	9.03%	6.70%
Upper RTI	7.90%	9.70%	2.80%	4.14%

BSC, best supportive care; excl., excluding; MACE, major adverse cardiac events; NMSC, nonmelanoma skin cancer; RTI, respiratory tract infection; UPA, upadacitinib; VTE, venous thromboembolic events.

Patient population

The model considers patients from 12 years of age with moderate to severe AD who are candidates for systemic treatment, that is the same population for which Rinvoq is approved. The clinical data from Measure UP 1 and 2 are included in the NMA analyses used in the model. As seen in Table 35, a comparison between the baseline patient characteristics in these trials for EASI, PSA, DLQI-score and POEM score, and the criteria used for treatment initiation in Danish clinical practice show that patients in the Measure UP 1 and 2-trials would be treated with advanced systemic treatment in Denmark, as patients in the clinical trials have higher scores (more severe) than the Danish guidelines require to initiate treatment.

Data on age for patients with moderate to severe AD in Denmark have been identified for the adult population, see Table 35. Considering that Rinvoq will be used from age 12, the mean age of patients in the clinical practice will be the model base-case. In line with the patient population included in the Measure Up 1 and 2 trials, the mean age of the patients was 33.8 years. There are no gender differences in any of the model inputs except mortality, an equal gender distribution have been used.

Table 35. Comparison between the baseline patient population in clinical trials and Danish clinical practice.

	MEASURE UP 1			**MEASURE UP 2**			**DDS (54)**	**Treatment of adult atopic dermatitis (58) Moderate/severe***	**AbbVie report Danish Skin Cohort Moderate/severe***
	PBO	**UPA 15 mg**	**UPA 30 mg**	**PBO**	**UPA 15 mg**	**UPA 30 mg**			
Age – years	34.4 (12-75)	34. (12-74)	33.6 (12-75)	33.4 (13-71)	33.3 (12-74)	34.1 (12-75)		46. 0 (13.7)/ 47.3 (15.1)	45.2 (34.9; 55.0)/ 46.2 (33.8; 58.6)
Gender (male) n (%)	144 (51%)	157 (56%)	155 (54%)	154 (55%)	155 (56%)	162 (57%)		31.9%/ 32.2%	31.8% / 31.4%
Duration of AD – years	21.3 (15.9)	20.5 (14.3)	20.4 (15.3)	21.1 (13.6)	18.8 (13.3)	20.8 (14.3)			39.6 (28.8; 49.9) 39.1 (27.1; 50.9) (SD)
EASI	28.8	30.6	29.0	29.1	28.6	29.7	> 16		
DLQI score	17.0	16.2	16.4	17.1	16.9	16.7	> 10	6.7(5.0)/	

	(6.8)	(7.0)	(7.0)	(7.2)	(7.0)	(6.9)		12.2(6.0)	
POEM score	21.5 (5.4)	21.2 (4.8)	21.4 (5.1)	21.8 (4.8)	21.2 (5.1)	21. (5.2)	> 16		
BSA, %	45.7 (21.6)	48.5 (22.2)	47.0 (22.0)	45.1 (22.4)	45.1 (22.4)	47.6 (22.7)	> 10%	17.9 (24.2)/ 41.3 (32.7)	

**Based on Scorad*

Intervention

Upadacitinib is available in two doses (15 mg and 30 mg), where the lower dose is considered the standard starting dose and maintenance dose according to dosing instructions and clinical expertise. Therefore, a distribution between patients using the lower dose of 15 mg daily and the higher dose of 30 mg daily can be expected.

In Danish clinical practice, the efficacy should be evaluated at 16 weeks after initiation of treatment. The criteria reaching treatment goals are (54):

- EASI 75 **or**
- At least 50% reduction of EASI compared to when treatment was initiated and at least 4-point reduction of DLQI.

The results for these outcomes presented in Table 36 show that most patients will reach the treatment goals used in Danish clinical practice and will continue treatment, when treated with 15 mg upadacitinib in monotherapy. Based on this data, an assumption is made that at least 70 % of patients will be treated with 15 mg in monotherapy when upadacitinib is used to treat AD in Denmark. Note that this is likely a conservative assumption, as in addition to the proportion reaching treatment goals, all patients aged 12 to 17 years and 65 years and older should be treated with 15 mg. Data from the Swedish prescription registry also supports the assumptions of the dose split. After the reimbursement decision in the end of January 2022, the proportion between the strengths, prescribed by dermatologists (which is seen as a proxy for patients with AD) is [redacted] and [redacted] for February and March. (Abbvie data on file).

Table 36. Proportion of patients reaching the criteria for response according to Danish treatment guidelines.

Definition of response (54):	**Measure-Up1**	**Measure-Up2**	**Measure-Up1**	**Measure-Up2**	**Ad-UP**	
	15 mg		30 mg		15 mg	30 mg
EASI 75	69.9 % (62.2 – 75.0)	60.1 % (54.4 – 65.9)	79.9 % (75.0-84.4	72.9 % (67.7 – 78.2)	64,4 % (59,1 – 70,0)	77,1 % (72,3 – 81,9
EASI50 + ≤4-point reduction of DLQI:	71.3 % (65.5 to 77.1)	63.7% (57.6 to 69.8)	79.9 % (74.8 to 85.0)	74.2% (68.6 to 79.8)	75.4 % (70,0 to 80,7)	82,0% (77,3, to 86,8)

To reflect this, a mixed analysis, taking a weighted average of cost and benefits for UPA 15 and UPA 30, is presented as the base case. For this weighted analysis, a conservative assumption of a 70% - 30% distribution between 15 mg and 30 mg is used. Se further information on the distribution in section 5.3.1 and 7.1.

Comparators

The model uses dupilumab as comparator. Dupilumab is dosed as an introduction dose 600 mg and after that every other week 300 mg subcutaneous. For patient weight under 60 kg an introduction dose of 400 mg should be used, and 200 mg every other week. However, most patient in Danish clinical practice will weight above 60 kg. The cost for the doses are the same (57). The efficacy from the pivotal trials SOLO-1 and 2 was included in the NMA.

8.3 Extrapolation of relative efficacy

No extrapolations are used in the model.

8.4 Documentation of health-related quality of life (HRQoL)

In accordance with DMC guidelines, health effects in the economic evaluation are expressed in terms of QALYs, which account for both health-related quality of life and life expectancy.

Utility data was collected in Measure Up 1 and 2 and Ad-UP, and assessment from patients with data from both baseline and the study visit at week 16 are used in the analysis, see data in Table 37. The number of patients with data for both baseline and week 16 are lower in the placebo group. The analyses used a Mixed Model Repeated Measures (MMRM) where patients contribute all their available data post-baseline. This assumed data missing at random.

Table 37. EQ-5D-5L data collected at baseline and week 16

EQ-5D-5L Index, Baseline and week 16 (visit mean)				Within Group Difference			Between Groups Difference			
				---- Change from Baseline ----			---------- Compared to Placebo ----------			
	N	Baseline Mean	Visit Mean	LS Mean	[95% CI]	SE	LS Mean	[95% CI]	SE	P-value
Measure-UP 1										
XXXXX	[redacted]									
XXXXXXXX	[redacted]									
XXXXXXXX	[redacted]									
[redacted]										
Placebo	[redacted]									
UPA 15 mg	[redacted]									
UPA 30 mg	[redacted]									
AD-Up										
Placebo + TCS	[redacted]									
UPA 15 mg QD + TCS	[redacted]									
UPA 30 mg QD + TCS	[redacted]									

Utility data was obtained from pooling data from all the pivotal trials. Utility data were analyzed using Ordinary Least Squares (OLS) regression ('reg' in STATA). The best fitting model according to Aikake's Information Criterion (AIC) was a model with only EASI response as a covariate. A complete case analysis was performed where only patients with available utility data at baseline and week 16 were included in analysis to determine health-state utility values.

The Furnival-Wilson leaps-and-bound algorithm was employed to determine the specification with the best goodness-of-fit using the 'gvselect' command in STATA. STATA 'gvselect' performs best subsets variable selection. The Furnival-Wilson leaps-and-bounds algorithm is applied using the log likelihoods of candidate models, allowing variable selection to be performed. This method is described in Lawless and Singhal. The log likelihood, Akaike's information criterion, and the Bayesian information criterion are reported for the best regressions at each predictor quantity. Essentially, the algorithm runs through a series of forward selection procedures to find the best fitting model. (158).

The following covariates were included in the selection process in addition to response levels used in the base case analysis (i.e., EASI-50, -75 and -90):

- Baseline utility
- Baseline EASI level
- An indicator for whether the patient had TCI/TCS intolerance
- An indicator for whether the patient was an adult (>18 years of age)
- An indicator for whether the patient was considered to have severe AD at baseline
- An indicator for whether the patient was female
- Patient age

Based on the Akaike's information criterion (AIC) and Bayesian information criterion (BIC), the best-fit version of the model included baseline utility and the indicators for response levels (EASI-50, -75, and -90). Using the coefficients for covariates included in the final best-fit model and the baseline patient characteristics, utility values for all health states were calculated. The EQ-5D-5L instrument was valued using the DK tariff (164) in line with the DMC guidelines.

8.4.1 Overview of health state utility values (HSUV)

The analysis described above results in the below health stare utility values (Table 38). Please not that these health states are not all used in the model, but are included here to present a complete description.

Table 38. Health state utility values

	Results, mean (SD)	Description	Used in model	Instrument	Value set	Reference
Baseline	[redacted]	Mean value of all observations at baseline	Yes	EQ-5D-5L	DK	AbbVie Confidential Data
Overall Week 16	[redacted]	Mean value of all observations at 16 weeks	Yes	EQ-5D-5L	DK	AbbVie Confidential Data
EASI-50	[redacted]	Mean value of all patients reaching EASI50	No	EQ-5D-5L	DK	AbbVie Confidential Data
EASI-75	[redacted]	Mean value of all patients reaching EASI75	Yes	EQ-5D-5L	DK	AbbVie Confidential Data
EASI-90	[redacted]	Mean value of all patients reaching EASI90	Yes	EQ-5D-5L	DK	AbbVie Confidential Data

Non-responders EASI50	[redacted]	Mean value of patients not reaching EASI 50	No	EQ-5D-5L	DK	AbbVie Confidential Data
Non-responders EASI75	[redacted]	Mean value of patients not reaching EASI 75	Yes	EQ-5D-5L	DK	AbbVie Confidential Data

8.4.2 Health state utility values used in the health economic model

Although EASI-75 is used as the threshold for response and for continued treatment, some patients will achieve an even better outcome and reach EASI-90. Reaching EASI-90 does not affect health care resource use but will provide additional utility gain. To address this, the utility from reaching EASI-75 [redacted] and EASI-90 [redacted] was weighted according to the proportion of responders reaching EASI-75 and EASI-90 for each treatment option (Table 39). Hence, the utility for reaching a specific response state is independent on treatment but the proportion of patients in different response states is determined by treatment choice, thus affecting responder utility for each treatment.

Table 39: Calculation of weighted responder utilities

	Utility from UPA trials		Efficacy		Proportion of responders		Weighted responder utility
Treatment	**EASI-75**	**EASI-90**	**EASI-75**	**EASI-90**	**EASI-75**	**EASI-90**	
UPA 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 30			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DUPI			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC, best supportive care; EASI, Eczema Area Severity Index; UPA, upadacitinib.

Since data on health utilities were collected in the clinical trials, no disutilities for adverse events was included in the model. The assumption was made that there is no difference in how adverse events impact health utilities between upadacitinib and dupilumab. However, upadacitinib has a more favourable route of administration. It has been shown that the route of administration has an impact in quality of life and administration of drug via injection has a negative impact. The model includes a disutility for injection for dupilumab based on a study investigating the preferences for different type of administration of biological treatments. The study derives the utilities associated with the route, frequency and location of administration, independent of the disease area. The resulting utility loss for subcutaneous injection at home every 2 weeks is applied for dupilumab in the model (159)

The threshold for response is set to EASI75 to in accordance with the Danish clinical practice. Utility was related to treatment response, non-responder, EASI-75 or EASI-90, and was assumed to not differ by trial and not be affected by any concomitant treatment. All patients start out at baseline utility [redacted] and remain there until the estimated time of early response where all patients move to the average utility at 16 weeks [redacted]. After assessment of response at 16 weeks, non-responders have reduced utility to 0.7696 while responders experience an increase to responder utility (see below). Non-responders remain on BSC and will, due to waning, eventually return to baseline utility. The resulting health state utility values used in the model are shown in Table 40.

Table 40. Utility values used in the model

Health state	Utility value	Instrument	Tariff (value set) used	Source
Baseline	[redacted]	EQ-5D-5L		AbbVie confidential data
Early response	[redacted]	EQ-5D-5L		AbbVie confidential data

(before week 16)				
Non-responder EASI 75 (from week 16)	[redacted]	EQ-5D-5L		AbbVie confidential data
Responder EASI75 (from week 16)	[redacted]			
UPA 15 mg	[redacted]	EQ-5D-5L	DK	AbbVie confidential data
UPA 30 mg	[redacted]	EQ-5D-5L	DK	AbbVie confidential data
DUPI	[redacted]	EQ-5D-5L	DK	AbbVie confidential data
(Dis)utility				
Injection dupilumab	[redacted]			Jørgensen et al (159)

8.5 Resource use and costs

In a health technology assessment (HTA), performed by TLV within the area of atopic dermatitis, TLV estimated healthcare resource use of patients with AD by control (responders and non-responders) of disease, based on dialogue with external Swedish experts (157). A Danish external expert in AD has confirmed to AbbVie that the resource use estimated by TLV may also be relevant in Denmark[2].

The treatment patterns in 8213 Danish patients with atopic dermatitis before and after hospital referral has been studied in a registry-based study. The authors suggest that the dramatic increase in use of drugs in the 3-6 months prior to the first visit are in part driven by un-controlled disease. In the years following the first hospital visit, the use of health-care resources decreased.

Hence, patients with uncontrolled disease will consume more health care resources, including health care visits and pharmaceutical treatments, as compared to patients with controlled disease. For model inputs on resource use and costs, the DMC, TLV and NICE assessments of dupilumab was used (157, 160, 161), and consisted of a combination of visits to GP, dermatologists, and dermatology nurses, as well as emollient products, emollient baths, UV treatments, TCI treatments, blood tests, and psychology visits.

8.5.1 Dosing

Dosing of upadacitinib is done according to the approved label in the model:

For adults he recommended dose of upadacitinib is 15 mg or 30 mg once daily based on individual patient presentation.

- A dose of 30 mg once daily may be appropriate for patients with high disease burden.
- A dose of 30 mg once daily may be appropriate for patients with an inadequate response to 15 mg once daily.
- The lowest effective dose for maintenance should be considered.

For patients ≥ 65 years of age, the recommended dose is 15 mg once daily.

For adolescents (from 12 to 17 years of age) the recommended dose of upadacitinib is 15 mg once daily for adolescents weighing at least 30 kg.

[redacted]

According to the label the lowest effective dose should be used. As discussed previously, most patients will have a sufficient response in monotherapy. The proportion of patients on 15 mg upadacitinib reaching the composite endpoint of **EASI50 + ≤4-point reduction of DLQI** was **71,3 %** (65.5 to 77.1) and **63,7%** (57,6 to 69,8) in Measure-UP 1 and 2, respectively. For the two studies pooled together, about [redacted] of patients reached the treatment goals on 15 mg upadacitinib in monotherapy. The proportion is higher for 30 mg, [redacted] respective [redacted] in the two studies.

These results show that most patients will reach the treatment goals used in Danish clinical practice treated with 15 mg upadacitinib in monotherapy. Patients not reaching the treatment goals can increase the dose to 30 mg, which will increase the proportion of patients reaching treatment goals. Based on these data, an assumption is made that at least 70 % of patients will be treated with 15 mg in monotherapy when upadacitinib is used to treat AD in Denmark. Note that this is likely a conservative assumption, as in addition to the proportion reaching treatment goals, all patients aged 12 to 17 years and 65 years and older should be treated with 15 mg. Data from the Swedish prescription registry also supports the assumptions of the dose split. After the reimbursement decision in the end of January 2022, the proportion between the strengths, prescribed by dermatologists and likely to be for the indication AD, is [redacted] and [redacted] for February and March. (Abbvie data on file)

Based on the described dosing and clinical relevance, a focused advisory board with Swedish dermatology experts indicated that 75% of the patient population can be estimated to use the lower 15 mg daily dose at any given time. This is supported by the 15 mg dose being considered the standard initial dose as well as the maintenance dose, and in line with the proportion of patients reaching a clinically important improvement in highly relevant patient reported outcomes such as DLQI (DLQI improvement ≥4) and POEM (POEM improvement ≥4), being 75% and 72% in Measure Up 1 and Measure Up 2, respectively. Furthermore, adolescents and elderly should always use the lower dose.

8.5.2 Adherence

Data on treatment adherence were derived from clinical trials, from published literature and from assumptions. Adherence data is presented separately for the decision tree (year 1) and the Markov (year 2+) parts of the model. For UPA 15 and UPA 30, adherence data was derived from the pivotal trials Measure Up 1 and 2 and is shown in Table 41.

Table 41: Adherence

Treatment	Model part	Adherence	Source
UPA 15	Decision tree	[redacted]	Measure Up 1 and Measure Up 2, Abbvie confidential data
UPA 30		[redacted]	Measure Up 1 and Measure Up 2 Abbvie confidential data
DUPI		95.20%	Kuznik et al., Dermatol Ther 2017
UPA 15	Markov	[redacted]	Assume the same as in decision tree
UPA 30		[redacted]	Assume the same as in decision tree
DUPI		98.60%	Kuznik et al., Dermatol Ther 2017

UPA, upadacitinib. DUPI, dupilumab.

8.5.3 Response and non-response

Resource use for patients defined as responders or non-responders were derived from the DMC (27), TLV(157)] and NICE (156) assessments of dupilumab and were then validated by a Danish clinician. The included resources were GP visits, outpatient visits to dermatologist, hospital admissions, outpatient visits to dermatology nurse, UV treatments, emollient baths, psychologist visits, emollient cream use, TCI treatment, and full blood counts. The annual resource use for responders and non-responders are given in Table 42 below. Two additional outpatient visits to dermatologist

were added to the resource use for responders during the first year of treatment with UPA and DUPI, irrespective of dose. Note that this constitutes a conservative assumption since dupilumab is an injection treatment while RINVOQ is a tablet where the need for additional visits will be less pronounced.

The resource use given for controlled patients was assumed to be equal to that of a responder to treatment while that of an uncontrolled patient was assumed to be equal to a non-responder.

Table 42: Resource use - responders and non-responders

Resources	Non-responders	Responders – year 1	Responders – year 2+	Reference
GP visits	1.25	0.50	0.50	(157)
Outpatient visits to dermatologist	6	4.5	2.5	
Outpatient visits to dermatology nurse	3.5	2.5	2.5	
A&E attendance	1.25	0	0	
Inpatient admissions	0.50	0	0	
UV treatments	39	6	6	
Emollient baths	6	0	0	
Psychologist visits	2	0	0	
Cream emollients (g per week)	500	250	250	(156)
TCI (g per week)	1.75	0	0	
Full blood counts (UPA)	4	0	0	
Full blood counts (DUPI)	4	0	0	
Full blood counts (BSC)	4	4	4	(27)

A&E, acute and emergency; BSC, best supportive care; GP, general practitioner; UPA, upadacitinib; UV, ultraviolet; VTE, venous thromboembolic events.

8.5.4 Adverse events

Resource use for treating adverse events is given in Table 43 below. When available, the resource use was based on relevant DRG codes. 50% of patients getting conjunctivitis will also have to have an eyecare visit.

Table 43: Resource use - adverse events

Adverse event	Resource use
Allergic conjunctivitis	Visit to GP + 50% Eyecare
Infectious conjunctivitis	Visit to GP + 50% Eyecare
Oral herpes	Visit to GP
Herpes zoster	Visit to GP
Adjudicated MACE	Mean DRG 05MP32-37
Adjudicated VTE	Mean DRG 04MA04 and 05MA12
Malignancies excl. NMSC	Kruse and Hostenkamp
Acne	DRG 09MA98 - MDC09 1. dagsgruppe, pat. Mindst 7 år

Nasopharyngitis	Visit to GP
Upper RTI	DRG 03MA98: MDC03 - 1-dagsgruppe, pat. Mindst 7 år

DRG, diagnosis related group; MACE, major adverse cardiac events; NMSC, nonmelanoma skin cancer; RTI, respiratory tract infection; UPA, upadacitinib; VTE, venous thromboembolic events

8.5.5 Drug costs

Cost for UPA 15 mg and UPA 30 mg are given

Cost for UPA 15 mg and UPA 30 mg are given in Table 44. PPP prices were used in the base case analysis.

Table 44: Unit cost - drugs (AIP)

Treatment	Cost per package (DKK)	Units	Cost per unit (DKK)
UPA 15	6.641,45	28	237,19
UPA 30	13.282,90	28	474,39
DUPI 300 mg	9.128,1	2	4.564,05

8.5.6 Responder and non-responder costs

Unit costs for resources used for responders and non-responders were obtained from the Danish healthcare authorisation (Sundhedsdatastyrelsen) using activity-based costing (DRG tariffs) when possible. Otherwise, general tariffs for visits to specialist are used. All unit costs are shown in Table 45.

Table 45: Unit costs: responders and non-responders

Resource	Cost (DKK)	Source/comment
GP visit	146,79	https://www.laeger.dk/sites/default/files/honorartabel_01.10.20.pdf
Outpatient visit to dermatologist	229,33	https://www.laeger.dk/sites/default/files/dermatologi_takstkort_pr_040121.pdf
Outpatient visit to dermatology nurse	554	DMC's catalogue of unit cost
Emergency attendance	1.735	DRG2021 09MA98 MDC09 1-dagsgruppe, pat. mindst 7 år
Hospital admission	33.855	DRG2021: 09MA02
UV treatment	1.939,45	https://www.laeger.dk/sites/default/files/dermatologi_takstkort_pr_040121.pdf
Emollient bath	161,5	https://www.laeger.dk/sites/default/files/dermatologi_takstkort_pr_040121.pdf
Psychologist visit	675	https://www.krl.dk/#/sirka/ovk
Cream emollients (cost per g)	0,83	Medicinpriser.dk (Betnovate)
TCI (cost per g)	4,13	Medicinpriser.dk
Full blood count	256	Rigshospitalets(State hospital) labportal

A&E, acute and emergency; BSC, best supportive care; GP, general practitioner; UPA, upadacitinib; UV, ultraviolet; VTE, venous thromboembolic events.

8.5.7 Travel and patient cost

Travel costs were added to all healthcare. For primary care, a one-way distance of 14 km was assumed for each visit. For visits to specialised care, a one-way distance of 14 km was assumed. This corresponds to total amount of 100 DKK forth and back from hospital. The costs per km (car allowance of 3,52 DKK per km) based on the DMC catalogue for unit cost.

Based on the DMC's catalogue of unit cost, a one-hour salary cost of 179 DKK is used for patient time. Also, medicine cost for Oftagel (patient with conjunctivitis) and Acivir (patient with herpes) are included. For time estimation and total cost see Table 46.

Table 46: Patient time and costs used in the model

	Total time estimate per visit/AE (hour)	Patient cost DKK per visit
Visit to GP	1,81	422,55
Visit to dermatologist	1,81	422,55
Emergency attendance	1,56	377,80
Hospital admission	24,56	4.494,80
Visits to dermatology nurse	1,56	377,80
UV treatments	2,56	556,80
Emollient baths	1,56	337,8
Psychologist visits	1,56	337,8
Injection site reaction	2,56	556,8
Allergic conjunctivitis	1,06	337,55
Infectious conjunctivitis	1,56	427,05
Oral Herpes	0,81	274,30
Herpes Zoster	1,06	319,05
MACE	24,56	4.494,80
Venous thromboembolic	4,56	914,80
Acne	0,81	243,55
Nasopharyngitis	1,06	288,30
Upper respiratory tract infection	4,56	914,80

8.5.8 Flares

In the Danish treatment guidelines for AD, treatment of flares is described to be 1-4 weeks with once daily administration with a topical corticosteroid. (54)

number of grams of TCS per week was calculated based on BSA involvement at baseline from pooled UPA trials and the assumption that 0.25 g of product from a tube with a standard 5 mm diameter nozzle is sufficient to cover an area the size of the flat adult handprint (palm and fingers). Furthermore, one handprint is assumed to be 0.87% of the area of an adult BSA. The amount of TCS per day was calculated to 13.77 g and the weekly amount to 96.41 g. The costs have been calculated per the dosing recommendations in the SPC for Betnovat creme/salve which is 1-4 weeks, 1-2 applications daily. Assuming that mean treatment length of flares is 2,5 weeks and the total amount of TCS for treating a flare is 241.01 g.

The unit costs used for estimating the cost for treating a flare is given in Table 47. Price is calculated assuming that half the patients need salve (for dry lesions), and half the patients need creme (wet lesions). The mean cost per gram of Betnovat crème or salve is 1.14 DKK and the total cost for TCS in treatment of flares is 275.18 DKK. No wastage of product is calculated as patients are assumed to use any surplus at another episode of flare.

Table 47: Costs - flares

Resource	Cost (DKK)	Cost per g (DKK)	Source/comment
Betnovat crème 100 g	145,11	1.45	Medicinpriser.dk
Betnovat salve 100 g	83,35	0.83	Medicinpriser.dk

8.5.9 Adverse events costs

Unit costs for AEs were obtained from publicly available price lists and are shown in Table 48.

Table 48: Unit costs - adverse events

Resource	Cost (DKK)	Source/comment
Injection site reaction	9.601	21MA05: Forgiftning og toksisk virkning af lægemiddel, øvrige
Allergic conjunctivitis **+ 50% eyecare visit and treatment with ultracortenol**	146,75 1.283*50%	GP visit Eyecare visit
Infectious conjunctivitis **+ 50% eyecare visit and treatment with ultracortenol**	146,75 1.283*50%	GP visit Eyecare visit
Oral herpes	146,75	GP visit
Herpes zoster	146,75	GP visit
Adjudicated MACE	56.979	Average of DRG tariffs 05MP32-05MP37
Adjudicated VTE	25.852,39	Average of DRG tariffs 04MA04 and 05MA12
Malignancies excl. NMSC	52.277,39	Kruse and Hostenkamp
Acne	1.800	09MA98 - MDC09 1. dagsgruppe, pat. Mindst 7 år
Nasopharyngitis	146,75	GP visit
Upper RTI	1.862	03MA98: MDC03 - 1-dagsgruppe, pat. Mindst 7 år

DRG, diagnosis related group; excl., excluding; MACE, major adverse cardiac events; NMSC, nonmelanoma skin cancer; RTI, respiratory tract infection; UPA, upadacitinib; VTE, venous thromboembolic events.

8.6 Results

8.6.1 Base case overview

A base case overview is shown in Table 49.

Table 49: Base case overview

		Upadacitinib	Dupilumab
Type of model		Decision tree + Markov model	Decision tree + Markov model
Time horizon		70 years (life time)	70 years (life time)
Treatment line		1st line. Subsequent treatment lines not included.	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Utilities	Health-related quality of life measured with EQ-5D-5L in studies Measure-UP 1 &2 and Ad-UP. Danish population weights were used to estimate health-state utility values.	Health-related quality of life measured with EQ-5D-5L in study Measure-UP 1 &2 and Ad-UP. Danish population weights were used to estimate health-state utility values. Disutility for route of administration.
	Efficacy (EASI)	NMA including Measure-UP 1 & 2, SOLO-1 & 2 and HEADS-UP	NMA including Measure-UP 1 & 2, SOLO-1 & 2 and HEADS-UP
Included costs		Active treatment costs Administration costs Adverse events costs Treatment related costs and monitoring costs Patient costs	Active treatment costs Administration costs Adverse events costs Treatment related costs and monitoring costs Patient costs
Dosage of pharmaceutical		15 mg (70%) and 30 mg (30%)	600 mg (int), 300 mg EOW
Average time on treatment		No stopping rule is applied	No stopping rule is applied

8.6.2 Base case results

The base case results per patient are shown in Table 50.

Table 50: Base case results

Cost (DKK)	UPA	DUPI	Incremental
Active treatment costs	759 009	698 588	60 421
Administration costs	0	868	-868
Adverse events costs	5 841	9 699	-3 858
Treatment related costs and monitoring costs	2 061 263	2 141 641	-80 377
Patient costs	582 594	605 168	-22 574
Total costs	3 408 707	3 455 963	-47 256
QALYs	16,407	16,046	0,362
Cost/QALY (ICER)			Dominant

8.7 Sensitivity analyses

In order to evaluate the effect of parameter uncertainty on outcomes, it is necessary to perform univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA). A univariate sensitivity analysis varies each of the variables in turn to identify the main drivers in the model while the PSA evaluates the underlying uncertainty in the model.

8.7.1 Deterministic sensitivity analysis

Univariate sensitivity analysis is used to determine the key drivers in the model; each variable is varied individually to see the proportional effect on model results. Deterministic sensitivity analyses (DSA) were performed by varying a number of parameters as described in Table 51 below.

Table 51. DSA parameters

Analysis	Base case	Variation
Costs		
GP visit	146,79	+/- 20 %
Outpatient visit to dermatologist	229,33	+/- 20 %
Outpatient visit to dermatology nurse	559,29	+/- 20 %
Emergency attendance	1735	+/- 20 %
Inpatient admission	33855	+/- 20 %
UV treatment	1939,45	+/- 20 %
Medical bath	161,50	+/- 20 %
Psychologist visit	681,45	+/- 20 %
Cream emollients	629,90	+/- 20 %
TCI	247,71	+/- 20 %
Full blood count	256	+/- 20 %
Treatment of flare	275,18	+/- 20 %
Travel (per visit)	98,56	+/- 20 %
Adverse event cost	Varies	+/- 20 %
Clinical parameters		
UPA 15 efficacy EASI-75	0.613	CI
UPA 30 efficacy EASI-75	0.718	CI
UPA 15 efficacy EASI-90	0.465	CI
UPA 30 efficacy EASI-90	0.604	CI
Active treatment discontinuation	0.063	+/- 20 %
BSC waning	On	On or Off
Utilities		
Baseline	0.613	CI
Average at 16 weeks	0.858	CI
EASI-75	0.888	CI
EASI-90	0.929	CI
Non-responders	0.770	CI

Results from the DSA is presented in Table **52** below.

Table 52. DSA results

Parameter	Analysis	Incremental costs (DKK)	Incremental QALYs	ICER (DKK)
Costs				
GP visit	Low	-47 237	0.362	Dominant
	High	-47 275	0.362	Dominant
Outpatient visit to dermatologist	Low	-47 127	0.362	Dominant
	High	-47 386	0.362	Dominant
Outpatient visit to dermatology nurse	Low	-47 160	0.362	Dominant
	High	-47 353	0.362	Dominant
Emergency attendance	Low	-46 882	0.362	Dominant
	High	-47 630	0.362	Dominant
Inpatient admission	Low	-44 335	0.362	Dominant
	High	-50 177	0.362	Dominant
UV treatment	Low	-36 212	0.362	Dominant
	High	-58 300	0.362	Dominant
Medical bath	Low	-47 089	0.362	Dominant
	High	-47 423	0.362	Dominant
Psychologist visit	Low	-47 021	0.362	Dominant
	High	-47 491	0.362	Dominant
Emollients	Low	-46 298	0.362	Dominant
	High	-48 214	0.362	Dominant
TCI	Low	-47 191	0.362	Dominant
	High	-47 321	0.362	Dominant
Full blood count	Low	-47 217	0.362	Dominant
	High	-47 296	0.362	Dominant
Treatment of flares	Low	-47 229	0.362	Dominant
	High	-47 283	0.362	Dominant
Travel	Low	-46 446	0.362	Dominant
	High	-48 066	0.362	Dominant
Adverse event	Low	-46 485	0.362	Dominant
	High	-48 028	0.362	Dominant
Patient time	Low	-43 555	0.362	Dominant
	High	-50 958	0.362	Dominant
Clinical parameters				
UPA 15 efficacy EASI-75	Low	-25 705	0.224	Dominant
	High	-67 405	0.490	Dominant
UPA 30 efficacy EASI-75	Low	-56 325	0.312	Dominant
	High	-39 210	0.405	Dominant
UPA 15 efficacy EASI-90	Low	-47 256	0.334	Dominant
	High	-47 256	0.391	Dominant
UPA 30 efficacy EASI-90	Low	-47 256	0.350	Dominant
	High	-47 256	0.372	Dominant

DUP efficacy EASI-75	Low	-51 283	0.547	Dominant
	High	-43 321	0.180	Dominant
DUP efficacy EASI-90	Low	-47 256	0.397	Dominant
	High	-47 256	0.322	Dominant
Active treatment discontinuation	Low	-52 595	0.411	Dominant
	High	-43 013	0.322	Dominant
BSC waning	Low	-47 256	0.253	Dominant
	High	-47 256	0.362	Dominant
Utilities				
Baseline	Low	-47 256	0.370	Dominant
	High	-47 256	0.353	Dominant
Average at 16 weeks	Low	-47 256	0.361	Dominant
	High	-47 256	0.362	Dominant
EASI-75	Low	-47 256	0.369	Dominant
	High	-47 256	0.354	Dominant
EASI-90	Low	-47 256	0.351	Dominant
	High	-47 256	0.372	Dominant
Non-responders	Low	-47 256	0.363	Dominant
	High	-47 256	0.360	Dominant

A&E, acute and emergency; BSC, best supportive care; EASI, Eczema Area Severity Index; GP, general practitioner; TCI, Topical calcineurin inhibitor; UPA, upadacitinib; UV, ultraviolet.

8.7.2 Scenario analysis

As described in section 5 above, AD carries a substantial economic burden with a large share in the form of indirect costs, i.e., costs due to productivity losses. These costs can come both from absenteeism (sickness absence) and presenteeism (reduced work capacity while at work). To evaluate the impact of including costs for productivity loss, a scenario analysis was performed.

A Danish registry-based cohort study found that AD patients were associated with increased risk of receiving paid sick leave or disability pension compared to controls. (72). In detail, the results showed that the average (SD) number of weeks per year of long-term sick leave for older patients (born 1964-1976) was 2.03 (2.75) for mild/moderate AD and 2.99 (6.00) for severe AD. Corresponding numbers for younger patients (born 1977-1999) were 1.69 (2.62) and 2.12 (2.76), respectively. The results show a relation between disease severity and sick leave but to properly conduct an analysis using a true societal perspective, additional information is needed. Firstly, data stratified by controlled and uncontrolled disease is needed to correlate the reduced work productivity to disease control and treatment efficacy. Secondly, the study report data on sick leave which, while highly relevant, do not provide the full picture on reduced work productivity for these patients. This can be achieved by instead looking at data on absenteeism, i.e., the reported number of days where a patient was unable to work, not completely captured by data on sick leave.

In the absence of Danish data sources that splits data into controlled and uncontrolled needed for the health economy model (nor includes absenteeism, i.e., the reported number of days where a patient was unable to work, instead of only sick leave), data on production loss was sourced from a Dutch publication. Data for controlled patients were assumed to be representative for responders, while data for uncontrolled patients were assumed to be representative for non-responders. As a conservative estimate, only productivity loss due to absenteeism was included although data

on presenteeism (reduced work capacity while at work) was also reported. Looking solely at absenteeism, the number of working days lost per year was 1.5 for controlled patients while it was 28.9 for uncontrolled.

The daily cost for productivity loss was estimated from a mean monthly wage in Denmark of 43 487 DKK (standardized monthly earnings, all sectors, all forms of pay, employees [excluding young people and trainees], men and women), equal to a mean yearly wage of 521 844 DKK (162) (Statistics Denmark 1). Assuming a mean of 213 working days per year (DMC guidelines), the mean wage per day was estimated to 2 453 DKK. Assuming a 93.6% employment rate (Statistics Denmark 2) (163), the annual costs for productivity losses for responders and non-responders were calculated to 3 444 DKK and 66 351 DKK, respectively.

Based on these inputs, the productivity loss for upadacitinib is estimated to 1 456 407 DKK while the corresponding number for dupilumab is 1 527 254 DKK, resulting in an incremental cost of -70 847 DKK per patient for productivity losses. Including costs for productivity losses, i.e., adopting a complete societal perspective, increases the total cost savings to -118 103 DKK per patient while the QALY gain is unchanged at 0.362 (Table 53).

Table 53. Scenario results

Cost (DKK)	UPA	DUPI	Incremental
Active treatment costs	759 009	698 588	60 421
Administration costs	0	868	-868
Adverse events costs	5 841	9 699	-3 858
Treatment related costs and monitoring costs	2 061 263	2 141 641	-80 377
Patient costs	582 594	605 168	-22 574
Indirect costs	1 456 407	1 527 524	-70 847
Total costs	4 865 114	4 983 217	-118 103
QALYs	16,407	16,046	0,362
Cost/QALY (ICER)			Dominant

8.7.3 Probabilistic sensitivity analysis

Parameter uncertainty was addressed using probabilistic sensitivity analysis (PSA), simulating the outputs from the model by sampling each parameter from chosen probabilistic distributions, reflecting both the central estimate (mean), variance (standard error) and anticipated shape of the data. The parameters included in the PSA and the distributions used are given in Table 54. 1,000 rounds of simulations were run.

Table 54. PSA distributions

Analysis	Distribution
GP visit	Gamma
Outpatient visit to dermatologist	Gamma
Outpatient visit to dermatology nurse	Gamma
Emergency attendance	Gamma
Inpatient admission	Gamma
UV treatment	Gamma
Medical bath	Gamma
Psychologist visit	Gamma
Cream emollients	Gamma
TCI	Gamma
Full blood count	Gamma
Treatment of flare	Gamma
Travel	Gamma
Adverse event cost	Gamma
UPA 15 efficacy EASI-75	Beta
UPA 30 efficacy EASI-75	Beta
UPA 15 efficacy EASI-90	Beta
UPA 30 efficacy EASI-90	Beta
Active treatment discontinuation	Beta

PSA results

PSA outputs are represented graphically by plotting incremental cost and effectiveness pairs on the cost-effectiveness plane. Figure 32 graphically summarises the results of the probabilistic analysis.

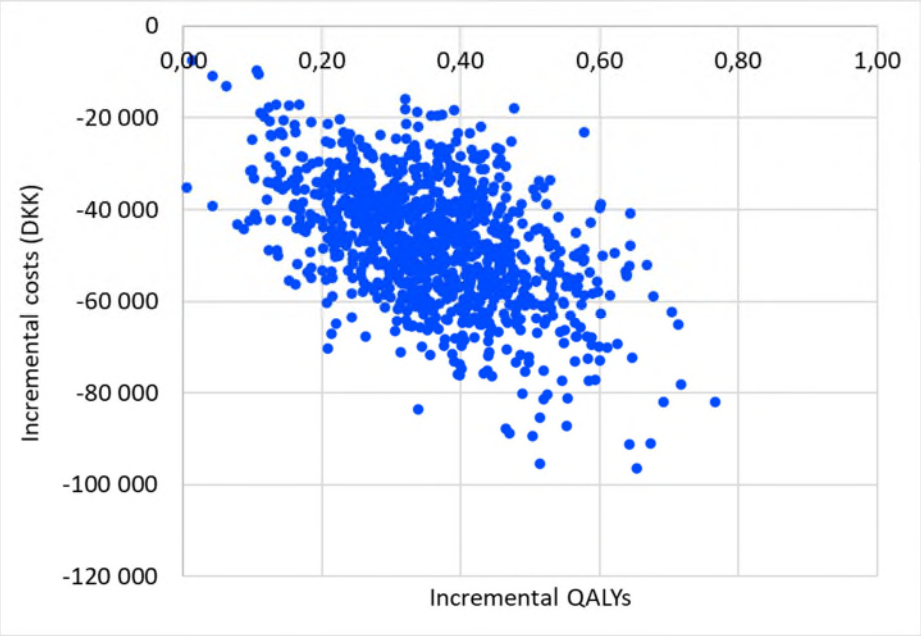


Figure 32. PSA results, cost-effectiveness plane

All simulations showed dominant results, being both more effective as well as cost saving. For the cost results, the simulations ranged from savings of DKK 7415 to savings of DKK 96361. For the QALY results, the QALY gains from the simulations ranged from 0.005 to 0.766 QALY. The cost-effectiveness plane results were converted into a cost-effectiveness acceptability curve (CEAC) that shows that there is a 100% likelihood that UPA, when compared to DUP, will be a cost-effective option in Denmark (Figure 33).

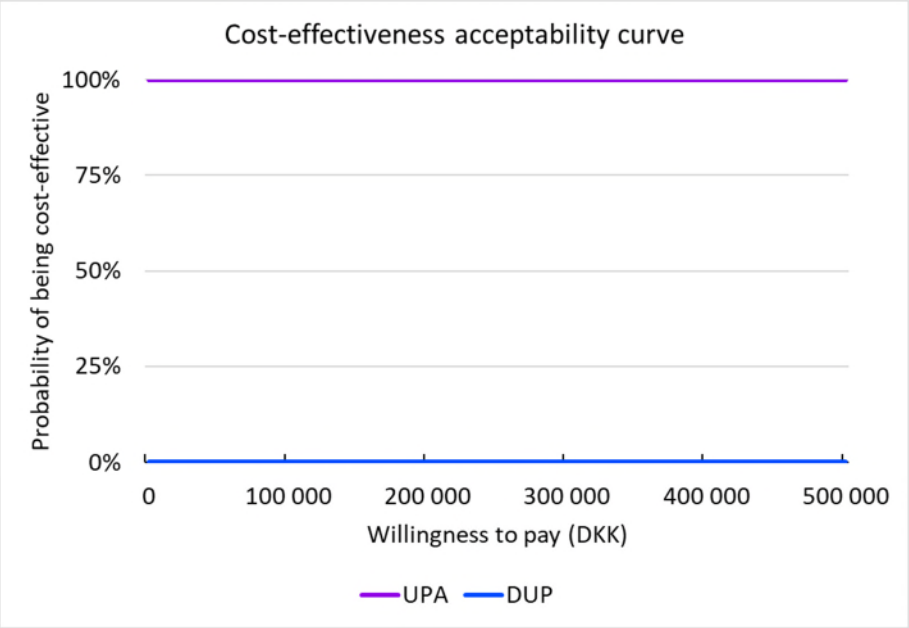


Figure 33. PSA results, CEAC

9. Budget impact analysis

The budget impact of introducing upadacitinib has been calculated as a separate functionality in the cost-utility analysis model. The budget impact model utilizes the same source of cost and efficacy-data as the cost-utility analysis. Patients will start on either upadacitinib or dupilumab in the budget impact model. Evaluation of efficacy is done after 16 weeks, whereafter patients are either responders or non-responders to treatment. Response is defined as EASI75, and both the response definition and the time to evaluation concurs with the Danish specialist associations guidelines. Two scenarios have been analyzed, where upadacitinib is either recommended, or not recommended for use in Denmark. The analysis is done per year, for five years.

9.1 Expected number of patients and market share uptake

The assumption of the patient number is estimated based on previous assessment reports of AD from the DMC. In the assessment report for baricitinib the expert committee estimated the patient population already treated with dupilumab and candidates for baricitinib (prevalence) to be 225 patients and 30 new patients per year (incidence) (27). For the patient population 12-17 years old (adolescents) 50 patients are candidates for treatment, and with an incidence of 13-16 new patients per year based on the assumptions made by the expert committee in the evaluation of dupilumab (57). For adolescents patients treated with dupilumab is 11, and new patients per year (incidence) is expected to be 13-16. The resulting patient numbers are summarized in Table 55.

Table 55. Prevalence and incidence used in budget impact calculation

	Adults	Adolescents	Total
Prevalence, n	225	11	236
Incidence, n	30	16	46

For both adults and adolescents, a market uptake of 30 % year 1, 40 % year 2, 50 % year 3, 75 % year 4 and 80 % in year 5 is assumed for upadacitinib. The resulting yearly patient numbers for the two scenarios are shown in Table 56 and Table 57.

Table 56. Number of patients expected to be treated if UPA is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
UPA	85	103	126	161	197
DUPI	197	225	248	260	269
Total patient number	**282**	**328**	**374**	**420**	**466**

Table 57. Number of patients expected to be treated if UPA is *not* recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
UPA	3	3	4	5	6
DUPI	279	325	370	415	460
Total patient number	**282**	**328**	**374**	**420**	**466**

9.2 Budget impact results

Table 58. Cost per patient if UPA is recommended, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
UPA	84.155	130.774	194.118	260.663	389.917
DUPI	208.438	265.693	325.173	349.272	371.296
Total cost	292.593	396.468	519.291	639.935	761.214

Table 59. Cost per patient if UPA is *not* recommended, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
UPA	2.805	3.892	5.121	7.746	10.206
DUPI	294.790	396.822	519.817	640.561	760.790
Total cost	297.596	400.714	524.938	648.307	770.996

Table 60: Expected Budget Impact if UPA is recommended, mio. DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommended	41,2	42,1	47,6	53,0	58,4
Not recommended	41,9	42,4	47,9	53,4	58,9
Total cost	-0,7	-0,3	-0,3	-0,4	-0,5

10. Discussion on the submitted documentation

Upadacitinib has shown high response rates for the primary endpoints in the pivotal clinical trials. The EASI75 response was between 71-80% in patients treated with upadacitinib 30 mg and between 60-70% in patients treated with upadacitinib 15 mg at week 16. Similarly, vIGA-AD responses were between 52-62% in patients treated with the higher 30 mg upadacitinib dose, for the lower 15 mg dose the vIGA-AD response was between 42-53%. Importantly, data also supports a rapid onset of effect, already significantly higher compared to placebo at week 1, and is fully achieved at week 8 to week 12. Most patients will reach the treatment goals used in Danish clinical practice (EASI 75 or EASI 50 + ≥ 4 point improvement in DLQI), treated with 15 mg upadacitinib in monotherapy. These outcomes form the major assumptions in the health economic analysis carried out in this application.

Dupilumab was recommended by the Medicines council in 2019 for patient over 18 years and in 2020 for adolescents (12-17 years) to treat moderate to severe AD when local and systemic treatment are inefficient. Dupilumab is the relevant comparator to upadacitinib as it is the advanced systemic treatment used in clinical practice in Denmark. Based on Danish registry data more patients are treated with systemic treatments alone than treated in combination with TCS in Danish clinical practice. Most patients also have an infrequent use of TCS, and overall TCS use is lower after hospital referral where treatment with systemics will be initiated. Therefore, in clinical practice it seems likely that upadacitinib and dupilumab will be used predominantly in monotherapy.

The cost effectiveness of treating moderate to severe AD patients who are candidates for systemic treatment with UPA as compared to dupilumab was evaluated using a cost utility approach to upadacitinib for adult patients and adolescents from 12 years of age with moderate to severe AD.

Relevant studies for the indirect treatment comparison with dupilumab was identified in a comprehensive systemic literature review. The identified studies were included in a network meta-analysis to quantify the relative efficacy of upadacitinib compared to dupilumab. The monotherapy network including studies where TCS could be used as a rescue therapy is the network AbbVie considers reflects both how upadacitinib will be used in clinical praxis and how TCS is used in clinical praxis based on Danish treatment recommendations for dupilumab, and Danish registry data. Results from the network metanalysis comparing upadacitinib and dupilumab in monotherapy is the available evidence that best mimic the relative efficacy in clinical practice and is therefore used to inform the cost-utility analysis.

In the network, there appears to be some heterogeneity in dupilumab response rates across Heads UP, SOLO 1 and SOLO 2 trials. A statistical assessment of the degree of disagreement between the direct and indirect evidence was performed alongside, considering the impact of removing Heads UP from the NMA. There are no differences in the trial design in terms of research objective or selection criteria when comparing Heads UP and other trials. Patient characteristics at baseline, and primary endpoints do not differ. One RCT design issue that is different between Heads UP and the SOLO 1 and SOLO 2 trials was that dupilumab patients in Heads UP received their self-administered dose at the trial site by a trained professional, while SOLO 1 and SOLO 2 patients in the dupilumab arm did not have to receive their dose at the trial site by a trained professional. Thus, it is possible the compliance and adherence of dupilumab injection administration was greater in Heads UP, which could explain some of the variation in outcomes reported for dupilumab. Following these considerations, Heads UP was not removed from the NMA on the basis that the inconsistency was borderline and that excluding Heads UP from the NMA would favour upadacitinib. Overall, the inclusion of Heads UP in the NMA leads to more conservative estimates of the efficacy of upadacitinib.

Data on utility was derived from pooled data from three UPA trials (Measure-UP 1 and 2 and AD-UP). In the cost-effectiveness analysis, utility was determined by health state, i.e., response to treatment, and was assumed to not differ by treatment.

Although 15 mg is expected to be the most used dose in clinical practice, a proportion of patients will receive 30 mg. Based on the results in the clinical trials it is assumed 70 % of patients treated with 15 mg will reach the treatment goals defined by the Danish specialist's association in the pivotal clinical trials for upadacitinib. The remaining 30 % of patients will be treated with 30 mg in the model. A weighted efficacy analysis demonstrated that an expected in label treatment dosing of upadacitinib (70% 15mg, 30% 30mg) is significantly more effective than dupilumab using EASI-75 as endpoint. This analysis demonstrates that upadacitinib when used at the expected dosing will allow more patients to reach treatment goals while at the same time constituting a cost-effective treatment option.

The model includes costs for active treatment, administration, health care utilization, adverse events, and patient-costs, in line with DMC guidelines. In addition, model details on discounting and age adjustment of utility are performed using relevant guidelines. Health care resource use for controlled and uncontrolled patients was sourced from the TLV and NICE evaluations of dupilumab and validated by Danish clinical experts and combined with relevant Danish tariffs and cost.

The cost effectiveness result is dominated which means that UPA is showing better efficacy and is cost saving. Also, all sensitivity analyses resulted in maintained dominance demonstrating that the results are robust and that changes to specific variables does not have an impact on the result. Additionally, a probabilistic sensitivity analysis was conducted, and the results build on those obtained in the DSA. All simulations showed more effective and cost saving results. Adopting a true societal perspective to include the full impact of AD results in more than two-fold increased cost savings due to reduced costs for productivity losses for upadacitinib as compared to dupilumab.

The CUA is evaluated with list prices and UPA is today available under a discounted agreement. The cost is therefore even lower than these analyses show.

In the base case analysis, treatment with UPA is dominant, resulting in cost savings and substantial QALY gains. The results are robust through all sensitivity analyses showing that UPA constitutes a cost effective and valuable treatment options for patients with moderate to severe AD in Denmark. An integrated budget impact model was developed and resulted in a net/cumulative cost saving of 2,3 million DKK. Including productivity losses would lead to substantially higher cost savings also in the budget impact calculations as the cost saving per patient more than doubled in the cost effectiveness analysis when including productivity losses. Overall, the analyses demonstrate that UPA is a cost-effective treatment option for patients with moderate to severe AD that are candidate for systemic treatment, while at the same constituting an attractive treatment option from a health care budget perspective.

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