Medicinrådet

Application for the assessment of abrocitinib for moderate to severe atopic dermatitis in adults

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Lægmandsresumé

Atopisk eksem, også kaldet atopisk dermatitis eller børneeksem, er en kronisk inflammatorisk hudlidelse, som kan forekomme i alle aldre og er karakteriseret ved generende udslæt. Moderat til svær atopisk eksem viser sig ved udtalt kløe, tør hud, rødme, afskalning, hævet udslæt evt. med blærer, fortykkelse og kradsning af huden. Derudover er atopisk eksem forbundet med nedsat livskvalitet for patienterne, samt der ses en øget forekomst af psykiske sygdomme, som angst og depression. Nuværende behandling i Danmark er blandt andet dupilumab som anvendes til størstedelen af patienterne med moderat til svær atopisk eksem. Det er dog ikke alle patienter som opnår tilstrækkelig effekt eller tåler behandlingen.

Der er derfor et stort behov for effektive, tålelige og let administrerbare behandlinger til moderat til svær atopisk eksem. Abrocitinib er en ny tabletbehandling med en hurtigt indsættende effekt. Abrocitinib har vist at kunne reducere kløe efter 1 døgns behandling, forbedre eksem med 75% efter 12 ugers behandling og patienterne opnår en forbedret livskvalitet. Tabletbehandling med abrocitinib er desuden en fordel for de patienter som ikke ønsker eller tåler injektioner.

Abrocitinib er undersøgt i et bredt klinisk studieprogram som blandt andet omfatter syv fase 3 studier, herunder et studie der evaluerer den kliniske effekt og sikkerhed af abrocitinib og dupilumab ved behandling af voksne med moderat til svær atopisk eksem, som samtidig anvender lokalbehandling med binyrebarkhormon.

I denne rapport sammenlignes abrocitinib med dupilumab. Efter 2 ugers behandling ses, at abrocitinib har en hurtigere indsættende effekt på kløe sammenlignet med dupilumab. Behandling i 12 uger viser, at abrocitinib og dupilumab over længere tid har sammenlignelig effekt og sikkerhed. Sundhedsøkonomisk er abrocitinib et omkostningsbesparende behandlingsalternativ til dupilumab.

Abrocitinib er en attraktiv ny behandlingsmulighed både for patienter, hospitaler og samfund, idet effekt og sikkerhed er sammenlignelig med dupilumab, abrocitinib er omkostningsbesparende i forhold til dupilumab og abrocitinib giver mulighed for fleksibel administration.

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Cibinqo
Generic name	Abrocitinib
Marketing authorization holder in Denmark	Pfizer Europe
ATC code	D11AH08
Pharmacotherapeutic group	Agents for dermatitis, excluding corticosteroids
Active substance(s)	Abrocitinib
Pharmaceutical form(s)	Film-coated tablet
Mechanism of action	Abrocitinib is a Janus kinase (JAK)1 inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Inhibition of JAK1 modulates the signalling pathways by preventing the phosphorylation and activation of STATs.

Overview of the pharmaceutical	
Dosage regimen	The recommended starting dose is 200 mg once daily. • A starting dose of 100 mg once daily is recommended for patients ≥ 65 years of age. For other patients who may benefit from a starting dose of 100 mg refer to SmPC section 4.4 and 4.8. • During treatment, the dose may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Abrocitinib is indicated for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy.
Other approved therapeutic indications	No
Will dispensing be restricted to hospitals?	Expected to be restricted to dermatologist - NBS
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	Polyvinylidene chloride (PVDC) blister with aluminium foil lidding film containing 7 film-coated tablets. Each pack contains 28 film-coated tablets.
Orphan drug designation	No

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2. Abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse event
ALC	Absolute Lymphocyte Count
ANC	Absolute Neutrophil Count
BSA	Body surface area
CI	Confidence interval
CPK	Creatine phosphokinase
DLQI	Dermatology life quality index
EASI	Eczema area severity index
EPAR	European public assessment report
FAS	Full analysis set
Hb	Haemoglobin
IFN	Interferon
IGA	Investigator's global assessment
IL	Interleukin
JAK	Janus kinase
LSM	Least squares mean
LTE	Long-term extension
MoA	Mode of action
NMA	Network meta-analysis
PSAAD	Pruritus and Symptoms Assessment for AD
PO-SCORAD	Patient oriented scoring atopic dermatitis
POEM	Patient oriented eczema measure
PP-NRS	Peak pruritus numerical rating scale
PT	Preferred term
QD	Once a day
QoL	Quality of life
QW	Once weekly
Q2W	Once every 2 weeks
RCT	Randomised controlled trial
SAE	Serious adverse event
SCORAD	Scoring atopic dermatitis
SmPC	Summary of product characteristics
SOC	System organ class
SUCRA	Surface under the cumulative ranking curve
TEAE	Treatment emergent adverse event
TCI	Topical calcineurin-inhibitors
TCS	Topical corticosteroids
TSLP	Thymic stromal lymphopoietin
TYK	Tyrosine kinase

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3. Tables and Figures

3.1 Tables in main report

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3.2 Figures in main report

3.3 Tables in appendices

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4. Summary

Atopic dermatitis (AD; also known as atopic eczema) is a chronic inflammatory disorder of the skin, characterized by the presence of red and itchy lesions that can occur anywhere on the body, in a persistent or relapsing manner. The pathophysiology of AD is characterized by abnormalities of the structure and function of the epidermis and inappropriate immune responses to antigens in the skin. Atopic dermatitis is the most common chronic inflammatory skin disease in the developed world, with primary onset in childhood affecting up to 25 % of children. Atopic dermatitis is however also very prevalent in adults with rates of 7–10 %. Up to approximately 85% of adult AD patients have mild to moderate severity and up to 60% have moderate to severe disease worldwide.

Atopic dermatitis results in a substantial clinical, health-related quality of life (QoL) and psycho-social burden on patients, as well as an impact on families, caregivers, and society. An uncontrollable and relentless itch (pruritus) and the appearance of red and inflamed lesions on the skin are the two most critical contributors to clinical, HRQL and psycho-social burden for patients with AD. Together, itch and skin appearance play a causative role in many of the key features of AD including skin damage, risk of infection, sleep disturbance, difficulty with mood and attention, negative effects on social and intimate relationships, depression and anxiety, and poor work or school performance.

Current treatment options for adults (≥18 years) with moderate to severe AD who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated, are limited to dupilumab and baricitinib. Dupilumab is available only as a subcutaneous injection, a dosage form often not preferred by patients. Dupilumab is also associated with injection site reactions, eye complications and face and neck erythema which can cause burning and itching, and therefore may not be appropriate for all patients. Baricitinib has recently been recommended by the Danish Medicines Council as a treatment option for atopic dermatitis although it is not yet widely established in clinical practice. In the baricitinib appraisal the expert committee views that data on efficacy, including EASI (eczema area severity index) and SCORAD (scoring atopic dermatitis), indicates that baricitinib is less effective than dupilumab. Accordingly, dupilumab is chosen as a single comparator for this submission, and is also included as an active control-arm in the JADE COMPARE trial, one of the pivotal trials for abrocitinib.

Many of the inappropriate immune responses in AD are mediated by the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. The JAK family is a group of cytoplasmic tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase (TYK)2) that mediate signalling pathways activated by various cytokines. Upon cytokine binding and receptor activation JAKs dimerise (as homo-or heterodimers) to form receptor complexes for signal transducer and activator of transcription proteins (STATs), which then phosphorylate, dimerise and translocate to the nucleus to regulate transcription of genes involved in various inflammatory responses. JAK inhibitors improve the signs and symptoms of atopic dermatitis (including skin inflammation and itch) by inhibiting the cytokine signalling pathways, including interleukin (IL)-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin (TSLP) and interferon (IFN)-ɣ implicated in atopic dermatitis pathogenesis.

Given the current treatment landscape, there is a need for further efficacious, tolerable, and easily administered treatments at this point in the pathway of care. Abrocitinib is an oral, JAK1-selective inhibitor that inhibits several key cytokine signalling pathways known to have an important role in the pathophysiologic characteristics of atopic dermatitis. Despite current treatment options there remains a substantial unmet need for treatments that better address the two major drivers of disease burden in atopic dermatitis: itch and the appearance of the skin.

The clinical development program for abrocitinib (CIBINQO®) in moderate to severe atopic dermatitis includes phase 2 studies and seven phase 3 studies (included in this submission; JADE COMPARE, JADE MONO-1 and JADE MONO-2,)

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evaluating abrocitinib in adults and adolescent patients. JADE COMPARE evaluates the efficacy and safety of abrocitinib and dupilumab in the treatment of adults with moderate to severe AD on background topical therapy. The anticipated marketing authorisation for abrocitinib (CIBINQO®) is treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy. However, in a Danish context the proposed positioning is for adults who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. This is in line with the positioning of dupilumab and baricitinib. Hence, this represents a subgroup of both the anticipated licensed population and the population studied in the clinical trial programme (in total 43.2% of patients had received prior systemic therapy in the JADE COMPARE trial). This submission focus on the population studied in the clinical trial programme, which are patients who had a prior inadequate response or for whom topical treatments were medically unadvisable, or who had received systemic therapies. By dividing the clinical trial population into subgroups this will increase uncertainty in the results and therefore no attempt has been made to perform the analysis on a subgroup level.

In this submission adult patients with moderate to severe atopic dermatitis are explored. Further, as per trial data the use of abrocitinib and comparator treatments in combination with background medicated topical therapy and as monotherapies is considered. At 12 weeks of therapy, compared with placebo, both doses (i.e., 100 mg QD and 200 mg QD) of abrocitinib evaluated in the pivotal trials demonstrated significantly greater improvements in skin clearance in both the Investigator's Global Assessment (IGA) and 75% improvement in EASI-75 responses both in combination with background topical therapies and as monotherapy. Also, abrocitinib 200 mg QD in combination with medicated topical therapy showed significantly greater improvements in IGA and EASI-75 compared to dupilumab at week 12. Abrocitinib has also demonstrated a fast onset of itch relief, with greater proportions of patients in both abrocitinib 100 mg QD and 200 mg QD groups achieving PP-NRS4 (Peak pruritus numerical rating scale; an improvement in PP-NRS of ≥4 points from baseline) compared with placebo as early as week 2 of treatment. The fast onset of action with abrocitinib was noted as early as after one day of treatment. In comparison to dupilumab, a significantly greater proportion of patients treated with abrocitinib 200 mg QD achieved PP-NRS4 at two weeks of therapy. Additionally, as early as two weeks of treatment, patients treated with abrocitinib experienced greater improvements in QoL (i.e., Dermatology Life Quality Index [DLQI],) which was sustained throughout week 12 compared with placebo in pivotal trials.

The Integrated Safety Summary demonstrates the safety and tolerability of abrocitinib 100 mg and 200 mg QD for the treatment of patients with moderate to severe AD in adults, both in combination with topical therapy and as monotherapy. The evaluation of the abrocitinib tolerability and safety profile is primarily drawn from safety assessments in six studies in the AD clinical development program (Phase 2b dose ranging study, JADE MONO-1, JADE MONO-2, JADE COMPARE, JADE REGIMEN, and JADE EXTEND).

Acute and long-term use of abrocitinib is well-tolerated and has a safety profile that supports use in patients with moderate to severe AD. Most AEs were mild, self-limited, and seldom required interruption or permanent discontinuation of therapy. The most common AEs associated with abrocitinib were nausea and headache, which tended to occur in the first few weeks of therapy. In JADE COMPARE study, the percentages of subjects reporting SAEs, severe AEs, and AEs leading to study discontinuation were low and similar across the abrocitinib, placebo, and dupilumab treatment groups. Abrocitinib treated subjects were more likely to experience nausea, herpes simplex, acne, and herpes zoster. Dupilumab-treated subjects were more likely to experience conjunctivitis.

In summary, abrocitinib is a highly effective, oral, selective JAK1 inhibitor that fulfills a significant unmet need in moderate to severe AD through its rapid onset (itch relief by day 2) and sustained skin clearance, while offering a convenient treatment option and manageable safety profile for adults. Moreover as demonstrated by analysis on data

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from JADE COMPARE the clinical efficacy and safety of abrocitinib is comparable to that of dupilumab, which is supported by evidence from JADE MONO-1 and JADE MONO-2.

Given the overall comparability between abrocitinib and dupilumab in both clinical efficacy and safety, a cost-minimization analysis is chosen to estimate the economic impact of recommending abrocitinib as standard of care in Denmark, as in accordance with the Medicines Council's method guideline. The cost-minimization analysis shows that under the assumption of equivalent efficacy, abrocitinib is a highly cost-saving alternative to dupilumab. All relevant cost differences between the relevant alternatives were considered, and the majority of the sensitivity analyses fall fairly close to the base case confirming that this analysis is robust. Given that abrocitinib have similar clinical effect compared with existing treatments, is cost-saving compared with existing treatments, and is a flexible oral administration, abrocitinib is an attractive treatment option for both patients, hospitals and the healthcare sector in general.

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

5.1 The medical condition and patient population

Atopic dermatitis (AD) is a relapsing inflammatory pruritic skin condition with immune dysfunction that affects lesional and nonlesional skin (1). AD is the most common chronic inflammatory skin disease in the developed world, with primary onset in childhood affecting up to 25 % of children. AD is however also very prevalent in adults with rates of 7–10 % (2, 3). In a Danish study the calculated incidence rate of atopic dermatitis from 14 to 29 years was found to be 8.9/1000 person-years (2).

AD has a complex, not yet fully understood pathogenesis with genetic, immunological, and environmental factors resulting in skin barrier dysfunction and immune dysregulation. Impairment of epidermal barrier function, for example, owing to deficiency in the structural protein filaggrin, can promote inflammation and T cell infiltration. The immune response in AD is skewed towards T helper 2 cell-mediated pathways and can in turn favour epidermal barrier disruption (3). Many cytokines implicated in the pathophysiology of AD, including skin barrier disruption, inflammation, and itch, require JAK1 for signal transduction. Key inflammatory cytokines involved in atopic dermatitis are IL-4, IL-13, IL-22 IL-31 and TSLP, all which require JAK-STAT downstream signalling for their biological function (4). Therefore, inhibition of JAK1 can block the downstream effects of cytokine signalling, leading to improvement in signs and symptoms of atopic dermatitis.

AD is characterized by pruritus, skin pain and eczematous lesions. Notably clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification, but these vary by patient age and chronicity of lesions (5). Lesions can affect any part of the body, but distribution and morphology are distinguishably different between pediatric and adult populations (6, 7). AD has three recognized clinical phases: infant (aged 3 to 6 months to <2 years), childhood (aged 2 to <12 years) and adult (aged 12 years and older) (6). Adolescents and adults are grouped together in the adult phase based on the similarity of the clinical pattern and predominant areas of AD involvement. Adolescents and adults often present with lichenified and excoriated plaques at flexures, wrists, ankles, and periorbital regions and can also occur in the head and neck (in the head and neck type, the upper trunk, shoulders, and scalp are involved) (7). Patients with adult-onset disease experience more lesions on the feet and fewer lesions on the eyelids, ears, and face than adult, childhood-onset patient (8). Pruritis is a hallmark of the condition that is responsible for much of the disease burden and a key symptom in AD. Severity of pruritus increases with disease severity in AD. In a multicenter US study of adult patients with AD (2013 to 2014), patients with moderate to severe

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AD (based on patient oriented (PO)-SCORAD) reported more days of itch per week than those with mild AD, in addition to higher mean peak pruritus numerical rating scale (PP-NRS) scores (9). According to the Danish guideline for Atopic dermatitis, pruritis is probably the most important parameter for monitoring disease activity (10).

AD has a profound negative impact on patient's quality of life (QoL). Symptoms of pruritus and sleep disturbances, negatively impact the patients' QoL and the burden of illness also extends to patients' families and caregivers (11). Patients with increased severity of AD experience a more negative impact on their health related QoL compared to their counterparts experiencing decreased lower disease severity (12, 13). Moderate to severe AD severely impairs QoL (14) and impacts emotional well-being, with over 50% of patients experiencing depression, anxiety, and sleep disruption (15), leading to worse overall mental health than patients suffering from diabetes or hypertension (16). In a Danish study both depression and anxiety were found to be prevalent among patients with AD, particular among those with severe disease where they reached the estimates for psoriasis (17). Comorbid conditions that may also affect patients with AD besides depression and anxiety include genetically-related atopic disorders e.g., asthma and allergic conditions (7).

Patients with moderate to severe AD who are candidates for systemic treatment are candidates for abrocitinib according to the anticipated label of abrocitinib. In Denmark, abrocitinib provides a treatment option for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. Hence, abrocitinib provides an alternative treatment option and dosage form to subcutaneous dupilumab and also an alternative treatment option to baricitinib for moderate to severe AD patients ≥ 18 years.

Up to approximately 85% of adult AD patients have mild-to-moderate severity and up to 60% have moderate to severe disease worldwide (18, 19). To our knowledge there are no registry data or published literature on the incidence and prevalence of moderate to severe atopic dermatitis in Denmark for the past 5 years. Thus, according to the Medicines Councils protocol for baricitinib, the Medicines Council's Expert Committee for Atopic Dermatitis has estimated that 225 patients will currently be candidates for dupilumab or baricitinib, though some may already have initiated treatment. It is further estimated that 250 patients has started dupilumab treatment since the recommendation for use by the Medicines Council and of those 60 patients will stop treatment due to adverse events or lack of efficacy. The Expert Committee has also estimated that 30 new patients per year will be candidates for dupilumab or baricitinib (20) and hence will also be candidates for abrocitinib.

Table 1 Estimated number of patients eligible for treatment

Year	[Year, i.e. 2022]	[Year, i.e. 2023]	[Year, i.e. 2024]	[Year, i.e. 2025]	[Year, i.e. 2026]
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	225 adults	255 adults	285 adults	315 adults	345 adults

Numbers of patients are estimated based on "Medicinrådets protokol for vurdering af baricitinib til behandling af moderat til svær atopisk eksem"(20).

5.1.1 Patient populations relevant for this application

The patient population relevant for this submission consist of adults with moderate to severe atopic dermatitis who previously had inadequate response to medicated topical therapy or are eligible for systemic treatments.

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The proposed positioning for abrocitinib is for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated (see also section 5.3 and 7.1.3). This represents a subgroup of both the anticipated license population and the population studied in the clinical trial program for abrocitinib, which across all trials was patients who previously had inadequate response to medicated topical therapy or were eligible for systemic treatment.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

There is currently no known cure for AD (21). The pharmacological treatment of atopic dermatitis is based on managing long term symptoms or resolving them acutely and aims to prevent episodes of flares and, when such episodes occur, to shorten the period until the disease has stabilized again. The goals for treatment of atopic dermatitis are (10):

- Control of acute flares
- Maintenance treatment when the skin is in remission
- Treatment of complications such as infections or allergies

Treatment of atopic dermatitis can be topical, systemic or both. Current treatments for AD include topical moisturizers and anti-inflammatory agents such as corticosteroids, calcineurin inhibitors, phototherapy in addition to topical treatment and systemic immunosuppressants. Topical corticosteroid (TCS) is first choice of treatment for moderate to severe AD. Second choice is calcineurin-inhibitors (TCI) (10). Although topical therapies can be effective for some patients, in others they have limited efficacy (21). Prolonged use of potent TCS should be avoided due to potential side effects including skin atrophy, skin bleaching, and the worsening or spreading of skin infections (22, 23). If topical treatment is inadequate, systemic treatment such as methotrexate, azathioprine, mycophenolate mofetil, cyclosporin or dupilumab can be used (10). Since May 2021 baricitinib has also been a treatment option for adults with moderate to severe AD in Denmark (24). Of the systemic treatments, only cyclosporine, baricitinib and dupilumab are approved for AD. Dupilumab is indicated for patients ≥ 6 years whereas cyclosporin is indicated for patients ≥ 16 years (25, 26). Baricitinib is indicated for adults ≥ 18 years with atopic dermatitis (27). According to a Danish study, patients with AD who are managed with systemic immunosuppressants are most often treated with methotrexate and azathioprine rather than cyclosporine (28). Use of cyclosporine is limited by nephrotoxicity with time and can be used for a maximum of 2 years in a patient's lifetime (10). While both methotrexate and azathioprine can be very effective in the management of AD, the drug survival is not always good (29). Also a Danish study found a disconnection between the severity of atopic dermatitis signs and symptoms, and use of atopic dermatitis therapies, suggesting that these drugs are not used widely enough, and that patients with moderate to severe disease in most cases are left with topical medication and UV treatment (30). Hence in 2019, only 7 % of Danish patients with severe AD were treated with a systemic therapy (31).

Given the current treatment landscape, there is a need for further efficacious, tolerable, and easily administered treatments at this point in the pathway of care.

5.2.2 Choice of comparator(s)

Dupilumab is chosen as comparator for the assessment of abrocitinib given that it has been standard of care in Denmark since 2018. Baricitinib has recently been recommended by the Medicines Council, 26 May 2021, as standard of care, though taking the short period that baricitinib has been available in Denmark into account, the vast majority

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of Danish AD patients who are candidates for systemic therapy will currently be treated with dupilumab. Also, in the baricitinib appraisal the expert committee views that data on efficacy, including EASI and scoring atopic dermatitis (SCORAD), indicates that baricitinib is less effective than dupilumab, though no significant differences were seen in the indirect comparisons between baricitinib and dupilumab (24). Accordingly, dupilumab and not baricitinib is chosen as a single comparator for this submission. Moreover, dupilumab is included as an active control-arm in the JADE COMPARE study assessing efficacy and safety of abrocitinib in adults with moderate to severe AD. No clinical study has assessed the efficacy and safety of both abrocitinib and baricitinib.

5.2.3 Description of the comparator

Generic name(s) (ATC-code) – Dupilumab (D11AH05)

Mode of action – Dupilumab is a fully humanized antibody to IL-4 receptor alpha subunit, which block both IL-4 and IL-13 signalling

Pharmaceutical form – solution for injection

Posology - 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.

Method of administration – subcutaneous injection

Should the pharmaceutical be administered with other medicines? Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Treatment duration/criteria for end of treatment – Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

Necessary monitoring, both during administration and during the treatment period – Not according to the SmPC, thus approximately 1.5% of patients is estimated to receive help from a nurse with administration (verified by clinical expert). In Denmark one blood test before initiating treatment with dupilumab is taken routinely by most clinicians (Clinical expert verification).

Packaging - 2 pieces of prefilled Dupilumab, either 200 mg or 300 mg

5.3 The intervention

Abrocitinib is indicated for moderate to severe atopic dermatitis in adults who are candidates for systemic therapy. Abrocitinib is an oral, JAK1-selective inhibitor that inhibits several key cytokine signalling pathways known to have an important role in the pathophysiologic characteristics of atopic dermatitis (32). The JAK family is a group of cytoplasmic tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) that mediate signalling pathways activated by various cytokines. Upon cytokine binding and receptor activation JAKs dimerize (as homo-or heterodimers) to form receptor complexes for signal transducer and activator of transcription proteins (STATs), which then phosphorylate, dimerize and translocate to the nucleus to regulate transcription of genes involved in various inflammatory responses (4, 33). Various cytokines relevant to the pathophysiology of atopic dermatitis, including IL-4, IL-13, IL-22, IL-31, TSLP and IFN-ɣ activate JAK1-containing heterodimeric receptors (4).

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- IL-4 and IL-13 contribute to the negative effect on skin barrier integrity by downregulating barrier proteins filaggrin, loricrin and involucrin, making the epidermis more penetrable by allergens and pathogens
- IL-4 is also a key player in antibody switching to IgE class and promoting T helper type 2 (Th2) cell differentiation, which in turn produce additional cytokines e.g., IL-4, IL-5, IL-13 and IL-31, leading to further skin inflammation and worsening of the AD condition
- IL-22 is associated with epidermal thickening, skin barrier disruption and increased expression of other pro-inflammatory cytokines e.g., TSLP and IL-33
- IL-31 and TSLP are pruritogenic cytokines that are heavily involved in triggering of inflammatory itch
- Th1 cell-derived IFN-ɣ, which is dominant in the chronic phase of AD, promotes exaggerated production of proinflammatory cytokines in keratinocytes (4, 33, 34).

Therefore, by inhibiting JAK1, abrocitinib inhibits the downstream functions of inflammatory cytokines in AD, reducing AD symptoms (including itch) and severity of the disease.

Posology – The recommended starting dose is 200 mg once daily.

- A dose of 100 mg once daily is recommended for patients ≥ 65 years of age. For other patients who may benefit from a starting dose of 100 mg, please refer to the SmPC.
- During treatment, the dose may be decreased or increased based on tolerability and efficacy. The lowest effective dose for maintenance should be considered. The maximum daily dose is 200 mg.

Method of administration – Abrocitinib is to be taken orally once daily with or without food at approximately the same time each day. In patients who experience nausea, taking tablets with food may improve nausea.

Treatment duration/criteria for treatment discontinuation - Discontinuation of treatment should be considered in patients who show no evidence of therapeutic benefit after 24 weeks.

Should the pharmaceutical be administered with other medicines? – Abrocitinib can be used with or without medicated topical therapies for atopic dermatitis.

Necessary monitoring, during administration, during the treatment period, and after the end of treatment –

- Lipid parameters should be assessed approximately 4 weeks following initiation of abrocitinib therapy and there after according to their risk for cardiovascular disease. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia.
- Please see table 2 below for recommended laboratory monitoring in accordance with the SmPC.

Need for diagnostics or other tests (i.e. companion diagnostics) – Screening prior to initiation of treatment:

- Patients should be screened for TB before starting treatment and yearly screening for patients in highly endemic areas for TB should be considered. Abrocitinib must not be given to patients with active TB.
- Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy and during therapy with abrocitinib.

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Table 2 Laboratory monitoring

Laboratory Measure	Monitoring guidance	Action
Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC), Absolute Neutrophil Count (ANC), and Haemoglobin (Hb)	Before treatment initiation, 4 weeks after initiation and thereafter according to routine patient management.	Platelets: Treatment should be discontinued if platelet counts are <50×103/mm^3.
		ALC: Treatment should be interrupted if ALC is < 0.5 × 103/mm^3 and may be restarted once ALC returns above this value. Treatment should be discontinued if confirmed.
		ANC: Treatment should be interrupted if ANC is <1 × 103/mm^3 and may be restarted once ANC returns above this value.
		Hb: Treatment should be interrupted if Hb < 8 g/dL and may be restarted once Hb returns above this value.
Lipid parameters	Before treatment initiation, 4 weeks after initiation and thereafter according to clinical guidelines for hyperlipidaemia.	Patients should be monitored according to clinical guidelines for hyperlipidaemia.

Atopic dermatitis is a common disease affecting the skin that often starts in early childhood. The clinical picture differs depending on the affected subjects age, infants and toddlers have different locations on the body affected by the disease compared with adolescents and adults. In some cases, the disease disappears during puberty, however, there are many individuals with the more severe forms of AD that respond inadequately to standard treatment, most often emollients and topical corticosteroids of different potency. There is a substantial unmet need in moderate to severe AD for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated given the limitations of existing treatments. Currently dupilumab is used as standard of care in Denmark, and baricitinib has recently also been recommended by the Medicines Council as standard of care. Notably, there is an unmet need for treatments that better address the two major drivers of disease burden in AD: itch and the appearance of the skin.

A proportion of patients in the Phase 3 dupilumab trials, 31%–56% of adults and 59% of adolescents treated with dupilumab did not achieve an EASI-75 response at Week 16 highlighting the need for additional treatment options (35-38). In a UK real-world study of dupilumab for the treatment of severe AD, some patients reported poor disease control prior to their fortnightly injections (39). The emergence of anti-drug antibodies seems to increase with shorter intervals in dupilumab dosing (40). Furthermore, dupilumab treatment is also associated with injection site reactions, eye complications (e.g., dry eyes, conjunctivitis, keratitis) and face and neck erythema (associated with burning and itching), potentially limiting treatment for some patients (41-45). Real-world studies have highlighted high rates of conjunctivitis, leading to discontinuation in some patients (46, 47).
Dupilumab is also only available as a subcutaneous injection, a dosage form often not preferred by patients, given the inconvenience of injections and for some needle phobia. A systematic literature review reported that multiple studies have shown that patients prefer oral formulations to injectable dosage forms, even when the oral medications were administered more frequently (47).

Abrocitinib is a new treatment option for moderate to severe AD, for which there are few current therapies. Abrocitinib, an oral JAK1 selective inhibitor, provides an alternative treatment and dosage form to subcutaneous Dupixent (dupilumab) and an alternative treatment option to Olumiant (baricitinib) for patients ≥ 18 years with moderate to severe AD. The proposed positioning for abrocitinib is for patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. Hence abrocitinib is relevant for the same patients who are candidates for dupilumab/baricitinib, are receiving dupilumab/baricitinib or have failed dupilumab/baricitinib. This represents a subgroup of the population studied in the clinical trial programme for abrocitinib, which across all trials was patients who previously had inadequate response to medicated topical therapy or were eligible for systemic treatments. However, clinical data for the full trial population for both abrocitinib and the comparator dupilumab will be presented in this appraisal as this represents the strongest data set. The data are in line with the proposed license for abrocitinib and the licensed indication for dupilumab. See App. K for our suggestion for implementation

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The primary efficacy studies on abrocitinib are summarized below. Two of these studies, the JADE MONO-1 and JADE MONO-2 do not include a comparison to other treatments. Only one study includes an active control arm of dupilumab, the most relevant comparator in a Danish setting. This pivotal phase 3 study JADE COMPARE explores efficacy and safety of abrocitinib in combination with topical medicated therapy in adults. JADE COMPARE is currently the best supportive evidence for a comparison between abrocitinib and dupilumab for the adult population receiving combination therapy. Systemic therapy combined with topical medicated therapy is standard treatment in Denmark and a further search for literature encompassing the adult population has not been performed. The JADE MONO-1 and MONO-2 studies have been included as supportive evidence and additional evidence for abrocitinib as these studies demonstrates the value of abrocitinib as monotherapy, though this is not common practice in Denmark.

6.2 List of relevant studies

A list of identified studies included can be seen in table 3. For detailed information about included studies, refer to appendix B. Refer to appendix A for a list of ongoing and completed studies investigating abrocitinib not included in this application.

Besides the randomised controlled trials JADE COMPARE, JADE MONO-1 and JADE MONO-2, a Pfizer sponsored network meta-analysis (48) is included as supportive evidence for the comparative analyses in section 7.1.4.

Table 3 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
(49) Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis, Bieber, NEJM, 2021	JADE COMPARE	NCT03720470	Completed (October 29, 2018 – December 27, 2019)	abrocitinib vs. dupilumab in combination with background medicated topical therapy for

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
				adults (≥ 18 years) with moderate to severe AD
(50) Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial, Simpson, Lancet, 2020	JADE MONO-1	NCT03349060	Completed (December 7, 2017 – March 26, 2019)	abrocitinib vs. dupilumab monotherapy for adults with moderate to severe AD
(51) Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis, Silverberg, JAMA Dermatol., 2020	JADE MONO-2	NCT03575871	Completed (June 29, 2018 – August 13, 2019)	abrocitinib vs. dupilumab monotherapy for adults with moderate to severe AD

7. Efficacy and safety

The abrocitinib trial program includes a vast number of outcomes, for simplicity, we focus on primary and most relevant secondary outcomes and endpoints considered important in national and international guidelines and by the Medicines Council as described in assessments of dupilumab and baricitinib. See appendix A table A1a for list of outcomes and measure and appendix D for further description of the outcomes included in this submission.

Trials in the clinical development program for abrocitinib in moderate to severe AD relevant for this appraisal are summarized in section 7.1 and further detailed in appendix B and C. At 12 weeks of therapy, compared with placebo, both doses (i.e., 100 mg QD and 200 mg QD) of abrocitinib evaluated in the pivotal trials demonstrated significantly greater improvements in skin clearance in both the Investigator's Global Assessment (IGA) and 75% improvement in Eczema Area Severity Index score (EASI-75) responses both as monotherapy and in combination with background topical therapies. Abrocitinib has also demonstrated a fast onset of itch relief, with greater proportions of patients in both abrocitinib 100 mg QD and 200 mg QD groups achieving PP-NRS4 (an improvement in PP-NRS of ≥4 points from baseline) compared with placebo as early as week 2 of treatment (49-51). The fast onset of action with abrocitinib was also demonstrated in comparison to dupilumab, as a greater proportion of patients treated with abrocitinib 200 mg QD achieved PP-NRS4 at two weeks of therapy (49). Similarly, as early as two weeks of treatment, patients treated with abrocitinib experienced greater improvements in QoL (i.e., Dermatology Life Quality Index [DLQI]) which was sustained throughout week 12 compared with placebo in pivotal trials (52). After 12-16 weeks of treatment the overall efficacy of abrocitinib was comparable to dupilumab (49).

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The Integrated Safety Summary demonstrates the safety and tolerability of abrocitinib 100 mg and 200 mg QD for the treatment of patients with moderate to severe AD in adults, both and in combination with topical therapy and as monotherapy. The evaluation of the abrocitinib tolerability and safety profile is primarily drawn from safety assessments in six studies in the AD clinical development program (Phase 2b dose ranging study, JADE MONO-1, JADE MONO-2, JADE COMPARE, JADE REGIMEN, and JADE EXTEND) (53).
Acute and long-term use of abrocitinib is well-tolerated and has a safety profile that supports use in patients with moderate to severe AD. Most AEs were mild, self-limited, and seldom required interruption or permanent discontinuation of therapy. The most common AEs associated with abrocitinib were nausea and headache, which tended to occur in the first few weeks of therapy (32, 53).

7.1 Efficacy and safety of abrocitinib compared to dupilumab for adults with moderate to severe atopic dermatitis

7.1.1 Relevant studies

The efficacy and safety of abrocitinib in combination with background medicated topical therapies and as monotherapy over 12-16 weeks were evaluated in pivotal Phase 3 randomised, double-blind, placebo-controlled studies (JADE COMPARE, JADE MONO-1 and JADE MONO-2). The patients in these 3 studies were 18 (JADE COMPARE) or 12 years of age and older (only JADE MONO-studies) with moderate to severe atopic dermatitis as defined by Investigator's Global Assessment (IGA) score ≥ 3, Eczema Area and Severity Index (EASI) score ≥ 16, BSA involvement ≥ 10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) ≥ 4 at baseline prior to randomisation. Patients who had a prior inadequate response or for whom topical treatments were medically unadvisable, or who had received systemic therapies were eligible for inclusion. All patients who completed the parent studies were eligible to enroll into the long-term extension study JADE EXTEND.
For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C.

7.1.1.1 Relevant studies for intervention

JADE COMPARE (NCT03720470) was a Phase 3 multicenter, double-blind, double-dummy, parallel group, randomised, placebo-controlled, trial of the efficacy and safety of abrocitinib and dupilumab in the treatment of adults with moderate to severe AD on background topical therapy. The study design for JADE COMPARE is presented in figure 1. Following screening, subjects were randomised to one of three treatment groups: abrocitinib 100 mg QD, abrocitinib 200 mg QD, and dupilumab 300 mg once every two weeks, with an initial loading dose of 600 mg [dosing per label] – plus background topical therapy in all arms. Patients in each treatment group were also administered an oral or injectable dummy (patients in control groups were given placebos of both dosage forms) and treated for 16 weeks. The patients, investigators, and representatives of the sponsor were unaware of the trial-group assignments. After the 16-week treatment period, patients in the abrocitinib + background topical therapy treatment groups continued on their dose for another 4 weeks, patients in the placebo + background topical therapy group were randomised to either abrocitinib 100 mg or 200 mg QD for 4 weeks, and the patients in the dupilumab + background topical therapy group were administered an oral placebo QD at this time to allow for an injection washout period prior to entering the long-term safety study EXTEND.
The primary objective of JADE COMPARE was to evaluate the efficacy of abrocitinib vs placebo in adults with moderate to severe AD on background medicated topical therapy at 12 weeks. The secondary objective was to compare abrocitinib vs dupilumab in attaining a clinically meaningful pruritis response at 2 weeks. Patients were eligible to participate if they were 18 years of age or older and had at least a 1-year history of atopic dermatitis that was moderate to severe at baseline, as determined by a score of 3 or higher on the IGA (scored on a 5-point scale [0,

clear; 1, almost clear; 2, mild; 3, moderate; and 4, severe]); a score of at least 16 on the EASI (scores range from 0 to 72, with higher scores indicating greater severity); at least 10% body-surface area (BSA) involvement; and a score of at least 4 on the PP-NRS (scores range from 0 to 10, with higher scores indicating greater pruritus). During the 6 months before screening, all the patients had an inadequate response to topical medications that were given for at least 4 weeks or a need for systemic therapy to control their disease. The primary end points were an IGA response (defined as a score of 0 or 1 on the IGA, with an improvement of ≥2 points from baseline) and an EASI-75 response (defined as ≥75% improvement from baseline in the score on the EASI) at week 12. The three key secondary end points were itch response (defined as ≥4-point improvement from baseline in the score on the PP-NRS) at week 2 and IGA and EASI-75 responses at week 16 (49).

Figure 1 JADE COMPARE: Study design

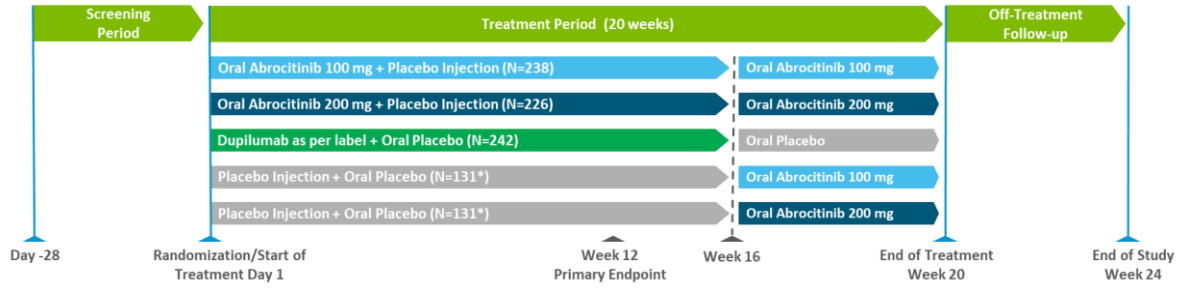

Figure source Pfizer Inc. * Both placebo groups combined included a sample size of 131. All treatment arms also received standardized topical therapies (medium or low potency topical corticosteroids, topical calcineurin inhibitors [e.g., tacrolimus, pimecrolimus], or a phosphodiesterase 4 inhibitor [e.g., crisaborole]) (49) .

JADE MONO-1 (NCT03349060) was a Phase 3 international, double-blind, parallel group, randomised, placebo-controlled, trial of the efficacy and safety of abrocitinib in the treatment of moderate to severe AD in adolescents (patients aged ≥12 years) and adults. Following screening, subjects were randomised 2:2:1 to one of 2 treatment groups (abrocitinib 100 mg and 200 mg) or placebo QD and treated for 12 weeks (Figure 2), using a central randomisation scheme provided by an interactive response technology system. Randomisation was stratified by baseline disease severity (Investigator Global Assessment score 3 or 4) and age group (<18 years or ≥18 years). Patients, investigators, and the funder of the study were masked to study treatment. The placebo tablets were identical to the abrocitinib 100 mg tablets in size, colour, shape, and odour. Patients were given two bottles, and were instructed to take one tablet from each bottle: for the 100 mg group, one bottle contained placebo and the other contained abrocitinib 100 mg tablets; for the 200 mg group, both bottles contained abrocitinib 100 mg tablets; and for the placebo group, both bottles contained placebo tablets. Follow-up was conducted through 28 days following the last dose. All eligible patients had a confirmed diagnosis of atopic dermatitis for at least 1 year before randomisation (according to Hanifin and Rajka diagnostic criteria); had moderate to severe AD (IGA score ≥3, EASI score ≥16, percentage of BSA affected ≥10%, and PP-NRS score ≥4) at the baseline visit. Eligible patients also had a documented recent history (in the 6 months before screening) of inadequate response to treatment with topical corticosteroids or topical calcineurin inhibitors given for at least 4 weeks, or were patients for whom topical treatments were otherwise medically inadvisable, or required systemic therapies to control their disease. The coprimary endpoints were the proportion of patients who had achieved an IGA response (score of 0 [clear] or 1 [almost clear] and a ≥2-grade improvement from baseline), and the proportion of patients who had achieved at least a 75% improvement in EASI score from baseline (EASI-75) at week 12 of treatment. Key secondary endpoints were the proportion of patients who achieved a PP-NRS response (≥4 point improvement from baseline in PP-NRS score) at weeks 2, 4, and 12, and least squares mean (LSM) change from baseline in PSAAD (11-item questionnaire developed to measure daily symptoms of atopic dermatitis) total score at week 12 (50).

Figure 2 JADE MONO-1: Study design

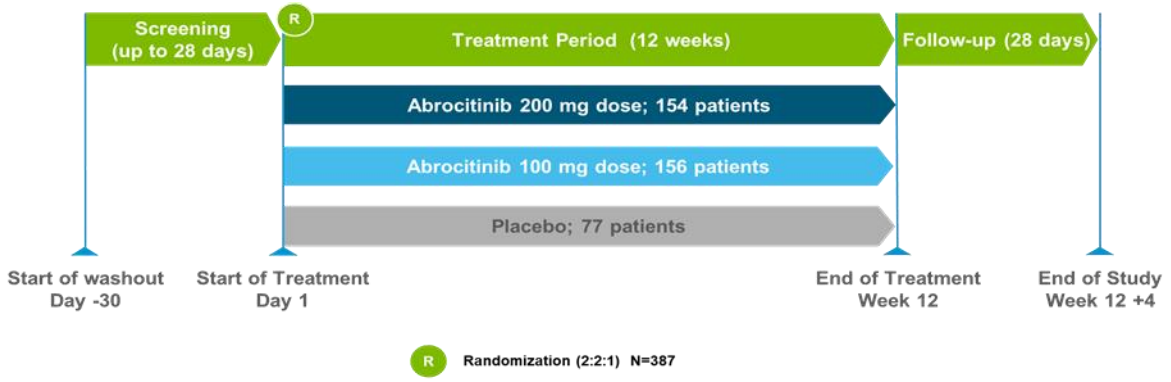

Figure source Pfizer Inc.

JADE MONO-2 (NCT03575871) study was identical to the study of JADE MONO-1, presented above. A diagram of the study design for JADE MONO-2 is presented in Figure 3 (51). JADE MONO-2 also included enrollment from Asian sites in contrast to JADE MONO-1 (50, 51).

Figure 3 JADE MONO-2: Study design

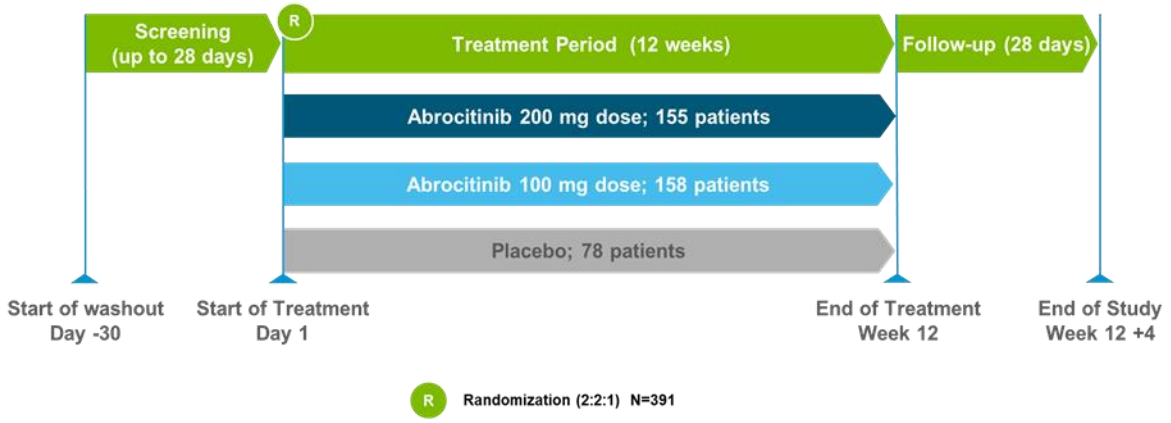

Figure source Pfizer Inc.

Supporting trials

In addition to the three pivotal studies for abrocitinib, data from a long-term extension study (JADE EXTEND) are included in the integrated safety summary. This trial was designed to explore the long-term safety and efficacy of abrocitinib for patients who completed a qualifying study (e.g. JADE MONO-1, JADE MONO-2 or JADE COMPARE) or the 12-week run-in period of the JADE REGIMEN study. Patients who were previously randomised to medicinal product 100 mg or 200 mg once daily in parent studies continued the same dose in JADE EXTEND as in the parent study. In JADE EXTEND, patients received double-blind treatment until the parent study was completed, after which patients received single-blind treatment (treatment assignment disclosed to the investigators but not to the patients). Those who received placebo or active comparator in the parent trial were randomised to receive either 100 mg or 200 mg abrocitinib (32).

A further study (JADE REGIMEN) is also summarised; following an open-label run-in period with abrocitinib 200 mg, responders (defined as those achieving an IGA of clear [0] or almost clear [1], a reduction from IGA baseline of ≥2 points, and reaching an EASI-75 response compared to baseline) were randomised to "dose down" to 100 mg or placebo in the maintenance period. If at any time during the maintenance period a flare was experienced (defined as a loss of response associated with a decrease of at least 50 % of the EASI response at Week 12 and an IGA score ≥2) the patient began a 12-week rescue treatment period (open-label abrocitinib 200 mg with concomitant medicated topical therapy). This study provides data on the ability to recapture response using abrocitinib 200 mg in combination with topical therapy as a rescue treatment for flares (54). JADE REGIMEN is included in the integrated safety summary.

7.1.1.2 Relevant studies for comparator

As JADE COMPARE includes the comparator dupilumab as an active control arm, this study is also relevant for the comparator. Please refer to section 7.1.1.1 for a description of the study.

7.1.1.3 Method of synthesis

The clinical effectiveness of abrocitinib in the treatment of moderate to severe AD has been assessed in an extensive clinical trial programme, including three pivotal Phase 3 clinical trials (considering both 200 mg and 100 mg doses of abrocitinib). Importantly, JADE COMPARE included a comparison between abrocitinib 100 mg/200 mg and dupilumab.

- JADE COMPARE evaluated 200 mg and 100 mg abrocitinib in combination with background medicated topical therapy vs each of dupilumab (300 mg according to label) and placebo in adults (≥18 years).
- JADE MONO-1 and JADE MONO-2 were replicate trials comparing 200 mg and 100 mg abrocitinib monotherapy with placebo in patients aged 12 years or older.

In all three trials, the use of rescue medication was prohibited.

In this submission, abrocitinib and the comparator treatment dupilumab for adults are explored in combination with background medicated topical therapy; further, the use of as monotherapy is considered in addition to the comparative analysis between abrocitinib and dupilumab with medicated topical therapy.

The JADE COMPARE support the adult combination therapy analysis respectively and are therefore most relevant to decision making and represents how these treatments are likely to be used in the clinical practice. In the JADE COMPARE study dupilumab is included as an active control-arm, though no formal multiplicity-adjusted comparisons were made between dupilumab and other treatment groups, except for PP-NRS4 response comparison at Week 2 between dupilumab and abrocitinib. Indirect comparisons on other included outcomes from the JADE COMPARE trial are made in appendix D "Results per study".

For JADE COMPARE, JADE MONO-1 and MONO-2 efficacy analysis were performed using the full analysis set (FAS), defined as all patients who were randomised and received ≥1 dose of treatment. The coprimary efficacy endpoints were analysed using the Cochran–Mantel–Haenszel test, adjusted by baseline disease severity (moderate/severe) and (for MONO trials only) age and for a given dose, both endpoints must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of patients achieving IGA response (similarly for EASI-75), along with a 95% confidence interval (using the normal approximation for the difference in binomial proportions) was reported. Key secondary endpoints and all other binary endpoints

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were also analysed using the Cochran–Mantel–Haenszel test. Missing responses for patients who had permanently withdrawn from the trial were defined as no response with respect to the primary endpoints at all visits after withdrawal; any observations that were missing intermittently (including baseline values) were considered to be missing complete at random and remained missing in the analysis. For continuous endpoints, a mixed-effects model with repeated measures that used all observed data was applied, including the factors (fixed effects) for treatment group, randomization strata (age, disease severity), visit, treatment-by-visit interaction, and relative baseline value. No imputations were made for missing data because the mixed-effect model with repeated measures yielded valid inferences under the assumption of a missing-at-random mechanism.

No indirect comparison is performed between abrocitinib and dupilumab regarding the monotherapy treatments as this is not standard treatment in Denmark. However data from the JADE MONO-1 and MONO-2 studies are included as supportive and additional evidence to present the value of abrocitinib as a monotherapy treatment option and therefore narratively described in section 7.1.3.1 and 7.1.3.2. The studies included both adolescents and adults and no rescue treatment were allowed in the trials (appendix C).

Safety data is described in section 7.1.3.3.

7.2 Efficacy and safety – results per study

The clinical effectiveness of abrocitinib in the treatment of moderate to severe AD was assessed in the three pivotal trials JADE COMPARE, JADE MONO-1, and JADE MONO-2. In all three trials the co-primary endpoints were proportions of patients who had achieved an;

- Investigator Global Assessment response (IGA 0 [clear] or 1 [almost clear] with ≥2-point improvement from baseline) and
- EASI-75= 75% improvement in Eczema Area Severity Index score

Analysis of the efficacy data was conducted on the full analysis set (FAS) consisting of all randomised patients who received at least one dose of the study drug with non-responder imputation for missing data. Description of outcomes in scope of this appraisal can be seen in appendix D.

The full trial populations for the pivotal RCTs included both patients who had received prior systemic therapy and patients who had not received prior systemic therapies. This population is broader than the proposed positioning corresponding to Danish clinical practice, where patients should previously have been treated with at least one systemic treatment for AD. However, no attempt has been made to stratify data from the JADE COMPARE trial as this will limit the population size which might increase uncertainty of the results.

7.2.1.1 Co-primary endpoints

IGA and EASI-75

IGA 0 (clear) or 1 (almost clear) with ≥2-point improvement from baseline and EASI-75 are the two co-primary endpoints included in all pivotal trials for abrocitinib. Higher proportions of abrocitinib treated patients than placebo treated patients achieved IGA and EASI-75 responses at week 12 in JADE COMPARE and both the coprimary endpoints were met. Both abrocitinib treatment groups were superior to placebo for IGA and EASI-75 response at Week 12 ($p<0.001$ for all comparisons; Table X):

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- IGA response (Week 12): statistically significantly higher proportions of patients achieved an IGA response of clear (0) or almost clear (1) with ≥2-point improvement from baseline for abrocitinib 200 mg (48.4%) and 100 mg (36.6%) compared with placebo (14.0%).
- EASI-75 response (Week 12): statistically significantly higher proportions of EASI-75 responders were observed for abrocitinib 200 mg (70.3%) and abrocitinib 100 mg (58.7%) compared with placebo (27.1%).

Although the primary objective for the co-primary endpoints was to compare abrocitinib doses with placebo, data is also presented for dupilumab. Significantly more patients receiving abrocitinib 200 mg than dupilumab achieved IGA and EASI-75 responses at Week 12. Response rates were similar between the abrocitinib 100 mg and the dupilumab treatment group (Table 4 and appendix D table A3a).

In addition, the JADE MONO-1 and JADE MONO-2 studies met both co-primary endpoints at week 12. In both MONO-1 and MONO-2 studies, the proportion of patients who achieved IGA and EASI-75 at week 12 were significantly higher for abrocitinib 200 mg and 100 mg compared with placebo (Appendix D table A3c and table A3d):

- IGA MONO-1; difference vs placebo 36.0% (95% CI, 26.2, 45.7) and 15.8% (95% CI, 6.8, 24.8) for abrocitinib 200 mg and 100 mg respectively,
- IGA MONO-2; difference vs placebo 28.7% (95% CI, 18.6, 38.8) and 19.3% (95% CI, 9.6, 29.0) for abrocitinib 200 mg and 100 mg respectively
- EASI-75 MONO-1; difference vs placebo 51.0% (95% CI, 40.5, 61.5) and 27.9% (95% Cl, 17.4, 38.3) for abrocitinib 200 mg and 100 mg respectively,
- EASI-75 MONO-2; difference vs placebo 50.5% (95% CI, 40.0, 60.9) and 33.9% (95% CI, 23.3, 44.4) for abrocitinib 200 mg and 100 mg respectively.

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Table 4 Co-primary endpoints at Week 12, JADE COMPARE, FAS (adults, combination therapy, full trial population)

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
IGA response				
IGA responders, n/N (%)	86/235 (36.6)	106/219 (48.4)	88/241 (36.5)	18/129 (14.0)
Difference from placebo, % (95% CI) p-value	23.1 (14.7, 31.4) p<0.001	34.8 (26.1, 43.5) p<0.001	22.5 (14.2, 30.9) NA†	–
Difference between abrocitinib and dupilumab	[redacted]	[redacted]	-	-
EASI-75 response				
EASI-75 responders, n/N (%)	138/235 (58.7)	154/219 (70.3)	140/241 (58.1)	35/129 (27.1)
Difference from placebo, % (95% CI) p-value	31.9 (22.2, 41.6) p<0.001	43.2 (33.7, 52.7) p<0.001	30.9 (21.2, 40.6) NA†	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–

†No formal multiplicity-adjusted comparisons were made between dupilumab and other treatment groups, except for PP-NRS4 response comparison at Week 2 between dupilumab and abrocitinib. Abbreviations: CI, confidence interval; EASI, Eczema Area Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; NA, not applicable.

7.2.1.2 Key secondary and other endpoints

EASI-75 at Week 16

Both doses of abrocitinib were superior to placebo for the key secondary endpoint EASI-75 response at Week 16 (p<0.001); Table 5). The proportion of EASI-75 responders was numerically greater for abrocitinib 200 mg compared with dupilumab, and numerically lower for abrocitinib 100 mg group compared with dupilumab; however no statistically significant differences were observed (Table 5 and appendix D table A3a).

Table 5 Co-primary endpoints at Week 16, JADE COMPARE, FAS (adults, combination therapy, full trial population)

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
EASI75 (key secondary endpoint)				
EASI-75 responders, n/N (%)	138/229 (60.3)	157/221 (71.0)	152/232 (65.5)	38/124 (30.6)
Difference from placebo, % (95% CI) p-value	29.7 (19.5, 39.9) p<0.001	40.4 (30.4, 50.4) p<0.001	34.7 (24.6,44.8) NA[†]	–
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	–	–

Abbreviations: CI, confidence interval; EASI, Eczema Area Severity Index; FAS, full analysis set.

SCORAD

SCORAD evaluates disease extent, clinical signs, and subjective symptoms. In this appraisal SCORAD is presented as least squares mean (LSM) change from baseline in appendix D table A3a for JADE COMPARE, given that these results are published (49). Overall, the reduction from baseline in SCORAD were similar between abrocitinib and dupilumab. The abrocitinib 200 mg group was associated with a numeric greater reduction from baseline compared to dupilumab and abrocitinib 100 mg were associated with a numeric lower reduction from baseline compared to dupilumab at week 12 (Table 6 and appendix D table A3a).

Table 6 SCORAD at Week 12, JADE COMPARE, FAS (adults, combination therapy, full trial population)

	Abrocitinib 100 mg N=237	Abrocitinib 200 mg N=225	Dupilumab 300 mg N=241	Placebo N=129
SCORAD (other secondary endpoint)				
LSM change from baseline at week 12	-36.6	-44.9	-39.7	-23.0
Difference from placebo, % (95% CI) p-value	-13.6 (-17.6, -9.7) <0.0001	-21.9 (-25.9, -18.0) <0.0001	-16.7 (-20.7, -12.8)	–
Difference between abrocitinib and dupilumab (95% CI)	[redacted]	[redacted]	–	–

Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least squares mean; SCORAD, scoring atopic dermatitis.

In JADE MONO-1 both abrocitinib treatment groups demonstrated significantly greater proportions of patients with SCORAD-75 responses compared with the placebo group at week 12, see appendix D table A3c (50). In JADE MONO-2, SCORAD is calculated as LSM percent change from baseline, where a negative change indicates improvement. The

LSM percent change was -45.8 in the abrocitinib 100 mg group, -56.2 in the abrocitinib 200 mg group and -22.7 in the placebo group, which for both abrocitinib doses showed a significantly greater reduction from baseline compared to placebo at week 12 (difference vs. placebo -23.1 (95% CI, (-32.3, -13.9) abrocitinib 100 mg and -33.4 (95% CI, (-42.6, -24.3) abrocitinib 200 mg), see also appendix D table A3d (51).

PP-NRS

PP-NRS is a measure for itch relief. Itch is a bothersome symptom in atopic dermatitis and is key to treat. In JADE COMPARE abrocitinib 200 mg was superior to dupilumab in the first key secondary endpoint of PP-NRS4 response at week 2 ($p<0.001$), indicating earlier onset of action in itch relief than dupilumab (table 7 and appendix D table A3a). Although not reaching statistical significance, the proportion of PP-NRS4 responders at Week 2 in the abrocitinib 100 mg treatment group was numerically higher vs dupilumab (31.8% vs 26.4%), see table 7 and appendix D table A3a. The median time to itch response in each trial group was 13.0 (10.0, 16.0) days for abrocitinib 200 mg, 29.0 (16.0, 56.0) days for abrocitinib 100 mg, and 31.0 (29.0, 57.0) days for dupilumab. At week 12 no significant differences was observed between abrocitinib 200 mg and dupilumab or between abrocitinib 100 mg and dupilumab which was maintained through week 16 (49) see table 7, appendix D table A3a.

In JADE MONO-1 and JADE-MONO-2, the PP-NRS scores decreased (improvement) between baseline and week 12 for both abrocitinib doses compared with placebo, and this reduction was observed within 1 day of the first dose of treatment (50, 51). In JADE MONO-1 for abrocitinib 200 mg differences vs. placebo at week 2 was 42.5% (95% CI, 33.6, 51.4) and at week 12 the difference was 41.7% (95% CI, 29.6, 53.9). For abrocitinib 100 mg differences vs. placebo at week 2 was 18.0% (95% CI, 10.2, 25.8) and at week 12 the difference was 22.5% (95% CI, 10.3, 34.8) (50) (appendix D table A3c). In JADE MONO-2 for abrocitinib 200 mg differences vs. placebo at week 2 was 31.2% (95% CI, 22.3, 40.2) and at week 12 the difference was 43.9% (95% CI, 32.9, 55.0). For abrocitinib 100 mg differences vs. placebo at week 2 was 19.2% (95% CI, 11.0-27.4) and at week 12 the difference was 33.7% (95% CI, 22.8, 44.7) (51) (appendix D table A3d).

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Table 7 PP-NRS4 at Weeks 2 and 12, JADE COMPARE, FAS (adults, combination therapy, full trial population)

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
PP-NRS4 response at week 2 (key secondary endpoint)				
PP-NRS4 responders, n/N (%)	75/236 (31.8)	111/226 (49.1)	63/239 (26.4)	18/130 (13.8)
Difference from placebo, % (95% CI) p-value	17.9 (9.5, 26.3) p<0.001	34.9 (26.0, 43.7) p<0.001	12.5 (4.4, 20.7) NA†	–
Difference between abrocitinib and dupilumab (95% CI)	5.2 (–2.9, 13.4) p=0.2	22.1 (13.5, 30.7) p<0.001	–	–
PP-NRS4 response at week 12 (other secondary endpoint)				
PP-NRS4 responders, n/N (%)	105/221 (47.5)	137/217 (63.1)	122/224 (54.5)	35/121 (28.9)
Difference from placebo, % (95% CI) p-value	18.5 (8.0, 28.9) p=0.0009	33.7 (23.4, 44.1) P<0.0001	25.5 (15.2, 35.9) NA†	-
Difference between abrocitinib and dupilumab (95% CI)	[redacted]	[redacted]	-	-

†No formal multiplicity-adjusted comparisons were made between dupilumab and other treatment groups, except for PP-NRS4 response comparison at Week 2 between dupilumab and abrocitinib.

Abbreviations: CI, confidence interval; FAS, full analysis set; PP-NRS, Peak Pruritus Numerical Rating Scale.

POEM

During the study treatment period up to Week 16 in JADE COMPARE, there was a clear separation in the change in POEM total score between the abrocitinib treatment groups and placebo. Abrocitinib 200 mg and 100 mg groups showed statistically significant improvement (reduction from baseline) compared with placebo at all time points. The POEM score was also significantly improved (lower) in abrocitinib 200 mg group than in dupilumab group at Week 12 (table 8 and appendix D table A3a). Despite numerical differences, no statistically significant differences were observed between abrocitinib 100 mg and dupilumab in this endpoint of symptom control at week 12 (49) see table 8 and appendix A3a.

Table 8 POEM at Week 12, JADE COMPARE, FAS (adults, combination therapy, full trial population)

	Abrocitinib 100 mg N=238	Abrocitinib 200 mg N=226	Dupilumab 300 mg N=241	Placebo N=131
POEM				
LSM from baseline at week 12	-9.6	-12.6	-10.8	**-5.1**
Absolute difference from placebo, % (95% CI) p-value	-4.4 (-6.0, -2.9) <0.0001	-7.5 (-9.1, -6.0) <.0001	-5.7 (-7.2, -4.2)	–
Absolute difference between abrocitinib and dupilumab (95% CI)	[redacted]	[redacted]	–	–

Abbreviations: CI, confidence interval; FAS, full analysis set; LSM, least squares mean; POEM, Patient oriented eczema measures.

The change from baseline in POEM scores were statistically significantly greater for both abrocitinib groups compared with placebo across all time points from week 2 to week 12 in both JADE MONO-1 and JADE MONO-2 (50, 51). At week 12, the LMS percent change from baseline was -6.8 in the abrocitinib 100 mg group (difference vs. placebo -3.1 (95% CI, -5.2, -0.9)), -10.6 in the abrocitinib 200 mg group (difference vs. placebo -6.9 (95% CI, -9.0, -4.7)) and -3.7 in the placebo group in the JADE MONO-1, see appendix D table A3c. In JADE MONO-2 the LMS percent change from baseline at week 12 was -8.7 in the abrocitinib 100 mg group (difference vs. placebo -5.1 (95% CI, -7.2, -3.1)), -11.0 in the abrocitinib 200 mg group (difference vs. placebo -7.4 (95% CI, -9.5, -5.3)) and -3.6 in the placebo group, see appendix D table A3d.

DLQI/CDLQI

During the study period, both abrocitinib treatment groups achieved significantly greater improvement vs placebo in health-related quality of life as assessed by DLQI in all trials (49-51). In JADE COMPARE a clinically meaningful, ≥4-point improvement in DLQI occurred in a statistically significantly greater proportion of patients in both abrocitinib + topical therapies groups compared with placebo + topical therapies at week 12. The abrocitinib 200 mg treatment group also had higher proportion of DLQI ≥4 responders than dupilumab at Week 12 (86.4% vs 81.8%, see table 9 and appendix A3a), although no statistical differences were observed (49).

Additionally, as early as two weeks of treatment, patients treated with abrocitinib experienced greater improvements in QoL (i.e., Dermatology Life Quality Index [DLQI]) which was sustained throughout week 12 compared with placebo in pivotal trials (52). In JADE MONO-1 and JADE MONO-2 both abrocitinib doses also showed a significantly greater improvement compared to placebo in both DLQI and CDLI at week 12 . Please refer to appendix D table A3c and A3d for results (50, 51).

Table 9 DLQI≥4 at Week 12, JADE COMPARE, FAS (adults, combination therapy, full trial population)

	Abrocitinib 100 mg	Abrocitinib 200 mg	Dupilumab 300 mg	Placebo
DLQI				
DLQI≥4 responders, n/N (%)	171/229 (74.7)	190/220 (86.4)	193/236 (81.8)	70/124 (56.5)
Difference from placebo, % (95% CI) p-value	18.3 (8.0, 28.6) p=0.0004	29.5 (19.7, 39.3) p<0.0001	25.3 (15.3, 35.3)	-
Difference between abrocitinib and dupilumab, % (95% CI)	[redacted]	[redacted]	-	-

Abbreviations: CI, confidence interval; DLQI, dermatology life quality index; FAS, full analysis set

7.2.1.3 Safety

Serious adverse events

Serious adverse events (SAE) are reported in the clinical trials, and data on SAE and not adverse reactions (AR) are therefore used in this submission for comparison on trial-arms. Data from JADE COMPARE are depicted in table 10 below. For additional analysis on the included trials refer to appendix E. The comparison indicates a non-statistically significant difference between abrocitinib and dupilumab in the proportion of patients experiencing serious adverse events, with an absolute risk difference between abrocitinib 200mg and dupilumab of 0.06% and a difference of 1.7% between abrocitinib 100 mg and dupilumab. Overall there were very few serious adverse events in the study arms.

Table 10 Serious adverse events, 16 weeks of treatment, JADE COMPARE, Safety analysis set (adults, combination therapy)

JADE COMPARE	Abrocitinib 100 mg N=238	Abrocitinib 200 mg N=226	Dupilumab 300 mg N=242	Placebo N=131
SAE				
Number of patients experience SAE (%)	6 (2.5)	2 (0.9)	2 (0.8)	5 (3.8)
Difference from placebo, % (95% CI)	-1.3 (-5.1, 2.5)	-2.9 (-6.43, 0.57)	-3.0 (-6.46, 0.48)	-
Difference between abrocitinib and dupilumab, % (95% CI)	1.7 (-0.60, 3.99)	0.06 (-1.61, 1.73)	-	-

Abbreviations: CI, confidence interval; SAE, serious adverse events

In JADE COMPARE, the percentages of patients who had serious or severe adverse events during the treatment period or adverse events that led to discontinuation of the trial regimen were similar across the trial groups. The incidence of

subjects reporting adverse events (AE) was higher in the abrocitinib 200 mg QD group compared to the abrocitinib 100 mg QD, dupilumab and placebo treatment groups.

Two malignant neoplasms (confirmed by the external data monitoring committee) were reported, one in the 200-mg abrocitinib group (cutaneous squamous-cell carcinoma) and one in the dupilumab group (invasive intraductal breast neoplasia) (49). In JADE MONO-1 SAEs were reported in five (3%) patients in the abrocitinib 100 mg group, five (3%) patients in the abrocitinib 200 mg group and three (4%) patients the placebo group. Among these only two SAEs were considered treatment related. One patient in the abrocitinib 200 mg group developed chronic inflammatory bowel disease during the treatment period, and one patient in the abrocitinib 100 mg developed acute pancreatitis. Treatment were discontinued in both cases (50). In JADE MONO-2 SAEs were reported for two (1.3%) patients in the 200-mg group, five (3.2%) in the 100-mg group, and one in the placebo group (1.3%). There were no treatment-related SAEs in the 200-mg group. SAEs that were considered related to treatment were reported for 2 patients in the 100-mg group. One patient developed herpangina, and 1 developed pneumonia. Two cases of serious adverse events considered related to treatment were reported for one patient in the placebo group. One case of eczema herpeticum and one case of staphylococcal infection. Treatment were discontinued in all cases (51). No malignancies were observed in either JADE MONO-1 and JADE MONO-2 (50, 51). No deaths, major cardiovascular adverse events, or thromboembolic events occurred during the treatment period in any of the trials (49-51).

Summary of the safety profile

In the placebo-controlled study JADE COMPARE which also included a dupilumab treatment group, the incidence of subjects reporting adverse events (AE) was higher in the abrocitinib 200 mg QD group compared to the abrocitinib 100 mg QD, dupilumab and placebo treatment groups. The percentages of subjects reporting SAEs, severe AEs, and AEs leading to study discontinuation were low and similar across the abrocitinib, placebo, and dupilumab treatment groups. Abrocitinib treated subjects were more likely to experience nausea, herpes simplex, acne, and herpes zoster. Dupilumab-treated subjects were more likely to experience conjunctivitis (49).

Abrocitinib

The abrocitinib Integrated Safety Summary addresses the safety and tolerability of abrocitinib 100 mg and 200 mg QD for the treatment of patients with moderate to severe AD in adults, both in combination with topical therapy and as monotherapy. A total of 3 128 patients were treated with abrocitinib in clinical studies in atopic dermatitis representing 2 089 patient-years of exposure. There were 994 patients with at least 48 weeks of exposure. Five placebo controlled studies were integrated (703 patients on 100 mg once daily, 684 patients on 200 mg once daily and 438 patients on placebo) to evaluate the safety of abrocitinib in comparison to placebo for up to 16 weeks. In addition also the LTE study, JADE EXTEND was included in the comprehensive review of longer term safety data (32). These data were included in two pre-specified pools to address specific goals: a Primary Safety Pool, this dataset was used to assess abrocitinib safety relative to placebo, dose–response relationships for frequent adverse drug reactions, and laboratory changes and an All Exposure Pool which enabled assessment of incidence rates, changes in laboratory parameters, and, where possible, risk factors for AEs (53).

The primary Safety Pool includes studies with a placebo comparator, of similar duration (12 to 16 weeks), same doses of abrocitinib, similar patient population, and comparable safety outcome assessment. Subjects in this pool included (53):

- Participants in the Phase 2b AD dose ranging study ((NCT02780167)
- Participants in the two pivotal monotherapy studies (JADE MONO-1 and MONO-2)
- Participants in the combination therapy study that included a dupilumab treatment arm (JADE COMPARE)

Table 11 Adverse events (by PT) in abrocitinib placebo controlled studies (Primary safety pool)

Adverse event	Placebo (N=342)	Abrocitinib 100 mg QD (N = 608)	Abrocitinib 200 mg QD (N = 590)
Acne	0	10 (1.6)	28 (4.7)
Blood Creatine Phosphokinase Increased	5 (1.5)	14 (2.3)	17 (2.9)
Dermatitis atopic	37 (10.8)	45 (7.4)	24 (4.1)
Diarrhea	10 (2.9)	10 (1.6)	16 (2.7)
Dizziness	3 (0.9)	11 (1.8)	17 (2.9)
Headache	12 (3.5)	36 (5.9)	46 (7.8)
Herpes Simplex[1]	3 (0.9)	10 (1.6)	17 (2.9)
Nasopharyngitis	27 (7.9)	75 (12.3)	51 (8.6)
Nausea	7 (2.0)	37 (6.1)	86 (14.6)
Vomiting	3 (0.9)	9 (1.5)	19 (3.2)
Upper respiratory tract infections	19 (5.6)	40 (6.6)	30 (5.1)
Urinary tract infection	4 (1.2)	10 (1.6)	13 (2.2)

AEs listed in the table appeared in ≥ 2% in the abrocitinib group (53). Marked in grey are AEs that are also listed as adverse reactions in the Cibinqo SmPC (see table 12) and used in the economic model described in section 8.2.2.5.

[1] Herpes Simplex includes oral herpes, genital herpes, herpes dermatitis, ophthalmic herpes simplex.

The system organ class (SOCs) with the highest proportion of events in abrocitinib treatment groups and greater frequency than placebo were Infections and infestations, Gastrointestinal disorders, Nervous system disorders, and Investigations. Events in the Skin and subcutaneous tissue disorders were more frequent in the placebo group. The most frequent events overall (≥ 2% in any treatment group) that occurred more commonly in the abrocitinib groups than placebo and in a dose-related fashion were nausea, headache, acne, vomiting, herpes simplex, blood creatine phosphokinase increase, and dizziness. In addition, abdominal pain upper, although occurring at a frequency < 2% in the primary safety pool, did appear to have a dose response and also occurred more commonly in the abrocitinib groups compared to placebo. Most of these events occurred in the first weeks of exposure. Nausea events occurred more frequently in female subjects (53).

The All Exposure Pool includes all subjects with AD who received at least one dose of abrocitinib in Phase 2b and 3 studies in the relevant dosing groups (100 mg QD and 200 mg QD), including the LTE study JADE EXTEND. For the ongoing JADE Extend study, the cut-off date was 22 April 2020. Day 1 for all subjects is the first day of exposure to abrocitinib 100 or 200 mg QD. Subjects in this pool included (53):

- Participants from the Primary Safety Pool (Phase 2b study, JADE MONO-1 and MONO-2, and JADE COMPARE)

- Participants from the initial open-label period of JADE REGIMEN prior to the randomised withdrawal period. Exposure after randomization in JADE REGIMEN was not included in this pool as this portion remained blinded.
- Participants who entered the ongoing LTE JADE EXTEND after the Phase 3 studies JADE MONO-1, JADE MONO-2, and JADE COMPARE and observed until 22 April 2020.

The SOCs with the highest proportion of events in abrocitinib treatment groups were Infections and infestations, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, and Investigations. The most frequent AEs by preferred term (PT) were similar to those in the Primary Pool. The only additional AE with a dose response was abdominal pain upper. Of treatment related treatment emergent adverse events (TEAEs) that occurred in ≥ 2% of subjects, nausea was most frequently reported. The majority of treatment related TEAEs were mild or moderate (53). The demographics in the safety pools represented a diverse group of subjects broadly representative of adult patients with AD. Acute and long-term use of abrocitinib is well-tolerated and has a safety profile that supports use in patients with moderate to severe AD. Most AEs were mild, self-limited, and seldom required interruption or permanent discontinuation of therapy. The most common AEs associated with abrocitinib were nausea and headache, which tended to occur in the first few weeks of therapy (53). Nausea may be mitigated by taking abrocitinib with food. Other frequent AEs included vomiting, upper abdominal pain, herpes simplex, increased blood creatine phosphokinase, dizziness, and acne (32).

Listed in Table 12 are adverse reactions observed in AD clinical studies presented by SOC and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness (32).

Table 12 Tabulated list of adverse reactions of abrocitinib

MedDRA SOC	Very common	Common	Uncommon
Infections and infestations		Herpes simplex[a] Herpes zoster[b]	Pneumonia
Blood and lymphatic system disorders			Thrombocytopenia Lymphopenia
Metabolism and nutrition disorders			Hyperlipidaemia[c]
Nervous system disorders		Headache Dizziness	
Vascular disorders			Venous thrombotic events including pulmonary embolism[d]
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain upper	
Skin and subcutaneous tissue disorders		Acne	
Investigations		Creatine phosphokinase increased > 5 × ULN[e]	

Source (32). a) Herpes simplex includes oral herpes, ophthalmic herpes simplex, genital herpes, and herpes dermatitis, b) Herpes zoster includes ophthalmic herpes zoster, c) Hyperlipidaemia includes dyslipidaemia and hypercholesterolaemia, d) Venous thrombotic events include deep vein thrombosis e) Includes changes detected during laboratory monitoring (see text in description of selected adverse reactions)

Description of selected adverse reactions - abrocitinib

Infections
In placebo controlled studies, for up to 16 weeks, infections have been reported in 27.4% of patients treated with placebo and in 34.9% and 34.8% of patients treated with abrocitinib 100 mg and 200 mg, respectively. Most infections were mild or moderate. The percentage of patients reporting infection related adverse drug reactions in the 200 mg and 100 mg groups compared to placebo were: herpes simplex (4.2% and 2.8% vs 1.4%), herpes zoster (1.2% and 0.6% vs 0%), pneumonia (0.1% and 0.1% vs 0%). Herpes simplex was more frequent in patients with a history of herpes simplex or eczema herpeticum. Most of the herpes zoster events involved a single dermatome and were non serious. All the opportunistic infections were cases of multidermatomal cutaneous herpes zoster (0.6%), most of which were non-serious. The incidence rate of herpes zoster in patients 65 years of age and older (7.40 per 100 patient-years) was higher than that of patients 18 to less than 65 years of age (3.44 per 100 patient years) and less than 18 years of age (2.12 per 100 patient years). The incidence rate of herpes zoster in patients with severe atopic dermatitis at baseline (4.93 per 100 patient-years) was higher than that of patients with moderate atopic dermatitis at baseline (2.49 per 100 patient-years) (32).

In placebo controlled studies, for up to 16 weeks, the rate of serious infections was 1.81 per 100 patient-years in patients treated with placebo, 3.32 per 100 patient-years in patients treated with 100 mg, and 1.12 per 100 patient-years in patients treated with 200 mg. Among all patients treated with abrocitinib, including the long-term extension study, the rate of serious infections was 2.65 per 100 patient-years treated with 100 mg and 2.33 per 100 patient-years treated with 200 mg. The most commonly reported serious infections were herpes simplex, herpes zoster, and pneumonia (32).

Creatine phosphokinase elevations (CPK)
In placebo controlled studies, for up to 16 weeks, significant increases in CPK values (> 5 × ULN) occurred in 1.8% of patients treated with placebo, 1.8% of patients treated with 100 mg and 3.8% of patients treated with 200 mg of abrocitinib, respectively. Most elevations were transient and none led to discontinuation (32).

Nausea
In placebo-controlled studies, for up to 16 weeks, nausea was reported in 1.8% of patients treated with placebo and in 6.3% and 15.1% of patients treated with 100 mg and 200 mg, respectively. Discontinuation due to nausea occurred in 0.4% of patients treated with abrocitinib. Among patients with nausea, 63.5% of patients had onset of nausea in the first week of therapy. The median duration of nausea was 15 days. Most of the cases were mild to moderate in severity. In patients who experience nausea, taking abrocitinib with food may improve nausea (32).

Lipid elevations
In placebo controlled studies, for up to 16 weeks, there was a dose-related increase in low density lipoprotein cholesterol (LDL-c), total cholesterol, and high-density lipoprotein cholesterol (HDL-c) relative to placebo at Week 4 which remained elevated through the final visit in the treatment period. There was no meaningful change in the LDL/HDL ratio in patients treated with abrocitinib relative to patients treated with placebo. Events related to hyperlipidaemia occurred in 0.4% of patients exposed to abrocitinib 100 mg, 0.6% of patients exposed to 200 mg and 0% of patients exposed to placebo (32).

Dupilumab

The safety of dupilumab was evaluated in four randomised, double-blind, placebo-controlled studies and one dose-ranging study in patients with moderate to severe atopic dermatitis. In these 5 trials, 1,689 subjects were treated with subcutaneous injections of dupilumab, with or without concomitant topical corticosteroids (TCS). A total of 305 patients were treated with dupilumab for at least 1 year (25).

The most common treatment-related adverse events that occurred with a higher frequency with dupilumab than placebo were injection site reaction (see table 13). Besides injection site reactions, headache, conjunctivitis, and eosinophilia were identified as important treatment emergent adverse reactions. Some infections were more frequent in the dupilumab group compared to placebo, including conjunctivitis and oral herpes. Also allergic conjunctivitis and

other eye disorders were more prevalent with dupilumab treatment. The majority of cases were mild to moderate in severity and were self-limiting. As with all therapeutic proteins, there is a potential for immunogenicity with dupilumab.

Table 13 Adverse events in dupilumab placebo controlled studies (Primary safety pool)

Adverse event, %	Placebo (N=517)	Dupilumab 300 mg Q2W (N = 529)
Arthralgia	1.7	2.8
Conjunctivitis	0.6	4.0
Conjunctivitis allergic	1.0	3.0
Dermatitis atopic	30.6	13.2
Diarrhea	1.7	3.4
Fatigue	1.4	2.3
Headache	5.0	8.5
Injection site reactions	5.4	9.6
Nasopharyngitis	10.1	10.4
Oral herpes	1.5	3.8
Psychiatric disorders	4.6	2.1
Vascular disorder	1.9	2.6
Upper respiratory tract infections	2.9	3.4

AEs listed in the table appeared in ≥ 2% in dupilumab treatment group (55). Marked in grey are AEs that are also listed in the SmPC of Dupixent as adverse reactions (see table 14) and used in the economic model described in section 8.2.2.5.

The most common treatment-related TEAEs (≥1% in any treatment group) that occurred with a higher frequency in either dupilumab treatment groups (≥1% higher in either dupilumab treatment groups) than the placebo group were as follows:

- Injection Site Reaction: The incidence was higher in both dupilumab groups compared to placebo, with a higher incidence in the 300 mg QW group. These treatment-related TEAEs accounted for the majority of all reported ISR.
- Headache: 2.5% (13/529) in the dupilumab 300 mg Q2W group and 1.4% (7/517) in the placebo group.
- Conjunctivitis (Infections and Infestations SOC): 1.3% (7/529) in the dupilumab 300 mg Q2W group and 0% in the placebo group.
- Eosinophilia: 1.3% (7/529) in the dupilumab 300 mg Q2W group and 0.2% (1/517) in the placebo group.

The results for the treatment-related TEAEs during the 52-week treatment period were generally similar to the results observed for the first 16-weeks of treatment described above. In addition, as with all monoclonal antibodies, dupilumab has the potential to elicit an anti-drug antibodies (ADA) response. Approximately 5 % of patients with atopic dermatitis, asthma, or chronic rhinosinusitis with nasal polyposis who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies. ADA responses were not generally associated with impact on dupilumab exposure, safety, or efficacy (55).

Listed in Table 14 are adverse reactions observed in AD clinical trials and/or postmarketing setting presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness (25).

Table 14 Tabulated list of adverse reactions of dupilumab in atopic dermatitis

MedDRA SOC	Very common	Common	Uncommon	Very rare	Not known
Infections and infestations		Conjunctivitis Oral herpes			
Blood and lymphatic system disorders		Eosinophilia			
Immune systems disorders				Serum sickness/serum sickness-like reactions	Anaphylactic reaction* Angioedema*
Nervous system disorders		Headache			
Eye disorders		Conjunctivitis allergic Eye pruritus Blepharitis	Keratitis Ulcerative keratitis		
Musculoskeletal and connective tissue disorders					Arthralgia*
General disorders and administration site conditions	Injection site reactions				

Source (25). * From postmarketing reporting.

Description of selected adverse reactions – dupilumab

Conjunctivitis and keratitis related events

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis patients who received dupilumab. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period. Among asthma patients frequency of conjunctivitis and keratitis was low and similar between dupilumab and placebo (25).

Hypersensitivity
Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported following administration of dupilumab (25).

Eczema herpeticum
Eczema herpeticum was reported in < 1% of the dupilumab groups and in < 1 % of the placebo group in the 16-week atopic dermatitis monotherapy studies. In the 52-week atopic dermatitis dupilumab + TCS study, eczema herpeticum was reported in 0.2 % of the dupilumab + TCS group and 1.9 % of the placebo + TCS group (25).

Eosinophilia
Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. Eosinophil counts declined to near baseline levels during study treatment and returned to baseline during the asthma open-label extension safety study (TRAVERSE).

Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was reported in < 2 % of dupilumab-treated patients and < 0.5 % in placebo-treated patients (25).

7.2.2 Comparative analyses of efficacy and safety

Please refer to section 7.1.2 for comparison between abrocitinib and dupilumab from JADE COMPARE. In addition, supporting evidence by Silverberg et al. is presented below (48). This systematic literature review and network meta-analysis is however not compatible with the methods described by the Medicines Council, as it also contains in-development products, and thereby is not limited to active standard of care products. Hence, it is not considered part of the comparative analysis included in the Medicines Council assessment, but merely included as relevant information.

Network meta-analysis, description
A systematic literature review and network meta-analysis of randomised controlled trials (RCT) has recently been performed to compare the efficacy and safety of approved or in-development systemic therapies for moderate to severe AD when used as either monotherapy or in combination therapy (48). Trials included present data on treatment with abrocitinib, baricitinib, dupilumab, lebrikizumab, nemolizumab, tralokinumab and upadacitinib. Included RCTs were identified through a systematic literature review (SLR) in accordance with the guidelines and recommendations of The Cochrane Collaboration. The search was limited to RCTs in adolescents (aged 12–17 years) or adults (aged ≥18 years) with moderate to severe AD, included identified systemic monotherapy or systemic therapy with topical anti-inflammatory therapy (combination therapy) and reported efficacy and/or safety. Titles and abstracts of citations identified from searches and content of relevant full texts were evaluated. Screening was conducted by 2 investigators at each stage, with a third investigator resolving any disagreements. Primary outcomes of interest included EASI and IGA responses. Secondary outcomes included SCORAD-50 and PROs PP-NRS, POEM, DLQI, HADS, rates of treatment-emergent adverse events (TEAEs) and discontinuations owing to AEs. The authors conclusion: Results of this NMA highlight that efficacy outcomes of JAK1 inhibitors (abrocitinib and upadacitinib) were consistently higher than those of dupilumab and baricitinib in moderate to severe AD. No meaningful statistical differences in safety-related outcomes were observed (48).

Network meta-analysis, short summary of the results
This summary focus is on the approved treatments for AD, dupilumab and baricitinib compared to abrocitinib, thus dupilumab and baricitinib have been recommend as standard of care in Denmark. Other treatments included in the

NMA is not reported in this submission as these are either not approved for AD or recommended as standard therapy in Denmark.

IGA:

For IGA response in the monotherapy treatments baseline model, both abrocitinib 200 mg and abrocitinib 100 mg had a statistically significant, greater probability of a response compared with placebo, baricitinib 2 mg, and baricitinib 4 mg. No significant difference was seen between dupilumab or abrocitinib. For IGA response, abrocitinib 200 mg + topical therapy and abrocitinib 100 mg + topical therapy had a statistically significant, increased probability of a response compared with placebo + topical therapy in the base-case combination-therapy NMA, with no differences vs. active therapies being significant (48).

EASI-75

In the base case for monotherapy, abrocitinib 200 mg had a statistically significant, greater probability of achieving EASI-75 than placebo, abrocitinib 100 mg, baricitinib 2 mg, and baricitinib 4 mg. No other differences between active treatments were significant. In analyses of combination therapies, abrocitinib 200 mg + topical therapy had a statistically significant, higher probability of achieving EASI-75 compared with topical therapy + either placebo, baricitinib 2 mg, baricitinib 4 mg, with no other differences between active treatments being significant (48).

SCORAD-50

Data were only available on SCORAD-50 for both abrocitinib doses and dupilumab 300 mg in combination therapy. The greatest SCORAD-50 response compared with placebo were with abrocitinib 200 mg and dupilumab 300 mg (48).

PP-NRS4

In the monotherapy base case, both abrocitinib doses and dupilumab 300 mg had a statistically significant, increased probability of achieving PP-NRS4 compared with placebo. There were no significant differences between abrocitinib (both doses) and dupilumab. No data were available for baricitinib. No other differences being significant (48).

POEM

Greatest reduction in POEM score was found in the abrocitinib 200 mg versus placebo. No significant difference was found between any of the treatment groups; abrocitinib 200 mg, abrocitinib 100 mg, dupilumab 300 mg, baricitinib 4 mg and baricitinib 2 mg in monotherapy nor in combination therapy (48).

DLQI

Significant reductions in DLQI score were observed for abrocitinib 200 mg, abrocitinib 100 mg, dupilumab 200 mg and dupilumab 300 mg. No difference was found between any of the treatments. In the analysis of combination therapies abrocitinib 200 mg, abrocitinib 100 mg, dupilumab 300 mg and baricitinib 4 mg showed significant reductions in DLQI compared to placebo. Baricitinib 2 mg did not show a difference compared to placebo. No data were available for dupilumab 200 mg. Abrocitinib 200 mg and dupilumab 300 mg showed greater reduction in DLQI than baricitinib 2 mg, with no other differences between treatments being significant (48).

Safety outcomes

Regarding safety outcomes, no statistically significant differences in TEAEs or discontinuations due to AEs were found in either monotherapy or with combination therapy for abrocitinib 200 mg and abrocitinib 100 mg compared with placebo or active comparators. SAE were not analysed in the NMA (48).

The results of this NMA should be interpreted with caution due to its limitations, which include:

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- The results of the comparative analysis may be biased by misalignment in the type of data provided for studies and may result in overestimation or underestimation.
- AEs, TEAEs, and discontinuations due to AEs were generally undefined across studies and may contribute to the heterogeneity of results.
- Some safety outcomes had large credible intervals because there were few observed events (i.e., up to one event) in the analyzed treatment groups.

Please, see publication for detailed information and graphic presentation of outcomes (48).

8. Health economic analysis

8.1 Model

In the following section we present a cost-minimization analysis comparing abrocitinib with dupilumab for treatment of patients with moderate to severe AD who have been previously treated with at least one systemic immunosuppressant therapy. The cost-minimization analysis is chosen as the overall clinical efficacy and safety of treatment with abrocitinib is comparable to treatment with dupilumab, as shown in the JADE COMPARE study and supported by the network meta-analysis described in section 7. Clinical experts have verified that the safety of abrocitinib and dupilumab is comparable. According to the Danish Medicines Council's method guide, a cost-minimization analysis is to be used when comparable effect between the intervention and comparator is expected (56). Since the clinical efficacy and safety is comparable between the two treatments no clinical efficacy endpoints, e.g. response rates or conditional discontinuation rates, are included in the economic analysis.

The Abrocitinib Cost model has been developed in Excel for the purpose of this application. The model is fully flexible with modifiable cells and no hidden or blocked cells. In the base case analysis, the model has a time horizon of 52 weeks, assuming a year is 364 days corresponding to treatment with 13 packs of 28 day treatment usage of either abrocitinib or dupilumab. This time horizon is chosen as essential differences in costs are assumed covered within this time period, due to the comparable effect of abrocitinib and dupilumab. Furthermore, this time horizon is also in line with the one used in the Danish Medicines Council's assessment report for dupilumab in January 2018 (57) and baricitinib in May 2021 (24). Since the incremental cost per patient is slightly different between year 1 and all subsequent years, the model also presents the incremental cost over a two-year time horizon. The differences in costs are due to a few inherent differences related to treatment;

- patients treated with dupilumab only receives an induction dose at treatment initiation in year 1,
- monitoring costs related to the induction period are only included in year 1,
- it is assumed that adverse events only occur at treatment initiation.

Although, there are these minor differences in cost between year 1 and subsequent years, we have chosen the one year time horizon as this was the chosen time horizon by the Medicines Council for all previous assessments of treatments within atopic dermatitis. Furthermore, the use of an equivalent time horizon enables comparison across the treatment area. The results of the incremental cost per patient in subsequent years are therefore omitted in this report.

In the model all patients who are candidates for treatment with abrocitinib or dupilumab enters the model in week 0 and continues treatment until week 52. No discontinuation in either of the treatment groups are assumed, as the

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discontinuation rates are not expected to differ between the two groups (discontinuation rates were similar in JADE COMPARE (49). Furthermore, the model does not consider mortality as it is not expected to differ between the two groups.

The aim of the model is to calculate the incremental costs per patient of treatment with abrocitinib compared to treatment with dupilumab. A limited social perspective is used as described in the Danish Medicines Council's method guide (56). Costs included in the model are those expected to differ for the two treatment options, including drug acquisition costs, administration costs, resource use and patient costs. Costs related to treatment of adverse events are included to incorporate the differences in the safety profiles between abrocitinib and dupilumab, although the overall safety of the two treatments are comparable from a clinical practice perspective according to clinical experts. A micro-based cost approach is used to estimate hospital costs, including hourly costs for practitioners and examinations rooms, following the Danish Medicines Council's method guide (56).

Background therapy (TCS or TCI) and treatment to control flares are excluded from the model as these costs are anticipated to be similar for both treatment groups. This is also the approach used in the Danish Medicines assessment report for baricitinib in May 2021 (24). Outpatient follow-up visits with a dermatologist are disregarded in the analysis, as these are assumed to be similar for both treatment arms. However, we include visits related to the initiation of treatment during the induction period (16 weeks) including training in the use of subcutaneous injection. This is the same approach as seen in the Danish Medicines Council's assessment report for baricitinib (24). Discounting is not applied in the base case analysis as the time horizon is one year but it is included in the two-year time horizon analysis included in the model.

The model includes three sheets. A description of each sheet is listed in the table below.

Table 15 Overview of sheets included in Excel model

Sheet name	Description
Abrocitinib Cost Model	Model for the total cost and incremental cost per patient analysis comparing treatment of abrocitinib and dupilumab
Sensitivity Analysis	Description and calculation of one-way sensitivity analyses
Budget Impact Analysis	Budget impact analysis of introducing abrocitinib as standard of care in the coming 5 years
Sensitivity_Budget Impact	Sensitivity analysis of the budget impact model
Background	Background information including drugs, currency, discounting, calculations of time horizon, and micro-costing inputs

The Abrocitinib Cost Model is built in a continuously flow in one sheet in the same order in this health economic appraisal. A description of where to find all inputs is described below:

Table 16 Overview of inputs in Abrocitinib Cost Model

Row	Input
6-12	Explanation of cell formatting
13-32	Description of model
33-77	Drug costs

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78-295	Hospital costs
296-345	Cross sectional costs
346-526	Patient costs
527-701	Results

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

No clinical efficacy endpoints are included in the economic analysis due to the comparable effect of abrocitinib and dupilumab. This clinical equivalence is the basis for the choice of a cost-minimization analysis, and thus no data for relative efficacy will be presented.

Data on Danish clinical practice has been collected via expert opinion from two Danish dermatology specialists, see section 11, referred to as "clinical experts" in the model and in this report.

Data on costs are based on a micro-based cost approach, following the methodology specified in the Medicines Council's catalogue on unit costs (58) and pharmacy purchasing prices are retrieved from medicinpriser.dk. See micro-costing inputs and calculation of hourly cost for practitioners in row 21-84 in the "Background" sheet of the model. A micro-based approach is used as the DRG-rate are not representative of the actual costs associated with hospitals costs in this case, and will lead to an overestimation of hospital costs in the analysis. A micro-based approach is also used in Danish Medicines Council's assessment report for baricitinib (24), however a sensitivity analysis will be conducted estimating the costs of using DRG-rates instead of a micro-based approach, to assess the uncertainty related to different costs estimates and where the DRG-rate represents an upper estimate (see section 8.7.1).

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

8.2.2.1.1 The Danish patient population:

Atopic dermatitis is the most common chronic inflammatory skin disease in the developed world, with primary onset in childhood affecting up to 25 % of children. Atopic dermatitis is however also very prevalent in adults with rates of 7–10 %, and up to 60% have moderate to severe disease worldwide (18, 19). To our knowledge there are no registry data or published literature on the incidence and prevalence of moderate to severe atopic dermatitis in Denmark for the past 5 years.

The Medicines Council's Expert Committee for Atopic Dermatitis has estimated that 225 patients currently are candidates for advanced systemic treatment (e.g. candidates for dupilumab or baricitinib), although the majority of patients may already have initiated treatment. The Expert Committee has also estimated that 30 new patients will be candidates for advanced systemic treatment per year in the protocol for baricitinib (20).

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Based on this input, the expected number of moderate to severe atopic dermatitis patients eligible for advanced systemic treatment in a Danish setting is estimated as seen in Table 17Table 17 Number of moderate to severe atopic dermatitis patients in Denmark expected to use advanced systemic treatmentbelow:

Table 17 Number of moderate to severe atopic dermatitis patients in Denmark expected to use advanced systemic treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of moderate to severe atopic dermatitis patients in Denmark expected to use advanced systemic treatment	225 adults	255 adults	285 adults	315 adults	345 adults

8.2.2.1.2 Patient population in the clinical documentation submitted:

The population in the clinical documentation consists of adults with moderate to severe atopic dermatitis who previously had inadequate response to medicated topical therapy or were eligible for systemic treatments. This is a broader patient population than the population expected to be treated in a Danish clinical setting, and represents the population studied in the clinical trial programme for abrocitinib (see also section 5.3 and 7.1.3). However, as discussed previously in this report, this is also the case for the clinical programme for dupilumab (see section 4). Clinical experts have been consulted regarding this possible discrepancy in efficacy between the clinical studies and a Danish clinical setting. They assess this risk to be minor, as they currently do not see any discrepancy in efficacy between clinical practice and the clinical trials, and Danish patients are not very treatment refractory. No actions will therefore be taken to control for this, and no efficacy endpoints are included in this cost-minimization analysis.

8.2.2.1.3 Patient population in the health economic analysis submitted:

The population in the health economic analysis consists of adults with moderate to severe atopic dermatitis who have previously been treated with at least one systemic immunosuppressant therapy or discontinued treatment with dupilumab or baricitinib. This is in line with Danish clinical practice. Abrocitinib provides an alternative treatment option and dosage form to subcutaneous dupilumab and an alternative treatment option to baricitinib for moderate to severe AD patients ≥ 18 years.

Based on the estimates provided by the Medicines Council's Expert Committee for Atopic Dermatitis and as advised by the secretariat, it is estimated that 225 adults will be candidates for advanced systemic treatment in the first year with a yearly patient population growth of 30 new patients in the following years. A significant number of these patients will however already be treated with dupilumab, and as well-treated patients are not switched according to Danish clinical practise, it is expected that only 25% of the 225 patient will initiate treatment with abrocitinib in year 1. Furthermore, it is expected that all new patients will be treated with abrocitinib following a recommendation by the Danish Medicines Council. The number of patients expected to be treated with abrocitinib is seen in Table 18 below.

Table 18 Number of moderate to severe atopic dermatitis patients in Denmark expected to be candidates for abrocitinib

Year	Year 1	Year 2	Year 3	Year 4	Year 5

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New patients	56	30	30	30	30
Existing patients	0	56	86	116	146
Total number of abrocitinib patients	*56*	*86*	*116*	*146*	*176*

8.2.2.2 Intervention

8.2.2.2.1 Intervention as expected in Danish clinical practice (as defined in section 2.2)

Abrocitinib provides a new treatment option for patients with moderate to severe atopic dermatitis who have been previously treated with at least one systemic immunosuppressant therapy or discontinued treatment with dupilumab or baricitinib. Furthermore, abrocitinib provides an alternative treatment option and dosage form to subcutaneous dupilumab and an alternative treatment option to baricitinib for moderate to severe AD patients ≥ 18 years.

8.2.2.2.2 Intervention in the clinical documentation submitted

The comprehensive review of the clinical documentation submitted for abrocitinib can be found in section 5 of this report. Table 19 below presents the clinical inputs of the intervention, abrocitinib, relevant for the analysis.

Table 19 Clinical inputs of intervention relevant for the costs per patient analysis

Clinical input	Description
Generic name (ATC code)	Abrocitinib (D11AH08)
Mode of action	Abrocitinib is an oral, Janus kinase 1 (JAK1)-selective inhibitor
Posology	- The recommended starting dose is 200 mg once daily. A starting dose of 100 mg once daily is recommended for patients ≥ 65 years of age. For other patients who may benefit from a starting dose of 100 m. - During treatment, the dose may be decreased or increased based on tolerability and efficacy. - The lowest effective dose for maintenance should be considered. The maximum daily dose is 200mg.
Method of administration	Abrocitinib is to be taken orally once daily with or without food at approximately the same time each day.
Treatment duration/criteria for treatment discontinuation	Discontinuation of treatment should be considered in patients who show no evidence of therapeutic benefit after 24 weeks
Should the pharmaceutical be administered with other medicines?	Abrocitinib can be used with or without medicated topical therapies for atopic dermatitis
Necessary monitoring, during administration, during the treatment period, and after the end of treatment	- Complete blood count including platelet count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC) and haemoglobin (Hb) should be assessed before initiation of treatment, approximately 4 weeks following initiation of abrocitinib and thereafter according to routine patient management. - Lipid parameters should be assessed approximately 4 weeks following initiation of abrocitinib therapy and there after according to their risk for cardiovascular disease. The effect of these lipid parameter elevations on cardiovascular morbidity

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	and mortality has not been determined. Patients with abnormal lipid parameters should be further monitored and managed according to clinical guidelines, due to the known cardiovascular risks associated with hyperlipidaemia.
Need for diagnostics or other tests	- Patients should be screened for TB before starting treatment and yearly screening for patients in highly endemic areas for TB should be considered. Abrocitinib must not be given to patients with active TB. - Screening for hepatitis B and C should be performed in accordance with clinical guidelines before starting therapy and during therapy with abrocitinib
Packaging	28 filmcoated tablets

Source: (32)

8.2.2.2.3 Intervention as in the health economic analysis submitted

Abrocitinib is included as an alternative treatment option to dupilumab in the economic analysis. The recommended starting dose of abrocitinib is 200 mg once daily. We have therefore chosen only to include the 200 mg dosing in the economic analysis, as the price of abrocitinib will not change by dose (flat pricing) and thereby a total costs per patient analysis for the 100 mg and 200 mg will have the same result. Atopic dermatitis is a chronic disease and treatment can potentially be livelong, however as efficacy and discontinuations rates of abrocitinib and the comparator dupilumab are not expected to differ, a time horizon/length of treatment is assumed to be 52 weeks in the model, corresponding to one year of treatment. As mentioned in section 8.1, the model also presents the incremental cost over a two-year time horizon, as the incremental cost per patient is slightly different between year 1 and all subsequent years. However, these are omitted in this report.

A summary of the basic characteristics of abrocitinib is seen in Table 20 below:

Table 20 Intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	200 mg or 100 mg once daily Patients ≥ 65 y: 100 mg once daily	200 mg once daily for all patients	200 mg once daily as starting dose, 100 mg or 200 mg once daily as maintenance dose
Mode of administration	Oral	Oral	Oral
Length of treatment (time on treatment)	12-52 weeks	52 weeks	Until loss of therapeutic benefit or discontinuation due to adverse events
Criteria for discontinuation	Patients who show no evidence of therapeutic benefit after 24 weeks.	N/A – discontinuation is not included in the model as the discontinuation rate is expected to be similar for both intervention and comparator	Loss of therapeutic benefit or discontinuation due to adverse events
Monitoring	Complete blood count	Complete blood count	Complete blood count

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Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
	Lipid parameters	Lipid parameters	Lipid parameters
Diagnostics	Screening for tuberculosis Screening for hepatitis B + C	Screening for tuberculosis Screening for hepatitis B + C	Screening for tuberculosis Screening for hepatitis B + C
Packaging	28 filmcoated tablets	28 filmcoated tablets	28 filmcoated tablets
Source	JADE Compare and SmPC of abrocitinib	SmPC of abrocitinib	Clinical experts

8.2.2.3 Comparator

8.2.2.3.1 The current Danish clinical practice

Dupilumab is chosen as comparator for the assessment of abrocitinib given that it has been standard of care in Denmark since 2018. Baricitinib has recently been recommended by the Medicines Council, 26 May 2021, as standard of care. A tablet-to-tablet comparison of abrocitinib and baricitinib would be relevant, but taking the short period that baricitinib has been available into account, the vast majority of Danish atopic dermatitis patients who are candidates for systemic therapy will currently be treated with dupilumab. Also, in the baricitinib assessment report the Expert Committee views that data on efficacy, including EASI and SCORAD, indicates that baricitinib is less effective than dupilumab (24). Furthermore, it is expected that costs related to treatment with baricitinib is at par with abrocitinib due to the same route of administration. We have also been advised by the secretariat, that choosing dupilumab as the only comparator would be adequate. Accordingly, dupilumab and not baricitinib is chosen as a single comparator for this submission. Moreover, dupilumab is included as an active control-arm in the JADE COMPARE study assessing efficacy and safety of abrocitinib in adults with moderate to severe atopic dermatitis. No clinical study has assessed the efficacy and safety of both abrocitinib and baricitinib.

8.2.2.3.2 Comparator in the clinical documentation submitted

The comprehensive review of the clinical documentation submitted for abrocitinib can be found in section 5 of this report. Table 21 below presents the clinical documentation of the comparator, dupilumab, relevant for the analysis.

Table 21 Clinical documentation of comparator relevant for the costs per patient analysis

Clinical input	Description
Generic name (ATC code)	Dupilumab (D11AH05)
Mode of action	Dupilumab is a fully humanized antibody to IL-4 receptor alpha subunit, which block both IL-4 and IL-13 signalling
Posology	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.
Method of administration	Dupilumab is administered as subcutaneous injections.

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Treatment duration/criteria for treatment discontinuation	Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.
Should the pharmaceutical be administered with other medicines?	Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.
Necessary monitoring, during administration, during the treatment period, and after the end of treatment	- No necessary monitoring according to the SmPC, approximately 1.5% of patients is estimated to receive help from a nurse with administration (verified by clinical experts). - One blood test during treatment initiation (estimate provided clinical expert).
Need for diagnostics or other tests	No.
Packaging	2 pieces of 300 mg prefilled solutions for injection

Source: SmPC of dupilumab (25) and clinical experts

8.2.2.3.3 Comparator in the health economic analysis submitted

Dupilumab is chosen as comparator in the economic analysis. Dupilumab is administered as an induction dose of 600 mg followed by a 300 mg dose subsequently every other week. As dupilumab is administered as subcutaneous injections, some patients will require assistance by a nurse in administration of dupilumab. It is assumed that 1.5% of patients will be requiring assistance based on advice from clinical experts. Equally to treatment with abrocitinib, treatment of dupilumab can potentially be livelong, however as efficacy and discontinuations rate of both treatments are not expected to differ, a time horizon/length of treatment is assumed to be 52 weeks in the model, corresponding to one year of treatment.

A summary of the basic characteristics of dupilumab is seen in Table 22 below:

Table 22 Comparator

Dupilumab	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Initial dose 600 mg followed by 300 mg every other week	Initial dose 600 mg followed by 300 mg every other week	Initial dose 600 mg followed by 300 mg every other week
Mode of administration	Subcutaneous injections	Subcutaneous injections 1.5% of patients will be assisted in administration	Subcutaneous injections 1.5% of patients will be assisted in administration
Length of treatment	52 weeks	52 weeks	Until loss of therapeutic benefit or discontinuation due to adverse events

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Dupilumab	Clinical documentation	Used in the model	Expected Danish clinical practice
Criteria for discontinuation	Patients who show no evidence of therapeutic benefit after 16 weeks.	N/A – discontinuation is not included in the model as the discontinuation rate is expected to be similar for both intervention and comparator	Loss of therapeutic benefit or discontinuation due to adverse events
Monitoring	N/A	One blood test	One blood test
Diagnostics	No	No	No
Packaging	2 x prefilled injections equivalent to 28 days of treatment	2 x prefilled injections equivalent to 28 days of treatment	2 x prefilled injections equivalent to 28 days of treatment
Source	SmPC dupilumab	SmPC dupilumab + clinical experts	Clinical experts

8.2.2.4 Relative efficacy outcomes

The analysis carried out is a cost-minimization analysis. No clinical efficacy endpoints are included in the economic analysis due to the comparable effect of abrocitinib and dupilumab, as described in section 7 of this report.

8.2.2.5 Adverse event outcomes

Adverse events are included in the model to incorporate differences in relation to direct treatment costs. Thus, clinical experts have assessed the safety of abrocitinib and dupilumab to be overall comparable, the two treatments have different adverse events. Though these adverse events are different they are all manageable in a Danish clinical setting according to clinical experts. Thus we do not expect there to be any clinically relevant difference in the treatment of the included adverse events. A description of the safety profile of both abrocitinib and dupilumab is found in section 7 of this report.

Adverse events included in the economic model are adverse events from the primary safety pools, which occurred in ≥ 2% of either the abrocitinib-arm or the dupilumab-arm compared to placebo (53, 55), and are listed as adverse reactions in the SmPCs of abrocitinib or dupilumab (25, 32). In addition Herpes zoster is also included as this a common adverse reaction related to abrocitinib and JAK-inhibition. Herpes zoster is more likely to affect patients above 65 years of age, which is assessed to be a very minor share of patients in a Danish clinical perspective. A clinical expert assess that very few atopic dermatitis patients will be affected by herpes zoster in Denmark. It can also be mitigated by prophylactic herpes zoster vaccination. By selecting those adverse events which are deemed adverse reactions by the EMA, this analysis is more likely to represents clinical practice and the actual drug reactions associated with treatment. Adverse reactions have also been the required outcome measure by the Expert committee in the protocol for dupilumab >18 years and baricitinib (20, 59).

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It is assumed that adverse events occur at treatment initiation. For patients treated with abrocitinib we have included the highest frequency of adverse events from the primary safety pool of abrocitinib (53) irrespective of whether the patient received 100 mg or 200 mg daily, which is a conservative approach. For dupilumab adverse events are also retrieved from the primary safety pool (55).

Table 23 below shows an overview of included adverse events in the economic model. The included adverse events can be modified in row 215-226 of the "Abrocitinib Cost Model" sheet in the model. The last column in the table below indicates whether or not an adverse event requires treatment, as assessed by clinical experts. An alteration of which adverse events that requires treatment can be done in row 233-244 in the "Abrocitinib Cost Model" sheet in the model.

Table 23 Adverse event outcomes

Adverse event outcome	Clinical documentation	Used in the model (numerical value)		Requiring treatment
		Abrocitinib	Dupilumab	
Acne	Integrated safety analysis abrocitinib	4,7%	0,0%	Yes
Arthralgia	EPAR dupilumab	0,0%	2,8%	No
Blood creatine phosphokinase increase	Integrated safety analysis abrocitinib	2,9%	0,0%	No
Conjunctivitis	EPAR dupilumab	0,0%	4,0%	Yes
Conjunctivitis allergic	EPAR dupilumab	0,0%	3,0%	Yes
Dizziness	Integrated safety analysis abrocitinib	2,9%	0,0%	No
Headache	Integrated safety analysis abrocitinib and EPAR dupilumab	7,8%	8,5%	No
Herpes simplex	Integrated safety analysis abrocitinib and EPAR dupilumab	2,9%	3,8%	Yes
Herpes zoster	Integrated safety analysis abrocitinib	1,8%	0,0%	Yes
Injection site reactions	EPAR dupilumab	0,0%	9,6%	No
Nausea	Integrated safety analysis abrocitinib and EPAR dupilumab	14,6%	2,9%	No
Vomiting	Integrated safety analysis abrocitinib	3,2%	0,0%	No

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8.3 Extrapolation of relative efficacy

This section is not relevant with the analysis being a cost-minimization analysis.

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

This section is not relevant with the analysis being a cost-minimization analysis.

8.5 Resource use and costs

8.5.1 Drug costs

Table 24 below presents the drug costs associated with treatment of both abrocitinib and dupilumab. Pharmacy purchasing price (PPP) is used for drug costs in this analysis, and retrieved from Medicinpriser.dk. The usual starting dose for patients treated with abrocitinib is 200 mg which can be reduced to 100 mg. However, because the price of abrocitinib for both the 100 mg and 200 mg dose is the same (flat price), only the 200 mg dose is included in the model, as described in section 8.2.2.2.3. The price can be adjusted in row 39-40 of the "Abrocitinib Cost Model" sheet in the model.

Table 24 Drug costs, DKK

Product	Administration	Pharmaceutical form	Package (units per pack)	PPP per pack, DKK	PPP per unit, DKK
Abrocitinib	Oral	Tablets	28	7,012	250
Dupilumab 300 mg	S.C	Solution for injection	2	8,900	4,450

Source: Medicinpriser.dk, 11th of October 2021

The number of administrations per year is based on the SmPC of abrocitinib and dupilumab. As described in section 8.2.2.3, dupilumab has an initial dose of 2 x 300 mg for adult patients which results in one additional administration of dupilumab in the first year of treatment. The total number of administration included in the model can be found in Table 25 below. Number of administrations in year 1 can be adjusted in row 53-54 of the "Abrocitinib Cost Model" sheet in the model.

Table 25 Number of administrations

Product	Number of additional administrations at start-up	Number of annual administrations	Total number of administrations in year 1
Abrocitinib	0	364	364
Dupilumab 300 mg	1	26	27

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8.5.2 Hospital costs

Hospital costs are based on a micro-based cost approach, as we assume that the DRG-rate for an outpatient visit for an adult patient with moderate to severe of DKK 1.735 is not representative of the actual cost[1]. Instead we have used the approached described in the Medicines Council's catalogue on unit costs (58) to estimate the hourly costs of a doctor, nurse and use of a hospital examination room. The hourly cost for a doctor assumes that the treating physician is a resident (1. reservelæge). The estimated hourly cost is calculated based on the average monthly salary over the last 12 months with available data in the register (from June 2020 till May 2021) divided by the average working hours per month (58, 60). This calculated average salary per hour is then multiplied by 2 to include an overhead of 100% to accommodate costs held by the department, time spend on non-patient related tasks and other absence, c.f. the method specified in 'Medicinrådet, Værdisætning af enhedsomkostninger, v 1.3' (58). The cost for an examination room is based on the cost estimate presented in Jan Sørensen, 2014 (61) inflated to 2021 price level using the PL-adjustment factor. The inputs used to calculated the hourly costs is found from row 21 in the "Background" sheet in the model.

To assess the uncertainty related to the micro-based cost-approach we perform a sensitivity analysis where all hospital costs are based on the DRG-rate. The costs related to hospital costs can be found in Table 26 below, and adjusted in row 84-85 and 91 in the "Abrocitinib Cost Model" sheet in the model.

Table 26 Hourly costs related to hospital costs

	Cost per hour, DKK
Doctor	886
Nurse	580
Hospital examination room	55

Source: (58, 60, 61)

8.5.2.1 Administration costs

Administration costs are assumed to differ between abrocitinib and dupilumab due to the different routes of administration.

Abrocitinib is administered orally and do not incur any administration costs (DKK 0).

Dupilumab is administered as subcutaneous injections which requires training in self-administration and continuously administration assistance for a small proportion of patients. All patients treated with dupilumab will be assisted in administering the first infusions of dupilumab at treatment initiation (2 x 300 mg), and the majority of patients will afterwards be able to self-administer dupilumab. Costs related to treatment initiation and training in self-administration is included under "monitoring costs" in section 8.5.2.2 below. It is however assumed that 1.5% of the patients requires continuously administration assistance of treatment with dupilumab. Continuously administration is assumed to be 25 administrations equal to all administration after the initial double dose administration (e.g. the

[1] Source: DRG 2021, Principal diagnosis DL209 Atopic dermatitis. The cost per outpatient visit is estimated to be 1 contact day. Outpatient DRG-group 09MA98.

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entire time perspective). It is assumed that a nurse will assist the patient and the time consumption related to each administration is 15 minutes including preparation, administration and registration. This assumption is verified by clinical experts and also the same approach used in the Medicines Councils assessment report for baricitinib (24).

A sensitivity analysis will estimate a scenario where none of the patients receiving dupilumab will require administration assistance (e.g. 0%), as well as a scenario where 3% of the patients will require administration assistance. This is due to uncertainty relating to this estimate, as this assumption is highly related to the characteristics of the patient population, which might change over time. Please see section 8.7.2 on sensitivity analyses.

Table 27 below presents the percentage of patients requiring continuously administration assistance, the time consumption for a nurse related to administration and number of administrations requiring administration assistance in year 1. These estimates can be adjusted in row 99, 105-106 and 111-112 in the "Abrocitinib Cost Model" sheet in the model.

Table 27 Distribution of patients requiring administration assistance

Product	Patients requiring administration assistance	Time consumption for a nurse related to administration (minutes)	Number of administrations requiring administration assistance in year 1
Abrocitinib	0%	0	0
Dupilumab	1.5%	15	25

Source: Clinical expert and the Medicines Council's assessment report for baricitinib (24)

8.5.2.2 Monitoring costs

Costs related to monitoring includes treatment initiation visits where patients treated with dupilumab will receive training in self-administration and costs related to blood tests. Out-patient visits with a dermatologist after the initiation period of 16 weeks are not included in the analysis, as it is assumed that treatment with both abrocitinib and dupilumab requires routine controls every third month (32, 62). This is the same approach as in the Medicines Council's assessment report for baricitinib, where consultations with dermatologist were excluded from the analysis (24).

Monitoring costs related to treatment initiation and training in self-administration

It is assumed that monitoring visits are conducted by a nurse and time consumption related to monitoring visits is 20 minutes. This is the same time estimates as in the Medicines Council's assessment report for baricitinib (24). Patients treated with abrocitinib has an average of 1 monitoring visit in the induction period of 16 weeks. Patients treated with dupilumab has an average of 2 monitoring visits during the induction period of 16 weeks. This covers treatment initiation including two trainings in self-administration. These estimates are provided by a clinical expert, and can be adjusted in row 148 and 153-154 of the "Abrocitinib Cost Model" sheet in the model.

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Table 28 Monitoring costs related to treatment initiation

Product	Number of monitoring visits in induction period	Time consumption for nurse related to monitoring visits (minutes)
Abrocitinib	1	20
Dupilumab	2	20

Source: Clinical experts and the Medicines Council's assessment report for baricitinib (24)

Monitoring costs related to blood tests

Monitoring costs related to blood tests are based on the SmPC of abrocitinib and clinical experts. It is assumed that treatment with abrocitinib requires four blood tests (ALC, ANC and Hb) per year. One prior to treatment initiation and subsequently every three months. Furthermore patients treated with abrocitinib are assumed to require two blood tests for lipid parameters, one prior to treatment and one after initiation of treatment, which is expected to be taken simultaneously with the before mentioned blood test. Treatment with dupilumab requires one blood test taken prior to treatment initiation. However, according to clinical experts, the number of blood test required for treatment with dupilumab can vary between dermatology departments across Denmark, why we have included a sensitivity analysis exploring the impact of blood test for dupilumab patients on the total costs. See section 8.7.3.

Furthermore, screening for tuberculosis and hepatitis B and C is required prior to treatment initiation of abrocitinib. It is assumed that the results of the blood tests are discussed at an out-patient control visit, why no additional monitoring visits related to blood tests are included in the analysis.

Table 29 below shows the number of annual blood tests for each treatment. These estimates can be adjusted in row 181-186 in the "Abrocitinib Cost Model" sheet in the model.

Table 29 Number of blood tests per year

Blood test	Abrocitinib, number of tests per year	Dupilumab, number of tests per year
Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC)	4	1
Absolute Neutrophil Count (ANC), and Haemoglobin (Hb)	4	1
Lipid parameters	2	0
Tuberculosis	1	0
Hepatitis B	1	0
Hepatitis C	1	0
Source	SmPC abrocitinib	Clinical experts and Medicines Council's assessment report for baricitinib (24)

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Cost estimates for blood tests are based on estimates from Rigshospitalets Labportal, Sektion for Eksterne Projekter Afdeling 3014 and Viruslab at Rigshospitalet. Unfortunately, it was not possible to obtain a cost estimate for screening of tuberculosis although multiple attempts through different clinical departments at both Rigshospitalet and Amager and Hvidovre Hospital were tried. The costs estimate for tuberculosis screening is therefore calculated as the average of all other blood tests used. Table 30 below shows the costs per test. These estimates can be adjusted in row 172-177 of the "Abrocitinib Cost Model" sheet in the model.

Table 30 Cost per blood test, DKK

Blood test	Cost per test, DKK	Source
Complete blood count including Platelet Count, Absolute Lymphocyte Count (ALC)	60	'Sektion for Eksterne Projekter Afdeling 3014' RH, Sep 14th, 2021
Absolute Neutrophil Count (ANC), and Haemoglobin (Hb)	55	RH Labportal, NPU02902 & NPU02319
Lipid parameters	75	RH Labportal, NPU01568 & NPU04094
Tuberculosis	58	Due to unavailability of a cost estimate for tuberculosis the average of all other blood tests has been used
Hepatitis B	42	'viruslab' RH, Sep 15th, 2021
Hepatitis C	58	'viruslab' RH, Sep 15th, 2021

8.5.2.3 Adverse events costs

Adverse events included in the economic model are those which occurred in ≥ 2% in the primary safety pool of abrocitinib or dupilumab and are listed as adverse reactions in the SmPC of either abrocitinib or dupilumab, please see section 8.2.2.5 for a detailed explanation.

Treatment patterns among patients treated for an adverse events is guided by clinical experts. Adverse events requiring treatment included in the analysis are acne, conjunctivitis, allergic conjunctivitis, herpes simplex and herpes zoster. It is assumed that none of the adverse events require hospitalization. Treatment costs relating to private specialist will be covered under cross sectional costs and costs associated with treatment with prescription medicine is included under patient costs. It is assumed that 50% of patients experiencing acne, conjunctivitis and allergic conjunctivitis will require treatment. All patients requiring treatment for these three adverse event will require one visit to a private specialist. It is assumed that 100% of patients experiencing herpes simplex will require treatment, and will require two visits to a private specialist. It is assumed that 100% of patients experiencing herpes zoster will require treatment. Dependent on the severity, patients will either be treated with out-patient consultations or in a private practise. In the base case analysis, it is assumed that 50% of the patients require two out-patient consultations with a doctor and the remaining 50% of the patients requires two visits to a private specialist.

The assumptions on treatment of adverse reactions are associated with uncertainty as the severity and thereby extend of treatment for each adverse reaction can be varying. The majority of adverse reactions are mild to moderate

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and can be managed during routine visits according to clinical experts. It can therefore be argued that the included costs associated with adverse events are overestimated, if the majority of adverse events are managed during control visits, however these costs have very limited impact on the total cost per patient analysis. Included adverse events are found in row 215-226 in the "Abrocitinib Cost Model" sheet in the model.

Treatment patterns associated with adverse events can be modified in row 233-244 of the "Abrocitinib Cost Model" sheet in the model. Please note that for adverse events listed as not requiring treatment, cells will be shaded grey, and must be changed to "Yes" in column E in order to be included in the analysis. It is assumed that time consumptions related to treatment of adverse events in an out-patient setting is 20 minutes for both a nurse and a doctor. This is equivalent to the time consumption related to a monitoring visit. This assumption can be adjusted in row 252-263 in the "Abrocitinib Cost Model" sheet in the model. Table 31 below presents the treatment pattern for adverse reactions requiring treatment.

Table 31 Treatment pattern for adverse events requiring treatment

	Share of patient's treated at the hospital in an outpatient setting	Share of patient's treated at a private specialist	Number of outpatient visits with a doctor related to the treatment of the AE	Number of outpatient visits with a nurse related to the treatment of the AE
Acne	0%	50%	0	0
Conjunctivitis	0%	50%	0	0
Allergic conjunctivitis	0%	50%	0	0
Herpes simplex	0%	100%	0	0
Herpes zoster	50%	50%	2	0

Source: clinical experts

8.5.3 Cross sectional costs

Cross sectional costs associated with treatment of adverse reactions are included in this analysis. Type of private specialist is guided by clinical experts and cost estimates per visit are based on rates based on the applicable agreement between the Danish Regions and the Danish Medical Association, c.f. 'Værdisætning af enhedsomkostninger' from the Danish Medicines Council (58).

Table 32 shows the type of specialist and costs associated with treatment of each adverse reaction. Costs associated with adverse reactions can be adjusted in row 302-313 of the "Abrocitinib Cost Model" sheet in the model.

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Table 32 Type of specialist and costs per visits associated with treatment of adverse reaction

	Type of private specialist	Number of visits to a private specialist related to the treatment of the AR	Costs per visit, DKK	Source
Acne	GP	1	147,85	PLO, Honorartabel, 1. oktober 2021 til 31. marts 2022 (63)
Conjunctivitis	Eye	1	258,89	FAPS øjenlæge, Takstkort 14B, 1. oktober 2021 (64)
Allergic conjunctivitis	GP	1	147,85	PLO, Honorartabel, 1. oktober 2021 til 31. marts 2022 (63)
Herpes simplex	GP	2	147,85	PLO, Honorartabel, 1. oktober 2021 til 31. marts 2022 (63)
Herpes zoster	Dermatologist	2	535,62	FAPS Dermato-venerologi, kapitel 4, 1. oktober 2021 (65)

8.5.4 Patient costs

Patient costs (transport costs and direct time spent on receiving treatment) related to administration of treatment, monitoring and adverse reactions are included in the analysis. Patient costs are calculated as the patient's time consumption (DKK 179 per hour) plus a transportation cost per visit to the hospital (DKK 100 per visit), c.f. 'Værdisætning af enhedsomkostninger' from the Danish Medicines Council (58). It is assumed that the total average transportation time to and from the hospital is 30 minutes (corresponding to an average speed of 56 km/h with an average distance of 14 km). Furthermore, it is assumed the transportation time and transportation cost for the patient related to a private specialist visit is equivalent to a hospital visits. Table 33 shows the costs input related to patient costs, and can be adjusted in row 352-356 of the "Abrocitinib Cost Model" sheet in the model.

Table 33 Cost input related to patient costs

	Cost per hour, DKK	Source
Patient cost per hour	179	Medicinrådet, Værdisætning af enhedsomkostninger, v 1.3
Patients transportation cost to and from the hospital	100	Medicinrådet, Værdisætning af enhedsomkostninger, v 1.3
Patient time consumption on transport to and from the hospital	30	Assumption
Patients transportation cost to and from the private specialist	100	Assumption
Patient time consumption on transport to and from the private specialist	30	Assumption

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8.5.4.1 Patient costs related to administration

Patient costs related to administration is based on the input in section 8.5.2.1 Administration costs. It is assumed that patients receiving abrocitinib do not incur any administration costs, while 1.5% of the patients receiving dupilumab requires administration assistance and thereby incur costs related to administration. Time consumption related to administration assistance is 15 minutes. Inputs regarding patient costs related to administration can be adjusted in row 99 and 105-106 of the "Abrocitinib Cost Model" sheet in the model.

Table 34 Inputs for calculation of patient costs related to administration

Product	Patients requiring administration assistance	Time consumption for a nurse related to administration (minutes)
Abrocitinib	0%	0
Dupilumab	1.5%	15

8.5.4.2 Patient costs related to monitoring

Patient costs related to monitoring are based on the input in section 8.5.2.2 Monitoring costs. As described in section 8.1 and 8.5.2.2, it is assumed that patients receiving abrocitinib require one monitoring visit during the induction period, while patients receiving dupilumab require two monitoring visits during the induction period. It is assumed that treatment with both abrocitinib and dupilumab requires routine controls every third month, why out-patient visits with a dermatologist after the induction period of 16 weeks are not included in the analysis. Inputs regarding patient costs related to monitoring visits in the induction period can be adjusted in row 148 and 153-54 in the "Abrocitinib Cost Model" sheet in the model.

Furthermore, it is assumed that patient time related to blood tests is 10 minutes. This includes the actual time of test and waiting time in the testing facility. It is assumed that blood tests are taken at a point in time prior to out-patient follow-up visits (e.g. not the same day) and the results of blood testing is discussed at the out-patient follow-up visits, why the patient only incur time in relation to the actual testing. Furthermore, it is assumed that multiple blood tests are taken at the same time and thus the patient costs related to blood tests are calculated based on the blood test taken most times over a one-year period. Patient time relating to blood test can be adjusted in row 405 in the "Abrocitinib Cost Model" sheet in the model.

Table 35 Inputs related to patient costs associated with monitoring

Product	Monitoring visits during the induction period	Time consumption related monitoring (minutes)	Time consumption related to blood test (minutes)
Abrocitinib	1	20	10
Dupilumab	2	20	10

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8.5.4.3 Patient costs related to adverse events

Patient costs related to adverse events are based on the input in section 8.5.2.3 Adverse event costs and section 8.5.3 Cross sectional costs. Inputs regarding adverse events can be adjusted in row 215-226 and 233-244 of the "Abrocitinib Cost Model" sheet in the model.

As mentioned in section 8.5.2.3 Adverse events requiring treatment included in the analysis are acne, conjunctivitis, allergic conjunctivitis, herpes simplex and herpes zoster. It is assumed that adverse events requiring treatment in the private sector are treated with a 15 minutes consultation at the private specialist. The patient time consumption related to a visit at a private specialist can be adjusted in row 451-462 of the "Abrocitinib Cost Model" sheet in the model. Table 36 below shows the inputs related to treatment of adverse event at a private specialist.

Table 36 Inputs related to treatment of adverse event at a private specialist

	Type of private specialist	Number of visits to a private specialist related to the treatment of the AE	Time consumption related to a private specialist visit (minutes)
Acne	GP	1	15
Conjunctivitis	Eye	1	15
Allergic conjunctivitis	GP	1	15
Herpes simplex	GP	2	15
Herpes zoster	Dermatologist	2	15

Patient time consumption related to treatment of an adverse event in an out-patient setting are assumed to equivalent to the time consumption of an monitoring visit, i.e. 20 minutes. The patient time consumption related to a visit in an out-patient setting can be adjusted in row 252-263 of the "Abrocitinib Cost Model" sheet in the model.

Table 37 Inputs related to treatment of adverse event in an out-patient setting

	Number of out-patient visits to related to the treatment of the AE	Time consumption related to a out-patient visit (minutes)
Acne	0	20
Conjunctivitis	0	20
Allergic conjunctivitis	0	20
Herpes simplex	0	20
Herpes zoster	2	20

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Furthermore, it is assumed that patients carry the costs for prescription medicine related to treatment of an adverse event. Table 38 below presents the share of patients experiencing an adverse event treated with prescription medicine, the prescription medicines used to treat the adverse event and the cost of the prescription medicines. These input can be adjusted in row 499-510 of the "Abrocitinib Cost Model" sheet in the model.

Table 38 Patient costs related to prescription medicines, DKK

	Share of patients experiencing an AE treated with prescription medicine	Prescription medicine used to treat the AE (product)	Cost per package, DKK
Acne	10%	Isotretinoin	55,32
Conjunctivitis	100%	Oftagel + Ultracortenol (10% of patients)	63,04
Allergic conjunctivitis	100%	Oftagel	49,25
Herpes simplex	100%	Aciclovir	30,75
Herpes zoster	100%	Aciclovir	30,75

Source: medicinpriser.dk; webapoteket.dk, 11th October 2021

8.6 Results

8.6.1 Base case overview

Table 39 below shows an overview of the base case

Table 39 Base case overview

Comparator	Standard of care - dupilumab
Type of model	Cost minimization
Time horizon	52 weeks
Perspective	Limited societal perspective
Time on treatment	No difference between intervention and comparator
Included costs	Drug costs Hospital costs - Administrations cost - Monitoring costs - Adverse reaction costs Cross sectional costs Patient costs

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Dosage of pharmaceutical	Abrocitinib: 200 mg or 100 mg per day Dupilumab: 300 mg every 14th day
Concomitant treatment	Not included as the use of concomitant treatment is equal for both intervention and comparator
Discounting	Discounting is not included as the time horizon is less than a year

8.6.2 Base case results

In this section we present the results of the total cost per patients analysis, which is used to estimate the incremental costs of treatment with abrocitinib compared to dupilumab for moderate to severe atopic dermatitis patients over a one year time horizon. The included costs are not discounted, as the time horizon is less than a year. Table 40 below shows the base case results for the total costs per patient analysis.

Drug costs include the total cost for one year of treatment with abrocitinib and dupilumab based on PPP level. Drug costs are the primary driver for differences between abrocitinib and dupilumab.

Hospitals costs include costs associated with administration, monitoring and adverse reactions treated in a hospital setting. As seen in Table 40, hospital costs are primarily driven by monitoring costs for both abrocitinib and dupilumab. The average abrocitinib patient does not incur any administration costs and have very low costs associated with treatment of adverse events in a hospital setting. For the average dupilumab patient, few costs incur in relation to administration, due to the subcutaneous mode of administration which require facilitation of training in self-administration, and no costs is incurred in relation to treatment of adverse events in a hospital setting.

Cross sectional costs include costs related to treatment of adverse events in the primary care sector. Cross sectional costs incur for both abrocitinib and dupilumab, as the majority of adverse events are treated in a primary care setting, however cross sectional costs have a very little influence on the overall costs.

Patient costs include costs of patient time and transportation in relation to administration, monitoring, treatment of adverse events and costs of prescription medicines. The majority of patient costs are related to monitoring for both abrocitinib and dupilumab, reflecting the time used on blood tests for treatment with abrocitinib and training in self-administration for treatment with dupilumab.

Table 40 Total cost per patient over a one-year time horizon, DKK

		Abrocitinib	Dupilumab
Drug costs	Total drug cost	**91,152**	**120,149**
Hospital costs	Total administration cost	**0**	**60**
	Total monitoring cost	**980**	**539**
	Total hospital adverse events cost	**6**	**0**

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Cross sectional costs	Total cross sectional cost related to adverse events	22	19
Patient costs	Total patient costs related to administration	0	88
	Total patient costs related to monitoring	1,127	528
	Total patient costs related to treatment of an adverse event	28	26
	Total patient costs related to prescription medicine	2	5

Table 41 below shows the incremental costs of treatment with abrocitinib compared to dupilumab for moderate to severe atopic dermatitis patients over a one year time horizon. The total costs per patient including patient costs of treatment with abrocitinib are DKK 93,315, while the total costs per patient including patient costs of treatment with dupilumab are DKK 121,413, which gives an incremental cost of DKK -28,097. Excluding patient costs, gives an incremental cost of DKK -28,606 for treatment with abrocitinib compared to dupilumab.

Table 41 Total incremental costs per patient over a one-year time horizon, DKK

	Abrocitinib	Dupilumab	Incremental cost
Drug costs	91,152	120,149	-28,996
Hospital costs	985	598	387
Cross sectional costs	22	19	3
Patient costs	1,156	647	509
Total costs including patient costs	93,315	121,413	-28,097
Total costs excluding patient costs	92,159	120,765	-28,606

As seen in Figure 4 below, the incremental costs of treatment with abrocitinib compared to dupilumab are primarily driven by drug costs, 98-99% of the total costs are drug costs. Excluding patient costs will only alter the results minimally. Abrocitinib is a highly cost-saving alternative to dupilumab.

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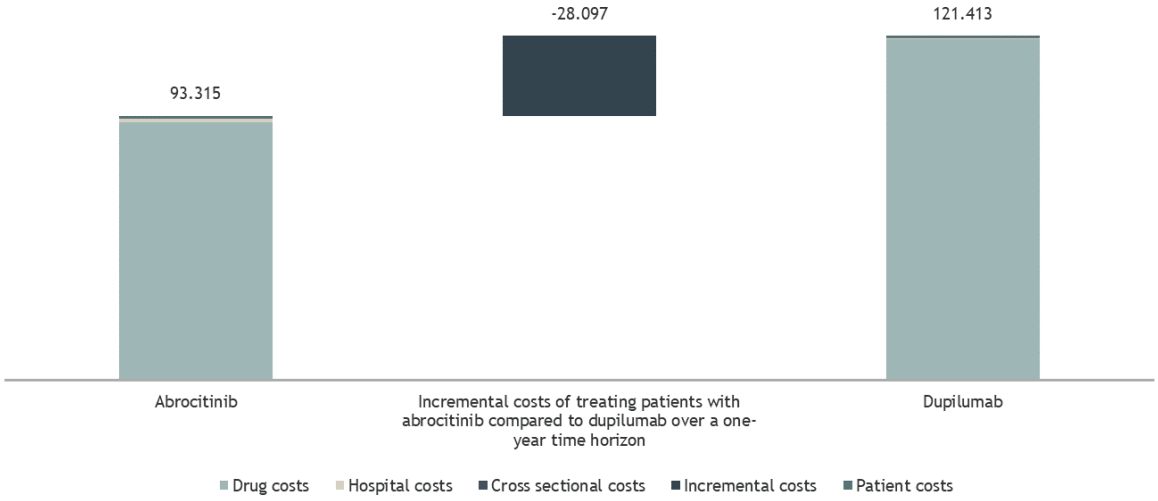
Figure 4 Incremental costs of treating patients with abrocitinib compared to dupilumab over a one-year time horizon



8.7 Sensitivity analyses

We have identified a number of uncertainties, which may impact the result from the base case analysis. In the following sections the conducted sensitivity analysis will be described and the results presented. Sensitivity analyses will be performed as one-way sensitivity analyses for each variable we have assessed as being uncertain. It is not possible to perform probabilistic sensitivity analyses, as the data basis for carrying out these analyses are not available.

The "Sensitivity analysis" sheet provides an overview of which parameters in the model we have adjusted to prepare a given sensitivity analysis. Based on the simple structure of the model, all sensitivity analyses are made by changing the relevant inputs in the sheet as described in the following section. Once inputs are adjusted in the model, push "run sensitivity analysis" in the top right corner of the sheet, to run the analyses.

8.7.1 DRG-rate instead of micro-costing

In the base case analysis, we have used a micro-costing approach to calculate hospital costs, which is equivalent to the approach used in the Medicines Councils assessment report for baricitinib (24). Alternatively, hospital costs can also be calculated using DRG-rates. We have therefore included as sensitivity analysis calculating hospital costs based on the DRG-rate of DKK 1,735 which is the DRG 2021 tariff for a patient with a primary diagnosis of atopic dermatitis (ICD-10 code DL209) in an outpatient setting with one contact day. The sensitivity analysis on the use of DRG-rate instead of micro-costing can be adjusted in row 27 and 50-61 in the "Sensitivity analysis" sheet in the model.

8.7.2 Number of monitoring visits during the induction period

In the base case analysis, we assume patients receiving abrocitinib have 1 monitoring visit during the induction period, and patients receiving dupilumab have 2 monitoring visits during the induction period, based on interviews with clinical experts. The additional monitoring visit for dupilumab treated patients covers training in self-administration of subcutaneous injections, however, we include a sensitivity analysis assuming dupilumab treated patients only have 1 monitoring visit during the induction period, and thereby there are no difference in monitoring visits between abrocitinib and dupilumab. The sensitivity analysis on number of monitoring visits can be adjusted in row 83-84 in the "Sensitivity analysis" sheet in the model.

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8.7.3 Number of blood tests per year for dupilumab patients

In the base case analysis, we assume that patients treated with abrocitinib requires 4 annual blood tests, and patients treated with dupilumab requires 1 annual blood test. However, based on inputs from clinical experts there can be difference in clinical practice regarding blood testing for dupilumab patients across dermatology departments in Denmark. We therefore have included a sensitivity analysis estimating the costs if the number of blood tests for dupilumab patients were increased to 2 annual blood tests. Furthermore, we have included a sensitivity analysis estimating the costs if no blood tests were taken for patients treated with dupilumab. The sensitivity analysis on number of blood tests for dupilumab patients can be adjusted in row 91-96 and 103-108 in the "Sensitivity analysis" sheet in the model.

8.7.4 Proportion of patients requiring assistance to administer dupilumab.

In the base case analysis, we have assumed that 1.5% of the patients treated with dupilumab require assistance in administration of dupilumab based on the Medicine Council's assessment report for baricitinib (24) and clinical experts. This assumption is highly correlated to the characteristics of the patient population, which might change over time. We have therefore included two sensitivity analyses to estimate the effect on the total costs per patient related to a change in the proportion of patients requiring administration assistance. The first scenario, no patients require assistance in administration of dupilumab, the second scenario 3% of the population require assistance in administration of dupilumab. The sensitivity analysis on proportion of patients requiring assistance to administer dupilumab can be adjusted in row 115-116 and 123-124 in the "Sensitivity analysis" sheet in the model.

8.7.5 Adverse events requiring treatment

In the base case analysis, we assume that only selected adverse events require treatment. These adverse events are acne, conjunctivitis, allergic conjunctivitis, herpes simplex and herpes zoster. However, treatment of adverse events are associated with uncertainty as the severity and thereby extend of treatment for each adverse event can be varying. We have therefore included an sensitivity analysis exploring the economic impact if all patients experiencing an adverse event had one additional out-patient visit compared to the base case analysis. The sensitivity analysis on additional out-patient visits related to adverse events can be adjusted in row 131-142 in the "Sensitivity analysis" sheet in the model.

8.7.6 Patient costs related to prescription medicines – acne treatment

In the base case analysis, we assume that 50% of the patients experiencing acne as an adverse reaction will need prescription medicine to treat it. The majority of acne reported for abrocitinib are mild to moderate cases, which do not require treatment as assessed by clinical experts. We have, however, included a sensitivity analysis estimating the costs if 100% of the patients experiencing acne as an adverse reaction will need prescription medicine to treat it. The sensitivity analysis on patient costs related to prescription medicines can be adjusted in row 149-160 in the "Sensitivity analysis" sheet in the model.

Table 42 One-way sensitivity analyses results

	Change	Incremental cost, DKK
Base case	-	**-28,097**

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	Change	Incremental cost, DKK
DRG-rate instead of micro-costing	Micro-costing → DKK 1,735	**-30,186**
Number of monitoring visits during the induction period for dupilumab patients	2 → 1	**-27,826**
Number of blood tests for dupilumab patients	1 → 0	**-27,763**
	1 → 2	**-28,432**
Proportion of patients requiring assistance to administer dupilumab.	1.5% to 0%	**-27,950**
	1.5% to 3%	**-28,245**
Adverse events requiring treatment	Selected reactions→ all reactions	**-28,053**
Patient costs related to prescription medicines – acne treatment	50% → 100%	**-28,095**

As seen in Table 42 above, all of the included sensitivity analyses fall fairly close to the base case result of an incremental cost of DKK -28,097 per patient. The results of the sensitivity analyses range from DKK -30,186 to DKK -27,763 per patient, corresponding to a difference from the base case of DKK -2,089 to DKK 334 per patient. The largest difference is seen in the sensitivity analysis of using a DRG-rate instead of the micro-costing approach, resulting in an incremental cost of DKK -30,186 per patient. Overall, the sensitivity analyses evaluating the impact of clinical inputs associated with uncertainty on the total incremental cost per patient, showed almost no difference from the base case. The results found in the base case analysis are therefore robust to changes in the included variables.

9. Budget impact analysis

The budget impact analysis follows the Medicines Council's methods guideline, which means that we do not include patient costs, and the costs are not discounted. The budget impact analysis is based on the cost model, and uses the results from the cost per patient analysis in the first treatment year. For subsequent treatment year, e.g. year 2-5, a few assumptions apply. Firstly, dupilumab has a double induction dose, which do not apply in subsequent years. Secondly, as it is assumed that monitoring of patients beyond the treatment induction period is similar for treatment with both abrocitinib and dupilumab, therefore no costs in relation to monitoring visits are included in the costs for subsequent years, however costs related to blood tests are included. Costs related to monitoring visits in subsequent years can be added in row 164-165 in the "Abrocitinib Cost Model" sheet. Lastly, as it is assumed that all adverse events occur at treatment initiation, as described in section 8.2.2.5, no costs related to treatment of adverse events are included in subsequent years. Hospital costs related to adverse events in subsequent years can be added in row 291-292, cross sectional costs related to adverse events in subsequent years can be added in row 341-342, patient costs related to treatment of adverse events in subsequent years can be added in row 490-491 and patients costs related to prescription medicine in subsequent years can be added in row 522-523 in the "Abrocitinib Cost Model" sheet.

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9.1 Number of patients

Table 43 below, shows the number of projected patients in the coming five years. The patient numbers are based on an estimation made by the Medicines Council's Expert Committee for Atopic Dermatitis in the protocol for baricitinib (20). This patient number has also been advised to use by the secretariat, as this number is still applicable and provides a common basis for comparison as these numbers were recently used in the Medicines Council's assessment report for baricitinib (24).

It is estimated that 225 patients will be candidates for advanced systemic treatment (e.g. candidates for dupilumab, baricitinib or abrocitinib), although the majority of patients may already have initiated treatment. The Expert Committee has also estimated that 30 new patients per year will be candidates for advanced systemic treatment (20).

Table 43 Number of moderate to severe atopic dermatitis patients in Denmark expected to use advanced systemic treatment

Year	Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Number of moderate to severe atopic dermatitis patients in Denmark expected to use advanced systemic treatment	225 adults	255 adults	285 adults	315 adults	345 adults

Based on the estimates provided by the Medicines Council's Expert Committee for Atopic Dermatitis as described above it is estimated that 225 adults will be candidates for advanced systemic treatment in the first year with a yearly patient population growth of 30 new patients in the following years. As described in section 8.2.2.1.3, a significant number of these patients are already treated with dupilumab, and as well-treated patients are not switched according to Danish clinical practise, it is expected that 25% of the 225 patient will initiate treatment with abrocitinib in year 1 following a positive recommendation of abrocitinib by the Danish Medicines Council. Furthermore, it is expected that 100 % of all new moderate to severe atopic dermatitis patients will be treated with abrocitinib following a positive recommendation by the Danish Medicines Council. This gives abrocitinib an expected market share of 25% in year 1 increasing to 51% in year 5. This growth in market share, is in line with the estimation of market shares provided by the Medicines Council's Expert Committee for Atopic Dermatitis in the Medicines Council's assessment report for baricitinib (24), however the distribution of number of patients are different. In the assessment report for baricitinib, it was assumed patients would initiate treatment on both baricitinib and dupilumab following a recommendation of baricitinib, leading to a large patient switch from dupilumab to baricitinib in year 5 (24). We have therefore assumed that all new patients initiate treatment with the current standard of care, either abrocitinib or dupilumab, dependent on the recommendation by the Danish Medicines Council. A sensitivity analysis estimating the budget impact of following the distribution of patients and market shares as presented in the Medicines Council's assessment report for baricitinib (24), can be found in section 9.4 Sensitivity analysis of budget impact in this report.

Table 44 below shows the number of patients expected to be treated over the next five-year period, if abrocitinib is introduced as standard of care. The patient numbers can be changed in row 17-20 and the share of patient expected to initiate treatment with abrocitinib and dupilumab, respectively, if abrocitinib is recommended as standard of care, can be change in row 11-12 in the "Budget Impact Analysis" sheet in the model.

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Table 44 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

		Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Abrocitinib	New patients	56	30	30	30	30
	Existing patients	0	56	86	116	146
	Total number of abrocitinib patients	*56*	*86*	*116*	*146*	*176*
Dupilumab	New patients	0	0	0	0	0
	Existing patients	169	169	169	169	169
	Total number of dupilumab patients	*169*	*169*	*169*	*169*	*169*
Total number of patients		225	255	285	315	345
Market share abrocitinib		25%	34%	41%	46%	51%
Market share dupilumab		75%	66%	59%	54%	49%

If abrocitinib is not introduced as standard of care, it is expected that no new moderate to severe atopic dermatitis patients will be treated with abrocitinib, e.g. the opposite situation. This gives dupilumab an expected market share of 100%. Table 45 below shows the number of patients expected to be treated over the next five-year period, if abrocitinib is not introduced as standard of care. The patient numbers can be changed in row 29-32 in the "Budget Impact Analysis" sheet in the model.

Table 45 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

		Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Abrocitinib	New patients	0	0	0	0	0
	Existing patients	0	0	0	0	0
	Total number of abrocitinib patients	0	0	0	0	0
Dupilumab	New patients	0	30	30	30	30
	Existing patients	225	225	255	285	315
	Total number of dupilumab patients	*225*	*255*	*285*	*315*	*345*
Total number of patients		225	255	285	315	345
Market share abrocitinib		0%	0%	0%	0%	0%

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	Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Market share dupilumab	100%	100%	100%	100%	100%

9.2 Expenditure per patient

In the base-case analysis of total costs per patient it was estimated that treatment with abrocitinib incurred DKK 92,159 per patient excluding patients costs, while treatment with dupilumab incurred DKK 120,765 per patient excluding patient costs. The costs included in the budget impact analysis therefore includes drug costs, hospital costs and cross-sectional costs, see Table 46. These results can also be found in row 44-45 in the "Budget Impact Analysis" sheet in the model.

Table 46 Total costs per patient treated with abrocitinib and dupilumab respectively, year 1, undiscounted, DKK

	Drug costs	Hospital costs	Cross sectional costs	Total costs per patient excluding patient costs
Abrocitinib	91,152	985	22	92,159
Dupilumab	120,149	598	19	120,765

For the calculation of treatment costs in subsequent years, a few assumptions apply as mentioned in section 8.1; 1) there are no double dose related to treatment initiation for dupilumab as no patients initiate treatment in subsequent years, 2) no costs in relation to monitoring visits are included in subsequent years, as these only incur in the induction period, 3) adverse events occurs at treatment initiation and no costs related to treatment of adverse reactions are included in subsequent years. Table 47 below shows the total cost per patient in subsequent years. These results can also be found in row 49-50 in the "budget impact analysis" sheet in the model.

Table 47 Total costs per patient treated with abrocitinib and dupilumab respectively, subsequent years, undiscounted, DKK

	Drug costs	Hospital costs	Cross sectional costs	Total costs per patient excluding patient costs
Abrocitinib	91,152	768	0	91,920
Dupilumab	115,699	177	0	115,876

9.3 Budget impact

The expected budget impact of recommending vs. not recommending abrocitinib as standard of care for patients with moderate to severe atopic dermatitis follows the number of patients and expenditure estimates presented in the two previous sections. The budget impact is shown in Table 48 below. Recommending abrocitinib as standard of care is estimated to result in an incremental cost of DKK -1,328,112 in year 1, increasing to DKK -4,355,674 in year 5. Accumulated, introducing abrocitinib is expected to lead to cost savings of DKK 14,438,831 over the five year period from 2022-2026.

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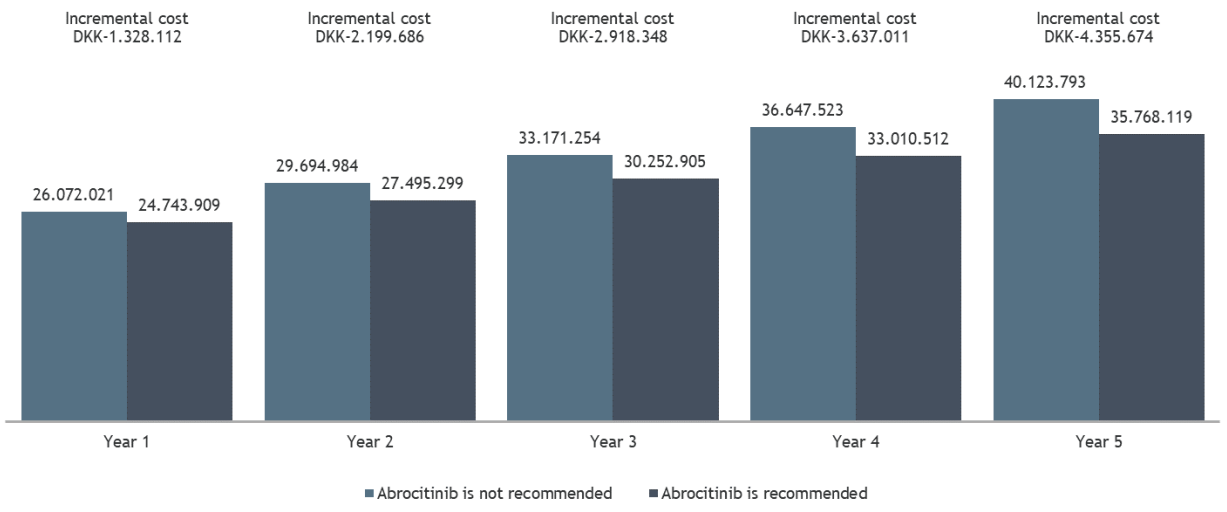
Table 48 Expected budget impact of recommending vs. not recommending the pharmaceutical for the current indication

	Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Abrocitinib is recommended	24,743,909	27,495,299	30,252,905	33,010,512	35,768,119
Of which: Drug costs	24,657,605	27,392,172	30,126,739	32,861,306	35,595,873
Of which: Hospital costs	85,089	102,476	125,516	148,556	171,596
Of which: Cross sectional costs	1,215	651	651	651	651
Minus:					
Abrocitinib is not recommended	26,072,021	29,694,984	33,171,254	36,647,523	40,123,793
Of which: Drug costs	26,032,208	29,636,667	33,107,628	36,578,589	40,049,550
Of which: Hospital costs	39,814	57,758	63,067	68,375	73,684
Of which: Cross sectional costs	0	559	559	559	559
Incremental costs	-1,328,112	-2,199,686	-2,918,348	-3,637,011	-4,355,674

Figure 5 below, illustrates the budget impact following a positive or negative recommendation of abrocitinib by the Danish Medicines Council.

Figure 5 Budget impact following a positive or negative recommendation of abrocitinib



9.4 Budget impact sensitivity analysis

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As mentioned in section 9.1 Number of patients, the budget impact analysis follows the patient estimate provided by the Medicines Council's Expert Committee for Atopic Dermatitis in the assessment report for baricitinib (24). This estimate was also advised to use by the secretariat. Our budget impact analysis follows the distribution of patients according to market share, however we have changed the distribution of number of patients in the base case analysis, meaning that all new patients initiate treatment with either abrocitinib or dupilumab and no patients switch treatment. In this sensitivity analysis, a budget impact analysis estimating the impact in costs following the distribution of patients and market shares as presented in the Medicines Council's assessment report for baricitinib (24) will be presented. In this scenario new patients will initiate treatment on both the existing standard of care as well as the new standard of care, and switch between treatments are allowed. Please not that this sensitivity analysis will only impact the expenditures in a scenario where abrocitinib is recommended as standard of care. The sensitivity analysis can be found in the "Sensitivity Budget Impact" sheet in the model.

Table 49 below show the distribution of patients used in the sensitivity analysis.

Table 49 Danish Medicines Council's estimate of the number of AD patients per year following a positive recommendation of baricitinib used to calculate the budget impact of recommending abrocitinib as standard of care

		Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Abrocitinib	New patients	56	21	23	26	46,5
	Existing patients	0	56	77	100	126
	Total number of abrocitinib patients	*56*	*77*	*100*	*126*	*173*
Dupilumab	New patients	0	10	6	4	-17
	Existing patients	169	169	179	185	189
	Total number of dupilumab patients	*169*	*179*	*185*	*189*	*173*
Total number of patients		225	255	285	315	345
Market share abrocitinib		25%	30%	35%	40%	50%
Market share dupilumab		75%	70%	65%	60%	50%

The same expenditures as used in section 9.2 are used to calculate the costs.

The sensitivity analysis of the expected budget impact of recommending vs. not recommending abrocitinib as standard of care for patients with moderate to severe atopic dermatitis is shown in Table 50 below. Recommending abrocitinib as standard of care is estimated to result in an incremental cost of DKK -1,328,112 in year 1, increasing to DKK -4,267,884 in year 5. Accumulated, introducing abrocitinib is expected to lead to cost savings of DKK 13,064,159 over the five year period from 2022-2026.

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Table 50 Sensitivity analysis of budget impact following the Medicines Council's estimate of AD patients used in the assessment report for baricitinib

	Year 1, 2022	Year 2, 2023	Year 3, 2024	Year 4, 2025	Year 5, 2026
Abrocitinib is recommended	24,743,909	27,873,519	30,663,857	33,508,223	35,855,909
Of which: Drug costs	24,657,605	27,773,289	30,546,182	33,370,035	35,681,785
Of which: Hospital costs	85,089	99,588	117,064	137,550	173,115
Of which: Cross sectional costs	1,215	642	611	638	1.009
Minus:					
Abrocitinib is not recommended	26,072,021	29,694,984	33,171,254	36,647,523	40,123,793
Of which: Drug costs	26,032,208	29,636,667	33,107,628	36,578,589	40,049,550
Of which: Hospital costs	39,814	57,758	63,067	68,375	73,684
Of which: Cross sectional costs	0	559	559	559	559
Incremental costs	-1,328,112	-1,821,466	-2,507,397	-3,139,300	-4,267,884

10. Discussion on the submitted documentation

Three randomised controlled studies from the abrocitinib pivotal clinical trial program and one RCT for dupilumab are used in this submission to evaluate the efficacy and safety of abrocitinib in adults compared to dupilumab. Results indicate that abrocitinib provides substantial benefit to adults with moderately to severely AD who are candidates for systemic treatment. Abrocitinib administered in combination with background topical treatment, mainly TCS or as monotherapy provided rapid, statistically significant, and clinically meaningful improvements in AD, itch and PROs demonstrated by pivotal clinical trials. Abrocitinib demonstrates well-defined tolerability and a manageable safety profile with or without topical background therapy. Most of the AEs associated with abrocitinib are mild and rarely require therapeutic interruptions or permanent discontinuation.

The main comparison between abrocitinib and dupilumab is done using the JADE COMPARE trial. Though there are some limitations to take into consideration. In terms of atopic dermatitis as a lifelong disease, this 16-week trial did not establish the long-term efficacy and safety of abrocitinib. The trial was not formally designed to evaluate the superiority of abrocitinib over dupilumab with respect to the two primary end points. The results from JADE COMPARE is supported by the NMA and demonstrates that abrocitinib matches up to dupilumab in treatment of moderate to severe AD. Abrocitinib 200 mg dose showed clinically significant difference for a range of endpoints vs dupilumab, and abrocitinib 100 mg was comparable to dupilumab.

Abrocitinib shows similar short-term rates of SAEs as dupilumab based on data from JADE COMPARE, JADE MONO-1, JADE MONO-2 and the NMA. Acute and long-term use of abrocitinib is well-tolerated and has a safety profile that supports use in patients with moderate to severe AD, similar to dupilumab.

The value of abrocitinib based on current evidence is a new mode of action, and thus adding a treatment option for moderate to severe AD patients. The oral administration form of abrocitinib offers clinical benefit of a magnitude that until now is only been observed with injectable biologics.

Our conclusion is that abrocitinib has shown a similar profile regarding efficacy and safety as dupilumab.

The cost-minimization analysis shows that under the assumption of equivalent efficacy, abrocitinib is a highly cost-saving alternative to dupilumab. All relevant cost differences between the relevant alternatives were considered, and the majority of the sensitivity analyses fall fairly close to the base case confirming that this analysis is robust.

There is a substantial unmet need in moderate to severe atopic dermatitis patients who have not responded to, or have lost response to, at least one systemic immunosuppressant therapy, or in whom these are contraindicated or not tolerated. Dupilumab may not be appropriate for all patients due to its side effect profile and route of administration, and abrocitinib represent a cost-saving alternative. Further, the 200 mg dose has been shown to be more effective than dupilumab at rapidly reducing itch and improving skin clearance, which are two major drivers of disease burden in AD. Hence, the cost-minimization analysis is a conservative modelling approach.

Given that both doses of abrocitinib have similar clinical effect compared with existing treatments (dupilumab and baricitinib), but are cost-saving compared with existing treatments, and with a flexible oral administration, they are attractive treatment options for both patients, hospitals and the healthcare sector in general.

11. List of experts

Two Danish clinical experts in dermatology has been consulted during development of this submission.

[redacted]

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Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Objective of the submission:
What is the value of abrocitinib compared to dupilumab for adults with moderate to severe atopic dermatitis who have had insufficient effect of optimized local treatment or who are candidates for systemic treatments.
Population: Adults with moderate to severe atopic dermatitis who are candidates for systemic treatment and who have had insufficient effect of optimized local treatment
Intervention: Abrocitinib 100 mg and 200 mg once daily
Comparator: Dupilumab 300 mg every other week, with and initial loading dose of 600 mg.
Outcomes: The outcomes in table A1a has been chosen for the assessment of the value of abrocitinib based on primary and key secondary outcomes included in the clinical trials. Also the Medicines Council previous evaluation of dupilumab and baricitinib has been taking into account, where the Expert Committee has chosen outcomes which best supports the assessment of the technologies value in atopic dermatitis.

Table A1a. Tabulated view of outcomes

Outcome	Measure
Eczema - distribution and severity	Proportion of patients achieving an IGA of 0 (clear) or 1 (almost clear)[¤]
	Proportion of patients who achieve a minimum of 75% reduction on the EASI scale (EASI75)
	Proportion of patients achieving 75 % reduction of SCORAD scale (SCORAD75) or least square mean change from baseline[#]
Eczema distribution and severity, patient reported	POEM, change from baseline
Side effects	Proportion of patients who experiences one or more serious adverse events
	Summary of long-term side effects, all degrees
Quality of Life	Patients with a ≥4-point decrease in DLQI total score (%) or DLQI change from baseline
	Patients with a ≥4-point decrease in CDLQI total score (%) or CDLQI change from baseline
Itch	Proportion of patients who achieve ≥4-point improvement in PP-NRS from baseline*

If not otherwise stated outcomes are assessed at the longest possible follow-up time
[¤]The primary outcome IGA is assessed at week 12.
[#] measure depends on data availability
* Itch is a key symptom of atopic dermatitis and important for evaluation of response to treatment. A fast and continuous relief in itch is essential and the outcome is thus assessed both at week 2 and week 12/16 (depending on study duration).

A literature search has not been performed as the study JADE COMPARE is used for the assessment of abrocitinib and includes the comparator dupilumab as an active study-arm. JADE COMPARE fulfills the PICO.

The US and EU clinical trial databases were searched for ongoing studies according to the Medicines Councils method guide (table A1b).

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Table A1b. Clinical trial registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Atopic dermatitis AND (Abrocitinib OR PF-04965842)	24.06.2021
EU Clinical Trials Register	EU Clinical Trials Register	Atopic dermatitis AND (Abrocitinib OR PF-04965842)	24.06.2021

Data from JADE REGIMEN and JADE EXTEND are included in the pooled safety analysis for abrocitinib and the studies are included in the integrated safety analysis for abrocitinib. However no efficacy data from the respective studies are used in this application, as the study designs are not eligible for comparison. The studies are listed in table A1c, with studies not included in the application.

Studies included in the application are not also listed in the search in the EU clinical trial register and US NIH registry & results database

Table A1c. List of ongoing or completed studies for abrocitinib not included in this application

NCT number / EudraCT number	Trial Name	Trial phase	Dates of study (start and expected completion date)	Reason for exclusion
NCT04065633	-	Phase 1	Completed (July 18, 2019 - December 14, 2019)	Healthy participants,
NCT04903093	-	Phase 1	Ongoing (June 4, 2021 - August 31, 2021)	Healthy participants,
NCT03796182	-	Phase 1	Completed (January 10, 2019 - March 12, 2019)	Healthy participants
NCT03358693	-	-	Ongoing (January 1, 2016 - December 31, 2025)	Observational
NCT03634345	-	Phase 1	Completed (September 12, 2018 - December 13, 2018)	Healthy participants
NCT03796676	JADE TEEN	Phase 3	Completed (February 18, 2019 – April 8, 2020)	Population
NCT03627767 / 2018-000501-23	JADE REGIMEN	Phase 3	Completed (June 11, 2018 - October 7, 2020)	Study design. Pooled safety data as assessed by the EMA included in the application
NCT03422822 / 2017-004851-22	JADE EXTEND	Phase 3	Ongoing (March 8, 2018 - December 1, 2023)	Study design. Pooled safety data as assessed by the EMA included in the application

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NCT02780167 / 2015-005513-72	-	Phase 2b	Completed (April 2016 - April 2017)	Population
NCT04345367 / 2019-004013-13	JADE DARE	Phase 3	Ongoing (June 11, 2020 - July 14, 2021)	Data not available
NCT04564755 / 2020-003610-1	-	-	-	Expanded access protocol
NCT03915496	JADE MOA	Phase 2	Ongoing (June 18, 2020 - October 4, 2021)	Population

No search for abstracts or conference material has been performed as results from non-peer-reviewed material will not be included.

List: Supplementary manual searches
EMAs webpage was manually searched on 15 June 2021 and the EPAR for Dupixient (55) has been retrieved and included. A newly published systematic review and network meta-analysis by Silverberg et al. 2021 has been manually searched and included in the application (48).

Search strategy

Not applicable.

Systematic selection of studies

Not applicable.

Quality assessment

Not applicable.

Unpublished data

Not applicable.

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Appendix B Main characteristics of included studies

Table A2a. Main characteristics of JADE COMPARE

Trial name: JADE COMPARE	NCT number: NCT03720470
Objective	*The primary objective of the JADE COMPARE trial was to evaluate the efficacy of abrocitinib as compared with placebo, at 12 weeks in patients with moderate-to-severe atopic dermatitis who were receiving background topical therapy. A key secondary objective was to evaluate the efficacy of abrocitinib, as compared with placebo and with dupilumab (an active comparator in another drug class), on the basis of a reduction in itch at 2 weeks.*
Publications – title, author, journal, year	*Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis, Bieber T. N Engl J Med 2021;384:1101-12.*
Study type and design	*A Phase 3 multicenter, double-blind, double-dummy, parallel group, randomised, placebo-controlled, trial of the efficacy and safety of abrocitinib and dupilumab in the treatment of adults with moderate-to-severe AD on background topical therapy. Patients were randomly assigned in a 2:2:2:1 ratio to receive 200 mg or 100 mg of abrocitinib orally once daily, 300 mg of dupilumab subcutaneously every other week (after a loading dose of 600 mg), or placebo for 16 weeks and allocated to treatment groups through the use of an Interactive Response Technology (IRT) system. The patients, investigators, and representatives of the sponsor were blinded as to the treatment group, throughout the treatment period.* *The study is completed.*
Sample size (n)	*838*
Main inclusion and exclusion criteria	*The table below provides an overview of the main inclusion and exclusion criteria. A full description of the inclusion and exclusion criteria is provided in the protocol which is published as supplementary material with the JADE COMPARE study by Bieber et al., NEJM, 2021 (49)* *JADE COMPARE main inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria

• Adults (≥18 years)
• Clinical diagnosis of moderate-to-severe AD ≥1 year before start of study
  ○ IGA score ≥3,
  ○ EASI ≥16;
  ○ BSA ≥10%,
  ○ PP-NRS ≥4
• Documentation within 6 months of screening of:
  ○ Inadequate response to TCS or TCI ≥4 weeks; or
  ○ Requiring systemic therapy to control disease
• Use of only non-medicated topical therapy during last seven days leading to Day 1 of study
• Stable medication regimens for non-AD indications
	• Acute or chronic medical or psychiatric conditions
	• Current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction
	• Other active inflammatory skin diseases or conditions affecting skin
	• Exposure to live or attenuated vaccine within six weeks before administration first dose of study drug
	• History of treatment with JAK inhibitors or dupilumab

AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; JAK = Janus kinase; PP-NRS = Peak Pruritus Numerical Rating Scale; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

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Trial name: JADE COMPARE	NCT number: NCT03720470
Intervention	*Abrocitinib 100 mg or 200 mg once daily. 238 patients were assigned to the 100-mg abrocitinib group and 226 patients were assigned to the 200-mg abrocitinib*
Comparator(s)	*Dupilumab 300 mg every 2 weeks with an initial loading dose of 600 mg. 243 patients were assigned to the dupilumab group*
Follow-up time	*16 weeks*
Is the study used in the health economic model?	*Yes*

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Primary, secondary and exploratory endpoints

Endpoints included in this application:

Primary endpoints: Response based on achieving the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline (pre-dose Day 1) of ≥2 points at Week 12; Response based on achieving the Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 12.

Secondary endpoints: Response based on achieving EASI-75 (≥75% improvement from baseline) at Week 16; Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at Week 2; Response based on achieving at least 4 points improvement in the severity of Pruritus NRS from baseline at all scheduled time points except Week 2 (week 16 will be used in this application); Change from baseline in Patient-Oriented Eczema Measure (POEM) at all scheduled time points (week 16 will be used in this application); Change from baseline in Dermatology Life Quality Index (DLQI) at all scheduled time points (week 16 will be used in this application); Response based on a ≥75% improvement in SCORAD (SCORAD75) from baseline at all scheduled time points (week 16 will be used in this application); Incidence of serious adverse event (SAE)s.

Other endpoints:

Endpoints not included in this application:

Secondary, safety and exploratory endpoints: Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of 2 points at Week 16; Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and ≥2 point reduction from baseline at all scheduled time points except Week 12 and Week 16; Response based on achieving a ≥75% improvement in the EASI total score (EASI-75) at all scheduled time points except Week 12 and Week 16; Response based on achieving a ≥50% and ≥90% improvement in the EASI total score (EASI-50 and EASI-90) at all scheduled time points; Time from baseline to achieve at least 4 points improvement in the severity of Pruritus NRS scale; Change from baseline in the frequency of itching due to AD; Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points; Change from baseline of Patient Global Assessment (PtGA) at all scheduled time points; Change from baseline in Health Care Resource Utilization (HCRU) questionnaire at all scheduled time points; Change from baseline in EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) at all scheduled time points; Change from baseline in Hospital Anxiety and Depression Scale (HADS) at all scheduled time points; Change from baseline in Patient-Oriented Eczema Measure (POEM) at all scheduled time points; Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at all scheduled time points; Response based on a ≥50% improvement in SCORAD (SCORAD50) from baseline at all scheduled time points; Change from baseline at all scheduled time points in SCORAD subjective assessments of itch and sleep loss; Steroid-free days at Week 16; Incidence of treatment-emergent adverse event (AE)s; Incidence of AEs leading to discontinuation; Incidence of clinical abnormalities and change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements, and vital signs; Response based on achieving at least 4 points improvement in the Night Time Itch Scale, for severity and frequency, from baseline at all scheduled time points; Time from baseline to achieve at least 4 points improvement in the Night Time Itch Scale for severity and frequency; Number of scratching episodes during the evening sleep period that occur pre-treatment versus on-treatment, as derived from data analysis using wearable accelerometry monitors; Duration of scratching episodes during the evening sleep period that occur pre-treatment versus on-treatment, as derived from data analysis using wearable accelerometry monitors; Compare change from pre-treatment to on-treatment measures of sleep quantity, total sleep time, wake after sleep onset (WASO), and sleep efficiency during the major rest period (night time sleep), from data obtained from wearable accelerometry monitors; Quantity of sleep, total sleep time, WASO, and sleep efficiency during the major rest period (night time sleep), from pre-treatment and on-treatment

Trial name: JADE COMPARE	NCT number: NCT03720470
	obtained from wearable accelerometry devices; Collection of banked biospecimens unless prohibited by local regulations or ethics committee decision.
Method of analysis	*The hypothesis objective:* • *To demonstrate superiority of 200 mg and 100 mg abrocitinib over placebo in adults (≥18 years) receiving background medicated topical therapy with moderate to severe AD.* • *To demonstrate superiority of abrocitinib over dupilumab in attaining a clinically significant improvement in severity of pruritus for adults with moderate to severe AD receiving background medicated topical therapy.* *A sequential Bonferroni-based iterative multiple testing procedure to strongly control the familywise Type 1 error at 5% was used for assessing the primary and key secondary endpoints.* *Total of 700 patients, with 200 each randomised to 200 mg abrocitinib, 100 mg abrocitinib, 300 mg dupilumab, and 50 patients each randomised to two sequences of matching placebo for 16 weeks, followed by a switch to receive 100 mg abrocitinib and 200 mg abrocitinib was planned. A combination of the two placebo sequences for analyses at all visits resulted in a 2:2:2:1 randomisation ratio, which provided ≥96% power to detect a difference of ≥20% in IGA response rate between either dose of abrocitinib and placebo, assuming the placebo response rate was 12% at Week 12. This also provided ≥99% power to detect a difference of ≥30% in EASI-75 response between either dose of abrocitinib and placebo, assuming placebo response rate is 23% at Week 12. In addition, the sample size provided ≥92% power to detect a difference of ≥15% in the proportion of patients with ≥4-point improvement in severity of pruritus PP-NRS between abrocitinib and dupilumab, assuming the dupilumab response rate is 18% at Week 2.* *Efficacy analyses were performed using the modified intented-to-treat (ITT) population, which included all the patients who had undergone randomization and received at least 1 dose of a trial drug or placebo. The modified-ITT would be expected to be identical to the full analysis set, defined as all randomised patients receiving at least one dose of study medication, because the first dose was administered in clinic.* *The coprimary efficacy endpoints were analysed using the Cochran–Mantel–Haenszel test, adjusted by baseline disease severity (moderate/severe) and for a given dose, both endpoints must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of patients achieving IGA response (similarly for EASI-75), along with a 95% confidence interval (using the normal approximation for the difference in binomial proportions) was reported. Additional secondary analyses utilised missing-at-random and missing-not-at-random approaches.* *Key secondary endpoints and all other binary endpoints were also analysed using the CMH test. For continuous endpoints, a mixed-effects model with repeated measures was applied, including the factors (fixed effects) for treatment group, randomisation strata (age, disease severity), visit, treatment-by-visit interaction, and relative baseline value. Within the framework of mixed-effect repeated measures, the treatment difference was tested at the pre-specified primary time point, Week 12, as well as other time points by time point-specific contrasts from the mixed-effect repeated measures model.*
Subgroup analyses	*NA*
Other relevant information	*No*

Table A2b. Main characteristics of JADE MONO-1 and MONO-2

Trial name: JADE MONO-1 and MONO-2	NCT number: NCT03349060 and NCT03575871
Objective	*The primary objective of the JADE MONO-1 and MONO-2 trials were to compare the efficacy of abrocitinib 200 mg and 100 mg once daily vs placebo in patients aged 12 years and older with moderate to severe AD.*
Publications – title, author, journal, year	*JADE MONO-1: Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): multicentre, double-blind, randomised, placebo-controlled phase 3 trial, Simpson EL. Lancet 2020;396:255-66.* *JADE MONO-2: Efficacy and Safety of Abrocitinib in Patients With Moderate-to-Severe Atopic Dermatitis A Randomised Clinical Trial, Silverberg JI. JAMA Dermatol. 2020;156(8):863-873.*
Study type and design	*JADE MONO-1 and MONO-2 were replicate phase 3 international, double-blind, parallel group, randomised, placebo-controlled, trials of the efficacy and safety of abrocitinib in the treatment of moderate-to-severe AD in adolescents (patients aged ≥12 years) and adults. Following screening, subjects were randomised 2:2:1 to one of 2 treatment groups (abrocitinib 100 mg and 200 mg) or placebo once daily and treated for 12 weeks, using a central randomisation sheme provided by an interactive response technology system. Patients, investigators, and the funder of the study were masked to study treatment.* *The studies are completed.*
Sample size (n)	*JADE MONO-1: 387* *JADE MONO-2: 391*

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Trial name: JADE MONO-1 and MONO-2	NCT number: NCT03349060 and NCT03575871

Main inclusion and exclusion criteria

The table below provides an overview of the main inclusion and exclusion criteria. A full description of the inclusion and exclusion criteria is published as supplementary material with the JADE MONO-1 and JADE MONO-2 study by Simpson et al., Lancet, 2020 and Silverberg JAMA Dermatol. respectively (50, 51).

JADE MONO-1 and MONO-2 main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Adolescents and adults (≥12 years)
• Body weight ≥40 kg
• Clinical diagnosis of moderate-to-severe AD ≥1 year before start of study
  ○ IGA score ≥3,
  ○ EASI ≥16;
  ○ BSA ≥10%,
  ○ PP-NRS ≥4
• Documentation within 6 months of screening of:
  ○ Inadequate response to TCS or TCI ≥4 weeks; or
  ○ Medically inadvisable to receive TCS or TCI, or
  ○ Requiring systemic therapy to control disease
	• Acute or chronic medical or psychiatric conditions
	• Current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction
	• Other active non-AD inflammatory skin diseases or conditions affecting skin
	• Any prior use of systemic JAK inhibitor or use of systemic corticosteroid within four weeks of study initiation
	• Use of dupilumab within six weeks of study initiation
	• Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use contraception

AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; JAK = Janus kinase; PP-NRS = Peak Pruritus Numerical Rating Scale; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Intervention

JADE MONO-1: Abrocitinib 100 mg or 200 mg once daily. 156 patients were assigned to the 100-mg abrocitinib group and 154 patients were assigned to the 200-mg abrocitinib

JADE MONO-2: Abrocitinib 100 mg or 200 mg once daily. 158 patients were assigned to the 100-mg abrocitinib group and 155 patients were assigned to the 200-mg abrocitinib

Comparator(s)

JADE MONO-1: Placebo once daily. 77 patients were assigned to the placebo group

JADE MONO-2: Placebo once daily. 78 patients were assigned to the placebo group

Follow-up time

12 weeks

Is the study used in the health economic model?

Yes

Primary, secondary and exploratory endpoints

Endpoints included in this application:

Primary endpoints: Response based on achieving the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline (pre-dose Day 1) of ≥2 points at Week 12; Response based on achieving the Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 12.

Secondary endpoints: Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at Week 2, 4, 8 and 12 (week 2 and 12 will be used in this application); Change from baseline in Patient-Oriented Eczema Measure (POEM) at week 2, 4, 8 and 12 (week 12 will be used in this application); Change from baseline in Dermatology Life Quality Index (DLQI) at Week 2, 4, 8 and 12 (week 12 will be used in this application); Percentage of Participants With Scoring Atopic Dermatitis (SCORAD) Response of >=75% Improvement From Baseline at Week 2, 4, 8 and 12 (week 12 will be used in this application for MONO-1); Change from baseline in SCORAD at Week 2, 4, 8 and 12 (week 12 will be used in this application for MONO-2); Incidence of serious adverse event (SAE)s.

Other endpoints:

Endpoints not included in this application:

Secondary, safety and exploratory endpoints: Change From Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) Total Score at Week 2, 4, 8 and 12; Time to Achieve >=4 Points Improvement From Baseline in Numerical Rating Scale for Severity of Pruritus uo to week 12; Percentage of Participants Achieving Eczema Area and Severity Index Response of >=75% Improvement From Baseline at Week 2, 4 and 8; Percentage of Participants Achieving Investigator's Global Assessment Response of Clear (0) or Almost Clear (1) and >=2 Points Improvement From Baseline at Week 2, 4 and 8; Percentage of Participants Achieving Investigator's Global Assessment Response of Clear (0) at Week 2, 4, 8 and 12; Percentage of Participants Achieving Eczema Area and Severity Index Response of >=50% Improvement From Baseline at Week 2, 4, 8 and 12; Percentage of Participants Achieving Eczema Area and Severity Index Response of >=90% Improvement From Baseline at Week 2, 4, 8 and 12; Percentage of Participants Achieving Eczema Area and Severity Index Response of 100% Improvement From Baseline at Week 2, 4, 8 and 12; Change From Baseline in Eczema Area and Severity Index Total Score at Week 2, 4, 8 and 12; Change From Baseline in Percentage Body Surface Area at Week 2, 4, 8 and 12; Percentage of Participants With Percentage Body Surface Area Less Than (<) 5% at Week 2, 4, 8 and 12; Percentage of Participants With Scoring Atopic Dermatitis (SCORAD) Response of >=50% Improvement From Baseline at Week 2, 4, 8 and 12; Change From Baseline in Scoring Atopic Dermatitis: Visual Analogue Scale of Sleep Loss at Week 2, 4, 8 and 12; Percentage of Participants Achieving >=1 Point Improvement From Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis at Week 2, 4, 8 and 12; Percentage of Participants With Baseline Dermatology Life Quality Index Score >=2 and Achieving <2 DLQI Score at Week 2, 4, 8 and 12; Percentage of Participants With Baseline Children's Dermatology Life Quality Index Score >=2 and Achieving <2 CDLQI Score at Week 2, 4, 8 and 12; Change from baseline in Children Dermatology Life Quality Index (CDLQI) at Week 2, 4, 8 and 12; Percentage of Participants With Baseline Dermatology Life Quality Index Score >=4 and Achieving >=4 Point Improvement From Baseline in DLQI Score at Week 2, 4, 8 and 12; Percentage of Participants With Baseline Children's Dermatology Life Quality Index Score >=2.5 and Achieving >=2.5 Point Improvement From Baseline in CDLQI Score at Week 2, 4, 8 and 12; Change From Baseline in Hospital Anxiety and Depression Scale (HADS): Depression Subscale at Week 2, 4, 8 and 12; Change From Baseline in Hospital Anxiety and Depression Scale: Anxiety Subscale at Week 2, 4, 8 and 12; Percentage of Participants With >=8 Points at Baseline and Achieving Score of <8 Points in Hospital Anxiety and Depression Scale: Anxiety Subscale at Week 2, 4, 8 and 12; Percentage of Participants With >=8 Points at Baseline and Achieving Score of <8 Points in Hospital Anxiety and Depression Scale: Depression Subscale at Week 2, 4, 8 and 12; Percentage of Participants With >=11 Points at Baseline and Achieving Score of <11 Points in Hospital Anxiety and Depression

Trial name: JADE MONO-1 and MONO-2	NCT number: NCT03349060 and NCT03575871

Scale: Anxiety Subscale at Week 2, 4, 8 and 12; Percentage of Participants With >=11 Points at Baseline and Achieving Score of <11 Points in Hospital Anxiety and Depression Scale: Depression Subscale at Week 2, 4, 8 and 12; Change From Baseline in Patient Global Assessment (PtGA) at Week 2, 4, 8 and 12; Percentage of Participants Achieving 'Clear' or 'Almost Clear' and >=2 Points Improvement From Baseline in Patient Global Assessment (PtGA) at Week 2, 4, 8 and 12; Change From Baseline in EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L): Index Value at Week 2, 4, 8 and 12; Change From Baseline in EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L)- Visual Analogue Scale Score at Week 2, 4, 8 and 12; Change From Baseline in EuroQol Quality of Life 5-Dimension Youth Scale (EQ-5D-Y): Index Value at Week 2, 4, 8 and 12; Change From Baseline in EuroQol Quality of Life 5-Dimension Youth Scale (EQ-5D-Y): Visual Analogue Scale Score at Week 2, 4, 8 and 12; Change From Baseline in Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) at Week 12; Change From Baseline in Pediatric Functional Assessment of Chronic Illness Therapy Fatigue Scale (Peds-FACIT-F) at Week 12; Change From Baseline in Short Form-36v2 (SF-36v2) Acute Summary Score at Week 12: Physical Component Summary; Change From Baseline in Short Form-36v2 Acute Summary Score at Week 12: Mental Component Summary; Plasma Concentration Versus Time Summary of abrocitinib.

Trial name: JADE MONO-1 and MONO-2	NCT number: NCT03349060 and NCT03575871
Method of analysis	*The primary analysis population for efficacy data in MONO-1 and MONO-2 was the full analysis set (FAS), defined as all randomised patients receiving at least one dose of study medication. The FAS would be expected to be identical to an intended-to-treat (ITT) population (randomised and dispensed study medication), because the first dose was administered in clinic.* *The hypothesis objective: To demonstrate superiority of 100 mg abrocitinib and 200 mg abrocitinib over placebo in the treatment of patients ≥12 years with moderate to severe AD.* *A sequential Bonferroni-based iterative multiple testing procedure to strongly control the familywise Type 1 error at 5% was used for assessing the primary and key secondary endpoints.* *Total sample of 225 participants, with 150 each randomised to abrocitinib 200 mg and 100 mg, and 75 assigned to placebo was planned for each of MONO-1 and MONO-2. This provided ≥95% power to detect difference in IGA response of ≥20% between treatment groups, assuming placebo response rate was 6% at Week 12. This provided at least 99% power to detect a difference in EASI-75 response rate of ≥30% between treatment groups, assuming placebo response rate was 15% at Week 12.* *Efficacy analyses were performed using the FAS population.* *The coprimary efficacy endpoints were analysed using the Cochran–Mantel–Haenszel test, adjusted by baseline disease severity (moderate/severe), age, and for a given dose, both endpoints must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of patients achieving IGA response (similarly for EASI-75), along with a 95% confidence interval (using the normal approximation for the difference in binomial proportions) was reported. Additional secondary analyses utilised missing-at-random and missing-not-at-random approaches.* *Key secondary endpoints and all other binary endpoints were also analysed using the CMH test.* *For continuous endpoints, a mixed-effects model with repeated measures was applied, including the factors (fixed effects) for treatment group, randomisation strata (age, disease severity), visit, treatment-by-visit interaction, and relative baseline value. Within the framework of mixed-effect repeated measures, the treatment difference was tested at the pre-specified primary time point, Week 12, as well as other time points by time point-specific contrasts from the mixed-effect repeated measures model.*
Subgroup analyses	*NA*
Other relevant information	*No*

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table A2c. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

JADE COMPARE

Characteristic	Placebo + topical therapies, QD (n = 131)	Abrocitinib 100 mg QD + topical therapies (n = 238)	Abrocitinib 200 mg QD + topical therapies (n = 226)	Dupilumab 300 mg Q2W + topical therapies (n = 242)
Age, yr*	37.4±15.2	37.3±14.8	38.8±14.5	37.1±14.6
Female sex, n (%)	54 (41.2)	118 (49.6)	122 (54.0)	134 (55.4)
Race, n (%)	—	—	—	
- White	87 (66.4)	182 (76.5)	161 (71.2)	176 (72.7)
- Black or African American	6 (4.6)	6 (2.5)	9 (4.0)	14 (5.8)
- Asian	31 (23.7)	48 (20.2)	53 (23.5)	46 (19.0)
- Other	7 (5.3)	2 (0.8)	3 (1.3)	6 (2.5)
Disease duration, yr*	21.4±14.4	22.7±16.3	23.4±15.6	22.8±14.8
IGA, %	—	—	—	
- Moderate	67.2	64.3	61.1	66.9
- Severe	32.8	35.7	38.9	33.1
EASI score*	31.0±12.6	30.3±13.5	32.1±13.1	30.4±12.0
BSA - %*	48.9±24.9	48.1±23.1	50.8±23.0	46.5±22.1
PP-NRS score*	7.1±1.8	7.1±1.7	7.6±1.5	7.3±1.7
SCORAD score	67.9±12.0	66.8±13.8	69.3±12.7	67.9±11.4
DLQI score*	15.2±6.9	15.5±6.4	16.3±6.6	15.6±6.7
POEM score	20.4±6.1	21.5±5.3	20.9±5.5	21.2±5.5
Co-existing medical conditions – no. (%)				
- Astma	48 (36.6)	79 (33.2)	82 (36.3)	75 (31.0)
- Allergic conjunctivitits	14 (10.7)	21 (8.8)	18 (8.0)	26 (10.7)
- Food allergy	14 (10.7)	36 (15.1)	39 (17.3)	36 (14.9)
Previous medications for AD				
- Topical agents only	83 (63.4)	139 (58.4)	122 (54.0)	129 (53.3)
- Sytemic agents	48 (36.6)	9 (41.6)	103 (45.6)	112 (46.3)
○ Nonbiologic	43 (32.8)	96 (40.3)	96 (42.5)	108 (44.6)
○ Biologic (excluding dupilumab)	5 (3.8)	3 (1.3)	7 (3.1)	4 (1.7)
○ Dupilumab	0	0	0	0

*Plus–minus values are means ±SD. BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Activity and Severity Index; IGA = Investigator's Global Assessment; POEM = Patient-oriented Eczema Measure; PP-NRS = Peak Pruritus Numerical Rating Scale; QD = once daily; SCORAD = Scoring of Atopic Dermatitis.

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Table A2d. Baseline characteristics of patients in studies included in the analysis of efficacy and safety - monotherapy				
	[JADE MONO-1]		[JADE MONO-2]	
	Abrocitinib 100 mg QD (n=156)	Abrocitinib 200 mg QD (n=154)	Abrocitinib 100 mg QD (n=158)	Abrocitinib 200 mg QD (n=155)
Age, mean (SD)	31.5 (14.4)	33.0 (17.4)	37.4 (15.8)	33.5 (14.7)
<18	34 (22%)	33 (21%)	17 (10.8%)	15 (9.7%)
Race (%)				
- *White*	113 (81)	104 (68)	101 (63.9)	91 (58.7)
- *Black*	15 (10)	11 (17)	9 (5.7)	6 (3.9)
- *Asian*	26 (17)	26 (17)	46 (29.1)	54 (34.8)
- *Other*	2 (1)	11 (7)	1 (0.6)	2 (1.3)
- *Not reported*	0	2 (1)	1 (0.6)	2 (1.3)
Gender – Male (%)	90 (58)	81 (53)	94 (59.5)	88 (56.8)
Disease duration , mean (SD), y	24.9 (16.1)	22.7 (14.5)	21.1 (14.8)	20.5 (14.8)
IGA (%)				
3 (moderate)	92 (59)	91 (59)	107 (67.7)	106 (68.4)
4 (severe)	64 (41)	63 (41)	51 (32.3)	49 (31.6)
EASI score, mean	31.3 (13.6)	30.6 (14.1)	28.4 (11.2)	29.0 (12.4)
BSA, mean (SD) %	50.8 (23.4)	49.9 (24.4)	48.7 (21.4)	47.7 (22.3)
PP-NRS score, mean (SD)	6.9 (2.0)	7.1 (1.9)	7.1 (1.6)	7.0 (1.6)
SCORAD score, mean (SD)	67.1 (13.7)	64.3 (13.1)	63.8 (11.4)	64.1 (13.1)
DLQI, mean (SD)	14.6 (6.5)	14.6 (6.8)	15.4 (7.3)	14.8 (6.0)
CDLQI, mean (SD)	11.7 (6.6)	13.2 (5.5)	13.8 (5.8)	12.9 (5.7)
POEM, mean (SD)	19.5 (6.5)	19.6 (5.9)	20.9 (5.7)	19.7 (5.7)
Previous medication for AD – no. (%)	155 (99)	154 (100)	157 (99.4)	153 (98.7)
- *Topical drugs alone*	69 (44)	82 (53)	87 (55.1)	93 (60.0)

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- *Systemic medications w/o topical drugs*	78 (50)	68 (44)	70 (44.3)	60 (38.7)
	13 (8)	9 (6)	7 (4.4)	5 (3.2)
- *Dupilumab*				

BSA = body surface area; CDLQI = Children Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Activity and Severity Index; IGA = Investigator's Global Assessment; NA = Not applicable; POEM = Patient-oriented Eczema Measure; PP-NRS = Peak Pruritus Numerical Rating Scale; QD = once daily; SCORAD = Scoring of Atopic Dermatitis.
*Baseline characteristics for dupilumab is only presented according to label = Patients weighing less than 60 kg received 200 mg every other week after a 400 mg loading dose on day 1, and patients weighing 60 kg or more received 300 mg every other week after an initial loading dose of 600 mg on day 1.

Comparability of patients across studies

In total 838 patients in the JADE COMPARE trial were randomly assigned to a trial group. 226 patients were assigned to the 200 mg abrocitinib group, 238 to the 100-mg abrocitinib group, 243 to the dupilumab group, and 131 to the placebo group. The baseline characteristics of the patients were similar across the groups.
Overall the baseline characteristics of the MONO studies are comparable with the characteristics of the JADE COMPARE study, thus the MONO studies also includes adolescents and the mean age is therefore lower compared to the COMPARE study as well as the duration of disease is longer for patients in the COMPARE study.
Data on the selected outcomes are depicted for JADE MONO studies and narratively compared with data from JADE COMPARE.

Comparability of the study populations with Danish patients eligible for treatment

Pfizer is positioning abrocitinib as an alternative to dupilumab and baricitinib for patients whose disease has not responded to at least one other systemic therapy, such as ciclosporin, methotrexate, azathioprine or mycophenolate mofetil, or if these treatments are contraindicated or not tolerated.
According to the DDS guideline for AD danish patients are eligible to dupilumab treatment when they do not respond to relevant topical therapy and one systemic treatment (azathioprine, methotrexate, ciclosporin or mycophenolate mofetil) and should prior to initiating treatment have AD with a severity corresponding to one or more of the following EASI > 16, BSA > 10%, DLQI > 10 and POEM > 16 (10). These criteria combine clinical signs of disease (EASI, BSA) as well as severity measure (POEM) and health-related quality of life through DLQI. Clinicians interviewed during development of this submission agreed that these eligibility criteria were generally aligned with those used in the Phase 3 clinical trial programmes and generalizable to the population expected to be treated with abrocitinib in clinical practice.

- Affected BSA ≥10%,
- IGA ≥3,
- EASI ≥16,
- Peak Pruritus Numerical Rating Scale (PP-NRS) ≥4

However in the Phase 3 clinical program it was not an exclusion criteria if patients were not previously treated with at least one systemic treatment for AD. In the JADE COMPARE trial 41.6%, 45,6% and 46.3% in the abrocitinib 100 mg, abrocitinib 200 mg and dupilumab group respectively had previously received prior systemic treatment. The

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population in the clinical trial program thereby differ from the danish population for whom abrocitinib is expected to be used, where at least one systemic treatment is required prior to treatment. However, clinical experts interviewed do not think that Danish patients will be treatment refractory due to prior use of systemic treatment, therefore this discrepancy between the study population and the danish population will most likely not have an impact. Also, proportion of patients receiving systemic treatment is comparable between the treatment-arms in the COMPARE study.

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Appendix D Efficacy and safety results per study

Table A3. Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition (from clinicaltrials.gov)	Validity	Clinical relevance
IGA response: an IGA score of 0 or 1 with a ≥2-point increase from baseline at evaluated time point(s)	IGA assessed severity of atopic dermatitis (AD) on a 5 point scale (0 to 4, higher scores indicate more severity). Scores: 0= clear, no inflammatory signs of AD; 1= almost clear, AD not fully cleared- light pink residual lesions (except post-inflammatory hyperpigmentation), just perceptible erythema, papulation/induration lichenification, excoriation, and no oozing/crusting; 2= mild AD with light red lesions, slight but definite erythema, papulation/induration, lichenification, excoriation and no oozing/crusting; 3= moderate AD with red lesions, moderate erythema, papulation/induration, lichenification, excoriation and slight oozing/crusting; 4= severe AD with deep dark red lesions, severe erythema, papulation/induration, lichenification, excoriation and moderate to severe oozing/crusting. Assessment excluded scalp, palms and sole.	Validated 5-point scale required by FDA as at least a co-primary endpoint (66).	Uses clinical characteristics to assess overall disease severity at any given timepoint. Provides a global clinical assessment of AD by investigators. A decrease in score relates to an improvement in signs and symptoms (66).
EASI75 response: an improvement of EASI score by ≥75% at the evaluated timepoint(s)	EASI evaluates severity of participants' AD (excluded scalp, palms, soles) based on severity of AD clinical signs and % of body surface area (BSA) affected. Severity of clinical signs of AD (erythema, induration/papulation, excoriation and lichenification) scored separately for each of 4 body regions (head and neck, upper limbs, trunk [including axillae and groin)] and lower limbs [including buttocks]) on 4-point scale: 0= absent; 1= mild; 2= moderate; 3= severe. EASI area score was based upon % BSA with AD in body region: 0 (0%), 1 (>0 to <10%), 2 (10 to <30%), 3 (30 to <50%), 4 (50 to <70%), 5 (70 to	EASI is a validated scoring system and the core outcome for measuring the clinical signs of eczema in all trials. Identified by the Expert Group on Harmonizing Outcome Measures for Eczema (HOME) as the preferred instrument for assessing objective evidence of atopic dermatitis (67).	Evaluates disease extent and clinical signs by grading the physical signs of atopic dermatitis/eczema (67, 68).

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Outcome measure	Definition (from clinicaltrials.gov)	Validity	Clinical relevance
	<90%) and 6 (90 to 100%). Total EASI score =0.1*Ah*(Eh+Ih+Exh+Lh) + 0.2*Au*(Eu+Iu+ExU+Lu) + 0.3*At*(Et+It+Ext+Lt) + 0.4*Al*(El+Il+Exl+Ll); A = EASI area score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs. Total EASI score ranged from 0.0 to 72.0, higher scores = greater severity of AD.		
SCORAD - **Change from baseline at evaluated time point(s)** - **SCORAD75 response: an improvement of SCORAD score by ≥75% at evaluated time point(s)**	Scoring index for AD combining extent, severity, subjective symptoms. Extent (A): rule of 9 was used to calculate BSA affected by AD as a % of whole BSA for each body region- head and neck 9%; upper limbs 9% each; lower limbs 18% each; anterior trunk 18%; back 18%; 1% for genitals. The score for each body region was added to determine A (0-100). Severity (B): severity of each sign (erythema; edema; oozing; excoriation; skin thickening; dryness) was assessed as none (0), mild (1), moderate (2) or severe (3). The severity scores added to give B (0-18). Subjective symptoms (C): pruritus and sleep loss, each of these 2 were scored by participant/caregiver using VAS where "0" = no itch or no sleeplessness and "10" = the worst imaginable itch or sleeplessness, higher scores worse symptoms. Scores for itch and sleeplessness added to give 'C' (0-20). The SCORAD for an individual was calculated: A/5 + 7*B/2 + C; range from 0 to 103; higher values of SCORAD = worse outcome.	SCORAD is a validated scoring tool identified by HOME and can be chosen to include in addition to the core outcome measure EASI in clinical trials (67).	Evaluates disease extent, clinical signs, and subjective symptoms. A difference of 8.7 points in SCORAD was estimated as the minimal clinical important difference for the patients with atopic eczema (69, 70).
POEM – Change from baseline at evaluated time point(s)	POEM is a 7-item participant reported outcome (PRO) measure used to assess the impact of AD (dryness, itching, flaking, cracking, sleep loss, bleeding and weeping) over the past week. Each item is scored as following: "no days (0)", "1-2	POEM is a validated scoring system were the measured domains derives from the patients themselves (70, 71). It is recommended as a	A questionnaire used in clinical trials to assess disease symptoms in children and adults with eczema from a patient perspective. The measure captures the

Outcome measure	Definition (from clinicaltrials.gov)	Validity	Clinical relevance
	days (1)", "3-4 days (2)", "5-6 days (3)" and "every day (4)". The score ranges from 0 to 28, where higher score indicated greater severity.	core tool for use in clinical trials by HOME (72).	fluctuating and chronic nature of atopic eczema. The minimal clinical important difference is estimated to be 3.4 points (70, 71).
DLQI - **Proportion of patients with ≥4-point decrease in total DLQI-score at evaluated time point(s)** - **Change from baseline at evaluated time point(s)**	DLQI is a 10-item questionnaire that measures the impact of skin disease on quality of life. Each question was evaluated on a 4-point scale ranging from 0 (not at all) to 3 (very much); where higher scores indicated more impact on quality of life. Scores from all 10 questions added up to give DLQI total score range from 0 (not at all) to 30 (very much). Higher scores indicated more impact on quality of life of participants.	DLQI is valid dermatology-specific quality-of-life instrument and is a widely used measure in clinical trials (73, 74).	Developed to measure dermatological patients' quality of life. It is not specific for atopic dermatitis. No MCID information was found for the patients with atopic dermatitis. Collectively for inflammatory skin diseases the MCID is estimated to be 3.3 but recommended to be 4 point change from baseline (73).
PP-NRS4 response: an improvement in PP-NRS of ≥4 points from baseline at the evaluated timepoint(s)	Percentage of patients with at least 4 points improvement in numerical rating scale (NRS) for severity of pruritis from baseline at evaluated timepoint(s). Participants were asked to assess their worst pruritus/itching due to AD over the past 24 hours on an NRS scale ranged from 0 (no itching) to 10 (worst possible itching), where higher scores indicated greater severity.	A validated tool for patients with atopic dermatitis to report the maximum intensity of their itch over the past 24 hours (75).	Chronic pruritus is a frequent symptom and one of the most bothersome (10). Pruritus is a subjective symptom with multiple dimensions that cannot be measured objectively. In PP-NRS patients record their pruritis intensity on a numerical rating scale (75). The minimal clinical important difference for clinical improvement in itch,

Outcome measure	Definition (from clinicaltrials.gov)	Validity	Clinical relevance
			as rated on the NRS, ranks between a decrease of 2–3 points (76).
SAE	A serious adverse event is any untoward medical occurrence at any dose that: Results in death; Is life-threatening (immediate risk of death); Requires inpatient hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); Results in congenital anomaly/birth defect or that is considered to be: An important medical event	N/A	Standard requirement according to clinical trials.

Results per study

Table A3a. Comparative Results of JADE COMPARE (NCT03720470)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IGA at week 12	Abrocitinib 200 mg	106/219	48.4%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	88/241	36.5%								

Table A3a. Comparative Results of JADE COMPARE (NCT03720470)												
IGA at week 12	Abrocitinib 100 mg	86/ 235	36.6%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	88/ 241	36.5%								
EASI75 at week 12	Abrocitinib 200 mg	154/ 219	70.3%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	140/ 241	58.1%								
EASI75 at week 12	Abrocitinib 100 mg	138/ 235	58.7%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	140/ 241	58.1%								
EASI75 at week 16	Abrocitinib 200 mg	157/ 221	71%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	152/ 232	65.5%								
EASI75 at week 16	Abrocitinib 100 mg	138/ 229	60.3%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	152/ 232	65.5%								

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Table A3a. Comparative Results of JADE COMPARE (NCT03720470)											
SCORAD change from baseline at week 12	Abrocitinib 200 mg	225	-44.9 LSM‡ (-47.3, -42.5)	[redacted]	[redacted]		NA	NA	NA	Mixed-effects model with repeated measures	(49)
	Dupilumab	241	-39.7 LSM‡ (-42.0, -37.4)								
SCORAD change from baseline at week 12	Abrocitinib 100 mg	237	-36.6 LSM‡ (-38.9, -34.3)	[redacted]	[redacted]		NA	NA	NA	Mixed-effects model with repeated measures	(49)
	Dupilumab	241	-39.7 LSM‡ (-42.0, -37.4)								
POEM change from baseline at week 12	Abrocitinib 200 mg	225	-12.6 LSM‡ (-13.6, -11.7)	[redacted]	[redacted]	-	NA	NA	NA	Mixed-effects model with repeated measures	(49)
	Dupilumab	241	-10.8 LSM‡ (-11.7, -9.9)								
POEM change from baseline at week 12	Abrocitinib 100 mg	238	-9.6 LSM‡ (-10.5, -8.6)	[redacted]	[redacted]	-	NA	NA	NA	Mixed-effects model with repeated measures	(49)
	Dupilumab	241	-10.8 LSM‡ (-11.7, -9.9)								
PP-NRS at week 2	Abrocitinib 200 mg	111/ 226	49.1%	22.1	13.5, 30.7	<0.001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	63/ 239	26.4%								

Table A3a. Comparative Results of JADE COMPARE (NCT03720470)											
PP-NRS at week 2	Abrocitinib 100 mg	75/ 236	31.8%	5.2	-2.9, 13.4	0.20	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	63/ 239	26.4%								
PP-NRS at week 12	Abrocitinib 200 mg	137/ 217	63.1%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	122/ 224	54.5%								
PP-NRS at week 12	Abrocitinib 100 mg	105/ 221	47.5%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	122/ 224	54.5%								
DLQI≥4 response at week 12	Abrocitinib 200 mg	190/ 220	86.4%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	193/ 236	81.8%								
DLQI≥4 response at week 12	Abrocitinib 100 mg	171/ 229	74.7%	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(49)
	Dupilumab	193/ 236	81.8%								

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Relative difference is calculated for selected endpoint with logistic regression by Pfizer Inc. for purpose of HTA only.

‡ Negative change indicates improvement. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; LSM, least squares mean; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, scoring atopic dermatitis.

Table A3b. Results of JADE MONO-1 (NCT03349060) at week 12, adolescents (≥12 years) and adults, FAS, Monotherapy

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IGA	Abrocitinib 200 mg	67/153	43.8%	36.0	26.2, 45.7	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	6/76	7.9%								
IGA	Abrocitinib 100 mg	37/156	23.7	15.8	6.8, 24.8	0.0037	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	6/76	7.9%								
EASI75	Abrocitinib 200 mg	96/153	62.7%	51.0	40.5, 61.5	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	9/76	11.8%								
EASI75	Abrocitinib 100 mg	62/156	39.7%	27.9	17.4, 38.3	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)

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Table A3b. Results of JADE MONO-1 (NCT03349060) at week 12, adolescents (≥12 years) and adults, FAS, Monotherapy											
	Placebo	9/76	11.8%								
SCORAD75	Abrocitinib 200 mg	45/ 146	30,8%	26.4	(17.6, 35.3)	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	3/73	4.1%								
SCORAD75	Abrocitinib 100 mg	18/ 145	12.4%	8.2	(1.0, 15.3)	0.0528	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	3/73	4.1%								
POEM	Abrocitinib 200 mg	153	-10.6 (-11.8, -9.4) LMS‡	-6.9	-9.0, -4.7		NA	NA	NA	Mixed-effects model with repeated measures	(50)
	Placebo	77	-3.7 (-5.5, -1.9) LMS‡								
POEM	Abrocitinib 100 mg	153	-6.8 (-8.0, -5.6) LMS‡	-3.1	-5.2, -0.9		NA	NA	NA	Mixed-effects model with repeated measures	(50)
	Placebo	77	-3.7 (-5.5, -1.9) LMS‡								
PP-NRS at week 2	Abrocitinib 200 mg	67/ 147	45.6%	42.5	33.6, 51.4	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	2/74	3%								

Table A3b. Results of JADE MONO-1 (NCT03349060) at week 12, adolescents (≥12 years) and adults, FAS, Monotherapy											
PP-NRS at week 2	Abrocitinib 100 mg	30/147	20%	18.0	10.2, 25.8	0.0004	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	2/74	3%								
PP-NRS	Abrocitinib 200 mg	84/147	57.2%	41.7	29.6, 53.9	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	11/74	15.3%								
PP-NRS	Abrocitinib 100 mg	55/147	37.7%	22.5	10.3, 34.8	0.0003	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(50)
	Placebo	11/74	15.3%								
DLQI	Abrocitinib 200 mg	119	-9.1 (-10.3, -8.0) LMS‡	-4.9	-6.9, -2.9	-	NA	NA	NA	Mixed-effects model with repeated measures	(50)
	Placebo	60	-4.2 (-5.9, -2.5) LMS‡								
DLQI	Abrocitinib 100 mg	121	–-7.0 (-8.1, -5.8) LMS‡	-2.8	-4.8, -0.8	-	NA	NA	NA	Mixed-effects model with repeated measures	(50)
	Placebo	60	-4.2 (-5.9, -2.5) LMS‡								

Result are at week 12 unless otherwise stated in the table. Relative difference is calculated for selected endpoint with logistic regression by Pfizer Inc. for purpose of HTA only.

‡ Negative change indicates improvement. CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LSM, least squares mean; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, scoring atopic dermatitis.

Table A3c. Results of MONO-2 (NCT03575871) at week 12, adolescents (≥12 years) and adults, FAS, Monotherapy

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**n/N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IGA	Abrocitinib 200 mg	59/155	38.1%	28.7	18.6, 38.8	<0.001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	7/77	9.1%								
IGA	Abrocitinib 100 mg	44/155	28.4	19.3	9.6, 29.0	<0.001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	7/77	9.1%								
EASI75	Abrocitinib 200 mg	94/154	61.0%	50.5	40.0, 60.9	<0.001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	8/77	10.4%								
EASI75	Abrocitinib 100 mg	69/155	44.5%	33.9	23.3, 44.4	<0.001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	8/77	10.4%								

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Table A3c. Results of MONO-2 (NCT03575871) at week 12, adolescents (≥12 years) and adults, FAS, Monotherapy											
SCORAD	Abrocitinib 200 mg	155	-56.2% LMS‡ (-61.2, -51.1)	-33.4	(-42.6, -24.3)	<0.0001	NA	NA	NA	Mixed-effects model with repeated measures	(51)
	Placebo	78	-22.7% LMS‡ (-30.4, -15.1)								
SCORAD	Abrocitinib 100 mg	158	-45.8% LMS‡ (-50.9, -40.7)	-23.1	(-32.3, -13.9)	<0.0001	NA	NA	NA	Mixed-effects model with repeated measures	(51)
	Placebo	78	-22.7% LMS‡ (-30.4, -15.1)								
POEM	Abrocitinib 200 mg	154	-11.0 (-12.1, -9.8) LMS‡	-7.4	−9.5, −5.3	-	NA	NA	NA	Mixed-effects model with repeated measures	(51)
	Placebo	78	-3.6 (-5.3, -1.9) LMS‡								
POEM	Abrocitinib 100 mg	156	-8.7 (-9.9, -7.5) LMS‡	−5.1	−7.2, −3.1	-	NA	NA	NA	Mixed-effects model with repeated measures	(51)
	Placebo	78	-3.6 (−5.3, −1.9) LMS‡								
PP-NRS at week 2	Abrocitinib 200 mg	54/ 153	35.3%	31.2	22.3-40.2	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	3/76	3.9%								

Table A3c. Results of MONO-2 (NCT03575871) at week 12, adolescents (≥12 years) and adults, FAS, Monotherapy											
PP-NRS at week 2	Abrocitinib 100 mg	36/ 156	23.1%	19.2	11.0-27.4	0.0002	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	3/76	3.9%								
PP-NRS	Abrocitinib 200 mg	85/ 153	55.3%	43.9	32.9, 55.0	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	9/76	11.5%								
PP-NRS	Abrocitinib 100 mg	71/ 156	45.2%	33.7	22.8, 44.7	<0.0001	[redacted]	[redacted]	[redacted]	Cochran–Mantel–Haenszel test	(51)
	Placebo	9/76	11.5%								
DLQI	Abrocitinib 200 mg	139	−9.8 (-10.7, -8.8) LMS‡	-5.9	-7.7, -4.2	-	NA	NA	NA	Mixed-effects model with repeated measures	(51)
	Placebo	70	-3.9 (-5.3, -2.4) LMS‡								
DLQI	Abrocitinib 100 mg	140	-8.3 (-9.3, -7.3) LMS‡	−4.4	-6.2, -2.7	-	NA	NA	NA	Mixed-effects model with repeated measures	(51)
	Placebo	70	-3.9 (-5.3, -2.4) LMS‡								

Result are at week 12 unless otherwise stated in the table. Relative difference is calculated for selected endpoint with logistic regression by Pfizer Inc. for purpose of HTA only.

‡ Negative change indicates improvement. CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LSM, least squares mean; POEM, Patient-Oriented Eczema Measure; PP-NRS, Peak Pruritus Numerical Rating Scale; SCORAD, scoring atopic dermatitis.

Appendix E Safety data for intervention and comparator(s)

Serious adverse events reported for abrocitinib in JADE COMPARE, JADE MONO-1 and JADE MONO-2 studies.

Table A4. Serious adverse events reported in JADE COMPARE, JADE MONO-1 and JADE MONO-2

				Estimated absolute difference		Estimated relative difference in effect			Description of methods used for estimation	References
Study	**Study arm**	**n/N**	**Result (%)**	**Difference**	**95% CI**	**Difference**	**95% CI**	***P* value**		
JADE COMPARE	Abrocitinib 200 mg	2/ 226	0.9	0.06	-1.61, 1.73	1.07	0.15, 7.54	0.47	Calculations based on n/N in respective arm of the trial.	(49)
	Dupilumab	2/ 242	0.8							
	Abrocitinib 100 mg	6/ 238	2.5	1.7	-0.60, 3.99	3.05	0.62, 14.96	0.08	Calculations based on n/N in respective arm of the trial.	(49)
	Dupilumab	2/ 242	0.8							
JADE MONO-1	Abrocitinib 200 mg	5/ 154	3%	-0.65	-5.80, 4.50	0.83	0.20, 3.4	0.4	Calculations based on n/N in respective arm of the trial.	(50)
	Placebo	3/77	4%							
	Abrocitinib 100 mg	5/ 153	3%	-0,63	-5.79, 4.53	0.84	0.21, 3.42	0.40	Calculations based on n/N in respective arm of the trial.	(50)

Table A4. Serious adverse events reported in JADE COMPARE, JADE MONO-1 and JADE MONO-2										
	Placebo	3/77	4%							
JADE MONO-2	Abrocitinib 200 mg	2/ 155	1.3%	-0.01	-3.10, 3.10	1.01	0.09, 10.93	0.5	Calculations based on n/N in respective arm of the trial.	(51)
	Placebo	1/78	1.3%							
	Abrocitinib 100 mg	5/ 158	3.2%	1.9	-1.82, 5.58	2.47	0.29, 20.77	0.20	Calculations based on n/N in respective arm of the trial.	(51)
	Placebo	1/78	1.3%							

For a summary of the safety profile please refer to section 7.1.3.1 Adverse reactions

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Appendix F Comparative analysis of efficacy and safety

Not applicable. Data from COMPARE are analysed in appendix D (efficacy) and E (safety).

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Appendix G – Extrapolation

This section is not relevant with the analysis being a cost-minimization analysis.

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Appendix H – Literature search for HRQoL data

This section is not relevant with the analysis being a cost-minimization analysis

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Appendix I Mapping of HRQoL data

This section is not relevant with the analysis being a cost-minimization analysis.

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Appendix J Probabilistic sensitivity analyses

This section is not relevant with the analysis being a cost-minimization analysis.

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Appendix K – Suggestion for Implementation of treatments for atopic dermatitis

Nedenfor er et forslag til implementering af nye lægemidler til behandling af atopisk eksem baseret på data fra en nyligt publiceret netværksmeta-analyse (77) . Denne NMA er inddraget da analysen indeholder data fra fase 3 studier for alle nye lægemidler som er blevet vurderet af Medicinrådet, dupilumab og baricitinib, samt igangværende processer for vurdering af lægemidlerne, abrocitinib, upadacitinib og tralokinumab. Tidligere beskrevet netværksmeta-analyse (afsnit 7.1.3) sponsoreret af Pfizer, indeholder ikke fase 3 data for upadacitinib og tralokinumab, da disse ikke var publiceret da analysen blev udarbejdet.

Netværksmeta-analysen indeholderogså data for lægemidler under udvikling til behandling af atopisk eksem, som endnu ikke er godkendt af EMA. Data for ikke godkendte EMA lægemidler og som ikke er i proces i Medicinrådet er undladt af nedenstående fremstilling af data, men kan ses i original publikationen. Netværksmeta-analysen er udarbejdet efter Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Data er medtaget for uge 16 for alle lægemidler, undtagen for abrocitinib, hvor data er medtaget for uge 12, grundet studiedesignet for abrocitinib. Dette betyder at behandlingstiden for patienterne i abrocitinib studierne er 4 uger kortere end for de øvrige lægemidler, hvilket muligvis kan have en indflydelse på data i form af lavere effekt for abrocitinib. For yderligere information om metode for udarbejdelsen af NMAen, se venligst publikation ” Short-Term Effectiveness and Safety of Biologics and Small Molecule Drugs for Moderate to Severe Atopic Dermatitis: A Systematic Review and Network Meta-Analysis, Pereyra-Rodriguez, J.-J, 2021” (77).

Tabel A5a og tabel A5b viser SUCRA-værdier på udvalgte effektmål for lægemidlerne, abrocitinib, baricitinib, dupilumab, tralokinumab og upadacitinib i monoterapi og i kombination med lokal behandling (77). Baseret på SUCRA-værdierne ses at abrocitinib, dupilumab og upadacitinib skiller sig ud ved at have bedre effekt end baricitinib og tralokinumab målt ud fra EASI-75 og IGA 0/1. For effektmålet kløe (NRSP) er lægemidlerne sammenlignelige, bortset fra tralokinumab som skiller sig ud ved at have dårligere effekt på kløe ved 16 uger. Der er ikke angivet data for abrocitinib i kombination med lokal behandling på kløe. I forhold til effektmålet, antal patienter som oplever uønskede hændelser er dupilumab og tralokinumab på niveau med placebo i monoterapi, og skiller sig ud ved være forbundet med færrest antal patienter oplever uønskede hændelser ved behandling. Baricitinib og dupilumab skiller sig ud ved at være forbundet med færrest svære uønskede hændelser i monoterapi, i forhold til de øvrige lægemidler. Dog ændres dette i kombination med lokal behandling hvor abrocitinib 100 mg og dupilumab skiller sig ud ved at færrest antal patienter oplever uønskede hændelser. I kombination med lokal behandling skiller abrocitinib 200 mg, tralokinumab og upadacitinib 30 mg sig ud ved at færrest antal patienter oplever svære uønskede hændelser. Ophør af behandling ses hyppigere ved baricitinib 4 mg, mens der ikke ses nævneværdig forskel mellem de øvrige lægemidler.

Overordnet set skiller abrocitinib, dupilumab og upadacitinib sig ud fra baricitinib og tralokinumab ved at have bedre effekt målt ved IGA 0/1 og EASI-75, mens sikkerhedsprofilen baseret på uønskede hændelser, svære uønskede hændelser, samt ophør af behandling vurderes at være sammenlignelig for alle lægemidlerne.

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Table A5a. SUCRA-værdier – Monoterapi. Modificeret fra Pereyra-Rodriguez, J.-J, 2021 .

	IGA 0/1	EASI75	NRSP	Any AE	Severe AE	Withdrawel
				SUCRA		
Abrocitinib 100 mg	0.50	0.55	0.35	0.71	0.64	0.17
Abrocitinib 200 mg	0.77	0.85	0.69	0.91	0.73	0.15
Baricitinib 2 mg	0.27	0.25	0.35	0.41	0.11	0.62
Baricitinib 4 mg	0.44	0.40	0.68	0.33	0.04	0.50
Dupilumab 300 Q2W	0.65	0.63	0.53	0.29	0.31	0.54
Placebo	0.05	0.01	0.00	0.27	0.63	0.58
Tralokinumab 300 Q2W	0.25	0.29	0.18	0.16	0.74	0.51
Upadacitinib 15 mg	0.86	0.83	0.78	0.54	0.35	0.31
Upadacitinib 30 mg	0.99	0.99	0.98	0.78	0.61	0.41

Source (77) AE: adverse event; NRSP; numerical rating scale for pruritus; SUCRA: surface under the cumulative ranking curve

Table A5b. SUCRA-værdier – Kombination med TCS. Modificeret fra Pereyra-Rodriguez, J.-J, 2021 .

	IGA 0/1	EASI75	NRSP	Any AE	Severe AE	Withdrawel
				SUCRA		
Abrocitinib 100 mg	0.55	0.57	-	0.28	0.60	0.36
Abrocitinib 200 mg	0.83	0.82	-	0.69	0.26	0.49
Baricitinib 2 mg	0.24	0.28	0.36	0.72	0.40	0.39
Baricitinib 4 mg	0.42	0.39	0.58	0.94	0.80	0.73
Dupilumab 300 Q2W	0.66	0.73	0.68	0.32	0.43	0.29
Placebo	0.02	0.04	0.03	0.23	0.61	0.59
Tralokinumab 300 Q2W	0.26	0.34	0.20	0.37	0.14	0.38
Upadacitinib 15 mg	0.77	0.73	0.71	0.42	0.50	0.44
Upadacitinib 30 mg	0.99	0.97	0.93	0.67	0.32	0.44

Source (77) AE: adverse event; NRSP; numerical rating scale for pruritus; SUCRA: surface under the cumulative ranking curve; TCS: topical corticosteroid

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