Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende ritlecitinib til svær alopecia areata (pletvist hårtab) hos patienter fra 12 år

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. ritlecitinib til svær alopecia areata (pletvist hårtab) hos patienter fra 12 år
2. Forhandlingsnotat fra Amgros vedr. ritlecitinib til svær alopecia areata (pletvist hårtab) hos patienter fra 12 år
3. Ansøgers endelige ansøgning vedr. ritlecitinib til svær alopecia areata (pletvist hårtab) hos patienter fra 12 år

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www.pfizer.dk
CVR.nr. 25 46 27 77

Till Medicinrådet,

Ballerup den 25. Marts 2025

Vi vil gerne starte med at takke Medicinrådet for en god process og et gennemarbejdet udkast til evalueringsrapporten. Vi har læst udkastet, og vi sætter pris på den grundige analyse samt beskrivelse af sygdomsbyrden og studiedata.

Vi har ved gennemlæsning af rapporten identificeret nogle områder, som vi læser som, at data er misforstået. Dette omfatter:

- Afklaring af anvendelse af livskvalitet i vignettestudiet
- Usikkerhed i forbindelse med "stopreglen"
- Forventning til behandling af Adverse Events (AEs)

Afklaring af anvendelse af livskvalitet i vignettestudiet
Medicinrådet har anført, at Pfizers *"vignette-studie medfører en væsentlig metodebetinget usikkerhed"* i forhold til vurderingen af nytteværdier. Derfor anvender Medicinrådet data fra Vañó-Galvan-studiet, og inkluderer vignettestudiet udelukkende til en sensitivetsanalyse.

Medicinrådet anerkender imidlertid, at *"effekten på både genvækst af hår og gevinst i livskvalitet kan være underestimeret i de sundhedsøkonomiske analyser. Det kan medføre en lavere ICER" sammenligned med i modellens base case"*.

Medicinrådet har besluttet ikke at bruge vignettestudiet af to årsager:

- Usikkerhed ved brugen af et redskab til indsamling af data for helbredsrelateret livskvalitet, som ikke er sammenligneligt med EQ-5D
- Vignettestudiet er ikke gennemført hos patienter med den pågældende sygdom, men hos et udsnit af den raske baggrundsbefolkning. Medicinrådet skriver, at *"Derfor er nytteværdierne estimeret i vignette-studiet svære at sammenligne med nytteværdierne fra henholdsvis ALLEGRO 2b/3 og studiet af Vañó-Galvan et al."*

Det er imidlertid en misforståelse, at vignettestudiet ikke er gennemført hos patienter med Alopecia Areata (AA). Både ansøgningen og den sundhedsøkonomiske model inkluderer livsksvalitetsdata fra vignettestudiet for AA-patienter.

Pfizers analyse i basisscenariet anvender nytteværdier fra en analyse i studiet, som er udført på den raske baggrundsbefolkning. Vignettestudiet indeholder imidlertid også en analyse med AA-patienter. Denne analyse er beskrevet i ansøgningens sektion 10.3 (samt mere detaljeret i den tekniske rapports sektion 5.3), og nytteværdierne indgår i den sundhedsøkonomiske model. Det er værdt at bemærke, at nytteværdierne fra vignettestudiet for patienter med AA ligger på samme niveau, omend en smule lavere, end dem for baggrundsbefolkningen.

Pfizer har brugt nytteværdierne for baggrundspopulationen af følgende årsager:

- Det er mere sammenligneligt med generiske målemetoder (som EQ-5D) og er i overensstemmelse med anbefalingen i NICE som medicinrådets metodevejledning henviser til: "*The elicitation of values from members of the general population provides greatest alignment with the methods used for EQ-5D.*"[1]

[1] D. Rowen, J. Brazier, R. Wong and A. Wailoo, *Measuring and valuing health-related quality of life*, NICE - Decision Support Unit, 2020. Section 3.1.1.1. DSU-hierarchy-of-evidence-report-310720-Final-for-website-1.pdf

- Nytteværdierne i begge undersøgelser er sammenlignelige, men resultaterne for baggrundspopulationen er lidt mere konservative.

Usikkerhed i forbindelse med "stopreglen"

Medicinrådet bemærker, at "*der er usikkerhed om hvorledes regler for behandlingsstop bedst giver mening i dansk klinisk praksis, da det forventes, at nogle patienter med delvist respons, som derved vil ligge i stadiet SALT 21-49, vil fortsætte behandling. På baggrund af erfaring fra dansk klinisk praksis forventes det, at nogle patienter kan få lov til at fortsætte behandlingen på trods af en SALT-score over 20, eksempelvis, hvis hårtabet kan skjules grundet placering. Dette er ikke muligt at modellere i den tilgængelige model, hvorfor betydningen heraf ikke kan afspejles i en følsomhedsanalyse. Medicinrådet forventer, at dette kan medføre højere omkostninger, ved fortsat behandling af nogle patienter, som ikke har fuldt respons*."(s33)

Pfizer ønsker at fremhæve at ALLEGRO-studiet tydeligt viser, at patienter enten opnår eller ikke opnår effekt af ritlecinib. Ved at sammenfatte tallene fra figur 3 i den tekniske rapport, fremgår det, at [redacted] af patienterne havde en score, der enten var i toppen eller bunden af skalaen (SALT 0-10 eller 50+) ved uge 48. Kun [redacted] af patienterne havde SALT 11-20, og [redacted] havde en score mellem 21 og 49. Data er ikke specificeret til at vise andelen af patienter med SALT 21-30 alene, men da patienterne generelt befinder sig i ekstremerne af skalaen, er det sandsynligt, at de fleste patienter i denne gruppe har SALT-værdier tættere på SALT 50 end SALT 20. Der er således tale om en marginal del af studiepopulationen.

Derudover er det relevant at bemærke, at patientpopulationen er lille og har en relativt beskeden budgetpåvirkning ([redacted] mio. DKK ved listepris). Det betyder, at selv hvis en fjerdedel af alle patienter med SALT 21-49 kom til at modtage behandling med ritlecinib, hvilket ville øge den samlede patientpopulation med omkring [redacted] så ville dette samlet set kun resultere i en øget budgetpåvirkning på [redacted] mio. DKK ved listepris i år 5.

Forventning til behandling af Adverse Events (AEs)

Modellen inkluderer alle bivirkninger, som opstår i forbindelse med behandlingen (uanset alvorlighedsgrad), der forekommer hos mere end 5% af patienterne, og alle alvorlige bivirkninger, der forekommer hos mere end 2% af patienterne. På grund af Litfulos bivirknings-profil er det dog kun milde bivirkninger, der er inkluderet i modellen: diarré, acne, hovedpine, infektioner i de øvre luftveje, forkølelse, udslæt, betændelse i hårsække og nældefeber.

De fleste personer med diarré, acne eller hovedpine opsøger normalt ikke læge, men bruger håndkøbslægemidler eller venter på, at det skal forsvinde af sig selv. Pfizer har dog medtaget disse bivirkninger i modellen og vurderet konservativt, at disse bivirkninger resulterer i et lægebesøg hos egen læge per bivirkning. Hvis bivirkningen er vedvarende, vil patienten sandsynligvis nævne det ved næste normale opfølgningsbesøg på sygehuset.

Medicinrådet mener imidlertid, at da patienter er i behandling med Litfulo under sygehusregi, kommer hver sådan bivirkning til at resultere i et ekstra sygehusbesøg. Dette mener vi ikke, at det er belæg for. Vi mener heller ikke at det er sandsynligt, at en patient, som klager over mild acne, får en konsultation med en speciallæge på sygehuset. Denne justering har minimal effekt på modelresultaterne, men vi anser disse antagelser for faktuelt urealistiske.

Venlig hilsen, Pfizer Danmark

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21.03.2025

DBS/MBA

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.04.2025
Leverandør	Pfizer
Lægemiddel	Litfulo (ritlecitinib)
Ansøgt indikation	Svær alopecia areata (pletvist hårtab) hos patienter fra 12 år
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Litfulo (ritlecitinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Litfulo	50 mg, kapsler (30 stk.)	6.686,52	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Litfulo indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

[redacted]

Konkurrencesituationen

På nuværende tidspunkt, er der ikke andre behandlingsalternativer til svær alopecia areata, som anbefalet af Medicinrådet.

Tabel 2 viser lægemiddeludgifter for Litfulo.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Litfulo	50 mg (30 stk.)	50 mg én gang dgl.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Status for vurdering ukendt	

Opsummering

[redacted]

Version log

Version log		
Version	**Date**	**Change**
2.5	10 September 2024	Section 3.4 and 3.4.1: new information regarding ATMP (Advanced Therapy Medicinal Products). Section 6.1.1 and 8.1: Updated text regarding data-cut. Section 4, 8, 10 and 12: Clarification regarding cost-minimization analysis.
2.4	5 July 2024	Section 11: Clarification in the text regarding costs and changes in the tables 26 and 30.
2.3	1 June 2024	Clarification regarding redaction of confidential information, clarification regarding EPAR, clarification regarding literature search and changes in the text regarding costs. New information about Joint Nordic assessments has been added.
2.2	3 November 2023	'Pharmaceutical' is exchanged with 'medicine'. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet 'Key Figures'
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.1	9 February 2022	Appendix K and onwards have been deleted (company-specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models

Version log		
		Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for the assessment of ritlecitinib for severe alopecia areata in adults and adolescent 12 years of age or older

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Table of contents

Tables and Figures

Abbreviations

AA	Alopecia Areata
AAPPO	Alopecia Areata Patient Priority Outcomes
AASIS	Alopecia Areata Symptom Impact Scale
AE	Adverse Event
AQoL-8D	Assessment of Quality of Life 8 dimensions
ALC	Absolute lymphocyte count
ANC	Absolute neutrophile count
AU	Alopecia Universalis
AT	Alopecia Totalis
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curves
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
cTTO	Composite time trade-off
DCE	Discrete-Choice Experiments
DLQI	Dermatology Life Quality Index
DMC	Danish Medicines Council
DSA	Deterministic sensitivity analyses
EBA	Eyebrow assessment
ELA	Eyelash assessment
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life Questionnaire - 5 Dimension - 5 Level
EQ-5D-5Y	European Quality of Life Questionnaire - 5 Dimension - Youth
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-Related Quality of Life
HSUV	Health State Utility Value
ICER	Incremental Cost-Effectiveness Ratio
IFN-γ	Interferon-gamma
IL-15	Interleukin 15
JAK	Janus Kinase
LOCF	Last observation carried forward
LT	Long-Term
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
NMSC	Non-Melanoma Skin Cancer
OWSA	One-Way Sensitivity Analysis
PGI-C	Patient Global Impression of Change
PPP	Pharmacy Purchasing Price
PRO	Patient Reported Outcome
PSA	Probabilistic sensitivity analysis

QALY	Quality Adjusted Life Years
QoL	Quality of Life
RWE	Real World Evidence
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SF-36	36-Item Short Form Survey Instrument
SLR	Systematic Literature Search
STAT	Signal transducer and activator of transcription
TEAE	Treatment Emergent Adverse Events
TTO	Time Trade-off
UK	United Kingdom
VAS	Visual Analogue Scale
VHP	Voluntary Harmonization Procedure

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Litfulo®
Generic name	Ritlecitinib
Therapeutic indication as defined by EMA	Litfulo is indicated for the treatment of severe alopecia areata (AA) in adults and adolescents 12 years of age and older.
Marketing authorization holder in Denmark	Pfizer Europe MA EEIG
ATC code	L04AF08
Combination therapy and/or co-medication	Not applicable
Date of EC approval	September 15, 2023
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	**No**
Orphan drug designation (include date)	**No**
Other therapeutic indications approved by EMA	**No**
Other indications that have been evaluated by the DMC (yes/no)	**No**
Joint Nordic assessment (JNHB)	No. The treatment is a primary care product in the other Nordic countries and is already assessed/under assessment.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Pack size: a pack of 30 hard capsules in a blister pack. Each capsule contains 50 mg of ritlecitinib.

2. Summary table

Summary	
Indication relevant for the assessment	The treatment of severe AA in adults and adolescents 12 years of age and older. This is in line with the EMA indication.
Dosage regiment and administration	The recommended dose is 50 mg once daily, administered orally.
Choice of comparator	Best supportive Care (BSC)/no treatment
Prognosis with current treatment (comparator)	AA is a chronic, autoimmune disease that does not affect survival. The course of AA is unpredictable and can be acute and self-limiting or follow a prolonged, relapsing-remitting course. Mild cases often go into spontaneous remission, while severe or long-lasting disease very rarely do so. Hair loss due to AA can cause low self-esteem and lead to social withdrawal, impact patient's relationships, education, and career. AA is associated with significant psychological distress including various psychiatric disorders, such as depression, anxiety, and paranoid disorders.
Type of evidence for the clinical evaluation	The pivotal phase 2b/3 randomized clinical trial ALLEGRO, and its long-term extension (ALLEGRO-LT) is used as evidence for the clinical evaluation.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Main efficacy results at week 24** SALT ≤20: Ritlecitinib 50 mg 23.39% vs placebo 1.54%. HR: 17.03 (4.07, 71.27), p< 0.0001 SALT ≤ 10: Ritlecitinib 50 mg 13.72% vs placebo 1.54% HR: 9.85 (2.29, 42.47), p= 0.0021 EBA: Ritlecitinib 50 mg 29.0% vs placebo 4.7% ELA: Ritlecitinib 50mg 28.9% vs placebo 5.2% **Main efficacy results at week 48** (active treatment vs baseline): SALT ≤20: Ritlecitinib 50 mg: 43.20% (34.52- 51.88) SALT ≤ 10: Ritlecitinib 50 mg 31.2% (23.08 - 39.32)
Most important serious adverse events for the intervention and comparator	Overall, 14 patients experienced 16 Serious Adverse Events (SAEs) up to Week 48. Of these, 10 patients experienced 11 SAEs (Placebo 3, Any dose Ritlecitinib 8) up to Week 24. In the ritlecitinib 50 mg arm, there were two reported SAEs. In 3 patients, the SAEs were considered related to treatment with ritlecitinib by the Investigator. No SAE had a frequency of ≥5% in any arm in the pooled safety analysis or in ALLEGRO 2b/3.
Impact on health-related quality of life	EQ-5D-5L was measured in ALLEGRO 2b/3 and is provided as a sensitivity analysis in the model. However, as it showed a lack

Summary	
	of construct validity for the AA population, it is not used in the base case. Base case analysis (TTO): [redacted] Scenario analysis (EQ-5D): [redacted]
Type of economic analysis that is submitted	Cost-utility analysis: semi-Markov model
Data sources used to model the clinical effects	Data for clinical effect in the health economic model is derived for the 50 mg and placebo arms in the ALLEGRO 2b/3 trial. For long term efficacy, i.e. beyond 48 weeks for ritlecitinib use, data from the ALLEGRO-LT trial is used.
Data sources used to model the health-related quality of life	Health-Related Quality of Life (HRQoL) from a Time-Trade-off (TTO) study for the United Kingdom (UK) population. The study is used with the UK population weights, as mapping to DK weights is not possible.
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	[redacted]
Number of eligible patients in Denmark	Approximately [redacted] patients with AA in Denmark are considered candidates for treatment. [redacted] new patients are estimated to be candidates for treatment each year.
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

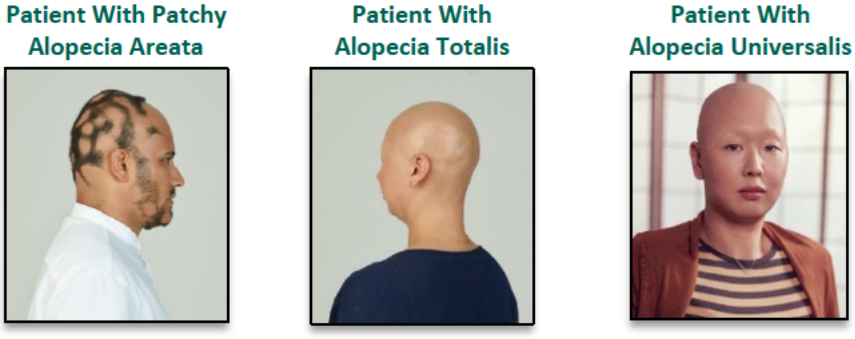
3.1 The medical condition

Alopecia areata (AA) is a T-cell mediated autoimmune disease characterized by nonscarring hair loss [1]. AA is unpredictable, but typically manifests as well-defined patches on the scalp (patchy AA). However, it can progress to alopecia totalis (AT), which is characterized by a complete hair loss on the scalp, or alopecia universalis (AU) which is complete loss of hair on all surfaces of the body, see Figure 1 [1]. **Patients with patchy AA have a 30-50% chance of spontaneous remission within the first 6-12 months. However, the risk of relapse is 85% and virtually all patients will have a relapse within 20 years [1, 2].** The prognosis of remission gets worsened by multiple factors, including familial predisposition, early onset, duration of AA >1-year, atopic dermatitis, involvement of the nails, ophiasis pattern, and AT or AU [1].

At onset of AA, patients usually report sudden and obvious loss of hair on the scalp. To determine a diagnosis of AA, the patients' medical history and an objective examination including a trichoscopy and pull test is often sufficient [1, 3].

The pathophysiology of AA is hypothesized to be a collapse of the immune privilege zone surrounding the hair follicle. This renders the hair follicle susceptible to attack by the immune system's natural killer cells and T-cells. These are activated by multiple cytokines, notably Interferon-gamma (IFN-γ) and Interleukin 15 (IL-15), through the JAK/STAT pathway. The attack does not destroy the hair follicle but rather promotes a premature switch from the anagen growth phase to the catagen and telogen phases, therefore, making it possible for hair regrowth in patients with AA [1, 4].

Figure 1 Overview Alopecia Areata subtypes



Source: Pfizer data on file (2022) [5].

The lack of hair on both the scalp and the rest of the body can greatly affect patients' physiological as well as psychological health. With the loss of hair on the scalp and skin, patients have an increased sensitivity to temperature and are more likely to get burned by the sun. As the eyebrows and eyelashes prevent sweat, water, and debris from getting in the eyes, loss of these can have significant impact on the eyes [6]. A large proportion (44.35%) of patients with AA in a Danish Skin Cohort study reported irritation of the eyes [7]. Furthermore, patients with AA can have problems with a runny nose and sneezing if the nasal hair is affected [6, 8]. Beyond hair loss, AA patients can also experience nail abnormalities, usually pitting of the nails, but they may also experience brittleness or breakage of the nails or even nail shedding which may be painful and make some activities hard to perform [9].

Although AA is neither life-threatening nor necessarily accompanied by physical pain, the condition can have a significant impact on patients' quality of life (QoL) [7]. Hair is one of the most powerful symbols of individual and group identity, regardless of culture or continent. Involuntary loss of hair can therefore have a significant negative impact on a person's psychological health and daily lives [6, 10].

In a survey by Muntyanu et al, including 216 adults with AA in the United States, almost two-thirds (62%) reported to have made different lives choices regarding relationships, education, or career because of AA [6]. Patients with AA have reported to withdraw from activities (62% of patients) and reducing interactions with friends (54%) after the first episode of hair loss [6]. This is supported by a recent survey of AA patients in Norway, which reported that 64,4% of respondents experience that the disease is having a significant impact on their daily lives due to shame and the feeling of being different [11].

Social isolation in particular, is a major burden for families and friends, who often feel like they are losing a part of the person they know, when patients with AA withdraw from social situations [11].

A recent scoping review found that work absenteeism and unemployment is also significantly higher in patients with AA compared to healthy controls matched for age, sex, and socioeconomic status [10]. Especially social anxiety is common in patients with AA and has been reported to be clinically significant in almost 50% of the patients, and depression was found to be up to 4 times more common in patients with AA when compared to healthy controls [10].

In the survey the vast majority of the patients (85%) reported that coping with AA was a daily challenge. Many patients try to conceal their hair loss. In the survey, concealment strategies were used by 90% of women and 72% of men, at the onset of hair loss [6]. In social settings a vast majority (86.7%) of patients use wigs, whereas over half of the patients (55.9%) use wigs at all times [10]. However, using wigs or hairpieces is not without problems. A large proportion of patients reported worrying that it may fall off (39%) or being noticed by others (47%). Furthermore, physical activity levels were reduced in 41% of the patients due to the concerns that the wig or hairpiece would become displaced doing the activity [10].

A recent Danish study, found that patients report, feeling stared at, harassed, ostracized, and meeting public stigma relating to other forms of illnesses and oncologic chemotherapy [2]. The American survey by Muntyanu et al confirms the impression from the Danish study, of a negative perception of severe AA on individuals unaware of the disease. In the study healthy individuals unaware of the disease described patients with severe hair loss with words such as: “sick”, “not attractive”, “contagious”, “unintelligent”, and “dirty”. They also reported not to wish to hire the patients [10]. When AA was recognized as a medical condition, the public stigma decreased [10].

Generally, psychological impact from AA seems to be more severe among women than men and among children and adolescents compared to adults [2, 6, 10]. Hair loss in children, adolescents, and young adults often has a big impact on patients’ self-esteem [7]. Some patients even correlated their hair loss with loss of their self-identity and described it as devastating and emotionally draining to the point where they could not look at themselves in the mirror [10]. Over half of affected children (51%) reported missing school and performing poorly (i.e., failing, having to repeat years, or stopping) due to the distress associated with AA [10]. Both anxiety and/or depression have been found to be more prevalent in patients with AA compared to gender- and age-matched controls and many relatives to the patients worry about the mental health of their adolescent children [10, 11].

3.1.1 Measurement of disease severity

Severity of Alopecia Tool (SALT) score is the most frequently used tool to measure the severity of AA and the recommended method to use when treating AA systemically in Denmark [1]. The SALT score is computed by measuring the percentage of hair loss in each of four areas of the scalp, and the composite total score is the SALT score. A SALT score of 100 denotes complete scalp hair loss, while a SALT score of 0, means that no hair is lost [1]. Severe AA, which is the focus of this application, is defined as a SALT score of 50 or more, i.e. a loss of 50% or more of all hair on the scalp.

3.2 Patient population

AA can impact at any age, although most patients develop the disease before the age of 40 years [12]. The highest incidence rate in Denmark is seen in patients aged 12-17, at 5.88 per 100,000 person-years in 2016 [13]. According to a recent Danish study on Epidemiology of Hospital-Treated AA in Denmark, the overall incidence rate of AA, in 2016, was 4.04 per 100,000 person-years, and the overall prevalence in 2016 was 71.7 per 100,000 persons [13]. Compared to men, women had a higher incidence and prevalence of 5.09 per 100,000 person-years and 89.7 per 100,000 persons, respectively [13]. However, most of these patients are not candidates for systemic treatment with ritlecitinib.

The DMC assumes that there are approximately 680 patients with severe AA, who would be candidates for systemic treatment in Denmark. Of these, a share of patients has lived with AA for many years and are expected to have accepted the disease and therefore not wish to attempt treatment [14]. As ritlecitinib does not have any severe adverse events,

approximately [redacted]% of patients ([redacted] patients) are expected to be candidates for the treatment.

The DMC assumes that 200 new patients are diagnosed with severe AA each year. Almost all patients are expected to request treatment, and [redacted] new patients are expected to be candidates for treatment each year [14].

In Table 1, the incidence and prevalence of patients in the past 5 years is presented. The numbers are derived from the DMC assumption of the population size in 2023 [14], and adjusted with the population change in the relevant patient groups by DST [15].

In Table 2, the estimated number of patients eligible for treatment in the next 5 years is presented. The numbers are derived from the DMC assumption of the population size [14] and agreed with DMC at the dialogue meeting.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	195	196	196	198	200
Prevalence in Denmark	662	665	668	672	680

Reference: DMC [14] and Danmarks statistik. "Population growth" (BEFOLK1) from 2019 to 2023. [15]

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Reference: Calculation.

3.3 Current treatment options

The Danish Dermatological Society describes the treatment of AA in its guidelines from 2023 [1]. Currently, no curative treatment exists, and the treatment approach of AA depends on the severity of the disease, impact on patients' quality of life, and potential adverse reactions [1].

In cases where disease severity is limited and a need and wish for treatment exists, local treatment is a possibility. Possible local treatments include topical corticosteroids or intralesional corticosteroids, administered under careful monitoring for side effects as compared to effects. Evidence supporting the effect of corticosteroids is limited, however potent corticosteroids (Class III-IV) are usually administered once daily for 8-12 weeks. AA affecting the eyelashes or eyebrows can be treated using oral or topical minoxidil and bimatoprost ophthalmic solution [1].

In the case of more widespread AA, the administration of topical immunotherapy is an option. In Denmark the treatment would typically be conducted using diphenylcyclopropenone (DPCP), which is a powerful sensitizing contact allergen applied in increasing doses to the scalp. Treatment is carried out once weekly for a duration of 3 weeks up to 10 months. Effect should be observable no later than 6 months post initiation of treatment. If an effect is observed, the dose is reduced, while a lack of effect results in discontinuation of treatment [1].

In cases of long-term widespread disease, systemic treatment (methotrexate, prednisolone, ciclosporin, pulse therapy using i.v.-steroid, azathioprine) can be administered following thorough information and risk evaluation. Patients with indication for systemic treatment, should meet all the following criteria [1]:

- Definitive AA diagnosis (anamnesis and objective examination, including trichoscopy and pull test, in special cases biopsy).
- Duration of disease: Period without new hair growth lasting longer than 6 months and less than 8 years.
- Severe AA corresponding to hair loss encompassing more than 50% of the scalp (corresponding to a Severity of Alopecia Tool, SALT score of 50 or more).
- Reduced quality of life (corresponding to a minimum score of 10 on the Dermatology Life Quality Index (DLQI) [1].

Due to potential adverse events however, the use of systemic prednisolone is not considered as a long-term treatment option [1, 14]. And none of the conventional off label immunosuppressive treatments are considered as long-term options for AA.

3.4 The intervention

Overview of intervention	
Indication relevant for the assessment	Litfulo is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years of age and older.
ATMP	No
Method of administration	Oral administration
Dosing	50 mg once daily
Dosing in the health economic model (including relative dose intensity)	50 mg once daily, RDI: 100%
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	EMA label: Discontinue if no evidence of therapeutic benefit at week 36.

Overview of intervention	
	ALLEGRO study: Increasing efficacy observed through week 48 in Allegro 2b/3.
Necessary monitoring, both during administration and during the treatment period	Screening and monitoring as current clinical practice for JAK-inhibitors and biologics: Before administration; Tuberculosis infection evaluation, Viral hepatitis screening, absolute lymphocyte count, platelet count, update immunizations according to current immunization guidelines. Four weeks after initiation; lymphocyte and platelet count.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Not applicable.
Package size(s)	30 hard capsules in a blister pack.

3.4.1 The intervention in relation to Danish clinical practice

Ritlecitinib will not replace any other treatment. Ritlecitinib is a JAK-inhibitor, a new class of drug for AA, and will be considered as a systemic treatment option for patients with more than 50 % hair loss meeting the criteria from the Danish treatment guidelines, mentioned in section 3.1.1. Initiation of treatment and monitoring will require screening and follow-up as for other JAK-inhibitors used for dermatological conditions such as atopic dermatitis.

Before administration, tuberculosis infection evaluation, viral hepatitis screening, absolute lymphocyte count, platelet count and immunizations according to current immunization guidelines is required. Four weeks after initiation lymphocyte and platelet counts are required again.

3.5 Choice of comparator(s)

There is no recommended long-term treatment for Danish patients with severe AA. In this application, ritlecitinib will therefore be compared to Best Supportive Care (BSC).

Overview of comparator	
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A

Overview of comparator	
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

As the comparator is BSC, this section is not applicable.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
SALT ≤ 20 Primary trial endpoint	Week 24	Proportion of participants with response based on an absolute SALT score ≤ 20 at Week 24. FAS**	Investigator assessed at visit.
SALT ≤ 10 Key secondary endpoint	Week 24	Proportion of participants with response based on an absolute SALT score ≤ 10 at Week 24. FAS**	Investigator assessed at visit.

PGI-C response Key secondary endpoint	Week 24	PGI-C response defined as a score of “moderately improved” or “greatly improved” at Week 24. FAS**	Patient reported at visit.
SALT ≤ 20 Other endpoints	Week 48	Proportion of participants with response based on an absolute SALT score ≤ 20 at Week 48. FAS**	Investigator assessed at visit.
SALT ≤ 10 Other endpoints	Week 48	Proportion of participants with response based on an absolute SALT score ≤10 at Week 48. FAS**	Investigator assessed at visit.
PGI-C response Other endpoints	Week 48	PGI-C response defined as a score of “moderately improved” or “greatly improved” at Week 24. FAS**	Patient reported at visit.
EBA (eyebrow assessment) response Other endpoints	Week 24	Response based on at least a 2-grade improvement or a score of 3 in EBA score.	Investigator assessed at visit.
ELA (Eyelash assessment) response Other endpoints	Week 24	Response based on at least a 2-grade improvement or a score of 3 in ELA score.	Investigator assessed at visit.
EBA (eyebrow assessment) response Other endpoints	Week 48	Response based on at least a 2-grade improvement or a score of 3 in EBA score.	Investigator assessed at visit.
ELA (Eyelash assessment) response Other endpoints	Week 48	Response based on at least a 2-grade improvement or a score of 3 in ELA score.	Investigator assessed at visit.
HADS Other endpoints	Week 24	LSM of change from baseline for depression and anxiety subscales.	Patient reported at visit.
HADS	Week 48	LSM of change from baseline.	Patient reported at visit.

Other endpoints			
EQ-5D-5L Exploratory endpoints	Week 24	Absolute and Change from Baseline in EQ-5D-5L VAS and Index Value.	Patient reported at visit.
EQ-5D-5L Exploratory endpoints	Week 48	Absolute and Change from Baseline in EQ-5D-5L VAS and Index Value.	Patient reported at visit.

* Time point for data collection used in analysis (follow up time for time-to-event measures); ** Full analysis set (FAS) defined as all randomized subjects, regardless of whether they received study medication. Excludes missing data due to COVID-19, missing data due to reasons unrelated to COVID-19 are considered as non-response. Hazard ratio and its associated confidence intervals (CI) are estimated from a Cox regression model including fixed effects of treatment. SALT = Severity af Alopecia Tool; EBA = Eyebrow assessment score; ELA = Eyelash assessment score; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels.

Validity of outcomes

Clinical outcomes

Severity of Alopecia Tool (SALT): Primary endpoint. Validated for AA. Clinician reported quantitative assessment of AA severity, measures the amount of scalp hair loss [16]. SALT less than 20 and less than 10 defined as primary endpoint in Allegro 2b/3 and by EMA, respectively.

Eyebrow assessment score (EBA): Validated for AA. Clinician reported. Characterizes eyebrow hair loss, numeric rating scale developed to characterize eyebrow hair loss. The numeric rating scale ranges from 0 (none) to 3 (normal) [17]. Response based on at least a 2-grade improvement or a score of 3 in EBA score secondary endpoint of relevance for patients experiencing loss of eyebrow hair.

Eyelash assessment score (ELA): Validated for AA. Clinician reported. Characterizes eyelash hair loss, numeric rating scale developed to characterize eyelash hair loss. The numeric rating scale ranges from 0 (none) to 3 (normal) [17]. Response based on at least a 2-grade improvement or a score of 3 in ELA score. Secondary endpoint of relevance for patients experiencing loss of eyelash hair.

Patient reported outcomes

Patient's Global Impression of Change (PGI-C): Key secondary endpoint. AA-specific but not validated. Assesses patient impression on improvement or worsening of AA since start of treatment. The PGI-C asks the patient to evaluate the improvement or worsening of their AA as compared to the start of the study using a single-item, "Since the start of the study, my AA has…". The patients select 1 of 7 responses ranging from "greatly improved" to "greatly worsened".

The EuroQol 5 Dimensions (EQ-5D-5L, EQ-5DY): Generic tool. Validated, though not for AA. Five domains that cover mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [18]. Please note that EQ-5D-5L does not capture all the domains which are relevant to patients with AA and is therefore insensitive to Health-Related Quality of Life (HRQoL) in this patient population. Therefore, it lacks content validity and

potential responsiveness to changes in HRQoL for patients with AA, please see section 10.3.

Hospital Anxiety and Depression Scale (HADS): Generic tool. Validated, but not for AA. HADS is a participant rated questionnaire (for ages 12 and older) with 2 subscales. HADS-A assesses state of generalized anxiety; HADS-D assesses state of lost interest and diminished pleasure response. Each subscale comprised of 7 items with range 0 (no presence of anxiety or depression) to 3 (severe feeling of anxiety or depression). Total score 0 to 21 for each subscale; higher score indicates greater severity of anxiety and depression symptoms. Score of ≥8 a subscale indicates cases of anxiety or depression [19].

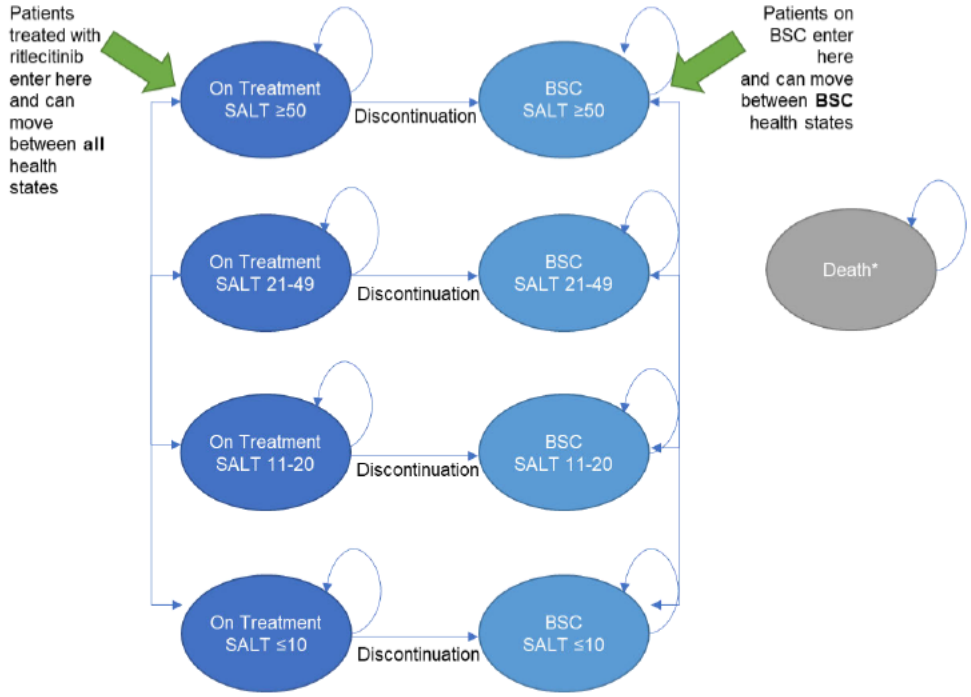
4. Health economic analysis

4.1 Model structure

A semi-Markov model was adopted to capture the long-term, chronic nature of AA. The model structure was based on scientific advice from NICE [5]. Please refer to the Technical Report for more detailed information on any part of the health economic model throughout.

The model structure, as described in Figure 2, simulates the movement of patients between health states based on the absolute SALT score of patients when treated with either ritlecitinib or BSC. Patients can move into the death state at any time in the model.

Figure 2 Model structure



*All patients can transition to death from any health state. BSC = best supportive care; SALT = Severity of Alopecia Tool.

Patients enter the model in the SALT ≥50 health state because the patient population being considered are required to suffer from severe AA, i.e. have ≥50% scalp hair loss (SALT ≥50). Patients treated with ritlecitinib begin on-treatment whereas those on BSC do not. Patients 'on treatment' can move to the BSC health states but not vice versa. The health states are linked to patients' absolute SALT scores, as detailed in Table 4.

Table 4 Health states used in the economic model

Health states	Definition
On Treatment; SALT ≥50	All patients receiving ritlecitinib treatment (i.e., not BSC) enter the model in this health state and remain on active treatment.
On Treatment; SALT 21-49	Patients in this health state are considered to have a partial response to ritlecitinib as their SALT score has improved from baseline (SALT 50-100). They remain on active treatment.
On Treatment; SALT 11-20	Patients in this health state are considered to have a response to ritlecitinib with SALT 11-20 and remain on active treatment.
On Treatment; SALT ≤10	Patients in this health state are considered to have a response to ritlecitinib with SALT ≤10 and remain on active treatment.
BSC; SALT ≥50	BSC patients enter the model in this health state. Furthermore, patients who stop active treatment will accumulate in this health state if they do not experience spontaneous remission.

BSC; SALT 21-49	Patients in this health state are not on active treatment.
BSC; SALT 11-20	Patients in this health state are not on active treatment.
BSC; SALT ≤10	Patients in this health state are not on active treatment and are assumed to have spontaneous remission.
Death	Death has occurred due to any cause. Patients can transition to the Death heath state from any health state.

BSC = best supportive care; SALT = Severity of Alopecia Tool

4.1.1 Time horizon, discounting, and perspective

A cycle length of 12 weeks was used in the model and a half-cycle correction was applied to both costs and health outcomes in the semi-Markov model to align with conventional modelling standards. A lifetime horizon was applied.

As per the DMC guidelines, the applied discount rates follow the guideline from the Danish Ministry of Finance [20]. The discount rate is 3.5% for all model years [20].

The model adopts a Danish limited societal perspective on costs, while the model considers all direct health effects for patients. In line with the DMC instructions, health effects to others than the patients themselves are not included in the evaluation [21].

4.1.2 Short-term health state membership and stopping rules

During the first 48 weeks (four cycles), patients treated with ritlecitinib are partitioned in SALT-based health states based on the ALLEGRO 2b/3 clinical trial. The distribution of patients treated with ritlecitinib across different SALT scores during the first 48 weeks is therefore defined and not linked to a previous health state. Hence the “semi” portion of the model.

An interim and final stopping rule is applied at Week 24 and Week 48 for patients treated with ritlecitinib and informs transitions to BSC health states. The interim stopping rule causes patients whose treatment results based on SALT score have worsened at Week 24 (2 cycles) of treatment compared to baseline (i.e., a worse SALT score), to discontinue treatment. The final stopping rule causes patients who do not achieve a SALT score ≤20 at Week 48 (4 cycles) to discontinue treatment.

A two-phase stopping rule is proposed because hair growth is not immediate, and patients continue to reach higher thresholds of response beyond Week 24. Patients who show no clinical meaningful response at Week 24 can go on to respond by Week 48, as shown in the ALLEGRO 2b/3 clinical trials and supported by the opinion of consultant dermatologists [22]. The interim stopping rule therefore prevents patients who are slower to respond to treatment from stopping treatment with ritlecitinib while alleviating the need to treat all eligible patients for at least 48 weeks.

4.1.3 Longer term transitions

After the final stopping rule at Week 48, all model transitions are handled through Markov processes.

At Week 48 (4 cycles), any ritlecitinib-treated patient who move to a health state where their SALT score is >20 is assumed to stop treatment due to loss of response. Patients who are treated with ritlecitinib can move between the on-treatment health states.

From Week 48 until Week 96 (24 months), transition matrices for patients treated with ritlecitinib were derived from the ALLEGRO-LT clinical trial to calculate the transitions between health states.

Given that no waning effect has been observed in the ALLEGRO-LT study, it is assumed that patients remain within the same health state after Week 96 (8 cycles) unless they stop treatment.

4.1.4 Treatment stop

Patients who stop treatment with ritlecitinib, for any reason initially enter the BSC health state with the same SALT score range they were in while on treatment with ritlecitinib for one cycle, before gradually transitioning through the health states with a greater SALT score each cycle until reaching a SALT score of ≥50. This is in line with the natural course of the disease, described in section 3.1.

The exception to this is patients who are assumed to be in spontaneous remission after stopping treatment; patients on BSC, whether they had previously received ritlecitinib treatment or not, can experience spontaneous remission by moving to the 'BSC SALT ≤10' health state. As it is not known how durable spontaneous remission in clinical practice is, it was assumed some patients lose spontaneous remission over time and an equal number of patients gain spontaneous remission over time. The share of BSC patients with spontaneous remission therefore remains constant amongst those alive. This means that patients treated with BSC (i.e., those who begin on BSC or who have stopped ritlecitinib treatment to BSC and returned to their baseline SALT score) do not move between health states in the model after Week 24 unless they die.

4.1.5 Discontinuation for any reason other than lack of effect

All ritlecitinib-treated patients who transfer to a health state score >20 stopped treatment due to lack of effect. However, even patients within a health state with a SALT score of ≤20 may discontinue ritlecitinib treatment for other reasons.

The share of patients discontinuing treatment for reasons other than a loss of treatment effect is modelled by extrapolating time on treatment in ALLEGRO-LT amongst patients with a SALT score ≤20.

4.2 Model features

The model features are described in Table 5.

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Patients from 12 years, with severe AA.	In line with label population
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	12 weeks	Able to capture the short-term treatment decisions in clinical practice and the long-term extrapolation of response following the final discontinuation rule
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Ritlecinib 50 mg once daily	This is the EMA approved dose for ritlecitinib.
Comparator(s)	BSC, i.e. no active treatment.	There is no other treatment recommended for long term treatment of AA. Prednisolone and Methotrexate are included for costs only.
Outcomes	SALT score	SALT is a clinically relevant outcome. SALT scores formed part of the primary endpoint in the ALLEGRO 2b/3 trial.

5. Overview of literature

5.1 Literature used for the clinical assessment

The application is based on a head-to-head study vs placebo. This is deemed relevant for Danish clinical practice. For the clinical assessment, data from the pivotal phase 2b/3 ALLEGRO, and its long-term extension (ALLEGRO-LT) is used as evidence for the clinical evaluation.

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
King B., Zhang X., Harcha W. G. et al. *Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomised, double-blind, multicenter, phase 2b–3 trial*. Lancet. 2023 401. 1518-1529 [4]. King B., Soung J.; Tziotzios C. et al. *Integrated Safety Analysis of Ritlecitinib, an Oral JAK3/TEC Family Kinase Inhibitor, for the Treatment of Alopecia Areata from the ALLEGRO Clinical Trial Program.* American Journal of Clinical Dermatology. 2024 Mar;25(2):299-314 [23].	Allegro 2b/3	NCT03732807	Start: 03/12/2018 Completion: 24/06/2021	Ritlecitinib vs placebo for adults and adolescents (12 years and older) with AA who have ≥50% scalp hair loss.
A Phase 3 open-label, multicenter, long-term study investigating the safety and efficacy of PF-06651600 (ritlecitinib) in adult and adolescent participants with alopecia areata. Piliang M., Soung J. King B., et al. *Efficacy and safety of the oral JAK3/TEC family kinase inhibitor ritlecitinib over 24*	Allegro-LT	NCT04006457	Start: 18/07/2019 Estimated completion: Jan 2026 Interim efficacy and safety result up to Month 24 from a pooled analysis of ritlecitinib 50 mg QD accepted.	Open label Ritlecitinib in adults and adolescents (12 years and older). Roll-over participants from ALLEGRO receiving 50mg once daily as maintenance treatment. De novo participants (new patients, not part of the ALLEGRO studies) receiving 200 mg once daily for 4 weeks, followed by 50 mg once daily thereafter.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
months: integrated analysis of the ALLEGRO phase 2b/3 and long-term phase 3 clinical studies in alopecia areata. Br J Dermatol. 2024 [24].				

5.2 Literature used for the assessment of health-related quality of life

A systematic literature search (SLR) was undertaken to identify and summarize the best available HRQoL evidence available for the treatment of AA, the methodology is summarized in Appendix I. The objective of the SLR was to assess the HRQoL and utility of patients with AA from interventional or Real World Evidence (RWE) studies. Searches were performed in October 2021. The search was updated in October 2024, to accommodate the time gap.

The original SLR from 2021 yielded three publications reporting utility data based on HRQoL scales, including EQ-5D-5L and Assessment of Quality of Life 8 dimensions (AQoL-8D):

- Burge et al (2021): EQ-5D-5L results showed that QoL decreased with increasing severity (mild 0.95 [0.14] vs moderate 0.93 [0.13] vs severe 0.87 [0.21]) [25]. However, the decrement was small despite using 5L, which is more sensitive to changes in HRQoL. Given the insensitivities of the EQ-5D (see section 10.3), these utility values were not suitable to be used in the cost-effectiveness model.
- Lai et al (2019): The AQoL-8D scale is a generic instrument which enables comparison across diseases measures on a scale from 0 (death) to 1 (full health) meaning positive values reflect an improvement in HRQoL. Mean (SD) overall AQoL-8D score for patients with AA was 0.748 (0.206) at baseline [26]. At 3 months, a patient group treated with ciclosporin showed a trend greater improvement in HRQoL across 6 of 8 AQoL-8D dimensions, compared to those treated with placebo. However, the results were not significantly different. This study was not suitable for use in the model as aggregate utilities only for moderate to severe patients with AA were described.
- Lai et al (2021): For patients with AA with <50% reduction in SALT score to ciclosporin in a preceding trial who were treated with sublingual tofacitinib in an open-label, roll-over clinical trial, changes in HRQoL were assessed using the AQoL-8D score. The mean change from baseline in AQoL-8D score was -0.0148 (0.0515) [27]. These utility values were not suitable for use in the cost-effectiveness model as only a mean reduction from baseline on treatment was described without disaggregation by SALT score.

The updated SLR from 2024 yielded one publication evaluating the relationship between AA severity and utility scores in EQ-5D and Skindex-16 AA. Vañó-Galván et al. (2023) report EQ-5D scores ranging from mild AA (0.90) to severe AA (0.78) among patients from five European countries [28]. The observed range of values across severity further supports the EQ-5D lacking sensitivity in this population. However, the study did not include SALT scores to grade patients. Instead, physicians categorized patients as “mild”, “moderate”, or “severe” according to their own definitions. It is possible that grading severity based on clinician judgment produced bias. Furthermore, as previously mentioned, EQ-5D was not considered a suitable tool to be used in the cost-effectiveness model.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Aggio D, Dixon C, Law EH, Randall R, Price T, Lloyd A. Estimation of health utility values for alopecia areata. Qual Life Res. 2024 Jun;33(6):1581-1592. doi: 10.1007/s11136-024-03645-9. Epub 2024 Mar 29. PMID: 38551802; PMCID: PMC11116246. [29]	All SALT health states used in the economic model	Section 10.3
Pfizer Inc, *Data on file,* 2024	All SALT health states used in the economic model	Section 10.3

5.3 Literature used for inputs for the health economic model

No literature search has been conducted for inputs for the health economic model, as no input data was derived from the literature.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

Efficacy and safety of ritlecitinib (PF-06651600) in patients with AA and ≥50% scalp hair loss was demonstrated in the international ALLEGRO phase 2b/3 randomized, double-blind, placebo-controlled study. The study is described in detail in Appendix A.

6.1 Efficacy of ritlecitinib compared to placebo for alopecia areata

6.1.1 Relevant studies

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ALLEGRO Phase 2b/3 Pivotal Study NCT03732807	24 weeks randomized, double-blind, placebo-controlled, followed by 24 weeks dose-ranging study	24 weeks placebo-controlled period followed by 24-weeks extension phase (up to 48 weeks)	718 adults and adolescents ≥12 years with AA who had ≥50% scalp hair loss	ritlecitinib (50 mg or 30 mg [with or without initial one month of once daily ritlecitinib 200 mg] or 10 mg*). 24-week extension phase: placebo patients transferred to one of two ritlecitinib regimens: 50 mg for 24 weeks or 200 mg for 4 weeks followed by 50 mg for 20 weeks.	Placebo for the first 24 weeks	At week 24: SALT score ≤20, SALT score ≤10, PGI-C response, ELA, EBA, AAPPO, HADS At week 24: SALT score ≤20, SALT score ≤10, PGI-C response, EBA, ELA, AAPPO, HADS

*The ritlecitinib 10 mg treatment group was assessed for dose-ranging only and was not tested for superiority to placebo. SALT = Severity af Alopecia Tool; PGI-C = Patient's Global Impression of Change; EBA = Eyebrow assessment score; ELA = Eyelash assessment score; AAPPO = Alopecia Areata Patient Priority Outcome; HADS = Hospital Anxiety and Deprission Score.

6.1.2 Comparability of studies

As the assessment is based on a head-to-head study this is not relevant.

6.1.2.1 Comparability of patients across studies

The assessment is based on a head-to-head study, so ALLEGRO 2b/3 is the only relevant study. The ALLEGRO 2B/3 study included several different dosing regimens in different treatment arms. In the clinical assessment, including Table 10, we only include data for the approved dose of ritlecitinib, i.e. 50 mg daily (no loading dose).

In the ALLEGRO-LT study, patients who were previously treated with other dosing regimens, or new to the study were assigned 50 mg daily with or without a loading dose. We have only included patients who received 50 mg without a loading dose.

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

ALLEGRO 2b/3		
	Placebo (N=131)	Ritlecitinib 50mg (N=130)
Age, Median (IQR)	32.0 (22.0–44.0)	30.0 (22.0–42.0)
Adolescents (12-17 years)	19 (15%)	18 (14%)
Adults (≥18 years)	112 (86%)	112 (86%)
Sex, Female/Male	66%/34%	55%/45%
Patients with alopecia totalis or alopecia universalis	60 (46%)	60 (46%)
Baseline SALT score, mean (SD)	93.0 (11.5)	90.3 (14.7)
Patients without normal eyebrow assessment score	107 (82%)	106 (82%)
Patients without normal eyelash assessment score	97 (74%)	95 (73%)
Disease duration since diagnosis, years,		
Median (IQR)	7.4 (2.6–14.4)	6.3 (2.6–10.9)
Mean (SD)	11.0 (11.8)	8.7 (8.7)
Duration of current AA episode, years		
Median (IQR)	2.5 (1.1–4.9)	2.2 (1.0–5.1)

Mean (SD)	3.2 (2.7)	3.2 (2.7)

ALLEGRO-LT	**Ritlecitinib 50mg N=191**
Age, Median (range)	31.0 (12.0–70.0)
Adolescents (12-17 years)	27 (14.1)
Adults (≥18 years)	164 (85.9)
Sex, Female/Male	56%/44%
Baseline SALT score, mean (SD)	90.8 (14.1)
Patients without normal eyebrow assessment score	154 (80.6%)
Patients without normal eyelash assessment score	139 (72.8%)
Disease duration since diagnosis, years, median (range)	6.9 (0.3–58.2)
Duration of current AA episode (years), median (range)	2.2 (0.0–10.0)
Prior pharmacological treatment for AA	145 (75.9%)

Reference: King et al (2023) [30]. Piliang et al (2024) [24].

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 11 shows important characteristics of AA patients included in a Danish skin cohort study [2], compared to those in the health economic model, i.e. from the ALLEGRO 2b/3 trial.

The main differences between populations are related to disease severity: patients in ALLEGRO 2b/3 and ALEGRO-LT have more severe disease, illustrated by the larger proportion of patients who have AU/AT, and that only patients with SALT ≥50 is included in the study. This is also reflected in the EMA label for ritlecitinib, where only patients with severe disease are potential candidates for treatment. Further, ALLEGRO 2b/3 contains a larger proportion of patients with involvement of eyebrow and eyelashes, which is also an indication of severity, see section 3.

Patients included in the ALLEGRO trial arms have had the disease for a median of 6.9 (0.04-60.11) years, [4] [redacted] This seems to be in line with severe patients in the Danish skin cohort [2] but many patients have endured AA for longer than what is recommended in the Danish guidelines for AA, which

recommend that systemic advanced treatment can be given to patients with a disease duration between 6 months and 8 years [1]. Therefore, it is likely that treatment start will be limited to patients with a disease duration of less than 8 years, i.e., a population that has had the disease for a shorter time than the trial population. This is important as disease duration is correlated with a worsening of the prognosis for disease [1].

Patients in the study are therefore likely to have a worse disease prognosis, and less likelihood of responding to treatment compared to the Danish AA population. As the health economic model is using efficacy data from the ALLEGRO trial, these differences are also valid in relation to the model.

Table 11 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish severe AA (>50% hair loss) population	Value used in health economic model
Age at AA onset/inclusion, mean (SD)	35 (20, 47)	33.7
AU/AT	Not available	46%†
Gender	Female: 69%Male: 31%	Female: 62,1% Male: 37,9%
Median disease duration	86% with AA for ≥8 years.	Across all treatment groups in ALLEGRO 2b/3: 6.9 years†
Median duration of current episode	Not available	Across all treatment groups in ALLEGRO 2b/3: 2.5 years†
No/barely no eyelashes	89% report involvement of eyelashes	74.7%†
No/barely any eyebrow hairs	94% report involvement of eyebrows	83.0%†

Reference: data from the Danish Skin cohort is derrived from Clemmensen et al (2024) [2]. Value used in the health economic model are in line with the ALLEGRO 2b/3 trial [32]. †Marked information is not specified in the model but comes from ALLEGRO 2b/2 [32]. AU = Alopecia Universalis; AT = Alopecia totalis; SALT = Severity af Alopecia Tool.

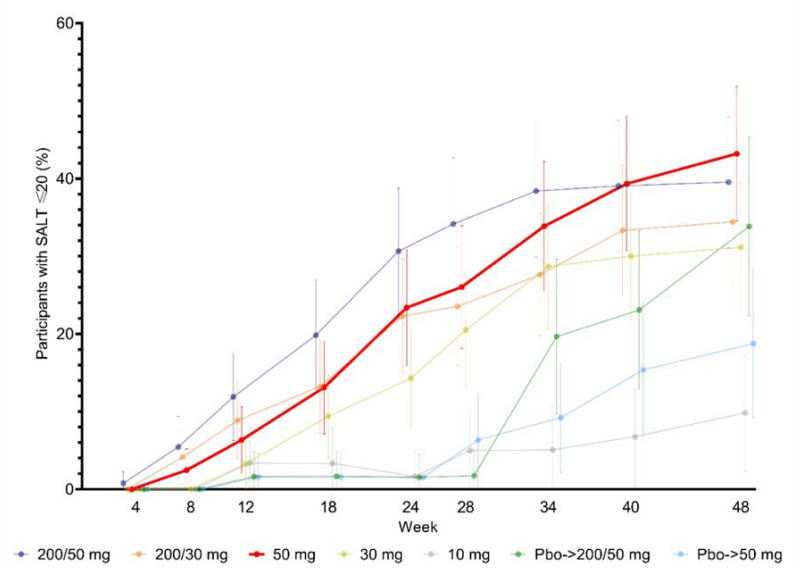
6.1.4 Efficacy – results per ALLEGRO 2/3b

The ritlecitinib 50 mg group met the primary endpoint of response based on SALT ≤20 at Week 24. Ritlecitinib also met the secondary endpoints based on SALT ≤10, Patient's Global Impression of Change (PGI-C), EBA and ELA week 24 [4]. The most relevant clinical and patient reported endpoints are presented in Table 12.

The Allegro 2b/3 study reports efficacy and safety up to week 48. The first 24 weeks of the trial were placebo controlled, after which all patients in the placebo group switched to active treatment with 50 mg (with or without a loading dose of 200 mg) [4].

Efficacy, measured by SALT score, continued to increase up to week 48, and response, measured as proportion of patients reaching a score of SALT 20 or less almost doubled in absolute terms, from week 24 (23.4%) to week 48 (43.2%) in the 50 mg dose group (see Figure 3 and Table 12) [4]. It is therefore clear that 24 weeks of follow up is not enough, but that the full study duration is taken into account.

Figure 3 Response based on SALT ≤20 up to Week 48



Reference: King et al (2023) [4]. Full analysis set: treatment group listed as loading dose if applicable/ maintenance dose. Participants were randomized to one of seven groups, 200/50 mg, 200/30 mg, 50 mg, 30 mg, 10 mg, Placebo to 200/50 mg, and Placebo to50 mg. Cases with missing data at a timepoint due to COVID related reasons are excluded. Cases with missing data at a timepoint due to reasons unrelated to COVID are considered as non-response. Abbreviations: Pbo = placebo; SALT =Severity of Alopecia Tool.

6.1.5 Efficacy – results per ALLEGRO LT

The Allegro LT study is ongoing. An integrated analysis of data up to 24 months is available and has been accepted for publication [24]. Patients aged ≥12 years with AA and ≥50% scalp hair loss from ALLEGRO-2b/3 who rolled over to ALLEGRO-LT after up to 48 weeks were included. The objective was to assess efficacy and safety of ritlecitinib through month 24. Proportions of patients with SALT ≤20 and ≤10, EBA, ELA and PGI-C responses are reported through month 24. Safety was assessed throughout month 24 [24].

At Month 24, proportion of patients with SALT ≤20 for ritlecitinib 50mg (no loading dose) was 46.1%. Patients with abnormal EBA or ELA scores at baseline achieved responses at month 24 of 46.8% and 43.2% and PGI-C response was achieved by 56.6% [24]. The safety profile was consistent with the known safety profile of ritlecitinib as reported in the pooled integrated safety analysis [23].

7. Comparative analyses of efficacy

Not applicable.

7.1.1 Differences in definitions of outcomes between studies

Not applicable.

7.1.2 Method of synthesis

Not applicable.

7.1.3 Results from the comparative analysis

Not applicable.

Table 12 Results from the comparative analysis of ritlecitinib vs. placebo for patients with severe AA

Outcome measure	Ritlecitinib 50mg (N=130)	Placebo (N=131)	Difference from placebo (95% CI),
SALT ≤ 20 response, week 24 Primary study endpoint.	23.39%	1.54 %	21.85 (14.65 to 30.23) p<0.0001 [redacted]
SALT ≤10 response, week 24 Primary endpoint, EMA	13.71 %	1.54%	11.88 (5.42, 18.33) P=0.000311 [redacted]
PGI-C response, week 24 Key secondary endpoint	49.17%	9.23%	39.96 (28.85 to 51.06) P<0·0001 [redacted]
EBA response, week 24	29.0%	4.7%	24.3 (14.8; 34.5)
ELA response, week 24	28.9%	5.2%	23.7 (13.6; 34.5)
SALT ≤ 20 response, week 48	43.20%	N/A	N/A
SALT ≤ 10 response, week 48	31.2%	N/A	N/A
PGI-C response, week 48	56.0%	N/A	N/A

Outcome measure	Ritlecitinib 50mg (N=130)	Placebo (N=131)	Difference from placebo (95% CI),
EBA response, week 48	43.6%	N/A	N/A
ELA response, week 48	40.0%	N/A	N/A
HADS, LSM of change from baseline			
Depression subscale, week 24	-0.3	0.0	-0.2 (-0.84, 0.37), p=0.443913
Depression subscale, week 48	-0.3	N/A	N/A
Anxiety subscale, week 24	-0.8	-0.6	-0.2 (-0.92, 0.50), p= 0.563896
Anxiety subscale, week 48	-0.7	N/A	N/A

Full analysis set, excludes missing data due to COVID-19. Missing data due to reasons unrelated to COVID-19 are considered as non-response. Hazard ratio: The analysis used first dosing date of randomized treatment as the starting point. Event is defined as the first occurrence of SALT ≤ 20 response/SALT ≤ 10 response/PGI-C response during the placebo-controlled period. Hazard ratio and its associated confidence intervals (CI) are estimated from a Cox regression model including fixed effects of treatment.; Only patient s treated with 50mg daily, without a loading dose are included in the ritlecinib treatment arm.

SALT = Severity af Alopecia Tool; PGI-C = Patient's Global Impression of Change; EBA = Eyebrow assessment score; ELA = Eyelash assessment score; AAPPO = Alopecia Areata Patient Priority Outcome. [4].

The share of patients with response are based on the number of participants with valid data at Week 24/48 (N1) (non-response for missing due to reasons unrelated to COVID-19; excludes missing due to COVID-19). Exact N1 numbers for each endpoint are presented in table 43. Please note that for endpoints such as EBA and ELA, the number of participants valid data at Week 24/48 (N1) will also be dependent on the number of patients with involvement of eyebrows/eyelashes at baseline.

Missing data due to COVID-19 is excluded at the specific timepoint but are still included in the other timepoints of data collection. Missing data due to reasons unrelated to COVID-19 are considered as non-response.

For the primary endpoint (SALT 10/20 at week 24), the Ritlecitinib 50mg treatment arm contained patients 6 missing due to COVID-19 (excluded from N) as well as 5 patients missing due to other reasons (considered as non-response). This corresponds to 4.8% missing data (130 randomized patients -5 missing due to covid: i.e. N1 =125. 6 patients missing due to other reasons: 6/125 = 4.8%) The placebo arm contained one patient missing due to COVID, and 5 patients missing due to other reasons. This corresponds to 3.8% missing data (131-1= N1=130. 5/130 = 4.8%).

For PGI-C response at week 24, 5 patients in the ritlecitinib 50mg treatment arm were missing due to COVID-19 (excluded from N), and 5 patients were missing due to other

reasons (considered as non-response), i.e. 4.0% missing data. In the placebo arm one patient was missing due to COVID-19, and 5 patients missing due to other reasons.

7.1.4 Efficacy – results per [outcome measure]

Not applicable.

8. Modelling of efficacy in the health economic analysis

Please refer to the Technical Report for more detailed information.

8.1 Presentation of efficacy data from the clinical documentation used in the model

The short-term Health State distribution was derived directly from the ALLEGRO 2b/3 trial i.e., data up to Week 48 for patients receiving ritlecitinib, and up to Week 24 for patients in the placebo arm [31]. These distributions of patients between health states are presented in Table 13.

Table 13 Short term distributions (up to week 48)

	Placebo				Ritlecitinib 50 mg			
SALT Health State	**Week 12**	**Week 24**	**Week 34***	**Week 48**	**Week 12**	**Week 24**	**Week 34**	**Week 48**
≤ 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11-20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment						[redacted]	[redacted]	[redacted]
Grand total						[redacted]	[redacted]	[redacted]

*Week 34 is assumed equal to week 36, to align with the 12-week cycle-length of the model. Source: health economic model. SALT = Severity af Alopecia Tool.

From Week 48 until Week 96 (24 months), transition matrices for patients treated with ritlecitinib were derived from the ALLEGRO-LT clinical trial to calculate the transitions between health states.

Patient level transition data between different health states after week 48 is based on modelled population, age group, and treatment response.

To calculate the transitions from Week 48 until Week 96, only data for patients with SALT ≤20 after 48 weeks of exposure to ritlecitinib were considered, ensuring that only patients who would have passed the final stopping rule were included.

Response was demonstrated to plateau in the ALLEGRO-LT trial, thus from Week 96 onwards, it is assumed that patients remain in state. This "stay in state"-approach assumes patients do not transition between health states after the LT data average after 24 months.

8.1.1 Extrapolation of efficacy data

As long-term efficacy data in the model is not derived through extrapolation, this section is only relevant for the measure of "discontinuations for any reason other than lack of response". Patients who stopped treatment due to a lack of response, are assumed to be captured by the stopping rules. Thus, only patients who had a SALT score of 20 or less at Week 48 were included in the analysis of patients discontinuing due to other reasons.

Data on discontinuation data was collected in the ALLEGRO 2b/3 trial and was extrapolated throughout the model duration.

8.1.1.1 Extrapolation of discontinuations

Based on visual inspection, the Generalized Gamma does not fit the data well, indicating a lack of convergence. As the exponential distribution is the next best statistically fitting to the data (according to AIC and BIC), the exponential distribution is used in the base case analysis.

According to the extrapolation made using the exponential curve, approximately [redacted] patients remained on treatment with ritlecitinib four years after achieving SALT score ≤20 following 48 weeks of ritlecitinib treatment.

Table 14 Summary of assumptions associated with extrapolation of discontinuation

Method/approach	Description/assumption
Data input	ALLEGRO 2b/3
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Intervention: Generalized Gamma*

Method/approach	Description/assumption
Function with best BIC fit	Intervention: Generalized Gamma*
Function with best visual fit	Intervention: No conclusion on best fit. However, the Generalized Gamma curve was excluded based on visual fit.*
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	No validation was made.
Function with the best fit according to external evidence	No validation based on external evidence was made.
Selected parametric function in base case analysis	Intervention: Exponential function*
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

*Please note, that as discontinuations can only occur in the active treatment arm, the BSC arm is not included in the table below.

Figure 4. The fit of parametric distributions to ALLERGO-LT discontinuations

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

Before week 48 transitions are not calculated but are taken directly from the ALLEGRO 2b/3-trial. Patient level transition data between different health states after week 48 is based on modelled population, age group, and treatment response.

Response was demonstrated to plateau in the ALLEGRO-LT trial, thus from Week 96 onwards, it is assumed that patients remain in state. This "stay in state"-approach assumes patients do not transition between health states after the LT data average after 24 months, see Table 15.

Table 15: Transitions in the health economic model from Week 96

		To SALT ≥50	To SALT 21-49	To SALT 11-20	To SALT ≤10
Ritlecitinib (From Week 48)	From SALT ≥50	[redacted]	[redacted]	[redacted]	[redacted]
	From SALT 21-49	[redacted]	[redacted]	[redacted]	[redacted]
	From SALT 11-20	[redacted]	[redacted]	[redacted]	[redacted]
	From SALT ≤10	[redacted]	[redacted]	[redacted]	[redacted]

As patients do not transition between health states beyond week 96 (model cycle 8), the distribution of patients in the different model stages over the time horizon (Figure 5 and Figure 6) is solely dependent on discontinuations and background mortality.

Figure 5. Distribution of patients in the model's stages over the model's time horizon, ritlecitinib

Figure 6. Distribution of patients in the model's stages over the model's time horizon, BSC

8.2 Presentation of efficacy data from [additional documentation]

Not relevant, as all efficacy data is derived from the ALLEGRO b2/3 trial and its extension trial, ALLEGRO-LT.

8.3 Modelling effects of subsequent treatments

Not relevant, as subsequent treatments are not included.

8.4 Other assumptions regarding efficacy in the model

No additional assumptions regarding efficacy are included in the model.

8.5 Overview of modelled average treatment length and time in model health state

Table 16 presents the modelled average and median time on treatment with ritlecitinib. All patients who do not reach SALT 20 at week 48 stop treatment, [redacted] Therefore, the median time on treatment [redacted] or approximately [redacted] years.

Table 16 Estimates in the model

	Modelled average time [effect measure]	Modelled median [effect measure]	Observed median from relevant study
Ritlecitinib	[redacted] years	[redacted] years	Not reached
BSC	Not relevant	Not relevant	Not relevant

Reference: see "DMC Results" in excel model.

The modelled average treatment length and time in model health states is presented in Table 17. These are derived in accordance with the modelling previously described. Only duration spent in each health state while on treatment is included in the table, hence BSC duration is entirely off treatment.

Table 17 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	On Trt SALT ≥50	On Trt SALT 21-49	On Trt SALT 11-20	On Trt SALT ≤10	Off Trt SALT ≥50	Off Trt SALT 21-49	Off Trt SALT 11-20	Off Trt SALT ≤10
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	0.00	0.00	0.00	0.00	0.00	[redacted]	[redacted]	[redacted]	[redacted]

Reference: see "DMC Results" in excel model. Abbreviations: trt = treatment.

9. Safety

9.1 Safety data from the clinical documentation

Safety data are based on an integrated analysis of data pooled from four clinical trials evaluating the safety of ritlecitinib in adults and adolescents with alopecia areata [23]:

- ALLEGRO phase 2a proof-of-concept study, NCT02974868, completed [33].
- ALLEGRO phase 2a safety (auditory) study, NCT04517864, completed [34].
- pivotal ALLEGRO phase 2b/3 study, NCT03732807, completed [4].
- long-term, open-label, phase 3 ALLEGRO-LT study, NCT04006457, ongoing [24].

It is comprised of a placebo-controlled pool of 881 patients and an all-exposure pool of 1294 patients.

The placebo-controlled pool thus included patients from the two phase 2a studies as well as the ALLEGRO-2b/3 study and ALLEGRO LT, who received ritlecitinib or placebo up to week 24 during the placebo-controlled period of each study. In the placebo-controlled pool, median [interquartile range (IQR)] exposure was 169 (167–173) days in each of the ritlecitinib and placebo groups. Data from the placebo-controlled pool are presented in Table 18, while safety data from ALLEGRO 2b/3 is presented in Table 19.

Table 18 Overview of safety events from pooled analysis with median (IQR) exposure 69 (167–173) days in each of the ritlecitinib and placebo groups.

	Placebo (n = 213)	Ritlecitinib 50 mg (n = 130)	Ritlecitinib all doses (n = 668)	Difference to 50 mg, % (95 % CI)
Number of adverse events, n	370	243	1273	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	148/213 (69.5)	98/130 (75.4)	[redacted]	5.9%
Number of serious adverse events*, n	4	0	[redacted]	N/A, few observations
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	4/213 (1.9)	0/130 (0.0)	[redacted]	N/A, few observations
Number of CTCAE grade ≥ 3 events,	2 (0.9%) CPK increase [23].	5 (1.5%) ALC decrease 16 (4.7%) CPK increase	[redacted]	N/A, few observations

	Placebo (n = 213)	Ritlecitinib 50 mg (n = 130)	Ritlecitinib all doses (n = 668)	Difference to 50 mg, % (95 % CI)
			[redacted]	
Number of adverse reactions, n	Not available	Not available	Not available	Not available
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	Not available	Not available	Not available	Not available
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	20 (9.4)	9 (6.9)	[redacted]	N/A, few observations
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	5/213 (2.3)	2/130 (1.5)	[redacted]	N/A, few observations

*A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect; N/A= Not applicable; ALC= Absolute Lymphocyte Count; ANC=Absolute Neutrophile Count. Reference: King et al. 2024 [23]. Numbers marked in yellow highlighter are not published, but are derrived from the ALLEGRO 2b/3 CSR [31].

Table 19 Overview of safety events ALLEGRO 2b/3 up to Week 48.

	Placebo (n = 131)	Ritlecitinib 50 mg (n = 130)	Ritlecitinib all doses (n = 584)	Difference to 50 mg, % (95 % CI)
Number of adverse events, n	Week 24: 223 Week 48: 372	Week 24: 243 Week 48: 363	[redacted]	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	Week 24: 93 (71) Week 48: 111 (85)	Week 24: 98 (75) Week 48: 110 (85)	[redacted]	N/A

	Placebo (n = 131)	Ritlecitinib 50 mg (n = 130)	Ritlecitinib all doses (n = 584)	Difference to 50 mg, % (95 % CI)
Number of serious adverse events*, n	Week 24: 3 Week 48: 3	Week 24: 0 Week 48: 2	[redacted]	N/A, few observations
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	Week 24: 3 (2) Week 48: 3 (2)	Week 24: 0 (0) Week 48: 2 (2)	[redacted]	N/A, few observations
Number of CTCAE grade ≥ 3 events, n	Week 24: 1 Week 48: 3	Week 24: 1 Week 48: 3	[redacted]	N/A, few observations
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	Week 24 1 (0.8%) CD4 lymphocyte decrease Week 48 1 (0.8) ANC decrease 1 (0.8) CD4 lymphocyte decrease	Week 24 1 (0.8) CD4 lymphocyte decrease. Week 48 1 (0.8) CD 4 Lymphocyte decrease 2 (1.5) ALC decrease	[redacted]	N/A, few observations
Number of adverse reactions, n	Not available	Not available	Not available	Not available
Number and proportion of patients with ≥ 1 adverse reaction, n (%)	Not available	Not available	Not available	Not available
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue	Week 48 14 (11)	Week 48 17 (13)	[redacted]	N/A, few observations

	Placebo (n = 131)	Ritlecitinib 50 mg (n = 130)	Ritlecitinib all doses (n = 584)	Difference to 50 mg, % (95 % CI)
treatment regardless of reason, n (%)				
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	Week 24: 2 (2) Week 48: 4 (3)	Week 24: 2 (2) Week 48: 4 (3)	[redacted]	N/A, few observations

Results are presented for baseline to week 24 and week 48 respectively.* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect; N/A= Not Applicable; ALC= Absolute Lymphocyte Count; ANC=Absolute Neutrophile Count. Reference: King et al. 2023 [4]. Numbers marked in yellow highlighter are not published, but are derrived from the ALLEGRO 2b/3 CSR [31].

The number of Serious Adverse Events (SAEs) were low in Allegro 2b/3 study and not enough to perform analysis compared to placebo. No serious adverse events occurred with more than 5% frequency [4]. Table 20 is therefore not applicable, but please see Appendix E for a full list of SAEs.

Overall, 14 patients experienced 16 SAEs up to Week 48. Of these, 10 patients experienced 11 SAEs (Placebo 3 SAEs, any dose Ritlecitinib 8 SAEs) up to Week 24. Of these, 2 occurred in the ritlecitinib 50 mg arm. In 3 patients, the SAEs were considered related to treatment with ritlecitinib by the Investigator [4].

Table 20 Serious adverse events (week 24 and 48)

Adverse events	Placebo (N=213)		Ritlecitinib 50 mg (N=130)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
No SAEs occurring in more than 5% of patients.				

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

In the health economic model, all AEs in the Full Analysis Set (FAS) population in the ALLEGRO 2b/3 trial fulfilling the following requirement were included:

- Treatment Emergent Adverse Events (TEAEs) occurring in ≥5% of patients in the ritlecitinib 50 mg arm, and
- SAEs occurring in ≥2 events in the ritlecitinib 50 mg treatment arm, and
- SAEs occurring in ≥2% in any treatment arm.

No SAEs were included based on this definition. The rate of adverse events at Week 48 were used for patients treated with ritlecitinib and adverse events at week 24 for BSC.

For both ritlecitinib and BSC, the risk of adverse events is assumed to be constant over the modelled time horizon, which is a simplifying assumption given the lack of longer-term data.

Table 21 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Acne	[redacted]	[redacted]	(Pfizer, data on file, 2022).	Most common AEs in the trial. In order not to miss important events, the threshold for including was lowered for inclusion of SAEs
Diarrhea	[redacted]	[redacted]		
Folliculitis	[redacted]	[redacted]		
Headache	[redacted]	[redacted]		
Nasopharyngitis	[redacted]	[redacted]		
Rash	[redacted]	[redacted]		
Upper respiratory tract infection	[redacted]	[redacted]		
Urticaria	[redacted]	[redacted]		

9.2 Safety data from external literature applied in the health economic model

Not relevant, as no external safety data is used in the health economic model.

Table 22 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

HRQoL was measured in the ALLEGRO 2b/3 study via the disease-specific Alopecia Areata Patient Priority Outcomes (AAPPO) and generic HRQoL instruments: EQ-5D-5L, EQ VAS, 36-Item Short Form Survey Instrument (SF-36), and HADS. In the following section, the EQ-5D results from ALLEGRO 2b/3 are described and discussed, in order to explain why the results, and specifically the EQ-5D results, cannot be used in the model. In section 10.3, the vignette study, informing the utilities in the model, is described.

Table 23 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
TTO	UK Vignette Study	Used in base case of Health-economic model.
EQ-5D-5L (& EQ-5D-5Y)	ALLEGRO 2b/3	DMC preferred tool. However, lacks content validity for AA.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

The change from baseline in EQ-5D-5L index score and Visual Analog Scale (VAS) scores, was included as one of the exploratory end points in the randomized, controlled ATTRACT 2b/3 trial.

EQ-5D-5L is a generic and validated instrument which is preferred by the DMC.

AA is a condition that is associated with a decrease in QoL, and HRQoL would be expected to have an inverse relationship to SALT scores (low SALT scores would be associated with high HRQoL). However, EQ-5D has been shown to have challenges with content validity in patients with AA (see section 3). Therefore, it was not used in the model base case.

10.1.2 Data collection

Patients completed the HRQoL assessments, including EQ-5D-5L and EQ-VAS, at the baseline visit and at subsequent visits (week 4, 12, 24, and for ritlecitinib alone week 48) [31].

Data in

Table 24 shows the pattern of missing data and completion of EQ-3D-5L for the AA population receiving any dose of ritlecitinib or placebo in the ALLEGRO 2b/3 trial.

There was no imputation of missing values, and it has not been possible to gain any data on characteristics of patients with missing data, however the share of patients missing is very small, so this is not expected to impact the analysis. Missing data from baseline to Week 24 ranges from 1-3% of the number of patients who are expected to complete at each timepoint, see

Table 24.

Missing data due to COVID-19 is excluded at the specific timepoint but are still included in the other timepoints of data collection. Missing data due to reasons unrelated to COVID-19 are considered as non-response.

Table 24 Pattern of missing data and completion in the adult population

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	620	[redacted]	[redacted]	[redacted]
Week 4	620	[redacted]	[redacted]	[redacted]
Week 12	620	[redacted]	[redacted]	[redacted]
Week 24	620	[redacted]	[redacted]	[redacted]
Week 48	620	[redacted]	[redacted]	[redacted]

[redacted]

Table 25 Pattern of missing data and completion in the adolescent population

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	98	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 4	98	[redacted]	[redacted]	[redacted]
Week 12	98	[redacted]	[redacted]	[redacted]
Week 24	98	[redacted]	[redacted]	[redacted]
Week 48	98	[redacted]	[redacted]	[redacted]

[redacted]

10.1.3 HRQoL results

The baseline EQ-5D-5L utility scores (for adults) and EQ-5D-Y (for adolescents) for all patients enrolled in the ALLEGRO 2b/3 study with EQ-5D showed a strong skew in values towards one i.e., the upper bound of utility index scores, and were similar to that of population norms. [redacted]

Similarly, the absolute EQ VAS scores in the ALLEGRO 2b/3 trial show little differentiation over time for all treatment groups, highlighting the limited sensitivity [31]. Please see the Technical Report for a thorough analysis of the EQ-5D results.

Figure 7 The mean change of EQ-5D-5L index-score from baseline through the different data collection time points for ritlecitinib and placebo

[redacted]

Figure 8 The mean change of EQ-5D-5L-VAS score from baseline through the different data collection time points for ritlecitinib and placebo

Table 26 HRQoL of EQ-5D-VAS score summary statistics

	Ritlecitinib		Placebo		Ritlecitinib vs. placebo	
	N	Mean (SE)	N	Mean (SE)	Difference	p-value*
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

SE was not available, therefore SD was provided. *As the p-values is not significant in any of the weeks, the 95% CI is not provided.

Table 27 HRQoL of EQ-5D-5L index summary statistics

	Ritlecitinib		Placebo		Ritlecitinib vs. placebo	
	N	Mean (SE)	N	Mean (SE)	Difference	p-value*
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

	Ritlecitinib		Placebo		Ritlecitinib vs. placebo
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	N/A	N/A	N/A

SE was not available, therefore SD was provided. *As the p-values is not significant in any of the weeks, the 95% CI is not provided.

Table 28 HRQoL of EQ-5D-Y-VAS score summary statistics

	Ritlecitinib		Placebo		Ritlecitinib vs. placebo
	N	Mean (SE)	N	Mean (SE)	Difference p-value*
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SE was not available, therefore SD was provided. *As the p-values is not significant in any of the weeks, the 95% CI is not provided

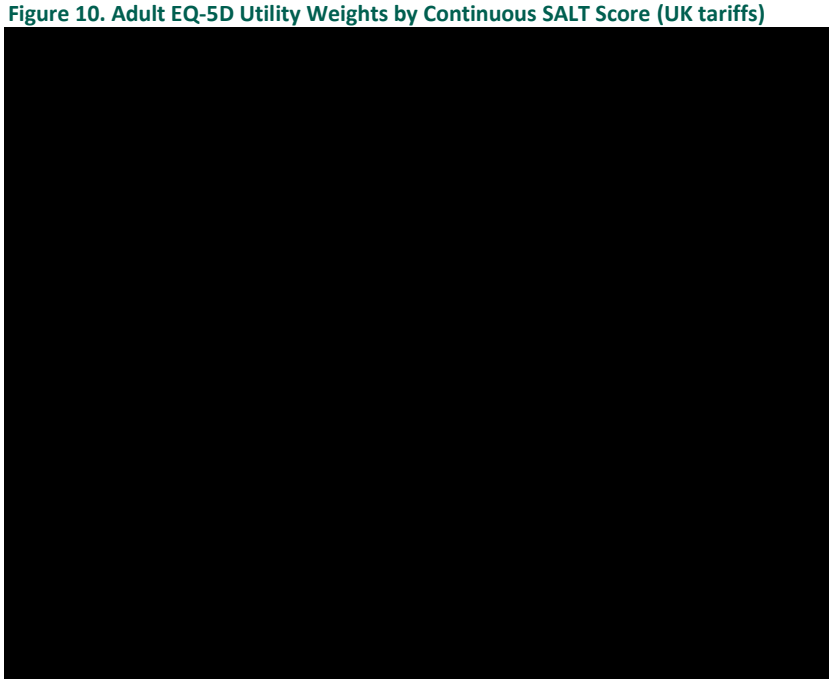
Figure 9 The mean change of EQ-5D-5L-VAS score from baseline through the different data collection time points for ritlecitinib and placebo

10.1.3.1 Analysis of the EQ-5D results

Initial investigation of the relationship between EQ-5D-5L utility weights and SALT scores was conducted on adult utility weights. Figure 10 is a scatter plot of UK adult utility

weights by SALT score. Note the horizontal cluster of utility weights of [redacted] Both indicates that utility weights derived from the EQ-5D are likely independent of SALT score.

Figure 10. Adult EQ-5D Utility Weights by Continuous SALT Score (UK tariffs)

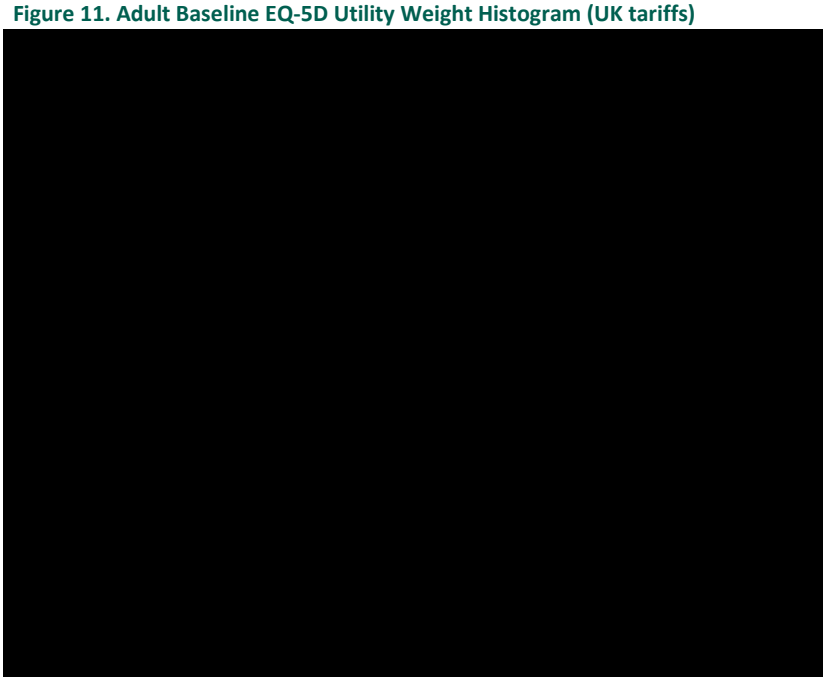


Reference: Pfizer 2023, data on file [35] (EQ-5D-3L Utility weights calculated via Hernandez et al. (2023) [36] algorithm).

The range of utility scores is larger for responses related to SALT scores [redacted] However, there are far fewer scores in that range compared with the number of observations [redacted] so the mean utility scores in patients with SALT 1-10 are [redacted]

Figure 11 shows the baseline count for observed EQ-5D utility scores (for adults) for all patients enrolled in the ALLEGRO 2b/3 study. The histograms highlight a skew in the baseline utility values towards one, the upper bound of utility index scores.

Figure 11. Adult Baseline EQ-5D Utility Weight Histogram (UK tariffs)

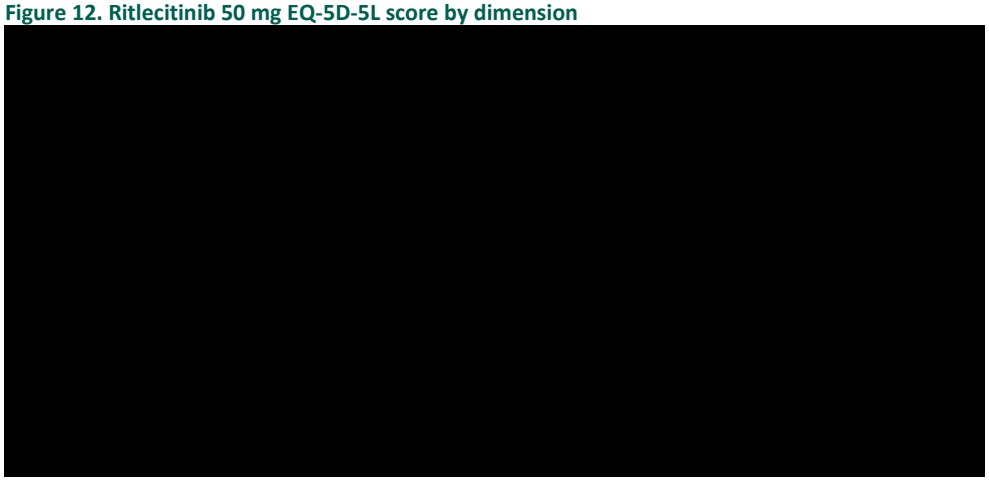


Reference: Pfizer 2023, data on file [35] (EQ-5D-3L Utility weights calculated via Hernandez et al. (2023) [36] algorithm.)

Figure 12 and Figure 13 show the scores across each of the five dimensions of EQ-5D for ritlecitinib 50 mg and placebo, respectively, across baseline, week 24, and week 48 [35].

Together these figures demonstrate that, according to the EQ-5D-5L questionnaire, perfect health at baseline was reported in of patients.

Figure 12. Ritlecitinib 50 mg EQ-5D-5L score by dimension



Reference: Based on Pfizer 2023, data on file [35].

Figure 13. Placebo EQ-5D-5L score by dimension

Reference: Based on Pfizer 2023, data on file [35].

Table 29 provides a [redacted] This demonstrates a pattern of improved outcomes with EQ-5D according to response, but this improvement is obstructed by high EQ-5D scores at baseline.

Table 29. Summary of Change from Baseline in EQ-5D Index Value by Treatment Group, Time Point and SALT Response (≤ 20 and >20) - Full Analysis Set (Overall)

The table includes data for all patients, not including data separately for patients with SALT ≤20 response).
Reference: Pfizer 2023, data on file [35].

All in all, the baseline EQ-5D utility scores for all patients enrolled in the ALLEGRO 2b/3 study with EQ-5D showed a strong skew in values towards one, the upper bound of utility index scores, [redacted]

[redacted] These results demonstrate that, according to the EQ-5D-5L questionnaire, perfect health was reported in a large proportion of patients throughout the study. This creates a ceiling effect, making it insensitive to changes. Additionally, trial EQ-5D appeared to not be sensitive to changes in AA severity because utility weights for all SALT score health states were very similar i.e., EQ-5D seem ill adapted to capture the burden of AA. This is further discussed in the section below and in 10.3.

10.1.3.2 Interpretation of the EQ-5D results

A substantial body of evidence exists that describes the burden that AA can have on patients' HRQoL. This includes the psychosocial burden but also a broader impact in terms of people's willingness to undertake daily activities. This evidence clearly suggests that the burden and impact of AA extends beyond simply hair loss resulting in a much wider impact on HRQoL [12, 39, 40].

Yet, the baseline EQ-5D-5L utility values derived from the ALLEGRO 2b/3 clinical trial ranged from [redacted] (UK value set). These values are relatively high, especially in the severe disease states with AA, compared UK population norms [16]. Though the different value sets make it necessary to be cautious, the trial utilities are still very high compared to the Danish general population [38], see Table 30.

Table 30. EQ-5D index value population norms by age group and total population (European VAS value set)

	18–24	25–34	35–44	45–54	55–64	65–74	75 +	Total
Argentina	0.907	0.889	0.869	0.849	0.829	0.796	0.724	0.856
Belgium	0.953	0.921	0.920	0.889	0.881	0.848	0.761	0.891
China	0.990	0.980	0.970	0.960	0.930	0.900	0.840	0.951
Denmark	0.914	0.914	0.881	0.861	0.845	0.818	0.753	0.866
Finland	N/A	0.919	0.891	0.853	0.805	0.762	0.573	0.815
France	0.924	0.921	0.883	0.893	0.836	0.804	0.756	0.872
Germany	0.950	0.949	0.943	0.908	0.881	0.838	0.771	0.902
Greece	0.979	0.972	0.957	0.916	0.817	0.793	0.739	0.913
Hungary	0.934	0.911	0.873	0.802	0.755	0.716	0.639	0.823
Italy	0.969	0.956	0.943	0.910	0.877	0.823	0.724	0.899
Korea	0.957	0.958	0.949	0.915	0.828	0.787	N/A	0.915
Netherlands	0.938	0.910	0.922	0.874	0.869	0.863	0.798	0.892
New Zealand	0.913	0.906	0.893	0.858	0.817	0.800	0.712	0.848
Slovenia	0.879	0.859	0.831	0.772	0.697	0.663	0.621	0.788
Spain	0.968	0.963	0.939	0.911	0.884	0.870	0.773	0.915
Sweden	0.888	0.893	0.868	0.835	0.813	0.836	0.701	0.851
Thailand	0.814	0.785	0.771	0.717	0.694	0.670	0.657	0.742
UK	0.934	0.922	0.905	0.849	0.804	0.785	0.734	0.856
UK—England	0.922	0.915	0.891	0.857	0.819	0.785	0.720	0.857
US	0.899	0.883	0.853	0.809	0.776	0.756	0.677	0.825

Reference: Janssen et al. 2019 [38].

As noted in the previous section, results from all PRO instruments across the ALLEGRO 2b/3 study, showed that there was a clear ceiling effect, as most patients reported maximal scores at baseline, indicating perfect health.

Overall, though SF-36 and AAPPO showed some difference between responders and non-responders, the ALLEGRO 2b/3 trial do not align with, or do not adequately capture, the detrimental burden patients with AA experience. The findings suggest a complexity around correctly estimating the burden of HRQoL, and therefore, alternative approaches were explored and are presented to connect the patient burden to utility elicitation.

One explanation may be that, even though depression and mental health of patients can be captured with EQ-5D-5L, other important aspects of HRQoL are not captured, which may explain the narrow range of observed utility values in the literature [18]. This suggests results from ALLEGRO-2b/3 are not the same as observed in the real-world setting [18, 25]. This was explored in section 10.1.3.310.1.3.3.

10.1.3.3 Important elements of HRQoL in AA – input from clinical experts

To understand the disconnect between the ALLEGRO 2b/3 HRQoL trial results and data from the literature, [redacted]

In summary, the PAG input suggested that generic preference-based measures that quantify the HRQoL of patients with AA are not able to overcome the complexity of correctly estimating the burden of AA. They are not specific or sensitive enough to comprehensively capture the full patient experience.

A recent Danish study that investigated the association between AA disease severity and HRQoL supports the suggestions from the PAGs. It highlighted the importance of using the proper tool for the intended measurement of quality of life (QoL). The study investigated multiple PRO measures in patients with AA, and showed how generic QoL tools were not able to distinguish between disease severity [2].

The limitation of content validity, also means that it is not feasible replacing trial EQ-5D with EQ-5D from the literature.

Overall, despite it being well known that the severity of AA has a meaningful impact on patients QoL, results reported using EQ-5D in the ALLEGRO 2b/3 trial do not adequately capture this. Since the issues are valid for EQ-5D in general, EQ-5D from the trial could not be replaced with EQ-5D from the literature.

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

EQ-5D was included in the study but not used in the model base case. The grounds for not using it in the base case are explained in section 3. In this section, the EQ-5D-5L values used in the scenario analysis are described.

The ALLEGRO trial measured EQ-5D-5L and produced the HSUVs through a post-hoc analysis of utility data in the trial by SALT score category, regardless of treatment or of assessment time point [31].

Model HSUVs are age adjusted.

10.2.1.1 Mapping

Since the ALLEGRO 2b/3 trial uses EQ-5D-5L, mapping is not necessary.

A study by Jensen et al (2021) was used to generate Danish utility values based on the imputed EQ-5D-5L data [48]. This study included a nationally representative sample based on age, gender, education, and region – and interviews were conducted using the EQ-VT 2.1. Respondents valued states based on composite time trade-off (cTTO) and discrete-choice experiments (DCE). A heteroscedastic censored hybrid model combining both the cTTO and DCE data was selected by the authors as the best fitting model, and the version with regular dummies was used for this analysis [48]. The resulting utility mean values with standard errors in brackets are presented in Table 31.

10.2.2 Disutility calculation

Not relevant. As the AEs are mild and transient, no disutilities were included in the model.

10.2.3 HSUV results

Table 31 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
SALT 0-10	[redacted]	EQ-5D-5L	DK	Derived from ALLEGRO 2b/3
SALT 11-20	[redacted]	EQ-5D-5L	DK	
SALT 21-49	[redacted]	EQ-5D-5L	DK	
SALT 50-100	[redacted]	EQ-5D-5L	DK	

95% CI was not available, therefore SE was provided. SALT = Severity af Alopecia Tool; EQ-5D-5L = EuroQoL 5 Dimensions 5 Levels. Reference: Pfizer data on file [31].

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

The ALLEGRO 2b/3 trial shows that ritlecitinib has a meaningful impact on hair regrowth in adults and adolescents with severe AA, and an acceptable safety profile. Additionally, a substantial body of evidence exists that describes the burden that AA can have on HRQoL [12, 43, 49]. Despite these clinical and physical symptom improvements, significant differences in EQ-5D-5L and SF-36 scores were not detected between the ritlecitinib 50 mg group and placebo from baseline to Week 24. Several factors may have contributed to this:

- **Generic Measures of HRQoL:** Generic measures of HRQoL, such as EQ-5D, may not capture all the domains which are relevant to patients with AA and are therefore insensitive to HRQoL in this patient population [25, 18]. A recent Danish study, investigating the association between AA disease severity and HRQoL, highlighted the importance of using the proper tool for the intended measurement of QoL. The study investigated multiple PRO (patient reported outcome) measures in patients with AA, and showed how generic QoL tools were not able to distinguish between disease severity [2].
  Whilst EQ-5D can capture depression and mental health of patients, it has been suggested that generic preference-based measures may not include all aspects of HRQoL, important to patients [18]. They do therefore not seem able to overcome the complexity of correctly estimating the burden of AA. Therefore, they lack

content validity and potential responsiveness to changes in HRQoL for patients with AA. Please see the Technical Report, for further details.

- **Ceiling Effect:** Most patients completing the EQ-5D-5L questionnaire in ALLEGRO 2b/3 reported the same score (no problems) across all domains at baseline, allowing no room for improvement up to Week 48. Similarly, patients completing the EQ-VAS had similar, high mean score at baseline through Week 48. This limits the room for improvements to be observed, creating a ceiling affect. Please see the analysis of trial EQ-5D results in the Technical Report.
- **Adaptation/Coping:** Across several studies, coping mechanisms are mentioned which offset the negative impact of AA on patients HRQoL the most extreme of which, after all other behaviors had been tried out, is acceptance [50, 51, 52, 53, 54]. Patients enrolled in ALLEGRO 2b/3 had AA for multiple years (mean [redacted] years since first diagnosis) across all trial arms. The lack of connection between treatment response and HRQoL may therefore partly be due to adaptation by patients who were enrolled to the study i.e., patients enrolled in the study may have learnt to cope with the way AA impacts their HRQoL.
- **ALLEGRO 2b/3 Design:** The higher HRQoL scores at baseline could be attributed to the data collection setting; first, the placebo-controlled period might also be too short to detect a meaningful difference (24 weeks). Secondly, the ALLEGRO 2b/3 study excluded [redacted] Finally, it is also relevant to consider that before patients were referred to the study, physicians would assess the ability of patients to participate in a clinical study. Patients who are unlikely to be able to comply with the follow ups and assessments of a clinical study, may not have been put forward, this being excluded even before inclusion assessment.

Overall, despite it being well known that the severity of AA has a meaningful impact on patients QoL (see section 3), HRQoL results reported using EQ-5D in the ALLEGRO 2b/3 trial do not adequately capture this. The DMC came to a similar conclusion in another recent evaluation for AA, that the quality of life among Danish patients in clinical practice is probably more negatively affected than in the study population [14].

The ALLEGRO study included several other tools for measuring HRQoL, the generic measures incurred the same challenges as EQ-5D (please see the Technical Report for details). The disease-specific AAPPO has been shown to be a reliable and valid measure and appears to be more sensitive to the burden for patients with AA. However, AAPPO cannot be used to describe utilities in an economic model, as it is not a preference-based measure.

Therefore, quality of life data from the clinical study were not used in the assessment. In line with NICE recommendations in cases where EQ-5D is not sensitive to the HRQoL impacts associated with the disease [55], a health state vignette approach was used to generate utility values by health state are used in the health economic analysis.

10.3.1 Study design

In accordance with the hierarchy of preferred HRQoL methods in the NICE guidance, a vignette study was designed in the United Kingdom (UK) [55], to capture the full impact

on HRQoL for patients who suffer from AA. The impact of AA on caregivers of adolescents was also explored within the vignette study but are not included in the model, in line with DMC guidelines [21].

The study design consisted of three main parts [5]:

The first part was designed to describe how key domains of HRQoL are affected by the disease for adults and adolescent patients with AA. These were informed by findings from three different sources:

1. Quantitative semi-structured interviews with adults and adolescent patients with AA were conducted to describe the impact of AA on their HRQoL and wellbeing.
2. A detailed literature review was completed to describe the impact of AA on HRQoL in patients.
3. Retrospective analysis of data from the AAPPO, SF-36 and the HADS from the ALLEGRO 2b/3 trial.

In part 2, a second round of interviews was conducted with adults and adolescent patients, caregivers, as well as health professionals, to obtain feedback on the draft vignettes and to determine the accuracy of the descriptions.

Part 3 consisted of a cross-sectional study in which the vignettes were reviewed and rated by the UK general population using the TTO valuation technique. Utilities were estimated for each of the patients' vignettes.

More information on the vignette methodology can be found in the Technical Report.

10.3.2 Data collection

Data on HRQoL was collected through TTO interviews conducted online via video conferencing software. The TTO interviews were conducted on the general population in the UK and on AA patients separately. In both populations an initial pilot was conducted with 20 participants to confirm comprehension of the vignettes. This data was pooled into the final sample of 100 participants in the general population (N=120) and 30 participants in the AA population (N=50) [29].

Prior to the TTO interview, participants were provided with information about the study and asked screening questions. If eligible, they were asked to sign a consent form and were asked to complete a brief background questionnaire [29].

Participants were initially asked to complete the EQ-5D-5L about themselves. They were then presented with the vignettes one-by-one and first asked to rate the severity of each vignette on the VAS from 0 (worst possible state) to 100 (full health). Secondly the participants completed the TTO exercise for each vignette, to generate the health state utilities [29].

A sensitivity analysis on the general population was also conducted to explore the impact of participants comprehension/understanding of the vignettes and TTO task on the

health state valuations. Six participants were excluded based on this exclusion criteria (N=114). The overall pattern of the results remained unchanged, with the sensitivity analysis showing larger range from the mildest to most severe health state [29].

More information on the vignette methodology can be found in the Technical Report.

10.3.3 HRQoL Results

The mean VAS ratings ranged from 77.6 (SALT 0-10) to 39.1 (SALT 50-100 + eyebrow/eyelash loss). The VAS ratings show that the perceived HRQoL burden increases as the level of scalp hair loss and associated impacts increase. The loss of eyebrows or eyelashes also increased the perceived HRQoL burden compared to scalp hair loss alone [29].

The TTO utility ratings ranged from 0.919 (SALT 0-10) to 0.502 (SALT 50-100 + eyebrow/eyelash loss. TTO utility weight data mirror the pattern observed for the VAS valuations, with a higher perceived HRQoL impact observed as the level of hair loss and associated impacts increase. The additional loss of eyebrows or eyelashes also increased the perceived HRQoL burden. Although utilities were obtained for a SALT score of 50-100 + eyebrow/eyelash loss, they are not included in the health economic evaluation, please see Table 32 [29].

10.3.4 HSUV and disutility results

The TTO utility weights of the full sample of people interviewed in the vignette study used in the model are presented in Table 32. The values are included in the model, using the UK tariff, as there is no method to map them to Danish values. Utilities in the model were age-adjusted.

More information in the vignette results can be found in the Technical Report.

Table 32 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs (N=120)				
SALT 0-10	0.919 [0.898-0.941]	TTO	UK	Based on general UK population
SALT 11-20	0.853 [0.812-0.894]	TTO	UK	
SALT 21-49	0.703 [0.647-0.759]	TTO	UK	
SALT 50-100	0.554 [0.471-0.638]	TTO	UK	
SALT 50-100 + eyebrow/eyelash loss*	0.502 [0.418-0.586]	TTO	UK	

*This health state was reported in the study but is not included in the economic model. SALT = Severity af Alopecia Tool; TTO = Time trade-off. Reference: Aggio 2024 [29].

Table 33 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				
N/A	N/A	N/A	N/A	N/A

11. Resource use and associated costs

All costs related to the treatment of patients with AA across all SALT health states with ritlecitinib and BSC were included in the model. To estimate the resource use and identify costs, input from clinical experts, the SmPC on ritlecitinib, data from the ALLEGRO 2b/3 trial, and assumptions were applied.

11.1 Medicines - intervention and comparator

The only medicine included in the model base case for the treatment group is ritlecitinib. The drug costs included in the model are based on the pharmacy purchase price (PPP) obtained in November 2024. The PPP of ritlecitinib is DKK 6,686.52 with a package size of 30 capsules.

Given that the model's cycle is 12 weeks (84 days) and one pack of ritlecitinib includes treatment for 30 days, the cost per cycle have been computed by first calculation the cost per capsule and thereafter multiplying the number of capsules needed per cycle.

In the first year of the model, drug costs for prednisolone and methotrexate are included for patients on BSC. Based on the doses and packaging sizes, this amounts to a combined cost per cycle of DKK 120 following the same calculation method as for ritlecitinib.

Table 34 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Litfulo (ritlecitinib)	50 mg	100 %	Once daily	Not relevant
Prednisolone (BSC)	3 x 5 mg	100%	once daily	Not relevant

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Methotrexate (BSC)	6 x 2.5 mg	100%	once weekly	Not relevant

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Ritlecitinib is administered orally, and patients can administer the medication at home. Therefore, no costs are associated with the administration of ritlecitinib.

Table 35 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A	N/A	N/A	N/A	N/A

11.4 Disease management costs

The resource use associated with disease management in the model is dependent on if patients receive treatment with ritlecitinib or BSC. The model assumes that resource use is health state independent.

Healthcare resource used by treatment arms in a Danish clinical practice was based on inputs from clinical experts (see section 14). According to the clinical experts, initiation of ritlecitinib treatment entails two ambulant hospital visits: one visit to evaluate eligibility and initiating the treatment, and one visit 4 weeks later, to evaluate the lab tests and adverse events. These visits would take place during the first treatment cycle only.

For patients in the BSC arm, treatment initiation would only entail one ambulant visit to the hospital during the first model cycle, when treatment would be discussed, and lab tests evaluated. As no treatment would be initiated, no second visit would be necessary.

Additionally, input from the clinical experts entailed that ritlecitinib treatment would be followed up with four lab tests annually: one connected with an ambulant hospital visit to see the specialist physician and three hospital visits to follow-up with a nurse. Laboratory tests in themselves are not included as costs, in line with DMC guidance [14] but are assumed to be included in the follow-up cost with the nurse or ambulant hospital visit. The clinicians only expected these four annual visits to be necessary for the first one or two years, and that visits would thereafter be once or twice per year. However, in order to be conservative, the model counts on 4 annual follow-up visits for the rest of the time on treatment.

According to the clinical experts, patients in the BSC treatment arm would not be followed up by a specialist, as BSC does not require specialist treatment. Instead, they would receive 2 annual visits to the general practitioner (GP).

Table 36 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Treatment assessment/initiation				
Ambulant hospital visit, BSC	Once in the first cycle	1,625.00	09MA98	DRG 2024 [56]
Ambulant hospital vists, ritlecitinib	Twice in the first cycle	1,625.00	09MA98	DRG 2024 [56]
Follow-up visits				
GP visit, BSC	2 times annually	160.72	No DRG	Gundydelse: 0101 Konsultation [57]
Ambulant control at hospital, ritlecitinib	1 time annually	1,625.00	09MA98	DRG 2024 [56]
Ambulant follow-up visits with nurse, ritlecitinib	3 times annually	231.00	No DRG	DMC [58]

The unit costs assigned to the resources utilized by patients were based on DRG codes, GP tariffs, and DMC valuation of unit costs. All ambulant visits at the hospital were assigned a unit cost of DKK 1,625.00 based on DRG code 09MA98 [56].This applies to the treatment assessment for both treatment arms as well as the annual monitoring visits for patients in the ritlecitinib arm. Monitoring visits performed by a GP for patients in the BSC arm were assigned a unit cost of DKK 160.72, based on the GP consultation fee [57].

Additional lab tests at a hospital for the ritlecitinib arm were assigned a unit costs of DKK 231.00 which is calculated by 1/2 of the hourly wage of DKK 462.00 for a nurse, as it is assumed that a lab test takes 30 minutes to perform by a nurse [58].

Total disease management costs per cycle were calculated, categorized by first and subsequent cycles, and divided by treatment arm. Resource use connected to the treatment assessment, was applicable for the first cycle in the model only. The number of ambulatory hospital visits was multiplied with the unit cost. These total treatment assessment costs were included as a one-time cost in the first cycle only.

The costs for each subsequent cycle were calculated by multiplying the monitoring frequencies with the relevant unit cost. These costs were added together and multiplied with a 'years per cycle' factor, converting the yearly costs to costs per cycle.

11.4.1 Costs associated with the use of wigs

Public funding of wigs was included as an added health care cost in the model. Patient's own expenses for wigs, or utilization of other hair-replacements were not included in the model, though they can be assumed to incur significant costs for patients [14]. In order to simplify the model, only wigs, and no other hair replacements, were considered.

Utilization of wigs was categorized based in SALT health states: Wig utilization for patients in health state SALT ≥50 was assumed to be 50%, in line with previous assumptions by the DMC [14]. Patients in SALT 11-20 and SALT ≤10 were not assumed to receive funding for wigs. Patients in SALT 21-49 were assumed to sometimes be entitled to public funding of wigs, i.e. 25% of patients were assumed to receive funding.

Patients can apply to their municipalities to have the cost of wig covered. However, the amount reimbursed varies between municipalities, and thus the regional subsidy for wigs was used instead. Annual reimbursement for a wig is assigned a unit cost of 4,170.00 DKK in accordance with sources from the Danish Cancer Society and Region North Jutland [59, 60].

11.5 Costs associated with management of adverse events

As the AEs included in the model were mainly mild, and none were serious, most could be handled by patients themselves. In order to be conservative however, all AEs, except for 'headache', were assumed to require the attention of a physician. Therefore, all AEs (except for headache) were assumed to generate one visit to a GP.

GP consultations unit cost of DKK 160.72 was applied in line with the Danish Medical Association costs [57]. Per cycle costs of an adverse event was calculated by multiplying the probability of the adverse event occurring per cycle with the respective resource use and the unit cost of a GP consultation.

Table 37 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Acne	GP consultations	DKK 160.72
Diarrhoea	GP consultations	DKK 160.72
Folliculitis	GP consultations	DKK 160.72
Headache*	N/A	N/A
Nasopharyngitis	GP consultations	DKK 160.72
Rash	GP consultations	DKK 160.72
Upper respiratory tract infection	GP consultations	DKK 160.72

	DRG code	Unit cost/DRG tariff
Urticaria	GP consultations	DKK 160.72

*Were assumed not to requre the attention of a physician.

11.6 Subsequent treatment costs

No subsequent treatment was included in the model for either treatment arm. If patients discontinued ritlecitinib, they would switch to BSC which does not include any active treatment.

Table 38 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A

11.7 Patient costs

In the model, patient-related time and costs were included for wig fittings, GP consultations, and hospital visits.

The patient-time associated with ritlecitinib treatment and BSC was based on the time spent on treatment-related activities and wig fitting and traveling to and from appointments.

For ambulant hospital appointment with a physician or nurse, patients spend 30 minutes on ambulant hospital visits and 60 minutes on transportation to and from the hospital [14]. Based on the input from a wig specialist (see section 14), wig fitting was assigned a time usage of 1,5 hours per wig (i.e. annually). The time for transportation to a wig specialist was assumed equal to time for transportation to a hospital, i.e. 60 minutes in total. For GP visits, it was assumed that patients spend 20 minutes on a GP consultation and 30 minutes on transportation to and from the GP.

In terms of transportation, a distance of 20 km to and from the hospital (40 km in total per visit) was assigned in accordance with the DMC valuation of unit cost [58]. The distance to a wig specialist was assumed equal to the distance to a hospital (40 km). A distance of 10 km to and from a GP (20 km in total per visit) was assumed as GPs are expected to be located closer to patients than hospitals.

A cost of DKK 188 per patient hour and 3.79 per kilometer was applied in accordance with DMC guidelines [21].

Total patient cost of time use was calculated. First, patient time use for each type of activity was multiplied with the average wage per hour to obtain the total patient time costs. Then, the distance to each type of facility in kilometers was multiplied with the

unit cost of transportation per kilometer, to obtain total transport costs. Finally, the patient time and transportation costs were added together.

Patient-related time for collection of Litfulo is not included in the model. It is assumed that patients receive their medication in connection with their doctor visit four times a year, as described in section 11.4.

Table 39 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Time spent at GP	0.3 hours
Transportation to GP	0.5 hours
Time spend at hospital	0.5 hours
Transportation to hospital	1.0 hour
Time spent at wig fitting	1.5 hours
Transportation to wig fitting	1 hour

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable, as no other cost is associated with and included in the model.

12. Results

The model results were driven by [redacted] These results were confirmed by the one-way sensitivity analysis (OWSA), which also showed that [redacted] were the main drivers of the ICER. The model results are consistent over the other probabilistic and deterministic sensitivity analyses and show that the model is generally robust.

Treatment with ritlecitinib for patients with severe AA generated an incremental cost of [redacted] gained at the current PPP. Ritlecitinib generated a total added cost per patient of [redacted] incremental QALYs.

In a scenario analysis, HSUVs were run using EQ-5D-5L values from ALLEGRO 2b/3. This scenario predictably generated a significantly higher ICER than the base case, since the main gain of treatment wasn't caught. The scenario resulted in an incremental cost of [redacted]

For all scenario analyses, please see section 12.2.3 .

12.1 Base case overview

Table 40 Base case overview

Feature	Description		
Comparator	BSC		
Type of model	Semi-Markov model		
Time horizon	Lifetime, i.e. until the potential age of 100 years.		
Treatment line	1st line. Subsequent treatment lines not included.		
Measurement and valuation of health effects	Health-related quality of life measured with a Time-Trade-off (TTO) [29] study for the UK population. UK population weights were used to estimate health-state utility values, as mapping to DK weights is not possible. EQ-5D-5L from ALLEGRO 2b/3 [31] are tested in a scenario analysis. Danish population weights were used to estimate health-state utility values.		
Costs included	Medicine costs Disease management costs Costs of adverse events Patient costs		
Dosage of medicine	Flat dosing		
Average time on treatment	Intervention: 70.48 months Comparator: Not relevant		
Parametric function for PFS	Not Relevant		
Parametric function for OS	Not Relevant		
Inclusion of waste	Not relevant		
Average time in model health state	Ritlecinib	Placebo	(months)
SALT ≥50	[redacted]	[redacted]	
SALT 21-49	[redacted]	[redacted]	
SALT 11-20	[redacted]	[redacted]	
SALT ≤10	[redacted]	[redacted]	
Death	[redacted]	[redacted]	

12.1.1 Base case results

In the base case, ritlecitinib generated an ICER of [redacted]. The incremental cost and incremental QALY per patient for ritlecitinib 50 mg compared to BSC was [redacted] respectively, over a lifelong time horizon. Table 41 presents an overview of the base case results.

Table 41 Base case results, discounted estimates

	Ritlecitinib 50 mg	BSC	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (SALT ≥50)	[redacted]	[redacted]	[redacted]
Life years gained (SALT 21-49)	[redacted]	[redacted]	[redacted]
Life years gained (SALT 11-20)	[redacted]	[redacted]	[redacted]
Life years gained (SALT ≤10)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs (SALT ≥50)	[redacted]	[redacted]	[redacted]
QALYs (SALT 21-49)	[redacted]	[redacted]	[redacted]

	Ritlecitinib 50 mg	BSC	Difference
QALYs (SALT 11-20)	[redacted]	[redacted]	[redacted]
QALYs (SALT ≤10)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

*Due to rounding.

12.2 Sensitivity analyses

Uncertainty in the input parameters in the model has been explored through deterministic sensitivity analyses (DSA) and a probabilistic sensitivity analysis (PSA).

12.2.1 Deterministic sensitivity analyses

A OWSA was used to assess the effect of parameter variation on the ICER. The OWSA was performed using a standard error approach. Where the standard error was not available for a parameter, the standard error was assumed to be 20% of the mean value. For resource healthcare resource utilization, variation in parameters were informed by clinical experts. Based on its mean and the standard error, the parameter was then varied using a 95% confidence interval based on the distribution of the parameter.

The results of the model were then evaluated using the upper and lower bounds for each parameter, fixing all other parameters' values, and recording the overall NMB value. This measures which variables have the largest impact on the overall cost-effectiveness analysis results and provides justification for estimates of the model's robustness to parameter variation. The results of the one-way sensitivity analysis for the 10 parameters with the largest impact on the ICER are presented in Table 42.

Table 42 One-way sensitivity analyses results, ritlecitinib 50 mg versus BSC

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/ QALY)
Base case	-	-	[redacted]	[redacted]	[redacted]
SALT ≥ 50 utility	2.5th percentile	See table note	[redacted]	[redacted]	[redacted]
	97.5th percentile	See table note	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/ QALY)
Ritlecitinib cost	80% of the cost	See table note	[redacted]	[redacted]	[redacted]
	120% of the cost	See table note	[redacted]	[redacted]	[redacted]
SALT ≤ 10 utility	2.5th percentile	See table note	[redacted]	[redacted]	[redacted]
	97.5th percentile	See table note	[redacted]	[redacted]	[redacted]
Spontaneous remission probability	Probability of [redacted]%	See table note	[redacted]	[redacted]	[redacted]
	Probability of [redacted]%	See table note	[redacted]	[redacted]	[redacted]
SALT 11-20 utility	2.5th percentile	See table note	[redacted]	[redacted]	[redacted]
	97.5th percentile	See table note	[redacted]	[redacted]	[redacted]
Follow-up visit (per 52 weeks)	1 visit	See table note	[redacted]	[redacted]	[redacted]
	2 visits	See table note	[redacted]	[redacted]	[redacted]
SALT 21-49 utility	2.5th percentile	See table note	[redacted]	[redacted]	[redacted]
	97.5th percentile	See table note	[redacted]	[redacted]	[redacted]
Cost of ambulant control at hospital	80% of the cost	See table note	[redacted]	[redacted]	[redacted]
	120% of the cost	See table note	[redacted]	[redacted]	[redacted]
Cost of wig reimbursement (per year)	80% of the cost	See table note	[redacted]	[redacted]	[redacted]
	120% of the cost	See table note	[redacted]	[redacted]	[redacted]
Cost of ambulant follow-up visit, nurse (per 52 weeks)	80% of the cost	See table note	[redacted]	[redacted]	[redacted]
	120% of the cost	See table note	[redacted]	[redacted]	[redacted]

SALT, Severity of Alopecia Tool; ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.

*To assess the impact of reducing/increasing the value of this parameter. SALT = Severity af Alopecia Tool.

The results were most sensitive to changes to the [redacted] Figure 14 illustrates the tornado diagram containing the results of the DSA.

Figure 14 One-way sensitivity analysis results for ritlecitinib 50 mg versus BSC

12.2.2 Probabilistic sensitivity analyses

A PSA was used to assess the effect of parameter uncertainty on the ICER. The PSA works by drawing a value for each parameter from their assumed probability distributions 1,000 times and evaluating the ICER obtained with each iteration. Where the standard errors for the parameters are unknown, they are assumed to be 20% of the parameter value for the purposes of defining the distributions for each parameter. In the interim plus final stopping rule modeling scenarios, counts of stable or improving SALT score patients are used at the interim stopping point. Final stopping rule patient counts are based on conditional counts given interim stable or improving SALT scores. Interim stopping rules use a beta distribution in probabilistic analyses, whereas the final stopping rule SALT score distribution is modeled via Dirichlet distributions. When there are 0 patients in a SALT category, a prior probability distribution informed by [61] that provides minimal information is used.

The cost-effectiveness acceptability curves (CEAC) in Figure 15, illustrates the cost-effectiveness probability at different willingness-to-pay thresholds, and Figure 16 presents the scatter plot from the PSA. As seen, all the simulated ICERs from the PSA are located in the north-east quadrant, where ritlecitinib is more effective and more costly compared to BSC.

Figure 17 presents a convergence plot of the estimated ICER mean as a function of the number of PSA simulations, and the impact of the PPP of ritlecitinib on the estimated ICER value can be found in Figure 18.

Figure 15 Cost-effectiveness acceptability curves

Figure 16 Scatter plot from PSA

Figure 17 Convergence plot for the estimated mean

Figure 18 Impact of PPP of ritlecitinib on the estimated ICER

12.2.3 Scenario analyses

The results of the sensitivity analyses for ritlecitinib are presented in Table 43. The table shows that most sensitivity analyses result in ICERs similar to the base case.

Predictably, the scenarios with a major impact on the ICER were those where the utility weights were varied, i.e. changing the source of the utility weights or where a waning effect was introduced on utilities.

Using trial EQ-5D-5L utility weights instead of the utilities from the TTO had the largest effect. As there was only a marginal difference between health states when using trial EQ-5D, the treatment gain was not captured by this scenario, causing a very high ICER.

Using utility weights from the study by Vañó-Galvan has a similar, though lesser effect. This can be explained by that though the study does not have the specific challenges with patient inclusion of the ALLEGRO study, it uses EQ-5D utility weights, the issues of which has been discussed in detail in section 10.1.3 and 10.3. The utility weights are thus marred by the shortcomings of generic HRQoL instruments, also noted by a recent Danish study by Clemmensen et al. [2].Furthermore, it's worth noting that the study does not use SALT scores, which introduces additional uncertainty to the utility scores.

Table 43 Results of scenario analyses

Scenario name	Variation	Incremental cost (DKK)	Incremental QALYs	ICER (DKK/QALY)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

13. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending ritlecitinib as standard treatment for patients with severe alopecia areata (SALT ≥50). The budget impact was estimated per year in the first 5 years after the recommendation of ritlecitinib. The budget impact analysis compares the expenditures in the scenario, where ritlecitinib is recommended as a possible standard treatment and the scenario, where ritlecitinib is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

The patient numbers in the budget impact model were agreed with DMC. It is estimated that there are currently around [redacted] patients with severe AA who are candidates to ritlecitinib treatment. In addition, it is expected that [redacted] new patients with severe AA each year will be candidates for ritlecitinib. In the scenario where ritlecitinib is recommended as standard treatment of people with severe AA, Pfizer expects a [redacted] uptake of candidates due to no other recommended alternatives. In the scenario where ritlecitinib is not recommended, a patient uptake of [redacted] was expected. The number of new patients expected to be treated over the next five years adjusted for market shares are presented in Table 44.

Table 44 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Ritlecitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

An overview of the results of the budget impact analysis is presented in Table 45. Based on the settings applied in the base case and the PPP on ritlecitinib, the budget impact was estimated to [redacted] in year 5 of the budget impact analysis.

Table 45 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Ritlecitinib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ritlecitinib is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

[redacted] Hud og kønssygdomme, Århus Universitetshospital

[redacted] Hudklinikken i Rødovre.

Toftild, wig specialist. Frederiksberg Allé 50, Frederiksberg.

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Appendix A. Main characteristics of studies included

Table 46 Main characteristic of studies included

Trial name: Allegro phase 2b/3	NCT number: NCT03732807
Objective	The objective of this study is to investigate the efficacy and safety of ritlecitinib, an oral, selective dual JAK3/TEC family kinase inhibitor, in patients with alopecia areata.
Publications – title, author, journal, year	Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomized double-blind, multicenter, phase 2b-3 trial Brett King, Xingqi Zhang et. al., The Lancet Volume 401, ISSUE 10387; https://doi.org/10.1016/S0140-6736(23)00222-2, published online 13th April 2023 [4].
Study type and design	Double blinded, randomized, placebo-controlled, multicenter, phase 2b/3 dose-ranging study
Sample size (n)	N=718. Patients were divided between the following treatment arms: • Ritlecitinib 200/50: 200 mg (loading dose; 4 weeks), followed by 50 mg maintenance dose (20 weeks) (n=132) • Ritlecitinib 200/30: ritlecitinib 200 mg (loading dose; 4 weeks), followed by 30 mg (maintenance dose; 20 weeks) (n=130) • **Ritlecitinib 50 mg (licensed dose) (n=130)** • Ritlecitinib 30 mg (n=132) • Ritlecitinib 10 mg (n=63) 50mg ritlecitinib: n=130, **Placebo (n=131).** At week 24, patients who were randomized to receive placebo were re-randomized to receive either 200 mg/50 mg (n=65) or 50 mg (n=66) ritlecitinib.
Main inclusion criteria	1. Male or Female, aged ≥ 12 years a. <18 years if permitted by the sponsor, local competent au<18 years if permitted by the sponsor, local competent authority, and Institutional Review Board/Independent Ethics Committee b. Within EU countries: aged 18-74 years (inclusive) 2. Meet reproductive criteria, including relevant contraceptive methods a. Non-pregnant or breastfeeding females using relevant contraceptive methods for women of childbearing potential during the intervention period and for at least 28 days after the last dose of study intervention

Trial name: Allegro phase 2b/3	NCT number: NCT03732807
	b. Male within Voluntary Harmonization Procedure (VHP) countries in the EMA, were required to use contraception during the intervention period and for at least 90 days after the last dose of study intervention 3. Meet the following AA criteria: a. Clinical diagnosis of AA with no other etiology of hair loss b. ≥50% hair loss of the scalp, including AT and AU without evidence of terminal hair regrowth within 6 months at both Screening and baseline visits. Current episode of hair loss ≤ 10 years.
Main exclusion criteria	1. Other types of alopecia, scalp disease, active systemic disease, that could impact AA assessment. 2. Any psychiatric condition, including recent or active suicidal ideation or behavior that meets any of the listed protocol criteria (including clinically significant depression indicated as a Patient Health Questionnaire-8 (PHQ-8) total score ≥ 15. 3. Auditory conditions considering acute, fluctuating, or progressive. 4. Known immunodeficiency disorder, including positive serology for HIV at screening or first-degree relative with hereditary immunodeficiency. 5. Present/past malignancies, except for adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ 6. Past/present lymphoproliferative disorder, lymphoma, leukemia 7. History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or recurrent (more than one episode of) localized, dermatomal herpes zoster. 8. Current/recent history of clinically significant severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, psychiatric, immunologic/rheumatologic, or neurologic disease 9. Age 12 to < 18 years without a documented history of varicella zoster virus vaccination or presence of varicella zoster virus immunoglobulin G antibodies 10. History of systemic infection requiring hospitalization, active acute or chronic infection requiring treatment within 4 weeks prior to baseline, or infection with hepatitis B or C virus according to protocol-specific testing algorithm. 11. Received any of the treatment regimens in the specified time frames a. At any time: previous use of any JAK inhibitor in any disease indication or any non-B-cell selective lymphocyte-depleting agent (e.g., alefacept, alemtuzumab)* b. Within 6 months of first dose of study drug or five half-lives (if known), or until lymphocyte count returns to normal, whichever is longer: any B-cell-depleting agents, including but not limited to rituximab

Trial name: Allegro phase 2b/3	NCT number: NCT03732807
	c. Within 12 weeks of first dose of study drug or five half-lives (if known), whichever is longer: other immunomodulatory biologic agents d. Within 8 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer: other systemic treatments that could affect AA e. Within 4 weeks of first dose of study drug: Ultraviolet B (UVB) phototherapy, Psoralen Ultraviolet A (PUVA) therapy, contact immunotherapy or topical irritants (e.g., anthralin) f. Within 2 weeks of first dose of study drug: topical treatments on areas under assessment, that could affect AA (e.g., steroid cream, medicated shampoo, minoxidil).
Intervention	Ritlecitinib mg once daily, divided into the following arms: • Ritlecitinib, 10 mg for 24 weeks, n = 62 • Ritlecitinib, 30 mg for 24 weeks, n = 132 • **Ritlecitinib, 50 mg for 24 weeks, n = 130** • Ritlecitinib, 200 mg for 4 weeks, then 30 mg for 20 weeks, n = 129 Ritlecitinib, 200 mg for 4 weeks, then 50 mg for 20 weeks, n = 131
Comparator(s)	Placebo for 24 weeks, n = 131
Follow-up time	Median duration of treatment at 48 weeks: 332.0 (19, 353) days for all ritlecitinib treatment groups.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint:** Response based on absolute SALT score of 20 or less (20% scalp hair loss or less) at week 24 from baseline. **Key secondary endpoints:** Response based on absolute SALT score of 10 or less (10% scalp hair loss or less) at week 24 from baseline. PGI-C response defined as a score of “moderately improved” or “greatly improved” at Week 24 from baseline. **Secondary endpoints:** Proportion with response based on SALT score ≤20 through Week 48 Proportion with response based on SALT score ≤10 through Week 48 Proportion with PGI-C response through Week 48

Trial name: Allegro phase 2b/3	NCT number: NCT03732807
	≥2-grade improvement or normal scores in eyelashes and eyebrows through Week 48 Change from baseline in AAPPO scales through Week 48. Change from baseline in the depression subscale score of the HADS through week 48. Change from baseline in the anxiety subscale score of the HADS through week 48. Improvement on HADS among participants with a baseline subscale score indicative of depression who achieved a "normal" subscale score indicative of an absence of depression through week 48. Improvement on HADS among participants with a baseline subscale score indicative of anxiety who achieved a "normal" subscale score indicative of an absence of anxiety through week 48. **Exploratory:** Change from baseline in EQ-5D-5L in adults and EQ-5D-5Y in adolescents at week 4,12,24, and 48 Exploratory: Change from baseline in SF36 in adults at week 4,12,24, and 48
Method of analysis	The analysis population for efficacy data was the FAS defined as all randomized subjects, regardless of whether they received study medication (N=718). In comparison to placebo, the data from the 2 placebo groups up to Week 24 were pooled to form the placebo group. The Miettinen and Nurminen method was used for calculation of 95% CIs and the Farrington-Manning method was used for the calculation of p values. The study was tested at an overall α=0.05. Missing data due to COVID-19-related reasons were excluded from the analysis, whereas patients with missing data due to other reasons were considered as non-responders. Dose-response analysis was done by use of a Bayesian three-parameter maximum drug effect (Emax) model. The safety analysis set (SAS) included all participants who received at least 1 dose of study medication (N=715).
Subgroup analyses	No predefined subgroups
Other relevant information	In the model, only patients receiving ritlecitinib 50mg and placebo to 50 mg ritlecitinib has been included. The entire study included the randomization of 718 patients to different treatment arms.

Table 47 Study Details

Trial name: Allegro-LT	NCT number: NCT04006457
Objective	The primary objective of ALLEGRO-LT is to evaluate the long-term safety and tolerability of ritlecitinib in adults and adolescents with AA up to Month 36. The secondary objective is to assess the long-term safety of ritlecitinib in adults and adolescents with AA for up to 60 months.
Publications – title, author, journal, year	A Phase 3 Open-Label, Multi-Center, Long-Term Study Investigating the Safety and Efficacy Of Pf-06651600 In Adult And Adolescent Participants With Alopecia Areata (NCT04006457). Piliang M., Soung J. King B., et al. *Efficacy and safety of the oral JAK3/TEC family kinase inhibitor ritlecitinib over 24 months: integrated analysis of the ALLEGRO phase 2b/3 and long-term phase 3 clinical studies in alopecia areata.* Br J Dermatol. 2024 [24].
Study type and design	ALLEGRO-LT is an ongoing, phase 3, open-label study investigating the long-term safety and efficacy of ritlecitinib in Alopecia Areata. ALLEGRO-LT is comprised of two cohorts: 1. Roll-over participants from ALLEGRO 2a and ALLEGRO 2b/3 2. De novo participants with ≥25% scalp hair loss who had not received treatment in either study.
Sample size (n)	*N=1051*
Main inclusion criteria	Patients ≥ 12 years Diagnosis of AA with ≥ 25% scalp hair loss due to AA, including AT or AU* No evidence of terminal hair regrowth within 6 months at both screening and baseline visits Maximum duration of current episode of hair loss ≤ 10 years For de novo participants: Clinical diagnosis of alopecia areata (AA) with no other cause of hair loss. Androgenetic alopecia coexistent with AA is allowed. De novo participants >=12 to <18 years of age: >=50% terminal hair loss of the scalp due to AA, including AT and AU De novo participants >=18 years of age: >=25% terminal hair loss of the scalp due to AA, including AT and AU No evidence of terminal scalp hair regrowth within 6 months (de novo only) Current episode of terminal scalp hair loss <=10 years

Trial name: Allegro-LT	NCT number: NCT04006457
Main exclusion criteria	Exclusion criteria for all participants: Participants who have previously taken Janus kinase (JAK) inhibitors other than PF-06651600 must have received the last dose >12 weeks prior to the screening visit Hearing loss with progression over previous 5 years, or sudden hearing loss, or middle or inner ear disease, or other auditory condition that is considered acute, fluctuating or progressive. History of or current malignancies with the exception of adequately treated or excised non metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ. History of a single episode of disseminated herpes zoster or disseminated herpes simplex, or a history of more than one episode of localized, dermatomal herpes zoster. g. Infection requiring hospitalization, or parenteral antimicrobial therapy within 6 months prior to Day 1.
Intervention	Daily ritlecitinib 50-mg with a 4-week 200-mg loading dose (200/50-mg) Daily ritlecitinib 50-mg with no loading dose (50-mg)
Comparator(s)	Not applicable, no comparator in the extension study.
Follow-up time	36 months (by the protocol). Protocol amendment: primary safety endpoints planned at month 36. Planned safety follow-up 60 months. Median follow up time (ritlecitinib treatment) is unknown, as the study is ongoing.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoints** Number of subjects reporting treatment-emergent adverse events from baseline through Month 36 Number of subjects reporting serious adverse events from baseline through Month 36 Number of subjects reporting adverse events leading to discontinuation from baseline through Month 36 Number of subjects with clinically significant abnormalities in vital signs from baseline through Month 36 Number of subjects with clinically significant abnormalities in clinical laboratory values from baseline through Month 36

Trial name: Allegro-LT	NCT number: NCT04006457

Vaccine sub-study: Percentage of subjects with a tetanus booster response at month 1

Secondary endpoints

Percentage of subjects with an absolute Severity of Alopecia Tool (SALT) Score <=10 [Time Frame: Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, and 36]

Percentage of subjects with an absolute SALT Score <=20 [Time Frame: Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, and 36]

Change from baseline in SALT score [Time Frame: Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, and 36]

Percentage of subjects with a 75% improvement in SALT score from baseline [Time Frame: Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 28, 32, and 36]

Percentage of subjects with at least a 2 grade improvement or a score of 3 in Eyebrow Assessment (EBA) score [Time Frame: Months 1, 3, 6, 12, 18, 24, and 36]

Percentage of subjects with at least a 2 grade improvement or a score of 3 in Eyelash Assessment (ELA) score [Time Frame: Months 1, 3, 6, 12, 18, 24, and 36]

Patient's Global Impression of Change (PGI-C) response, defined as PGI-C score of "moderately improved" or "greatly improved" [Time Frame: Months 1, 3, 6, 9, 12, 18, 24, and 36]

Change from baseline in Alopecia Areata Patient Priority Outcomes (AAPPO) domains [Time Frame: Months 1, 3, 6, 9, 12, 18, 24, and 36]

Change from baseline in the depression subscale score of the Hospital Anxiety and Depression Scale (HADS) [Time Frame: Months 1, 3, 6, 9, 12, 18, 24, and 36]

Change from baseline in the anxiety subscale score of the HADS [Time Frame: Months 1, 3, 6, 9, 12, 18, 24, and 36]

Improvement on HADS among participants with a baseline subscale score indicative of depression who achieved a "normal" subscale score indicative of an absence of depression [Time Frame: Months 1, 3, 6, 9, 12, 18, 24, and 36]

Improvement on the HADS among participants with a baseline subscale score indicative of anxiety who achieved a "normal" subscale score indicative of an absence of anxiety [Time Frame: Months 1, 3, 6, 9, 12, 18, 24, and 36]

Number of subjects reporting treatment-emergent adverse events [Time Frame: Month 37 through Month 60]

Number of subjects reporting serious adverse events [Time Frame: Month 37 through Month 60]

Trial name: Allegro-LT	NCT number: NCT04006457

	Number of subjects reporting adverse events leading to discontinuation [Time Frame: Month 37 through Month 60]
	
	Number of subjects with clinically significant abnormalities in vital signs [Time Frame: Month 37 through Month 60]
	
	Number of subjects with clinically significant abnormalities in clinical laboratory values [Time Frame: Month 37 through Month 60]
	
	Vaccine sub-study:
	
	- Percentage of subjects with:
	  - a meningococcal serogroup C response
	  - anti-tetanus antibody level ≥1.0 IU/mL
	  - anti-tetanus antibody level ≥0.1 IU/mL
	
	≥4x increase in anti-tetanus antibody level from baseline
	
	Fold increase in anti-tetanus levels above baseline values
	
	Geometric mean concentrations (GMCs) of anti-tetanus antibody levels
	
	Percentage of subjects with ≥1:4 hSBA (in subjects with undetectable pre-vaccination assay titers) for meningococcal serogroup C
	
	- Geometric mean titers (GMTs) of antibodies for meningococcal serogroup C
	- Number of subjects reporting serious adverse events
	- Number of subjects reporting adverse events
	- Number of subjects reporting adverse events leading to discontinuation

Method of analysis	The primary endpoints of incidence of TEAEs, SAEs, and AEs leading to discontinuation, clinically significant abnormalities in vital signs, and clinically significant abnormalities in laboratory values will be summarized using descriptive measures such as numbers and percentages. The safety summaries will be reported for all participants, as well as by de-novo participants (i.e., those who did not receive study intervention in Allegro studies) and participants originating from the Allegro study program. No formal statistical hypotheses will be tested. Secondary endpoints: Efficacy analyses are descriptive in nature (such as number and percent, mean, standard deviation) at each visit where measured; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported. Displays by de-novo participants (I.e., those who did not receive study intervention in the Allegro studies) and participants originating from the Allegro study program will also be included.
Subgroup analyses	No predefined subgroups

Trial name: Allegro-LT	NCT number: NCT04006457
Other relevant information	As the study is still ongoing, currently, only the interim analysis of the is available.

Appendix B. Efficacy results per study

Results per study

The following table highlights the results on the relevant effect-measures of the study.

Results are for primary and key secondary efficacy endpoints across treatment groups for the overall clinical study, for the FDA and the EMA, based on the respective planned analysis and significance levels (full analysis set). All p values presented in this table are nominal.

For primary and key secondary endpoints HR with CI and p-values are included. All other endpoints are reported as difference vs placebo only. Results compared to placebo until week 24, no placebo arm from week 24 up to week 48.

Results per study: ALLEGRO 2B/3

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Referenc es
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SALT ≤20 at week 24	Ritlecitinib 50 mg	124	23.39 % (15.94 to 30.84)	21.85%	14.65-30.23	<0.0001	[redacted]	[redacted]	[redacted]	Primary endpoint for overall clinical study (α=0.05) and for the FDA (α=0.00125). Miettinen and Nurimen method was used to calculate 95% CIs and Farrington-Manning	[4] NCT0373 2807

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	130	1.54 % (0.00 to 3.65)							method was used to calculate P-values for testing difference in the proportion of response between active treatment group and placebo. Data missing due to Covid-19 were excluded from this analysis, whereas patients with missing data due to other reasons were included in the analysis as non-responders.	
SALT ≤10 at week 24	Ritlecitinib 50 mg	124	13.71 % (7.66 to 19.76)	12.17 %	6.27-19.53	0.0002	[redacted]	[redacted]	[redacted]	Miettinen and Nurminen method was used to calculate 95% CIs and Farrington-Manning method was used to calculate P-values for testing difference in the proportion of response between active treatment group and placebo. Data missing due to Covid-19 were excluded from this analysis, whereas patients with missing data due to other reasons were included in the analysis as non-responders. Key secondary endpoint for the overall clinical study (α=0.05).	[4] NCT03732807
	Placebo	130	1.54 % (0.00 to 3.65)								

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PGI-C at week 24	Ritlecitinib 50 mg	125	49.17% (40.84 to 58.36)	39.96 %	28.85 - 51.06	<0.0001	[redacted]	[redacted]	[redacted]	PGI-C response was defined as a PGI-C score of moderately improved or greatly improved. Key secondary endpoint for the EMA (α=0.01). Cases with missing data at Week 24 due to reasons unrelated to COVID-19 are considered as non-response. Cases with missing data at Week 24 due to COVID-related reasons are excluded. Confidence Interval is calculated based on normal approximation.	[4]
	Placebo	130	9.23% (4.25 to 14.21)								
EBA at week 24	Ritlecitinib 50 mg	100	29.00 % (20.11 - 37.89)	24.33 %	14.82 - 34.48	0.000002	N/A	N/A	N/A	Confidence Interval is calculated based on normal approximation. Cases with missing data at that timepoint due to COVID-related reasons are excluded. Cases with missing data at that timepoint due to the reasons unrelated to COVID-19 are considered as non-response. Confidence Interval and p-value are	
	Placebo	107	4,67 % (0.67 - 8.67)								

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										calculated using Miettinen and Nurminen (MN) method.	
ELA at week 24	Ritlecitinib 50 mg	90	28.89 %	23.73 %	13.61 - 34.50	0.000013	N/A	N/A	N/A	Confidence Interval is calculated based on normal approximation. Cases with missing data at that timepoint due to COVID-related reasons are excluded. Cases with missing data at that timepoint due to the reasons unrelated to COVID-19 are considered as non-response. Confidence Interval and p-value are calculated using Miettinen and Nurminen (MN) method.	
	Placebo	97	5.15 %								
SALT ≤20 at week 48	Ritlecitinib 50 mg	125	43.20 % (34.52-51.88)	N/A	N/A	N/A	N/A	N/A	N/A	FAS, Confidence Interval is calculated based on normal approximation. Cases with missing data at that timepoint due to COVID-related reasons are excluded Cases with missing data at that timepoint due to reasons unrelated to COVID-19 are considered as non-response.	

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										95% confidence intervals are shown as percentage.	
SALT ≤10 at week 48	Ritlecitinib 50 mg	125	31.2% (23.08 - 39.32)	N/A	N/A	N/A	N/A	N/A		FAS, Confidence Interval is calculated based on normal approximation. Cases with missing data at that timepoint due to COVID-related reasons are excluded Cases with missing data at that timepoint due to reasons unrelated to COVID-19 are considered as non-response. 95% confidence intervals are shown as percentage.	
PGI-C at week 48	Ritlecitnib 50 mg	125	56.0% (47.30 - 64.70)	N/A	N/A	N/A	N/A	N/A	N/A	FAS, Confidence Interval is calculated based on normal approximation. Cases with missing data at that timepoint due to COVID-related reasons are excluded	

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										Cases with missing data at that timepoint due to reasons unrelated to COVID-19 are considered as non-response. 95% confidence intervals are shown as percentage.	
EBA response at week 48	Ritlecitinib 50mg	101	43.56% (33.89 - 53.23)	N/A	N/A	N/A	N/A	N/A	N/A	FAS	
ELA response at week 48	Ritlecitinib 50mg	90	40.00% (29.88 - 50.12)	N/A	N/A	N/A	N/A	N/A	N/A	FAS	
AAPPO, LSM of change from baseline											
	Ritlecitinib 50 mg	119	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	FAS, Mixed-effect model with repeated measures includes the fixed effects for	

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Emotional symptoms at week 24	Placebo	125	[redacted]				N/A	N/A	N/A	treatment group, baseline value, visit, treatment by visit interaction. Baseline is defined as the latest non-missing value from the pre-treatment period. Emotional Symptoms: Mean of Items 5, 6, 7, 8 on the AAPPO. Activity Limitations: Mean of Items 9, 10, 11 on the AAPPO. Missing rule: requires at least 2 non-missing responses; otherwise missing. Unstructured covariance matrix was used for model errors.	
Activity limitations at week 24	Ritlecitinib 50 mg	119	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	FAS, FAS, Mixed-effect model with repeated measures includes the fixed effects for treatment group, baseline value, visit, treatment by visit interaction. Baseline is defined as the latest non-missing value from the pre-treatment period.	
	Placebo	125	[redacted]								

Results of ALLEGRO 2b/3 (NCT03732807)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N1	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										Emotional Symptoms: Mean of Items 5, 6, 7, 8 on the AAPPO. Activity Limitations: Mean of Items 9, 10, 11 on the AAPPO. Missing rule: requires at least 2 non-missing responses; otherwise missing. Unstructured covariance matrix was used for model errors	

N/A = **N/A**; FAS = Full analysis set.; LOCF = Last observation carried forward. N=130 for Ritlecitinib 50 mg arm. N=131 for Placebo arm. Full analysis set, excludes missing data due to COVID-19. Missing data due to reasons unrelated to COVID-19 are considered as non-response. The share of patients with response are based on the number of participants with valid data at Week 24/48 (N1) (non-response for missing due to reasons unrelated to COVID-19; excludes missing due to COVID-19).

Table 48. Results per study: ALLEGRO-LT

Results of ALLEGRO-LT interim analysis up to month 24. (NCT04006457)*											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		

SALT score ≤20 Month 12 Month 24	Ritlecitinib 50 mg	191	 40.3 % 46.1%	N/A	N/A	N/A	N/A	N/A	N/A	LOCF
SALT score ≤10 Month 12 Month 24	Ritlecitinib 50 mg	191	 30.9% 37.7%	N/A	N/A	N/A	N/A	N/A	N/A	LOCF
EBA response Month 12 Month 24	Ritlecitinib 50 mg	154	 44.8% 46.8%	N/A	N/A	N/A	N/A	N/A	N/A	LOCF
ELA response Month 12 Month 24	Ritlecitinib 50 mg	139	 43.2% 43.2%	N/A	N/A	N/A	N/A	N/A	N/A	LOCF
PGI-C response Month 12 Month 24	Ritlecitinib 50 mg	189	 57.7% 56.6%	N/A	N/A	N/A	N/A	N/A	N/A	LOCF

*Ritlecitinib 50mg, rollover patients from Allegro 2b/3. N/A = Not Applicable, FAS = Full analysis set.; LOCF = Last observation carried forward.

Appendix C. Comparative analysis of efficacy

Not relevant, as the analysis is built on a head-to-head study.

Table 49 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

D.1 Extrapolation of discontinuations

D.1.1 Data input

Please note, that as discontinuations can only occur in the active treatment arm, the BSC arm is not included in this section.

Despite treatment response, some patients may choose to discontinue from treatment for any reason other than lack of treatment response.

In order to assess the number of patients discontinuing treatment for other reasons than a lack of response, patients treated with ritlecitinib during week 48 to 96 was used to inform time on treatment. In line with the calculation of long term transitions, all patients who received ritlecitinib 50 mg in the ALLEGRO-LT trial were considered in this step.

Those who stopped treatment due to a lack of response, are assumed to be captured by the stopping rules, thus only patients who had a SALT score of ⩽20 at Week 48 were included in the analysis of patients discontinuing due to other reasons, ensuring that patients were not double counted.

D.1.2 Model

To extrapolate the KM for discontinuations to a lifetime horizon for the model, the standard parametric survival models were curve fit to the individual patient data from the ALLEGRO 2b/3 study in accordance with the best practices from NICE Technical Support Document 14 for survival analysis alongside clinical trials [62]. Parameters and model fit statistics were calculated for each curve type. For the full explanation, please see the Technical Report.

D.1.3 Proportional hazards

Not relevant.

D.1.4 Evaluation of statistical fit (AIC and BIC)

After the Generalized Gamma, the best fit was the Exponential curve.

Table 50 AIC and BIC statistics for parametric distributions fit to ALLEGRO-LT discontinuation

Distribution	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

Lognormal	[redacted]	[redacted]
Generalized Gamma	[redacted]	[redacted]

D.1.5 Evaluation of visual fit

By visual inspection the Generalized Gamma curve did not fit the data, indicating a lack of convergence.

Figure 19 The fit of parametric distributions to ALLERGO-LT discontinuations

D.1.6 Evaluation of hazard functions

Not relevant.

D.1.7 Validation and discussion of extrapolated curves

By visual inspection the Generalized Gamma curve did not fit the data, indicating a lack of convergence. The most appropriate curve for data extrapolation was selected based on the goodness of fit for each parametric survival function based on statistical analyses of AIC and BIC and the log cumulative hazard plots.

D.1.8 Adjustment for background mortality

AA is assumed to not affect mortality. Thus, transitions to the Death health state are purely modeled via gender-specific annual death rates from life tables of the general Danish population [63]. A weighted average probability of death per model cycle is computed from the population characteristics from the baseline characteristics table. As no patients died during the ALLEGRO 2b/3 trial, a user option exists to disable death in the first 48 weeks so that the model results match the observed values in the clinical trial.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of [effect measure 2]

Not applicable.

Appendix E. Serious adverse events

This integrated safety analysis included data pooled from four studies: three randomized, placebo-controlled studies, and an ongoing long-term, open-label, phase 3 study of ritlecitinib in AA from the ALLEGRO clinical development program: ALLEGRO phase 2a proof-of-concept study (NCT02974868), ALLEGRO phase 2a safety study (NCT04517864), pivotal ALLEGRO phase 2b/3 study (NCT03732807), and long-term, open-label, phase 3 study (ALLEGRO-LT; NCT04006457; ongoing). ALLEGRO-LT enrolled patients into two arms: (1) rollover patients who had received treatment in the ALLEGRO phase 2a proof-of-concept or phase 2b/3 study and (2) de novo patients who had not received treatment in either study.

The all-exposure pool included all patients who received at least one dose of ritlecitinib in the ALLEGRO-2a, ALLEGRO- 2a safety, ALLEGRO-2b/3, or ALLEGRO-LT study. This pool included two cohorts based on ritlecitinib dose: an "any ritlecitinib" group comprising patients who received any dose of ritlecitinib and a "ritlecitinib 50-mg" group, including just the patients who received ritlecitinib 50 mg QD with or without an initial 200-mg QD loading dose in any of the four studies.

Safety data in table 45 is a summary of treatment-emergent adverse events (all causalities) in the all-exposure pool receiving any ritlecitinib dose [23].

In the recently accepted publication, an interim analysis was conducted, including efficacy and safety of ritlecitinib 50mg (with or without loading dose of 200mg) for 24 months [24]. No new safety signals were observed, and the safety results were in line with the comprehensive integrated pooled analysis of the Allegro studies [23] presented in Table 51.

Table 51 Summary of treatment-emergent adverse events (all causalities) in the all-exposure pool.

Preferred Terms	Number (%) of patients	IR (95% CI)
General information AEs		
Patients evaluable for AEs	1294	
AEs	5234	
Patients with AEs	1094 (84.5)	179.76 (169.33, 190.65)
Patients with SAEs	57 (4.4)	2.64 (2.01, 3.40)
Patients with severe AEs	83 (6.4)	3.91 (3.13, 4.83)
Deaths	2 (0.2)	0.09 (0.01, 0.31)
Patients discontinued from study or study drug due to AEs	78 (6.0)	3.59 (2.84, 4.45)
Patients with temporary discontinuation due to AEs	284 (21.9)	15.10 (13.42, 16.95)

AEs occurring in ≥5% of patients in any patient		
Headache	229 (17.7)	11.90 (10.43, 13.53)
Sars-CoV-2 positive test	201 (15.5)	9.75 (8.47, 11.18)
Nasopharyngitis	160 (12.4)	8.17 (6.97, 9.51)
Acne	135 (10.4)	6.75 (5.68, 7.97)
Upper respiratory tract infection	132 (10.2)	6.48 (5.44, 7.66)
Pyrexia	98 (7.6)	4.64 (3.79,5.64)
Cough	96 (7.4)	4.54 (3.70,5.53)
Fatigue	91 (7.0)	4.33 (3.51, 5.30)
Urticaria	88 (6.8)	4.25 (3.43, 5.22)
AEs of special interest		
Serious infections	14 (1.1)	0.64 (0.36, 1.06)
Opportunistic infections	1 (<0.1)	0.05 (0.00, 0.23)
Herpes zoster	20 (1.5)	0.92 (0.57, 1.40)
Herpes simplex	37 (2.9)	1.72 (1.22, 2.35)
Malignancies (excluding NMSC)	7 (0.5)	0.32 (0.14, 0.64)
Non-Melanoma Skin Cancer (NMSC)	3 (0.2)	0.14 (0.03, 0.38)
Breast cancer	4 (0.5)	0.35 (0.10, 0.85)
Major Adverse Cardiovascular Event (MACE)	3 (0.2)	0.14 (0.03, 0.38)
Thromboembolic event	1 (<0.1)	0.05 (0.00, 0.23)
Peripheral neuropathy	4 (0.3)	0.18 (0.05, 0.45)
Paresthesia and dysesthesia	26 (2.0)	1.20 (0.80, 1.75)
Sensorineural hearing loss	14 (1.1)	0.64 (0.36, 1.06)
All SAEs according to system organ class		
Cardiac disorders	2 (0.2)	0.09 (0.01, 0.31)
Eye disorders	1 (0.1)	0.05 (0.00, 0.23)
Gastrointestinal disorders	2 (0.2)	0.09 (0.01, 0.31)
General disorders and administration site conditions	1 (0.1)	0.05 (0.00, 0.23)
Hepatobiliary disorders	1 (0.1)	0.05 (0.00, 0.23)
Immune system disorders	2 (0.2)	0.09 (0.01, 0.31)
Infections and infestations	14 (1.1)	0.64 (0.36, 1.06)
Injury, poisoning and procedural complications	6 (0.5)	0.27 (0.11, 0.58)
Musculoskeletal and connective tissue disorders	4 (0.3)	0.18 (0.05, 0.45)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (0.6)	0.37 (0.17, 0.70)
Nervous system disorders	2 (0.2)	0.09 (0.01, 0.31)
Pregnancy, puerperium and perinatal conditions	3 (0.2)	0.14 (0.03, 0.38)
Psychiatric disorders	6 (0.5)	0.27 (0.11, 0.57)
Renal and urinary disorders	1 (0.1)	0.05 (0.00, 0.23)
Respiratory, thoracic and mediastinal disorders	4 (0.3)	0.18 (0.05, 0.45)
Skin and subcutaneous tissue disorders	1 (0.1)	0.05 (0.00, 0.23)
Vascular disorders	3 (0.2)	0.14 (0.03, 0.38)

NMSC = Non-Melanoma Skin Cancer. Reference: King et al. (2024), including the Supplementary Appendix [23].

Appendix F. Health-related quality of life

Not applicable, as no domain specific data is relevant for this application.

Appendix G. Probabilistic sensitivity analyses

Table 52. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Appendix H. Literature searches for the clinical assessment

Not applicable, as the included clinical data is based on a head-to-head study comparing ritlecitinib with placebo.

H.1 Efficacy and safety of the intervention and comparator(s)

Table 53 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

Abbreviations:

Table 54 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Abbreviations:

Table 55 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A	N/A	N/A	N/A	N/A

H.1.1 Search strategies

Table 56 of search strategy table for [name of database]

No.	Query	Results
N/A	N/A	N/A

H.1.2 Systematic selection of studies

Table 57 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
N/A	N/A	N/A	N/A

Table 58 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
N/A	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded full text references

H.1.4 Quality assessment

H.1.5 Unpublished data

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The objective of the SLR was to assess the HRQoL and utility of patients with AA from interventional or RWE studies. The research question of the SLR was the following: What is the health-related quality of life and utility in patients with alopecia areata in interventional and real-world studies?

The methodology of the SLR implements the principles outlined in Cochrane Handbook for Systematic Reviews of Interventions, Centre for Reviews and Dissemination (CRD)'s Guidance for Undertaking Reviews in Healthcare, and Methods for the Development of NICE Public Health Guidance [28, 29].

The key biomedical literature databases (Medical Literature Analysis and Retrieval System Online [MEDLINE®], Excerpta Medica Database [Embase®]) and Cochrane collaboration were consulted. This is in accordance with the list of databases suggested by the HTA organizations, such as the NICE. MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations was searched to ensure that non-indexed citations would be retrieved.

The Ovid platform was used to conduct searches in the literature databases mentioned.

Table 59 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	2000-2021	18.10.2021
Medline	Ovid	2000-2021	18.10.2021
Embase	Ovid	2021-2024	28.10.2024
Medline	Ovid	2021-2024	28.10.2024

Database	Platform	Relevant period for the search	Date of search completion
Specific health economics databases	N/A	N/A	N/A

Table 60 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Table 61 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A	N/A	N/A	N/A	N/A

I.1.1 Search strategies

The eligibility for studies to be included in the SLR was defined according to the PICOS criteria aligned to the review questions. The PICOS criteria considered to identify studies suitable for inclusion is presented in Table 62.

The original search from 2021 was updated in October 2024 to account for data published between 2021 and 2024. The updated search had the same inclusion and exclusion criteria; however, the search strategy was adjusted in that it only included the time period from 2021-2024. Furthermore, we limited the search based on region: Europe, United States, Canada, Australia, and New Zealand. The purpose of including a geographical limitation was to identify publications that

would be relevant specifically to the Danish population. Therefore, the search was geographically limited to countries with populations, treatment traditions, and healthcare systems closer to and more relevant for the Danish population.

The search strategy for the SLR, performed in OVID in 2021 and 2024 are reported in Table 63 and Table 64 respectively. The PRISMA diagrams corresponding each search is to be found in Figure 20 and Figure 21.

Table 62 PICOS inclusion and exclusion criteria

	Inclusion	Exclusion
Patient population	[redacted]	[redacted]
Intervention and Comparators	[redacted]	[redacted]
Outcomes measures	[redacted]	[redacted]
Study design	[redacted]	[redacted]
Other limits	[redacted]	[redacted]

Table 63 Search strategy for OVID conducted in 2021.

No.	Query	Results
#1	[redacted]	[redacted]
#2	[redacted]	[redacted]
#3	[redacted]	[redacted]
#4	[redacted]	[redacted]
#5	[redacted]	[redacted]
#6	[redacted]	[redacted]
#7	[redacted]	[redacted]
#8	[redacted]	[redacted]
#9	[redacted]	[redacted]
#10	[redacted]	[redacted]
#11	[redacted]	[redacted]
#12	[redacted]	[redacted]

No.	Query	Results
#13	[redacted]	[redacted]
#14	[redacted]	[redacted]
#15	[redacted]	[redacted]
#16	[redacted]	[redacted]
#17	[redacted]	[redacted]
#18	[redacted]	[redacted]
#19	[redacted]	[redacted]
#20	[redacted]	[redacted]
#21	[redacted]	[redacted]
#22	[redacted]	[redacted]
#23	[redacted]	[redacted]
#24	[redacted]	[redacted]
#25	[redacted]	[redacted]

No.	Query	Results
#26	[redacted]	[redacted]
#27	[redacted]	[redacted]
#28	[redacted]	[redacted]
#29	[redacted]	[redacted]
#30	[redacted]	[redacted]
#31	[redacted]	[redacted]
#32	[redacted]	[redacted]
#33	[redacted]	[redacted]
#34	[redacted]	[redacted]
#35	[redacted]	[redacted]

No.	Query	Results
#36	[redacted]	[redacted]
#37	[redacted]	[redacted]
#39	[redacted]	[redacted]

Table 64 Search strategy for OVID conducted in 2024.

No.	Query	Results
#1	[redacted]	[redacted]
#2	[redacted]	[redacted]
#3	[redacted]	[redacted]
#4	[redacted]	[redacted]
#5	[redacted]	[redacted]
#6	[redacted]	[redacted]
#7	[redacted]	[redacted]

No.	Query	Results
#8	[redacted]	[redacted]
#9	[redacted]	[redacted]
#10	[redacted]	[redacted]
#11	[redacted]	[redacted]
#12	[redacted]	[redacted]
#13	[redacted]	[redacted]
#14	[redacted]	[redacted]
#15	[redacted]	[redacted]
#16	[redacted]	[redacted]
#17	[redacted]	[redacted]
#18	[redacted]	[redacted]

No.	Query	Results
#19	[redacted]	[redacted]
#20	[redacted]	[redacted]
#21	[redacted]	[redacted]
#22	[redacted]	[redacted]
#23	[redacted]	[redacted]
#24	[redacted]	[redacted]
#25	[redacted]	[redacted]
#26	[redacted]	[redacted]
#27	[redacted]	[redacted]
#28	[redacted]	[redacted]

No.	Query	Results
#29	[redacted]	[redacted]
#30	[redacted]	[redacted]
#31	[redacted]	[redacted]
#32	[redacted]	[redacted]
#33	[redacted]	[redacted]
#34	[redacted]	[redacted]
#35	[redacted]	[redacted]
#36	[redacted]	[redacted]
#37	[redacted]	[redacted]
#39	[redacted]	[redacted]

I.1.1.1 Data extraction

Data from included studies in the original SLR, were extracted into a pre-defined Excel-based template, ensuring that data were extracted uniformly and were comparable across studies. Two analysts independently extracted data, and their results were checked and reconciled by a third independent analyst.

To ensure consistency of the process, training specific for researchers performing data extraction was conducted. Additional follow-up check-ins were organized to address any issues related to data extraction.

Data from the updated SLR in 2024 were reviewed by two reviewers by first title/abstract and then by full text.

I.1.1.2 Results

A total of 2,687 records were identified using the Ovid platform in 2021. Of these 121 records were selected for full text review, after screening by title/abstract. Overall, following full-text review a total of 35 records from 32 original studies were selected for data extraction in the QoL SLR. Details of the included and excluded studies are presented in the PRISMA flow diagram in Figure 20. None of the studies proved relevant due that they were either not based on SALT scores, or based on EQ-5D, which has been showed not to be appropriate for AA.

A total of 22 records were identified using the Ovid platform in 2024. Of these 10 records were selected for full text review, after screening by title/abstract. After full text review one record was selected for data extraction. However, the study was not included in the health economic model based on that it was not based on SALT scores and it used EQ-5D, which has been showed not to be appropriate for AA.

Details of the included and excluded studies are presented in the PRISMA flow diagram in Figure 21.

Table 65 Summary of studies included in the SLR from 2021

Reference	Subgroup	Study Design	Study Population	Scales Used	Summary of Outcomes for AA	Full reference

Lambert *et al.* (2011)	Adults	Cross-sectional study, survey	Adult patients with a chronic skin disease (including AA)	DLQI	Baseline DLQI, mean: 6.00 DLQI at follow-up: 0.00	Lambert J, Bostoen J, Geusens B, et al. A novel multidisciplinary educational programme for patients with chronic skin diseases: Ghent pilot project and first results. Archives of dermatological research 2011. 303: 57–63.
Nasimi *et al.* (2020)	NR	Cross-sectional study, survey	Patients ≥16 years old	DLQI	DLQI, mean (SD): 10.69 (5.93)	Nasimi M, Ghandi N, Torabzade L, et al. Alopecia Areata-Quality of Life Index questionnaire (reliability and validity of the Persian version) in comparison to Dermatology Life Quality Index. International Journal of Trichology 2020. 12: 227.
Willemse *et al.* (2019)	NR	Cross-sectional study, survey	Patients with AA	DLQI	DLQI, mean (SD): 0.76 (0.64)	Willemse H, van der Doef M & van Middendorp H. Applying the Common Sense Model to predicting quality of life in alopecia areata: The role of illness perceptions and coping strategies. Journal of Health Psychology 2019. 24: 1461–1472.
Qi *et al.* (2015)	Male, Female, Patchy AA, AT/AU	Cross-sectional study, survey	Patients ≥16 years diagnosed with AA	DLQI	DLQI, mean (SD): 5.8 (5.6)	Qi S, Xu F, Sheng Y, et al. Assessing quality of life in alopecia areata patients in China. Psychology, health & medicine 2015. 20: 97–102.
Ghajarzadeh *et al.* (2012a)	Male, Female	Cross-sectional study, survey	Patients with AA	DLQI, SF-36	DLQI, mean (SD): 6.4 (5.5) SF-36 score, mean (SD): 68.01 (15.1).	Ghajarzadeh M, Ghiasi M & Kheirkhah S. Associations between skin diseases and quality of life: a comparison of psoriasis,

Ghajarzadeh *et al.* (2012b)						vitiligo, and alopecia areata. Acta Medica Iranica 2012. 511–515. Ghajarzadeh M, Ghiasi M & Kheirkhah S. Depression and quality of life in Iranian patients with Alopecia Areata. Iranian Journal of Dermatology 2011. 14: 140–143.
Bae *et al.* (2021) (abstract)	NR	Cross-sectional study, survey	Patients with seven chronic skin diseases (AA, atopic dermatitis, chronic urticaria, psoriasis, rosacea, seborrheic dermatitis and vitiligo)	DLQI	DLQI, mean : 6.00	Bae JM, Kim JE, Lee RW, et al. Beyond quality of life: A call for patients' own willingness to pay in chronic skin disease to assess psychosocial burden—A multicenter, cross-sectional, prospective survey. Journal of the American Academy of Dermatology 2021. 85: 1321–1324.
Al-Mutairi *et al.* (2011)	Adult, Extensive AA, AT, AU	Cross-sectional study, survey	Patients with severe forms of AA	DLQI	DLQI, mean : 13.54	Al-Mutairi N & Eldin O. Clinical profile and impact on quality of life: Seven years experience with patients of alopecia areata. Indian Journal of Dermatology, Venereology and Leprology 2011. 77: 489.
Shi *et al.* (2013)	NR	Cross-sectional study, survey, secondary analysis of data	Patients with AA	DLQI	DLQI, mean (SD): 6.8 (4.8)	Shi Q, Duvic M, Osei JS, et al. Health-Related Quality of Life (HRQoL) in Alopecia Areata Patients—A Secondary Analysis of the National Alopecia Areata Registry Data. Journal of Investigative

						Dermatology Symposium Proceedings 2013. 16: S49–S50.
Russo *et al.* (2018)	NR	Cross-sectional study, survey	Patients diagnosed with AA, androgenetic alopecia, telogen effluvium	DLQI	DLQI, mean (SD): 3.0 (3.2)	Russo PM, Fino E, Mancini C, et al. HrQoL in hair loss-affected patients with alopecia areata, androgenetic alopecia and telogen effluvium: the role of personality traits and psychosocial anxiety. Journal of the European Academy of Dermatology and Venereology 2019. 33: 608–611.
Yu *et al.* (2016)	NR	Cross-sectional study, survey	Patients with AA for the first time	DLQI	DLQI, mean (SD): 7.21 (5.7)	Yu N-L, Tan H, Song Z-Q, *et al.* Illness perception in patients with androgenetic alopecia and alopecia areata in China. *Journal of psychosomatic research* 2016. 86: 1–6.
Temel *et al.* (2019)	NR	Cross-sectional study, survey	Patients with AA	DLQI	DLQI, mean (SD): 6.64 (6.1)	Temel AB, Bozkurt S, Senol Y, et al. Internalized stigma in patients with acne vulgaris, vitiligo, and alopecia areata. Turkish Journal of Dermatology 2019. 13: 109.
Qi *et al.* (2010) (abstract)	Patchy AA, AT/AU, Recurrent disease, Primary disease	Prospective study	Patients newly diagnosed with AA	DLQI	DLQI (Chinese version), mean (SD): 5.4 (5.5)	Qi S, Xu F, Yang Q, *et al.* Profile of alopecia areata in 655 Chinese patients. in *JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY* (MOSBY-ELSEVIER 360 PARK AVENUE SOUTH, NEW YORK, NY 10010-1710 USA, 2010). 62: AB75–AB75.

Velez-Muniz *et al.* (2019)[18]	Adults	Cross-sectional study, survey	Children and adults, with a clinical diagnosis of AA and clinical signs of active disease	DLQI	DLQI, mean (SD): 6.1 (5.1)	Vélez-Muñiz R d C, Peralta-Pedrero ML, Jurado-Santa Cruz F, *et al.* Psychological Profile and Quality of Life of Patients with Alopecia Areata. *Skin Appendage Disorders* 2019. 5: 293–298.
Abedini *et al.* (2018)[19]	Mild, Severe, Male, Female	Cross-sectional study, survey	Patients with definite diagnosis of AA	DLQI	DLQI, mean (range): 7.9 (0.3-15.5)	Abedini R, Hallaji Z, Lajevardi V, *et al.* Quality of life in mild and severe alopecia areata patients. *International journal of women's dermatology* 2018. 4: 91–94.
Jankovic *et al.* (2016)[20]	NR	Cross-sectional study, survey	Adult patients (aged over 16 years) with diagnosis of AA	DLQI, SF-36	DLQI subscales, mean (SD): Symptoms and feelings: 1.4 (1.1) Daily activities: 1.2 (1.7) Leisure: 1.1 (1.5) Work or school: 0.6 (1.0) Personal relationships: 0.5 (1.1) Treatment: 0.5 (0.9) SF-36 subscales, mean (SD): Physical functioning 89.3 (15.8) Role physical 73.1 (37.0) Bodily pain 82.3 (26.3) General health 61.1 (20.5) Vitality 59.3 (12.4) Social functioning 70.8 (27.0) Role emotional 65.6 (42.9) Mental health 50.1 (6.8)	Janković S, Perić J, Maksimović N, *et al.* Quality of life in patients with alopecia areata: a hospital-based cross-sectional study. *Journal of the European Academy of Dermatology and Venereology* 2016. 30: 840–846.

Gulec *et al.* (2004)	NR	Case-control study	Patients with AA	SF-36	SF-36 subscales for AA patient's vs Controls, mean (SD): Physical functioning: 90.19 (17.15) vs 8.85 (16.62) Pain: 76.31 (22.85) vs 77.23 (20.61) Vitality: 51.35 (20.68) vs 59.71 (18.48) Social functioning: 71.83 (24.47) vs 55.48 (20.31) Mental health: 55.69 (17.85) vs 67.23 (17.55) General health: 65.04 (19.99) vs 68.14 (18.21) Role limitations due to physical health: 83.17 (29.59) vs 78.37 (32.1) Role limitations due to emotional problems: 59.83 (42.22) vs 76.96 (51.76)	Güleç AT, Tanrıverdi N, Dürü Ç, *et al.* The role of psychological factors in alopecia areata and the impact of the disease on the quality of life. *International journal of dermatology* 2004. 43: 352–356.
Meier *et al.* (2015) (abstract)	Moderate-to-severe	Retrospective, single center	Patients with moderate-to-severe AA	DLQI	DLQI at baseline, mean: 9.95 DLQI at 24 weeks, mean: 5.3	Meier K, Mehra T, Mueller-Hermelink E, *et al.* Treatment of therapy resistant alopecia areata with fumaric acid esters. in *EXPERIMENTAL DERMATOLOGY* (WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 2015). 24: E12–E12.

Atis *et al.* (2021)	NR	Propective, single center	Patients with AA	DLQI	DLQI, mean (SD): 9.3 (5.3)	Atış G, Tekin A, Ferhatoğlu ZA, *et al.* Type D personality and quality of life in alopecia areata and vitiligo patients: A cross-sectional study in a Turkish population. *TURKDERM-Turkish Archives of Dermatology and Venereology* 2021. 55: 87–91.
Staumont-Salle *et al.* (2012)	Responder, Non-responder	Retrospective, single center	Patients with AA	DLQI	DLQI, mean 6	Staumont-Sallé D, Vonarx M, Lengrand F, *et al.* Pulse corticosteroid therapy for alopecia areata: long-term outcome after 10 years. *Dermatology* 2012. 225: 81–87.
Willemsen *et al.* (2011)	NR	Prospective cohort study	Patients with AA	SF-36	SF-36 at baseline/at follow-up, mean (SD): Physical functioning: 51.12 (6.64)/ 51.82 (7.28) Role physical: 47.76 (6.64)/ 48.81 (6.39) Bodily Pain: 49.56 (11.51)/ 52.04 (10.11) General health: 44.53 (10.14)/ 49.54 (9.39) Vitality: 48.51 (7.6)/ 56.55 (6.81) Social functioning: 45.69 (9.84)/ 49.84 (10.37) Role emotional: 39.41 (10.65)/ 49.26 (7.92)	Willemsen R, Haentjens P, Roseeuw D, *et al.* Hypnosis and alopecia areata: long-term beneficial effects on psychological well-being. *Acta dermato-venereologica* 2011. 91: 35–39.

					Mental Health: 41.17 (7.96)/ 49.60 (8.65)	
Saddouk 2021	NR	Retrospective, single center	Patients hospitalized or who consulted for AA	NR	At admission, 8% of patients had no effect on their quality of life, 16% had a small effect, 16% had a moderate effect, 56% had a large effect and 1 patient had an extremely large effect on quality of life. After treatment, 23% reported no effect on quality of life, 18% had a small effect, 23% had a moderate effect, 32% had a large effect and 1 patient retained the extremely large effect on quality of life.	Saddouk H, Khouna A, Ragragui H, *et al.* Alopecia areata and quality of life: The experience of a dermatology department. in *EADV* (2021).
Burge *et al.* (2021) (abstract)	Mild, Moderate, Severe	Cross-sectional study, survey	Patients with AA	EQ-5D-5L	EQ-5D-5L results showed that quality of life decreased with increasing severity (mild 0.95 (0.14) vs moderate 0.93 (0.13) vs severe 0.87 (0.21), p= 0.0070).	Burge R, Anderson P, Austin J, *et al.* The patient-reported burden of alopecia areata by current severity: a real-world study in the United States [Poster 26158]. in (2021).
Liu_JAAD (2018) Liu_PDC_2017 (abstract)	NR	Cross-sectional, survey	Children with AA ages 4 to 16	DLQI	DLQI/CDLQI, mean (SD): 6.3	Liu LY, King BA & Craiglow BG. Alopecia areata is associated with impaired health-related quality of life: a survey of affected adults and children and their families. *Journal of the American Academy of Dermatology* 2018. 79: 556-558. e1.

Lai *et al.* (2021) Lai *et al.* (2019	AT/AU, Patchy AA, Male, Female, Adults, Moderate to severe	RCT, double-blind, single center, placebo-controlled study	Adults, 18 to 65 years of age, with moderate to severe AA	AQoL-8D	AQoL-8D utility scores at baseline, mean (SD): 0.739 (0.207) vs 0.756 (0.218) QoL-8D utility scores at 3 months, mean (SD): 0.803 vs 0.806 Change from baseline in AQoL-8D score at 3 months, mean (SD): 0.064 (0.085) vs 0.050 (0.095)	Lai VWY, Chen G & Sinclair R. Impact of cyclosporin treatment on health-related quality of life of patients with alopecia areata. *Journal of Dermatological Treatment* 2021. 32: 250–257. Lai VWY, Chen G, Gin D, *et al.* Cyclosporine for moderate-to-severe alopecia areata: A double-blind, randomized, placebo-controlled clinical trial of efficacy and safety. *Journal of the American Academy of Dermatology* 2019. 81: 694–701.
Bilgic *et al.* (2013)	Children and adolescents (8–12 years, 13–18 years)	Cross-sectional study, survey	Children and adolescents with AA	PedsQL	Mean (SD) overall PedsQL-P and -C scores for all with AA were 70.3 (13.4), and 74.0 (13.4), respectively.	Bilgiç Ö, Bilgiç A, Bahalı K, *et al.* Psychiatric symptomatology and health-related quality of life in children and adolescents with alopecia areata. *Journal of the European Academy of Dermatology and Venereology* 2014. 28: 1463–1468.
Masmoudi *et al.* (2013)	Degree of scalp hair loss (SALT score: S1-S5), Adults	Cross-sectional study, survey	Newly diagnosed patients with AA	SF-36	Patient's quality of life, demonstrated by SF-36 scores, ranged from 38.54 to 92.7 with a mean (SD) of 68.95 (13.10).	Masmoudi J, Sellami R, Ouali U, *et al.* Quality of life in alopecia areata: a sample of tunisian patients. *Dermatol Res Pract* 2013. 2013: 983804.
Putterman *et al.* (2019)	Degree of scalp hair loss (SALT score: S1-S5),	Cross-sectional study, survey	Children >7 years of age with AA; English-speaking parents; legal guardians of	DLQI	CDLQI, mean (SD): 4.4 (4.9) FDLQI, mean (SD): 6.6 (5.3)	Putterman E, Patel DP, Andrade G, *et al.* Severity of disease and quality of life in parents of children with alopecia areata, totalis, and universalis: a prospective, cross-sectional study. *Journal of the*

	Children (≥7 years)		pediatric patients with AA, AT, or AU diagnosed for at least 1 month			*American Academy of Dermatology* 2019. 80: 1389–1394.
Balieva *et al.* (2016)	NR	Cross-sectional study, multicenter	Patients with AA	EQ-5D-VAS	Mean (SD) EQ-5D-VAS self-reported health status in AA was 69.7 (18.1)	Balieva F, Kupfer J, Lien L, *et al.* The burden of common skin diseases assessed with the EQ5D™: a European multicentre study in 13 countries. *British Journal of Dermatology* 2017. 176: 1170–1178.
Dubois *et al.* (2010)	NR	Cross-sectional study	Patients with AA	EQ-5D	Mean (SD) SF-36 dimensions scores ranged from 49.3 (20.4) to 88.2 (22.5), in which mental health and vitality were the most altered SF36 dimensions, whereas physical functioning, role physical and body pain were the least ones.	Dubois M, Baumstarck-Barrau K, Gaudy-Marqueste C, *et al.* Quality of life in alopecia areata: a study of 60 cases. *J Invest Dermatol* 2010. 130: 2830–3.
Lai *et al.* (2021)	Nonresponders, Adults (18-65 years), Moderate to severe	Open-label, roll-over clinical trial	Patients with AA	AQoL-8D	Change from baseline in AQoL-8D score, mean (n=13): -0.0148 (0.0515)	Lai VWY, Bokhari L & Sinclair R. Sublingual tofacitinib for alopecia areata: a roll-over pilot clinical trial and analysis of pharmacokinetics. *International Journal of Dermatology* 2021. 60: 1135–1139.
Jabbari *et al.* (2018)	Patchy AA/AT/AU	P2, single arm, open-label, single center	Moderate-to-severe AA	DLQI	DLQI at baseline, mean: 6.5 (5) DLQI at follow-up, mean: 6 (6.9)	Jabbari A, Sansaricq F, Cerise J, *et al.* An Open-Label Pilot Study to Evaluate the Efficacy of Tofacitinib in Moderate to Severe Patch-Type Alopecia Areata,

						Totalis, and Universalis. *Journal of Investigative Dermatology* 2018. 138: 1539–1545.
Mackay-Wiggan *et al.* (2021)	Adult, Moderate-to-severe	P2, single arm, open-label, single center	Moderate-to-severe AA, AT, and AU	DLQI	DLQI at baseline, mean: 4.21 (3.77) DLQI at follow-up, mean: 4.62 (3.82)	Mackay-Wiggan J, Sallee BN, Wang EHC, *et al.* An open-label study evaluating the efficacy of abatacept in alopecia areata. *Journal of the American Academy of Dermatology* 2021. 84: 841–844.

Table 66 Summary of studies included in the SLR from 2024

Reference	Subgroup	Study Design	Study Population	Scales Used	Summary of Outcomes for AA	Full reference
Vañó-Galván *et al.* (2023)	Mild, Moderate, Severe	Retrospective point-in-time cross-sectional survey	Patients with AA	EQ-5D-5L	EQ-5D-5L results showed that quality of life decreased with increasing severity (mild 0.89 vs moderate 0.85 vs severe 0.77, p< 0.001).	Vañó-Galván, S., Blume-Peytavi, U., Farrant, P. *et al.* Physician- and Patient-Reported Severity and Quality of Life Impact of Alopecia Areata: Results from a Real-World Survey in Five European Countries. *Dermatol Ther (Heidelb)* **13**, 3121–3135 (2023).

I.1.2 Quality assessment and generalizability of estimates

As the results from the SLR is not being used this section is not relevant.

I.1.3 Unpublished data

As the results from the SLR is not being used this section is not relevant.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

No literature search has been conducted for inputs for the health economic model. No data have been needed from the literature; therefore, no literature search has been conducted.

J.1.1 Example: Systematic search for [...]

Table 67 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

J.1.2 Example: Targeted literature search for [estimates]

Table 68 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Figure 20 PRISMA diagram for SLR in OVID from 2021

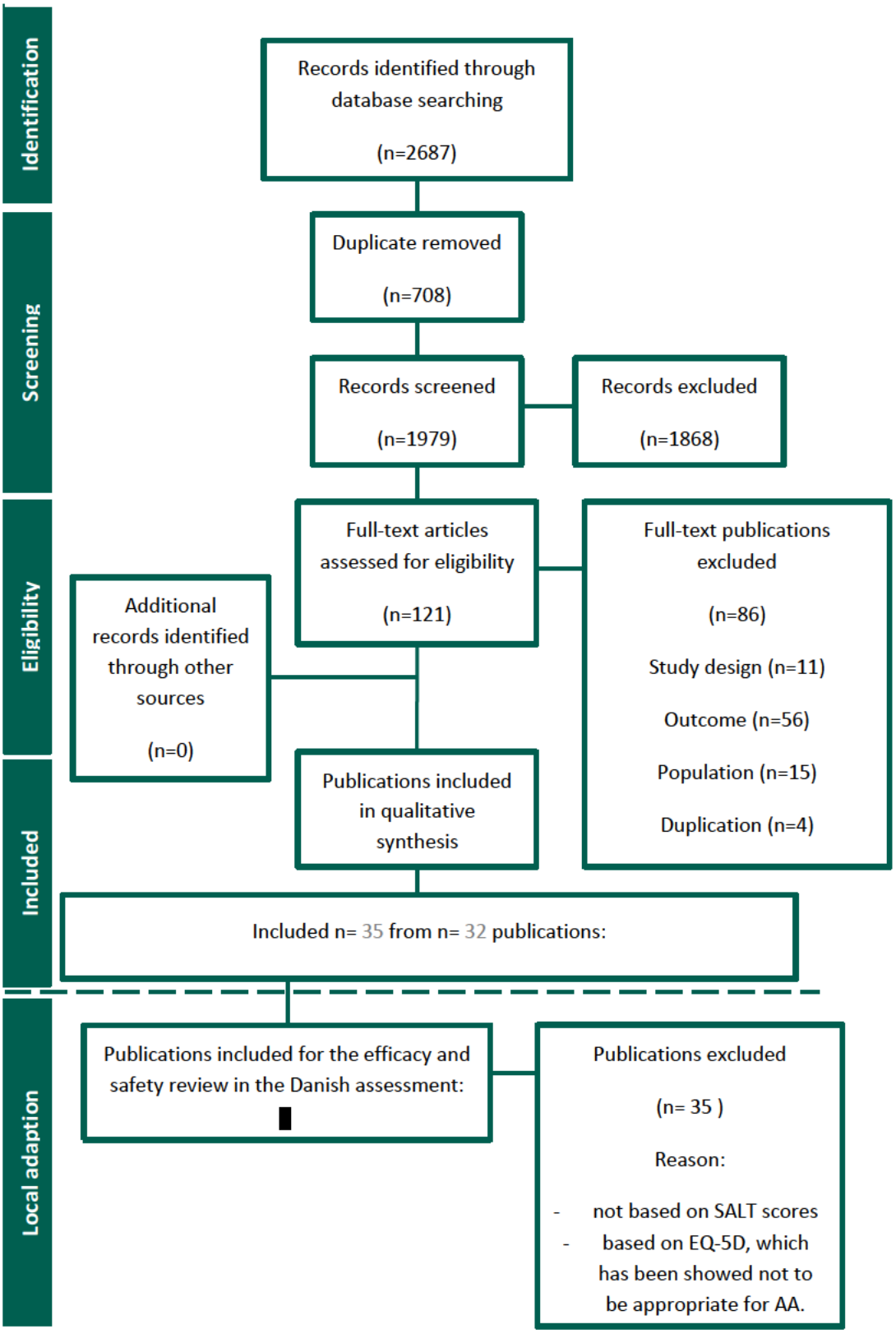
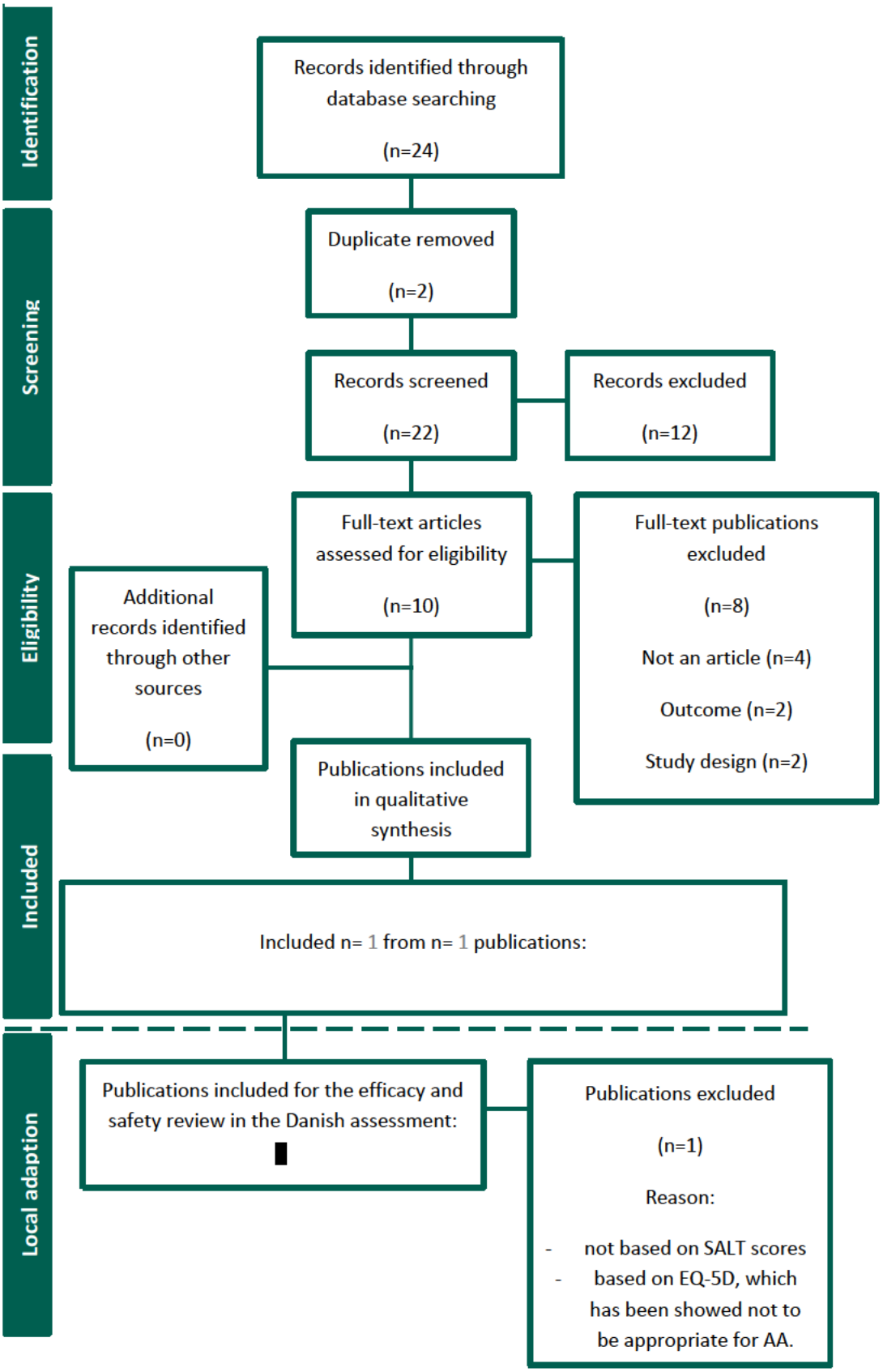


Figure 21 PRISMA diagram for SLR in OVID from 2024



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