

Bilag til Medicinrådets vurdering af mogamulizumab til behandling af mycosis fungoides og Sézarys syndrom

Vers. 2.0



Bilagsoversigt

1. Ansøgers notat til Rådet vedr. mogamulizumab
2. Amgros' forhandlingsnotat vedr. mogamulizumab
3. Ansøgers endelige ansøgning vedr. mogamulizumab

Kyowa Kirin comments on the Danish Medicines Council (DMC) assessment report of mogamulizumab for the treatment of patients with mycosis fungoides or Sézary syndrome, who have received at least one prior systemic treatment.

Kyowa Kirin would like to thank the DMC and acknowledge the significant work that the DMC has done during the assessment. We would like to clarify the points below where our perspectives differ, particularly in relation to certain assumptions in the health economic model and the clinical meaningfulness of treatment with mogamulizumab.

In summary, Kyowa Kirin considers the survival modelling assumptions to be the most important source of uncertainty in the assessment. While acknowledging the challenges associated with limited long-term data, the company believes that the selected extrapolation may underestimate the survival benefit of mogamulizumab and generate clinically implausible long-term outcomes. Kyowa Kirin therefore requests that greater weight be given to alternative extrapolations that better align with the observed data and clinical evidence.

Overall survival

The DMC assesses that the assumption of proportional hazards is not reasonable and has adopted separate models on that basis. Our concern is not this conclusion, but the basis on which the alternative specification was selected. The assessment states that the absolute survival level cannot be determined from the available data, and that the extrapolated curves have instead been chosen so to deliver a survival gain of approximately two years, drawn from clinical experience with mogamulizumab in third line. However, this inverts the conventional order of assessment where distributions are evaluated on statistical fit, visual fit to the observed data, on the clinical plausibility of the extrapolated hazard, and then compared against external expectations (as per DMC guidelines). If used as a post-analysis validation check, a two-year expectation is legitimate. However, used as the selection criterion, the different distributions simply become a tool for reaching a figure already pre-determined. Moreover, such expectation is drawn from third-line only experience and applied to an “at least one previous systemic treatment” setting, without statements or concerns of how many patients were assessed and against what comparator. There are also concerns on the fact that several combinations across extrapolations may generate gains of about two years.

We would like to point out that in Tables 12 and 13 the “Average” columns are not restricted mean survival times, and the values contradict the 2.1 years gain mentioned. These numbers align with a cell which includes averages of the time axis weighted by the proportion of patients alive, a quantity that rises with the dispersion of survival times rather than with their average. If we use restricted mean survival time, the DMC's selection generates

indeed 6.6 years for mogamulizumab against 4.5 for standard of care, which is aligned with the 2.1 gain mentioned in the report.

Nonetheless the Weibull specification is in our view not clinically plausible. With separate Weibull fits the survival curves cross at month 180, and beyond approximately five years the model implies a higher risk of death under mogamulizumab than under standard of care. From month 150, projected survival under mogamulizumab falls below the observed Kaplan–Meier estimate for Danish standard of care. The mogamulizumab data underlying Figure 33 extend to month 67 and the reversal lies beyond the observations on which the departure from proportionality is identified. No mechanism for it is proposed in the assessment. In addition, we would like to note that the Weibull distribution is associated with the worst AIC, among the available extrapolations, for the Danish comparator arm. Finally, we note that Table 34 contains no scenario varying the OS extrapolation, although it is one of the largest structural drivers of the incremental QALYs as also acknowledged by the DMC.

Weighting analysis and data sources

The DMC notes that disease stage and performance status are not included in the weighting model. These variables were not omitted by choice, they are not obtainable for this cohort. ECOG performance status is not systematically recorded in the Danish administrative health registers and is therefore not accessible for this population. The Danish National Lymphoma Registry (LYFO) does record it, but includes only patients managed in haematology departments; patients with MF or SS treated exclusively in dermatology may therefore not be comprehensively represented. MF and SS are staged according to the TNMB classification specific to cutaneous T-cell lymphomas, as applied in MAVORIC. TNMB stage is not routinely captured as a structured variable in the Danish national registers, and clinical stage consequently cannot be directly ascertained for the present population from the available sources.

We would note, however, that the Danish SoC population is defined by administration of systemic therapy in secondary care. In Danish clinical practice systemic therapy is reserved for advanced-stage MF and SS, so the cohort definition itself selects for more advanced disease, consistent with the relapsed or refractory MAVORIC population. Stage cannot be formally verified within the available data, but it is not an unconstrained source of imbalance. As to the analysis' magnitude, the survival difference in the weighted analysis is substantial and its confidence interval excludes the null by a wide margin. For unmeasured confounding to account for it entirely, any residual imbalance would have to be strongly associated with both treatment allocation and mortality, over and above the variables already balanced. Stage and performance status are themselves correlated with one another and with covariates already included in the weighting, which limits the additional imbalance they can independently carry, and the cohort definition further constrains the plausible range of stage. We do not suggest this removes the uncertainty the DMC identifies, but the direction of the estimated effect appears unlikely to rest on it.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

Forhandlingsnotat

28.09.2026

MBA/LSC

Dato for vurdering i Medicinrådet	28.10.2026
Leverandør	Kyowa Kirin
Lægemiddel	Poteligeo (mogamulizumab)
Ansøgt indikation	Behandling af voksne patienter med mycosis fungoides (MF) eller Sézarys syndrom (SS), der har fået mindst én tidligere systemisk behandling
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Poteligeo:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Poteligeo	4 mg/ml (5 ml)	10.686,53				

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

Aftaleforhold

Amgros har en eksisterende aftale på Poteligeo. Aftalen gælder til den 31.03.2027 med mulighed for at forlænge i alt 24 måneder (4*6 måneder). Der er inkluderet mulighed for prisregulering i aftalen.

[Redacted text]

Informationer fra forhandlingen

[Redacted text]

Konkurrencesituationen

Der er ingen etableret standardbehandling som alternativ til Poteligeo.

Tabel 2 viser de årlige lægemiddeludgifter ved behandling med Poteligeo.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Poteligeo	4 mg/ml (5 ml)	1 mg/kg ugentligt i de første 28 dage, og herefter hver 2. uge indtil progression, i.v.	[Redacted]	[Redacted]

*Medicinerådet antager en gennemsnitlig kropsvægt på 77 kg jævnfør vurderingsrapporten.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Opsummering

[Redacted text]



Application for the assessment of Poteligeo[®] (mogamulizumab) for treatment of patients with mycosis fungoides or Sézary syndrome, who have received at least one prior systemic treatment

Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information



Contact informationyear

Contact information	
Name	Charlotte Dawkins Kyowa Kirin
Title	Value & Access Specialist, Northern Cluster
Phone number	+44(0)7587 035123
E-mail	Charlotte.Dawkins@kyowakirin.com
Name (External representation)	N/A
Title	
Phone number	N/A
E-mail	



Table of Contents

Contact information	2
Tables and Figures	7
Abbreviations	12
1. Regulatory information on the medicine	14
2. Summary table	14
3. The patient population, intervention, choice of comparator(s) and relevant outcomes	16
3.1 The medical condition	16
3.2 Patient population	19
3.3 Current treatment options	20
3.4 The intervention	20
3.4.1 Description of ATMP Mechanism of action	21
3.4.2 The intervention in relation to Danish clinical practice	21
3.5 Choice of comparator(s)	22
3.6 Cost-effectiveness of the comparator(s)	33
3.7 Relevant efficacy outcomes	34
3.7.1 Definition of efficacy outcomes included in the application	34
4. Health economic analysis	35
4.1 Model structure	35
4.2 Model features	36
5. Overview of literature	37
5.1 Literature used for the clinical assessment	37
5.2 Literature used for the assessment of health-related quality of life	39
5.3 Literature used for inputs for the health economic model	41
6. Efficacy	42
6.1 Efficacy of mogamulizumab compared to vorinostat for patients with MF or SS who have received at least one prior systemic therapy	42
6.1.1 Relevant studies	42
6.1.2 Comparability of studies	44
6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment	44
6.1.4 Efficacy – results per MAVORIC trial	45
6.1.5 Efficacy – results per PROSPER and PROCLIP real-world data studies	50



7.	Comparative analyses of efficacy.....	51
7.1.1	DK SoC sample selection	51
7.1.2	Differences in definitions of exposures and outcomes between studies	52
7.1.3	Method of synthesis	53
7.1.4	Results from the comparative analysis	54
7.1.5	Efficacy – results per overall survival	56
8.	Modelling of efficacy in the health economic analysis	57
8.1	Presentation of efficacy data from the clinical documentation used in the model	57
8.1.1	Extrapolation of efficacy data	58
8.1.2	Calculation of transition probabilities.....	63
8.2	Presentation of efficacy data from London supra regional centre	63
8.3	Modelling effects of subsequent treatments	63
8.4	Other assumptions regarding efficacy in the model.....	66
8.5	Overview of modelled average treatment length and time in model health state	67
9.	Safety	67
9.1	Safety data from the clinical documentation.....	67
9.2	Safety data from external literature applied in the health economic model	73
10.	Documentation of health-related quality of life (HRQoL).....	76
10.1	Presentation of the health-related quality of life (EQ-5D).....	76
10.1.1	Study design and measuring instrument	76
10.1.2	Data collection	76
10.1.3	HRQoL results.....	77
10.2	Health state utility values (HSUVs) used in the health economic model	79
10.2.1	HSUV calculation	79
10.2.2	Disutility calculation.....	80
10.2.3	HSUV results.....	80
10.3	Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy	80
10.3.1	Swinburn et al. 2015 Study design.....	81
10.3.2	Swinburn et al. 2015 Data collection	81
10.3.3	Swinburn et al. 2015 HRQoL Results.....	81
10.3.4	Swinburn et al. 2015 HSUV and disutility results	81
10.3.5	Van Agthoven 2001 Study design	81
10.3.6	Van Agthoven 2001 Data collection.....	82
10.3.7	Van Agthoven 2001 HRQoL Results	82
10.3.8	Van Agthoven 2001 HSUV and disutility results	82
11.	Resource use and associated costs	83
11.1	Medicines - intervention and comparator	83
11.2	Medicines– co-administration	88



11.3	Administration costs	88
11.4	Disease management costs.....	88
11.5	Costs associated with management of adverse events	89
11.6	Subsequent treatment costs	90
11.6.1	Allogenic stem cell transplant.....	92
11.7	Patient costs.....	92
11.8	Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)	93
12.	Results	93
12.1	Base case overview	93
12.1.1	Base case results	93
12.2	Sensitivity analyses	94
12.2.1	Deterministic sensitivity analyses	95
12.2.2	Scenario analyses	96
12.2.3	Probabilistic sensitivity analyses	96
13.	Budget impact analysis	98
14.	List of experts	99
15.	References.....	100
Appendix A.	Main characteristics of studies included	105
Appendix B.	Efficacy results per study	112
Appendix C.	Comparative analysis of efficacy	114
C.1	Introduction	115
C.2	Study aim	115
C.3	Methods.....	116
C.4	MAVORIC trial data	116
C.4.1	Patient eligibility MAVORIC.....	116
C.4.2	Observation period MAVORIC	117
C.4.3	Data preparation MAVORIC	117
C.5	Danish real-world data.....	117
C.5.1	Patient eligibility Danish SoC	118
C.5.2	Observation period Danish SoC	119
C.5.3	Data preparation Danish SoC.....	119
C.6	Comparative study design.....	120
C.6.1	Outcomes.....	120
C.6.2	Exposure alignment	120
C.7	Statistical methods.....	121
C.7.1	Primary analysis	121
C.7.2	Outcome analyses.....	123



C.8	Results.....	124
C.8.1	Descriptive statistics	124
C.8.2	ATT weights.....	125
C.8.3	Balance assessment	126
C.8.4	Weighted efficacy outcomes results.....	128
C.8.5	Concluding remarks	129
C.9	Appendix A: Balance assessment.....	130
Appendix D. Extrapolation.....		132
D.1	Extrapolation of OS	132
D.1.1	Data input	132
D.1.2	Model.....	132
D.1.3	Proportional hazards.....	132
D.1.4	Evaluation of statistical fit (AIC and BIC).....	133
D.1.5	Evaluation of visual fit.....	133
D.1.6	Evaluation of hazard functions	135
D.1.7	Validation and discussion of extrapolated curves	137
D.1.8	Adjustment of background mortality.....	138
D.1.9	Adjustment for treatment switching/cross-over	138
D.1.10	Waning effect.....	138
D.1.11	Cure-point	138
Appendix E. Serious adverse events.....		139
Appendix F. Health-related quality of life		140
15.2	Longitudinal Mixed Model to Examine the Changes in QoL Endpoints Due to Treatment	142
15.2.1	Family 1 of Hierarchical Models.....	143
15.2.2	Family 2 of Hierarchical Models.....	146
15.2.3	Family 3 of Hierarchical Models.....	150
Appendix G. Probabilistic sensitivity analyses.....		159
Appendix H. Literature searches for the clinical assessment.....		166
H.1	Efficacy and safety of the intervention and comparator(s)	166
H.1.1	Search strategies.....	168
H.1.2	Systematic selection of studies.....	178
H.1.3	Excluded full-text references	201
H.1.4	Quality assessment	221
H.1.5	Unpublished data.....	229
H.1.6	Local adaptation.....	229
Appendix I. Literature searches for health-related quality of life		230
Appendix J. Literature searches for input to the health economic model.....		231



Appendix K. HES analysis	232
K.1.1 Data source	232
K.1.2 Cohort definition	232
K.1.3 Survival analysis	232

Tables and Figures

Table 1 EORTC proposed clinical staging for MF and SS	17
Table 2 Incidence and prevalence in the past 5 years	19
Table 3 Estimated number of incident patients eligible for treatment	19
Table 4 Description of bexarotene	22
Table 5 Description of acitretin	22
Table 6 Description of isotretinoin	23
Table 7 Description of alitretinoin	23
Table 8 Description of cyclophosphamide	24
Table 9 Description of liposomal doxorubicin	24
Table 10 Description of vincristine	25
Table 11 Description of prednisolone	25
Table 12 Description of gemcitabine	26
Table 13 Description of methotrexate	26
Table 14 Description of etoposide	27
Table 15 Description of chlorambucil	28
Table 16 Description of chlormethine	28
Table 17 Description of carmustine	28
Table 18 Description of peginterferon alfa-2a	29
Table 19 Description of extracorporeal photopheresis (ECP)	30
Table 20 Description of alemtuzumab*	30
Table 21 Description of brentuximab vedotin	31
Table 22 Description of pembrolizumab	31
Table 23 Description of phototherapy UV-A (PUVA)	32
Table 24 Description of local radiotherapy	32
Table 25 Description of total skin electron beam therapy (TSBET)	33
Table 26 Efficacy outcome measures relevant for the application	34
Table 27 Features of the economic model	36
Table 28 Relevant literature included in the assessment of efficacy and safety	38
Table 29 Relevant literature included for (documentation of) health-related quality of life (See section 10)	40
Table 30 Relevant literature used for input to the health economic model	41
Table 31 Overview of study design for studies included in the comparison	43
Table 32 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety	44
Table 33 Characteristics in the relevant Danish population and in the health economic model	45
Table 34 PFS in ITT population and pre-specified subgroups	45
Table 35 Exploratory analyses of OS results from the MAVORIC trial	49



Table 36 Descriptive statistics of the compared populations	54
Table 37 Distribution of treatments in the DK SoC arm	55
Table 38 Results from the comparative analysis of mogamulizumab vs. DK SoC	57
Table 39 Summary of assumptions associated with extrapolation of overall survival	59
Table 40 Goodness of fit for OS (mogamulizumab and DK SoC combined models)	59
Table 41 Summary of assumptions associated with extrapolation of next-treatment free survival	60
Table 42 Goodness of fit for NTFS (mogamulizumab)	61
Table 43 Summary of assumptions associated with extrapolation of time on treatment	61
Table 44 Goodness of fit for TOT (mogamulizumab)	62
Table 45 Transitions in the health economic model	63
Table 46 AIC and BIC statistics for PSMs fitted to digitised DFS and OS for aSCT	65
Table 47 Estimates in the model	67
Table 48 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction	67
Table 49 Overview of safety events in the MAVORIC trial.	67
Table 50 Grade ≥ 3 TEAEs reported in the trial, regardless of frequency	69
Table 51 Serious adverse events (Data cutoff, 31 December 2016)	70
Table 52 Adverse events used in the health economic model	70
Table 53 Grade 3+ adverse events (TEAEs) that appear in more than 5 % of patients	73
Table 54 Overview of included HRQoL instruments	76
Table 55 Pattern of missing data and completion, mogamulizumab	77
Table 56 Pattern of missing data and completion, vorinostat	77
Table 57 HRQoL EQ-5D-3L VAS summary statistics	78
Table 58 Overview of health state utility values [and disutilities]	80
Table 59 Overview of health state utility values [and disutilities] in Swinburn et al 2015.	81
Table 60 Overview of health state utility values [and disutilities] in Van Agthoven 2001.	82
Table 61 Overview of literature-based health state utility values	82
Table 62 Pharmaceutical costs used in the model	85
Table 63 Distribution of treatments under DK SoC and cost per administration	87
Table 64 Administration costs used in the model	88
Table 65 Disease management costs used in the model	88
Table 66 Cost associated with management of adverse events	89
Table 67 Medicines of subsequent treatments	91
Table 68 Costs of subsequent treatments	91
Table 69 Costs of aSCT	92
Table 70 Patient costs used in the model	92
Table 71 Base case overview	93
Table 72 Base case results, discounted estimates	93
Table 73 One-way sensitivity analyses results	95
Table 74 Scenario analyses	96



Table 75 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)	98
Table 76 Expected budget impact of recommending the medicine for the indication.....	98
Table 77 Main characteristics of studies included - MAVORIC	105
Table 78. Main characteristics of studies included - EORTC 21012	108
Table 79 Results per study - MAVORIC	112
Table 80. Results per study – EORTC 21012	113
Table 81 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]	114
Table 82: MAVORIC inclusion and exclusion criteria.....	116
Table 83: Data cleaning procedures.....	119
Table 84: Covariates included in the estimation of propensity scores	122
Table 85: Descriptive statistics.....	125
Table 86: Balance table for model covariates pre and post weighting	127
Table 87 Goodness of fit for OS (mogamulizumab separate models).....	133
Table 88 Goodness of fit for OS (DK SoC separate models)	133
Table 89. Overview of parameters in the PSA.....	159
Table 90 Bibliographic databases included in the literature search	166
Table 91 Conference material included in the literature search.....	167
Table 92 of Search strategy for Medline & EMBASE (conducted on 2 July 2019).....	168
Table 93 Search strategy for Medline In-Process (conducted on 2 July 2019)	171
Table 94 Search strategy for Cochrane (CENTRAL) (conducted on 2 July 2019)	171
Table 95 Search strategy for DARE (conducted on 2 July 2019).....	171
Table 96 Search strategy for Medline & EMBASE (conducted on 15 September 2020)	172
Table 97 Search strategy for Medline In-Process (conducted on 15 September 2020)	173
Table 98 Search strategy for Cochrane (CENTRAL) (conducted on 15 September 2020)	174
Table 99 Search strategy for Medline & EMBASE (conducted on 31 May 2021).....	174
Table 100 Search strategy for Cochrane (CENTRAL) (conducted on 31 May 2021)	176
Table 101 Search strategy table for Medline & EMBASE (conducted on 03 February 2025)	176
Table 102 Search strategy for Cochrane (CENTRAL) (conducted on 03 February 2025)	177
Table 103 Inclusion and exclusion criteria used for assessment of studies	178
Table 104 Overview of study design for studies included in the SLR	186
Table 105 Overview of study design for studies included in the analyses.....	201
Table 106 Overview of publications excluded at full-text screening from the SLR.....	201
Table 107 Study quality assessment of RCT's using the NICE checklist	221
Table 108 Quality assessment of outcomes used in the included RCT studies – GRADE (Comparison of Mogamulizumab vs. Vorinostat for Relapsed/Refractory Cutaneous T-Cell Lymphoma)	223



Table 109 Quality assessment of outcomes used in the included RCT studies – GRADE (Comparison of Brentuzimab vedotin vs. Physician’s Choise for Previously treated CD-30-positive Cutaneous T-Cell Lymphoma)	224
Table 110 Quality assessment of non-RCT’s using Downs and Black checklist	225
Figure 1 Disease-specific survival according to clinical stage	18
Figure 2 Antibody-dependent cellular cytotoxicity mechanism of action of mogamulizumab	21
Figure 3 Model structure	36
Figure 4 Overview of MAVORIC study design	42
Figure 5 Kaplan–Meier plot of investigator-assessed PFS for the ITT population	46
Figure 6 Kaplan–Meier survival analysis of OS (data cut-off 2 nd March 2019)	48
Figure 7 Kaplan–Meier curve of TTNT for the ITT population	50
Figure 8 Kaplan–Meier curve of NTFS for the ITT population	50
Figure 9 Distribution of winsorized ATT weights for the mogamulizumab arm	56
Figure 10 Unweighted Kaplan–Meier curves of OS by treatment arm	56
Figure 11 Weighted Kaplan–Meier curves of OS by treatment arm	57
Figure 12 Survival model selection process algorithm	58
Figure 13 Base-case model for OS; Log-normal adjusted for general population OS	60
Figure 14 NTFS extrapolated curves for mogamulizumab	61
Figure 15 TOT extrapolated curves for mogamulizumab	62
Figure 16 DFS following aSCT KM data, London supra-regional centre	63
Figure 17 OS following aSCT KM data, London supra-regional centre	64
Figure 18: DFS after aSCT – Digitised KM data and PSMs	64
Figure 19: OS after aSCT – Digitised KM data and PSMs	65
Figure 20 Base-case curves for OS and DFS after aSCT	65
Figure 21 Treatment Effect via Adjusted Mixed Model ¹ of QoL Symptoms Score Change from Baseline by Visit ² and Treatment Group of the LPP ³ for the EQ-5D-3L VAS Score ⁴	78
Figure 22 One way sensitivity analysis – tornado diagram	95
Figure 23 Incremental cost-effectiveness plane	96
Figure 24 Cost-effectiveness acceptability curve	97
Figure 25 Convergence plot	98
Figure 26. National Danish registers used to define the Danish real-world population	118
Figure 27: Flowchart of selected patients from the Danish registers	124
Figure 28: Distribution of winsorized ATT weights for the mogamulizumab arm	126
Figure 29: Distributional balance of age	126
Figure 30: Unweighted KM curves of OS by treatment arm	127
Figure 31: Log hazard over log time by treatment arm, unweighted	128
Figure 32: Weighted KM curves of OS by treatment arm	128
Figure 33: Log hazard over log time by treatment arm, weighted	129
Figure 34: Distributional balance of number of previous systemic treatments	130
Figure 35: Distributional balance of type of diagnosis	130
Figure 36: Distributional balance of sex	131
Figure 37 Log cumulative hazard for OS	132



Figure 38 Schoenfeld residuals	133
Figure 39 Extrapolated mogamulizumab curves (dependent fit, weighted).....	134
Figure 40 Extrapolated DK SoC curves (dependent fit, weighted)	134
Figure 41 Extrapolated mogamulizumab curves (independent fit, weighted).....	135
Figure 42 Extrapolated DK SoC curves (independent fit, weighted)	135
Figure 43 Extrapolated and observed hazard functions mogamulizumab (combined)	136
Figure 44 Extrapolated and observed hazard functions DK SoC (combined)	136
Figure 45 Extrapolated and observed hazard functions mogamulizumab (separate)	137
Figure 46 Extrapolated and observed hazard functions mogamulizumab (separate)	137
Figure 47: Families for Hierarchically Testing HRQoL Domains Related to CTCL	142
Figure 48: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Skindex-29 Symptom Scale Score	144
Figure 49: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus Itchy QoL Symptom Score	145
Figure 50: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus Likert Scale Score	146
Figure 51: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Skindex-29 Functioning Score.....	147
Figure 52: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus ItchyQoL Functioning Score.....	148
Figure 53: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Physical Well-Being Score	149
Figure 54: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Functional Well-Being Score	150
Figure 55: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Emotional Well-Being Score.....	152
Figure 56: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus ItchyQoL Emotion Score.....	153
Figure 57: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Skindex-29 Emotion Score	154
Figure 58: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Social Well-Being Score	155



Figure 59: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Total Score.....	156
Figure 60: Treatment Effect via Adjusted Mixed Model ^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the EQ-5D-3L Index Score	157
Figure 61: Treatment Effect via Adjusted Mixed Model of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the EQ-5D-3L VAS Score	158
Figure 62 PRISMA flow diagram for SLR conducted on 2 July 2019	182
Figure 63 PRISMA flow diagram for updated SLR conducted on 15 September 2020	183
Figure 64 PRISMA flow diagram for updated SLR conducted on 31 May 2021	184
Figure 65 PRISMA flow diagram for updated SLR conducted on 3 February 2025	185
Figure 66 Overall survival in DK SoC base case and HES	233

Abbreviations

Abbreviation term	Definition
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AFT	Accelerated failure time
aSCT	Allogeneic stem cell transplantation
BIA	Budget-impact analysis
BOR	Best overall response
CCR4	C-C chemokine receptor type 4
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisolone
CI	Confidence interval
CMA	Cost-minimization analysis
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CUA	Cost-utility analysis
DOT	Duration of treatment
ECOG	Eastern Cooperative Oncology Group
ECP	Extracorporeal photochemotherapy
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L	EuroQol Group 5-Dimension 3-Level Self-Report Questionnaire
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy - General
Fc	Fragment crystallizable
HR	Hazard ratio
HRQoL	Health-Related quality of life



HSUV	Health state utility value
IgG1	Immunoglobulin G 1
IQR	Interquartile range
ISCL	International Society for Cutaneous Lymphomas
ITC	Indirect treatment comparison
ITT	Intent-to-treat population
LDH	Lactate dehydrogenase
LS	Least square
LY	Life years
MF	Mycosis fungoides
MID	Minimally important difference
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NTFS	Next-treatment-free-survival
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PH	Proportional Hazards
PO	Per os
PR	Partial response
PSA	Prostate-specific antigen
PUVA	Psoralen plus ultraviolet-A radiation.
QALY	Quality-adjusted life years
QoL	Quality of Life
R/R	Relapsed/Refractory
RDI	Relative dose intensity
RWE	Real-World Evidence
SmPC	Summary of product characteristics
SoC	Standard of Care
SS	Sézary syndrome
TEAE	Treatment-emergent adverse event
TNMB	Tumour-node-metastasis-blood
TSEBT	Total skin electron beam therapy
TTF	Time-to-treatment failure
TTNT	Time-to-next treatment
TTR	Time to response
VAS	Visual analogue score



1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Poteligeo®
Generic name	Mogamulizumab
Therapeutic indication as defined by EMA	Mogamulizumab is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.
Marketing authorization holder in Denmark	Kyowa Kirin Holdings B.V. Bloemlaan 2 2132 NP Hoofddorp Holland
ATC code	L01FX09
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	22 November 2018
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, orphan drug designation was granted on October 14, 2016 (EU/3/16/1756).
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Treatment practices across the Nordic countries are aligned. However, since the product is already recommended in Sweden and Norway, this application for recommendation only concerns Denmark.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	20 mg vials of mogamulizumab in 5ml, corresponding to 4mg/mL

2. Summary table

Summary	
Indication relevant for the assessment	Poteligeo® is indicated for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.
Dosage regimen and administration	The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on Days 1 and 15



Summary	of each subsequent 28-day cycle until disease progression or unacceptable toxicity.
Choice of comparator	According to Danish treating dermatologists, haematologists, and oncologists, standard of care (SoC) in Denmark follows closely international guidelines from the European Society of Medical Oncology (ESMO) and the European Organisation for Research and Treatment of Cancer – Cutaneous Lymphoma Tumour Group (EORTC-CLTG). Systemic treatments include retinoids (bexarotene, acitretin, isotretinoin, and alitretinoin), chemotherapies (cyclophosphamide, doxorubicin, vincristine, prednisolone, gemcitabine, low and high dose methotrexate, etoposide, chlorambucil, chlormethine, and carmustine), interferon (alpha and pegylated), extracorporeal photopheresis (ECP), and immunotherapies (alemtuzumab, brentuximab vedotin, and pembrolizumab). Therefore, the base-case analysis relies on an indirect treatment comparison of mogamulizumab vs the basket of treatments that make up Danish SoC (DK SoC).
Prognosis with current treatment (comparator)	The prognosis of patients with MF/SS is dependent on stage. Patients with early-stage MF have a survival similar to that of the general population, however, median survival is reduced to 4.7 years for stage IIB patients, to 1.4 years for stage IVB patients, and to 3.1 years for patients with SS.
	Advanced MF and SS both impose a severe quality of life (QoL) burden on both patients and caregivers; patients face debilitating symptoms like persistent itching, skin discomfort, and sleep disruption, while caregivers are significantly impacted by the demanding, time-consuming nature of providing physical and emotional support.
Type of evidence for the clinical evaluation	Effect estimates from the pivotal phase III randomized controlled trial MAVORIC, adjusted using inverse probability of treatment weighting (IPTW) with an external control arm generated from Danish national register data on SoC.
Most important efficacy endpoints (Difference/gain compared to comparator)	Overall survival (OS) estimates adjusted to reflect outcomes had the DK SoC population received mogamulizumab. Median OS mogamulizumab not reached. Median OS Danish standard of care 17.94 months.
Most important serious adverse events for the intervention and comparator	Mogamulizumab demonstrated a tolerable and manageable safety profile in patients with MF and SS. The most common treatment-related serious adverse events (AEs) with mogamulizumab were pneumonia (2%) and pyrexia (2%). AEs were not assessed in the DK SoC external control arm. In the MAVORIC trial control arm (vorinostat), the most common serious AEs were pulmonary embolism (3%) and thrombocytopenia (2%).
Impact on health-related quality of life	Clinical documentation: In the phase III MAVORIC trial, mogamulizumab showed clinically meaningful HRQoL improvements, measured by FACT-G, Skindex-29, ItchyQoL, and EQ-5D-3L. Improvements were sustained longer with mogamulizumab than with vorinostat in MF/SS patients. Health economic model: Mogamulizumab generated more quality-adjusted life years (QALYs) compared to DK SoC, though at a higher cost.



Summary	
Type of economic analysis that is submitted	Cost-utility analysis using a partitioned survival model structure.
Data sources used to model the clinical effects	The phase III MAVORIC trial and real-world evidence data from Danish national registers.
Data sources used to model the health-related quality of life	The phase III MAVORIC trial with Danish specific tariff
Life years gained	5.04
QALYs gained	3.56
Incremental costs	DKK 1,151,759
ICER (DKK/QALY)	DKK 323,961
Uncertainty associated with the ICER estimate	Starting age in the model Mogamulizumab price State-specific utilities
Number of eligible patients in Denmark	55 patients in Year 5
Budget impact (in year 5)	11,644,100 DKK

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

3.1 The medical condition

Lymphoma is a hematologic cancer of the lymphocytes, a type of white blood cell, and can be classified as Hodgkin lymphoma or non-Hodgkin lymphoma (NHL) (1). Approximately 80% of lymphomas are NHL. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells). There are many different forms of T-cell lymphomas, and cutaneous T-cell lymphoma (CTCL) is a general term for T-cell lymphomas that involve the skin. CTCL combines a group of diseases which are defined by abnormal clonal proliferations of post-thymic mature T-cells that infiltrate the skin and eventually manifest into patches, plaques, tumours and/or erythroderma (2). However, CTCL also involves the blood, lymph nodes and viscera, and the level of involvement of the different compartments (skin, lymph, blood, and viscera) determine a patient's prognosis and are used in the disease staging system (3). Approximately 2/3 of CTCL are classified as either mycosis fungoides (MF) or Sézary syndrome (SS), which are fatal and debilitating haematological malignancies (4).

MF, which accounts for 50-60% of CTCL cases, has indolent clinical behaviour presenting as slightly scaly, pruritic, erythematous patches or thin plaques, which are frequently characterized by epidermal atrophy (3, 5, 6). This early presentation is highly variable and many



of its clinical and pathologic features are non-specific, mimicking a variety of inflammatory, infectious and malignant dermatologic disorders (2, 4). As such, a definitive diagnosis of MF is challenging, particularly in early stages, and is often delayed for years (median: 3–4 years) or even decades (more than 40 years in some cases) (4). While a definitive diagnosis of MF may be made based on clinical and histopathologic features alone (biopsies of suspected skin sites), molecular analyses to detect clonal T-cell receptor gene rearrangements is useful in confirming a diagnosis, especially considering the prognostic significance of peripheral blood involvement in MF (4, 7). The more advanced stages of MF are characterized by extracutaneous disease, including more significant blood involvement, lymph node involvement or visceral spread as malignant T-cells may lose their skin homing tendency, migrate back to blood and spread to other compartments (8). In the rare instances where visceral involvement occurs, the disease usually proves fatal (2).

SS is a rare, more aggressive, leukemic form of CTCL characterized by the presence of malignant lymphocytes called 'Sézary cells' in the peripheral blood ($> 1,000/\mu\text{L}$), erythroderma indicating blood involvement by malignant T-cells, and generalized lymphadenopathy (4, 8). Importantly, the morphologic detection of Sézary cells in the peripheral blood is not specific for CTCL; therefore, the detection of clonally related T-cells (Sézary cells) in the skin and lymph nodes is useful in confirming a diagnosis of SS (4, 7, 9). As with MF, there are delays in the diagnosis of SS (mean: 4.2 years overall) and variations in the diagnosis of SS can be determined by the presence or absence of erythroderma at initial presentation (10). Overall, differentiation from MF is not clear, and many studies categorise SS patients as advanced MF.

MF and SS have been staged according to the tumour-node-metastasis-blood (TNMB) classification system by the International Society for Cutaneous Lymphomas (ISCL) and the EORTC since 2007 which takes into account concurrent disease involvement in all four disease compartments (skin, lymph nodes, blood and viscera) and stratifies patients into nine stages (Stage IA–IVB) (11) (Table 1). Considering advanced disease is defined as Stage IIB or above, by definition all SS patients (Stage IVA1–IVB) are considered advanced. Management of MF and SS is stage dependent, therefore accurate staging is essential for best management (12).

Table 1 EORTC proposed clinical staging for MF and SS

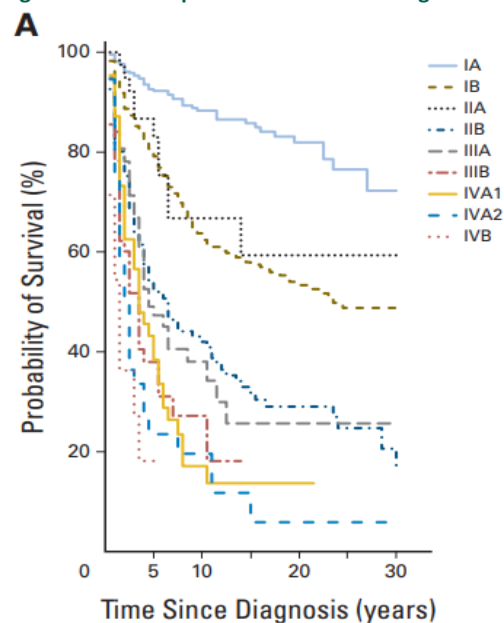
Subtype	Clinical stage	Skin	Node	Visceral	Blood
Mycosis fungoides Sézary syndrome	IA	T ₁	N ₀	M ₀	B _{0,1}
	IB	T ₂	N ₀	M ₀	B _{0,1}
	IIA	T _{1–2}	N _{1,2}	M ₀	B _{0,1}
	IIB	T ₃	N _{0–2}	M ₀	B _{0,1}
	IIIA	T ₄	N _{0–2}	M ₀	B ₀
	IIIB	T ₄	N _{0–2}	M ₀	B ₁
	IVA ₁	T _{1–4}	N _{0–2}	M ₀	B ₂
	IVA ₂	T _{1–4}	N ₃	M ₀	B _{0–2}
	IVB	T _{1–4}	N _{0–3}	M ₁	B _{0–2}

Abbreviations: B, blood; EORTC, European Organisation for Research and Treatment of Cancer; M, metastasis; MF, mycosis fungoides; N, node; SS, Sézary syndrome; T, tumour. Source: Olsen et al. (11).



Prognosis in MF and SS is highly dependent on disease stage at diagnosis, TNMB classification, and the extent of disease involvement (11-16). Advanced disease stages (IIB and beyond) correlate with notably reduced survival compared to early stages (IA–IIA), with survival outcomes worsening significantly as the disease progresses (16). Blood involvement, specifically at higher levels (B1 or B2), further reduces survival rates, and the presence of T-cell clones in blood is associated with a poorer prognosis (17). Skin involvement also impacts survival differently by disease stage, with advanced skin disease (T3–T4) associated with lower survival (18-20). Similarly, nodal (N1-N3) and visceral (M1) involvement are associated with increased mortality risk (12). Agar et al. reported a median overall survival (OS) of 4.7 years for stage IIB patients with 47% being alive five years after diagnosis. For SS, the median OS was 3.1 years, with 26% being alive five years after diagnosis. Late-stage disease (IVB) is associated with the lowest OS, a median of only 1.4 years (13). The variable prognosis is shown in Figure 1 below.

Figure 1 Disease-specific survival according to clinical stage



Source: Agar et al. (13)

CTCL imposes a substantial physical and psychological burden on patients, characterized by disfiguring skin manifestations, which significantly impair quality of life (QoL) (21). Due to its debilitating nature, the disease also impacts broader aspects of life, including family dynamics, occupational participation, and social interactions (21, 22). Additionally, caregivers experience substantial physical and emotional demands, particularly in managing practical care tasks which are time-intensive and contribute to a higher caregiver burden compared to other cancer types (23). As a result of the few treatment options available, patients can cycle through multiple treatments that have previously failed, imposing a substantial burden on individuals and health care systems (24). There is a clear unmet need for new treatment options for advanced MF and SS patients who require systemic therapy that can target all disease compartments (skin, blood, lymph nodes and viscera) and provide a durable response in order to extend patients' disease-free interval and, subsequently, time to receiving next therapy, as well as a meaningful OS benefit.



3.2 Patient population

There is a paucity of recent high quality epidemiological literature investigating the incidence, prevalence and regional variation of CTCL, MF, and particularly SS, making it difficult to define the current epidemiological landscape (25). Globally, CTCL incidence and prevalence appear to be increasing. In Europe, incidence has risen since the 1960s by 15–40% every five years, with the steepest increases in Central and Nordic countries (26).

In Denmark, the estimated incidence of MF is 0.3-0.5 per 100,000 individuals (27), corresponding to approximately 10 to 15 new cases annually. With 87% five-year survival, the estimated 5-year prevalence is $0.4 \times 100,000 \times 5 \times 0.87 = 1.7$ per 100,000. Based on Danish register data (28), the ratio of SS to MF patients receiving systemic therapy is 0.132 (SS:MF = 24/182, see section 7 for further details). Applying this ratio to the MF incidence (0.4 per 100,000) gives a SS incidence of 0.053 per 100,000.

Table 2 shows the expected incidence and prevalence of MF and SS in Denmark over the past five years. Notably, the 182 MF patients and 24 SS patients reported in the Danish register data represent a treated cohort used to estimate the SS:MF ratio, rather than the total national case count per year. The figures in Table 2, by contrast, are population-level estimates of annual incidence and 5-year prevalence derived from national rates. The two datasets are therefore conceptually aligned but not numerically comparable.

Table 2 Incidence and prevalence in the past 5 years

Year	2021	2022	2023	2024	2025
Danish population	5,873,623	5,934,002	5,964,059	5,995,628	6,004,342
SS incidence	3	3	3	3	3
SS prevalence	13	13	13	13	14
MF incidence	23	24	24	24	24
MF prevalence	100	101	101	102	102
Incidence in Denmark	27	27	27	27	27
Prevalence in Denmark	113	114	115	115	116
Global prevalence	Worldwide MF incidence of 0.36–0.64/100,000 (29)				

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome.

In line with its license (patients who have received one prior systemic treatment) not all patients will be eligible for mogamulizumab. Kyowa Kirin expects that approximately one third of MF patients and all SS would be receiving treatment with mogamulizumab in case of approval, corresponding to 11 patients per year (3 SS patients and ~8 MF patients).

Table 3 Estimated number of incident patients eligible for treatment

Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for treatment in the coming years	11	11	11	11	11



3.3 Current treatment options

Treatment of CTCL in Denmark, including MF and SS, is primarily carried out by dermatologists in collaboration with haematologists and oncologists, and follows international guidelines from the ESMO and the EORTC-CLTG (16, 30, 31). There is no single standard regimen; therapy is tailored to disease characteristics, stage, comorbidities, prior treatments, and patient preferences (32). With the exception of allogeneic stem cell transplantation (aSCT), available therapies are non-curative. The main goals are to delay progression, reduce tumour burden, improve quality of life, and minimise treatment-related toxicity. Response rates are generally below 50% and progression-free survival (PFS) is often less than six months, meaning most patients require sequential therapies (33).

Therapy for early-stage MF (IA-IIA) is typically skin-directed, including topical corticosteroids, chlormethine (nitrogen mustard), and phototherapy (narrow-band UVB or PUVA).

For advanced MF (IIB–IV) and SS, first-line therapy typically involves systemic agents (interferon- α , retinoids such as acitretin or bexarotene, or low-dose methotrexate), often in combination with local treatments or phototherapy. Radiotherapy and total skin electron beam therapy (TSEBT) are options for tumour control. For highly selected patients, aSCT may be considered with curative intent (33). Subsequent treatment decisions are discussed at multidisciplinary meetings. Immunotherapies include brentuximab vedotin (anti-CD30), alemtuzumab (anti-CD52), and pembrolizumab (PD-1 inhibitor). Of these, only brentuximab vedotin is EMA-approved for CD30-positive CTCL, including MF/SS (16, 34). Alemtuzumab and pembrolizumab require individual approval and are used off-label. In dermatology, off-label treatment is largely used due to a lack of evidence for treatment for given skin diseases (32). For mogamulizumab, the updated EORTC-CLTG guidelines specifically recommend its use as a second-line treatment in multiple stages of MF and SS (16).

3.4 The intervention

Overview of intervention	
Indication relevant for the assessment	Adult patients with MF or SS who have received at least one prior systemic therapy.
ATMP	N/A
Method of administration	Intravenous infusion.
Dosing	1 mg/kg IV over at least 60 minutes. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on Days 1 and 15 of each subsequent 28-day.
Dosing in the health economic model (including relative dose intensity)	1 mg/kg mogamulizumab administered as an intravenous infusion. Weekly administration on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every 2 weeks on days 1 and 15 of each subsequent 28-day cycle. Mean dose intensity of 94.4% (as reported during the randomized period of MAVORIC).
Should the medicine be administered with other medicines?	Pre-medication with antipyretic infusions and antihistamine is recommended for the first infusion. If an infusion reaction occurs, administration of pre-medication for subsequent infusions is recommended.



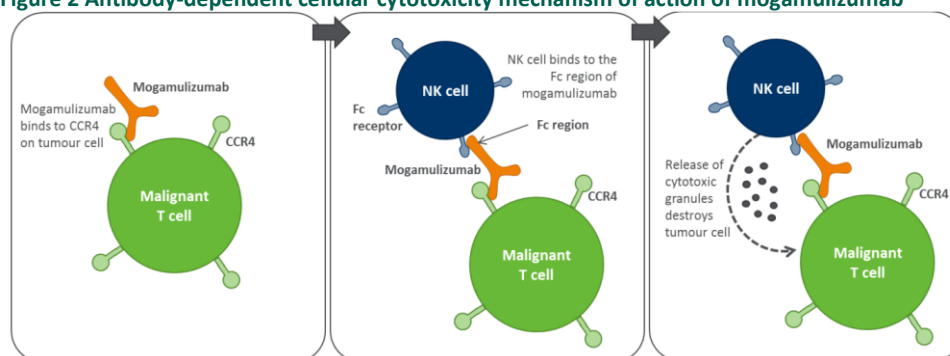
Overview of intervention	
Treatment duration / criteria for end of treatment	Disease progression, or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	20mg vials of mogamulizumab in 5ml, corresponding to 4mg/mL.

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome; mg, milligram; kg, kilogram; mL, millilitre. Source: (35).

3.4.1 Description of ATMP Mechanism of action

Mogamulizumab is a defucosylated, humanized, monoclonal antibody directed against CCR4, a G protein-coupled receptor for CC chemokines that is involved in the trafficking of lymphocytes to various organs including the skin, resulting in depletion of the target cells (36, 37). CCR4 is expressed on the surface of some cancer cells including T-cell malignancies, such as MF and SS (37). Upon binding to CCR4 on tumour cells, mogamulizumab facilitates natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) mechanism that destroys the cell (Figure 2) (38). NK cells bind by the fragment crystallizable (Fc) receptor to the Fc region of mogamulizumab on the tumour cell, which promotes the release of cytotoxic granules and causes tumour cell lysis (38).

Figure 2 Antibody-dependent cellular cytotoxicity mechanism of action of mogamulizumab



Abbreviations: CCR4, C-C chemokine receptor type 4; Fc region, fragment crystallizable region; NK cell, natural killer cell. Source: Kyowa Kirin – Data on file (38).

3.4.2 The intervention in relation to Danish clinical practice

In Danish clinical practice, mogamulizumab is anticipated to be incorporated as an additional option for patients with MF or SS who have progressed following first-line therapy and require alternative systemic treatment. Mogamulizumab is therefore expected to complement, rather than replace, existing agents and will expand the therapeutic armamentarium for advanced or refractory MF and SS, potentially delaying the need for high-toxicity treatments. Its introduction represents an incremental addition to established treatment protocols rather than a paradigm shift.



3.5 Choice of comparator(s)

According to Danish treating dermatologists, haematologists, and oncologists, MF and SS SoC in Denmark follows closely international guidelines from the ESMO and the EORTC-CLTG (see Section 14 for details on the experts who were consulted). For patients who have received at least one prior systemic therapy, SoC consists of other systemic treatments, including retinoids (bexarotene, acitretin, isotretinoin, and alitretinoin), chemotherapies (cyclophosphamide, doxorubicin, vincristine, prednisolone, gemcitabine, low and high dose methotrexate, etoposide, chlorambucil, chlormethine, and carmustine), interferon (alpha and pegylated), ECP, and immunotherapies (alemtuzumab, brentuximab vedotin, and pembrolizumab). Patients may continue to receive topical therapy, PUVA, localised radiotherapy, or TSEBT as part of routine management; however, inclusion in the DK SoC comparator arm was based solely on observed prior systemic treatment. The base-case analysis relies on the comparison between mogamulizumab and the basket of treatments that make up SoC in Denmark.

Table 4 Description of bexarotene

Overview of comparator – bexarotene	
Generic name	Bexarotene
ATC code	L01XF03
Mechanism of action	Selective retinoid X receptor (RXR α , β , γ) agonist regulating gene transcription involved in cell differentiation, proliferation, and apoptosis. Exact mechanism in CTCL unknown.
Method of administration	Oral capsules.
Dosing	300 mg/m ² /day; adjust for tolerability.
Dosing in the health economic model (including relative dose intensity)	600mg /m ² bexarotene administered orally once daily; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression or intolerable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	75 mg capsules, pack of 100.

Abbreviations: RXR, retinoid X receptor; CTCL, cutaneous T-cell lymphoma; mg, milligrams, m², squared meter.

Table 5 Description of acitretin

Overview of comparator – acitretin	
Generic name	Acitretin
ATC code	D05BB02
Mechanism of action	Synthetic retinoid that normalizes epidermal cell differentiation, keratinization, and proliferation. In MF/SS, retinoid-induced modulation of T-cell activity may contribute to anti-tumor effects.
Method of administration	Oral capsules.



Overview of comparator – acitretin

Dosing	10 to 30 mg daily for 2 to 4 weeks; may increase up to 75 mg/day depending on response and tolerability.
Dosing in the health economic model (including relative dose intensity)	30 mg orally once daily; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, lack of response, or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	25 mg capsules, 50 per blister pack.

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome; mg, milligram.

Table 6 Description of isotretinoin

Overview of comparator – isotretinoin

Generic name	Isotretinoin
ATC code	D10BA01
Mechanism of action	Retinoid and stereoisomer of tretinoin that modulates cell differentiation and proliferation. In MF/SS, proposed to induce apoptosis and alter malignant T-cell growth, though exact mechanism is unclear.
Method of administration	Oral capsules.
Dosing	0.5 mg/kg/day initially; adjust by response and tolerance.
Dosing in the health economic model (including relative dose intensity)	0.5 mg isotretinoin administered orally once daily; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, drug intolerance or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	20 mg capsules, 50 per blister pack.

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome; mg, milligrams; kg, kilograms.

Table 7 Description of alitretinoin

Overview of comparator – alitretinoin

Generic name	Alitretinoin
ATC code	D11AH04
Mechanism of action	Pan-retinoid receptor agonist (RAR and RXR) with immunomodulatory and anti-inflammatory effects. In MF/SS, may act by influencing malignant T-cell differentiation and apoptosis.
Method of administration	Oral capsules.



Dosing	30 mg once daily; reduce to 10 mg if not tolerated.
Dosing in the health economic model (including relative dose intensity)	30 mg orally once daily; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, lack of response, or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	30 mg capsules, 30 per blister pack.

Abbreviations: RAR, retinoic acid receptor; RXR, retinoid X receptor, MF, mycosis fungoides; SS, Sézary syndrome; mg, milligrams.

Table 8 Description of cyclophosphamide

Overview of comparator – cyclophosphamide	
Generic name	Cyclophosphamide
ATC code	L01AA01
Mechanism of action	Alkylating agent forming DNA cross-links that inhibit replication and transcription, leading to cell-cycle arrest and apoptosis. Active mainly in proliferating cells.
Method of administration	Intravenous infusion.
Dosing	600 mg/m ² IV every 3 to 4 weeks; adjust for hematologic toxicity and renal function.
Dosing in the health economic model (including relative dose intensity)	750 mg/m ² IV on day 1 of each 21-day cycle; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	Commonly used in combination regimens (e.g., CHOP) for MF/SS with systemic involvement.
Treatment duration/ criteria for end of treatment	Continue until disease progression, cumulative toxicity, or infection risk becomes unacceptable.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	500 mg powder for solution for injection.

Abbreviations: mg, milligrams; m², squared meter; IV, intravenous; MF, mycosis fungoides; SS, Sézary syndrome.

Table 9 Description of liposomal doxorubicin

Overview of comparator – liposomal doxorubicin	
Generic name	Liposomal doxorubicin
ATC code	L01DB01
Mechanism of action	Anthracycline that intercalates into DNA, inhibiting DNA and RNA synthesis and inducing strand breaks through topoisomerase II inhibition. Liposomal formulation alters tissue distribution and reduces cardiotoxicity.



Overview of comparator – liposomal doxorubicin

Method of administration	Intravenous infusion.
Dosing	20 to 50 mg/m ² IV every 3 to 4 weeks; slower infusion rates reduce infusion-related reactions.
Dosing in the health economic model (including relative dose intensity)	50 mg/m ² IV once every 21-day cycle; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No. However, non-liposomal doxorubicin is commonly used in combination regimens (e.g., CHOP) for MF/SS with systemic involvement.
Treatment duration/ criteria for end of treatment	Continue until disease progression, intolerance, or cumulative dose limit reached due to cardiotoxicity risk.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	100 mL vial, 2 mg/mL concentrate for infusion.

Abbreviations: mg, milligrams;m², squared meter; IV, intravenous;MF, mycosis fungoides; SS, Sézary syndrome;mL, millilitre.

Table 10 Description of vincristine

Overview of comparator – vincristine

Generic name	Vincristine
ATC code	L01CA02
Mechanism of action	Vinca alkaloid that binds tubulin, preventing microtubule formation and arresting mitosis in metaphase. Leads to apoptosis of dividing cells.
Method of administration	Intravenous Infusion.
Dosing	1 to 1.4 mg/m ² IV once weekly; adjust for toxicity and age.
Dosing in the health economic model (including relative dose intensity)	1.4 mg/m ² IV on day 1 of each 21-day cycle; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	Commonly used in combination regimens (e.g., CHOP) for MF/SS with systemic involvement.
Treatment duration/ criteria for end of treatment	Continue per regimen until disease progression, cumulative toxicity, or unacceptable neurotoxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	2 mL vial, 1 mg/mL solution for injection.

Abbreviations: mg, milligrams;m², squared meter; IV, intravenous;MF, mycosis fungoides; SS, Sézary syndrome;mL, millilitre.

Table 11 Description of prednisolone

Overview of comparator – prednisolone

Generic name	Prednisolone
ATC code	H02AB07



Mechanism of action	Synthetic glucocorticoid that binds cytoplasmic glucocorticoid receptors, altering gene expression to produce anti-inflammatory, immunosuppressive, and lympholytic effects.
Method of administration	Oral tablets.
Dosing	7.5 to 75 mg daily depending on disease severity; taper to lowest effective dose.
Dosing in the health economic model (including relative dose intensity)	40 mg/m ² orally on days 1–5 of each 21-day cycle; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	Commonly used in combination regimens (e.g., CHOP) for MF/SS with systemic involvement
Treatment duration/ criteria for end of treatment	Continue until inadequate response, toxicity, or transition to next therapy; minimize duration to reduce adverse effects.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	25 mg tablets, 100 per pack.

Abbreviations: mg, milligrams; MF, mycosis fungoides; SS, Sézary syndrome.

Table 12 Description of gemcitabine

Overview of comparator – gemcitabine	
Generic name	Gemcitabine
ATC code	L01BC05
Mechanism of action	Nucleoside analogue that inhibits ribonucleotide reductase and incorporates into DNA, leading to chain termination, impaired replication, and apoptosis of rapidly dividing cells.
Method of administration	Intravenous infusion.
Dosing	1,000 mg/m ² IV on days 1 and 8 of each 21-day cycle.
Dosing in the health economic model (including relative dose intensity)	1,000 mg/m ² IV on days 1 and 8 per 21-day cycle; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, cumulative toxicity, or intolerance.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	220 mL vial, 10 mg/mL concentrate for infusion.

Abbreviations: mg, milligrams; m², squared meter; IV, intravenous; mL, millilitre.

Table 13 Description of methotrexate

Overview of comparator - methotrexate	
Generic name	Methotrexate
ATC code	L04AX03



Overview of comparator - methotrexate

Mechanism of action	Antimetabolite that inhibits dihydrofolate reductase, blocking tetrahydrofolate formation and thereby impairing DNA and RNA synthesis in rapidly dividing cells, including malignant T cells.
Method of administration	Oral (low-dose) or intravenous (high-dose).
Dosing	Low-dose: 25 to 30 mg orally once weekly, typically used for MF/SS. High-dose: 1 to 3 g/m ² IV every 2 to 3 weeks in aggressive or refractory cases.
Dosing in the health economic model (including relative dose intensity)	30 mg orally once weekly; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, intolerance, or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	2.5 mg tablets, 100 per blister pack.

Abbreviations: mg, milligrams;g, grams; m², squared meter.

Table 14 Description of etoposide

Overview of comparator – etoposide

Generic name	Etoposide
ATC code	L01CB01
Mechanism of action	Topoisomerase II inhibitor that induces DNA strand breaks, preventing repair and replication, leading to cell-cycle arrest and apoptosis.
Method of administration	Oral capsules.
Dosing	50–100 mg/m ² /day on days 1–5 or 100–120 mg/m ² on days 1, 3, and 5 every 3–4 weeks; adjust for marrow suppression or prior therapy.
Dosing in the health economic model (including relative dose intensity)	40 mg/m ² orally on days 1 to 5 per 28-day cycle; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	Yes, commonly combined with other cytotoxic agents (e.g., CHOP-like regimens or platinum-based therapies) in advanced or transformed MF/SS.
Treatment duration/ criteria for end of treatment	Typically, 4–6 cycles given every 21–28 days; stop at disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	50 mg capsules, 20 per blister pack.

Abbreviations: mg, milligrams;m², squared meter;MF, mycosis fungoides; SS, Sézary syndrome.



Table 15 Description of chlorambucil

Overview of comparator – chlorambucil	
Generic name	Chlorambucil
ATC code	L01AA02
Mechanism of action	Alkylating agent that cross-links DNA strands at guanine residues, inhibiting replication and transcription, leading to cell-cycle arrest and apoptosis.
Method of administration	Oral tablets.
Dosing	0.1 to 0.2 mg/kg/day for 4–8 weeks when used as monotherapy for palliative treatment of advanced disease.
Dosing in the health economic model (including relative dose intensity)	10 mg orally once daily; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, hematologic toxicity, or intolerance.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	2 mg tablets, 25 per pack.

Abbreviations: mg, milligrams;kg, kilogram.

Table 16 Description of chlormethine

Overview of comparator – chlormethine	
Generic name	Chlormethine
ATC code	L01AA05
Mechanism of action	Bifunctional alkylating agent that cross-links DNA, inhibiting replication and inducing apoptosis in rapidly dividing malignant T cells in the skin.
Method of administration	Topical gel.
Dosing	Apply a thin layer once daily to affected skin areas.
Dosing in the health economic model (including relative dose intensity)	0.99 g topically once daily, up to 60 g six times per year; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Continue until adequate response or unacceptable local toxicity (e.g., ulceration, blistering, severe dermatitis). Resume at reduced frequency after improvement.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	60 g tube, 160 µg/g gel.

Abbreviations: g, grams; µg, microgram.

Table 17 Description of carmustine



Overview of comparator – carmustine	
Generic name	Carmustine
ATC code	L01AD01
Mechanism of action	Alkylating nitrosourea compound that forms interstrand DNA cross-links, inhibiting DNA and RNA synthesis and impairing repair mechanisms, leading to apoptosis.
Method of administration	Intravenous infusion .
Dosing	150 to 200 mg/m ² IV every 6 weeks, either as a single dose or split over two consecutive days.
Dosing in the health economic model (including relative dose intensity)	200 mg IV once every 6 weeks; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, cumulative myelosuppression, or unacceptable toxicity (particularly pulmonary or hepatic)
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	100 mg powder with solvent for reconstitution for IV infusion.

Abbreviations: mg, milligrams; m², squared meter; IV, intravenous.

Table 18 Description of peginterferon alfa-2a

Overview of comparator – peginterferon alfa-2a	
Generic name	Peginterferon alfa-2a
ATC code	L03AB11
Mechanism of action	Pegylated form of interferon alfa-2a with antiviral, antiproliferative, and immunomodulatory activity. Pegylation prolongs half-life and maintains interferon-mediated activation of immune effector cells that suppress malignant T-cell proliferation in MF/SS.
Method of administration	Subcutaneous injection.
Dosing	180 µg once weekly for 48 weeks; adjust based on tolerability and hematologic response.
Dosing in the health economic model (including relative dose intensity)	180 µg subcutaneously once weekly; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Continue until disease progression, intolerance, or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	Pack of 4 prefilled syringes, each containing 180 µg solution for injection.



Abbreviations: µg, microgram; MF, mycosis fungoides; SS, Sézary syndrome.

Table 19 Description of extracorporeal photopheresis (ECP)

Overview of comparator – extracorporeal photopheresis	
Generic name	Extracorporeal photopheresis
ATC code	N/A (DRG code: 16PR03)
Mechanism of action	Immunomodulatory therapy in which leukocytes are collected, exposed ex vivo to 8-methoxypsoralen and UVA light, then re-infused. Induces apoptosis of malignant T cells and promotes immune tolerance via activation of antigen-presenting cells.
Method of administration	Localised, device-based procedure performed in hospital.
Dosing	Typically administered on two consecutive days every 2 to 4 weeks; frequency may be adjusted by response.
Dosing in the health economic model (including relative dose intensity)	Two consecutive treatment days per 4-week cycle; mean dose intensity 100%.
Should the medicine be administered with other medicines?	Often combined with systemic agents (e.g., interferon, retinoids) in MF/SS for enhanced response.
Treatment duration/ criteria for end of treatment	Continue until disease progression, loss of response, or intolerance; responses often maintained with ongoing monthly cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	N/A

Abbreviations: DRG, diagnosis related groups; MF, mycosis fungoides; SS, Sézary syndrome.

Table 20 Description of alemtuzumab*

Overview of comparator - alemtuzumab	
Generic name	Alemtuzumab
ATC code	L04AG06
Mechanism of action	Monoclonal antibody targeting CD52 on B and T lymphocytes, monocytes, macrophages, NK cells, and some granulocytes. Induces antibody-dependent and complement-mediated lysis of malignant lymphocytes.
Method of administration	Intravenous infusion.
Dosing	12 mg/day IV for 5 consecutive days (first course), then 12 mg/day for 3 days at 12-month intervals; up to 4 total courses depending on response and tolerability.
Dosing in the health economic model (including relative dose intensity)	10 mg IV three times per week; mean dose intensity 94.4%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Up to 4 treatment courses or until disease progression, intolerance, or unacceptable toxicity.



Overview of comparator - alemtuzumab

Need for diagnostics or other tests (i.e. companion diagnostics) No.

Package size(s) 12 mg/1.2 mL vial, concentrate for infusion.

Notes: * Discontinued in Denmark as of June 23; previously available under compassionate use.

Abbreviations: mg, milligram; IV, intravenous; mL, millilitre.

Table 21 Description of brentuximab vedotin

Overview of comparator - brentuximab vedotin

Generic name Brentuximab vedotin

ATC code L01FX05

Mechanism of action CD30-directed antibody–drug conjugate consisting of a monoclonal antibody linked to monomethyl auristatin E (MMAE). After binding to CD30-positive cells, the complex is internalized and MMAE is released, disrupting microtubule formation and inducing apoptosis.

Method of administration Intravenous infusion.

Dosing 1.8 mg/kg IV every 3 weeks; reduce or delay doses for toxicity.

Dosing in the health economic model (including relative dose intensity) 1.8 mg/kg IV every 3 weeks; mean dose intensity 94.4%.

Should the medicine be administered with other medicines? No.

Treatment duration/ criteria for end of treatment Up to 16 cycles or until disease progression, intolerance, or unacceptable toxicity.

Need for diagnostics or other tests (i.e. companion diagnostics) No.

Package size(s) 50 mg vial, powder for concentrate for infusion.

Abbreviations: mg, milligram; kg, kilogram; IV, intravenous.

Table 22 Description of pembrolizumab

Overview of comparator - pembrolizumab

Generic name Pembrolizumab

ATC code L01FF02

Mechanism of action Humanized monoclonal antibody targeting PD-1 receptor, blocking its interaction with PD-L1 and PD-L2. This releases inhibitory signalling on T cells, restoring antitumor immune activity against malignant T cells in MF/SS.

Method of administration Intravenous infusion.

Dosing 200 mg IV every 3 weeks or 400 mg IV every 6 weeks.

Dosing in the health economic model (including relative dose intensity) 200 mg IV every 3 weeks; mean dose intensity 94.4%.

Should the medicine be administered with other medicines? No.



Overview of comparator - pembrolizumab

Treatment duration/ criteria for end of treatment	Continue until disease progression, intolerable immune-related toxicity, or completion of planned course (typically up to 2 years).
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	4 mL vial, 25 mg/mL concentrate for infusion.

Abbreviation: MF, mycosis fungoides; SS, Sézary syndrome; mg, milligram; IV, intravenous; mL, millilitre.

Table 23 Description of phototherapy UV-A (PUVA)

Overview of comparator - phototherapy UV-A

Generic name	Phototherapy UV-A
ATC code	N/A (DRG: 17MA98)
Mechanism of action	Combines oral or topical psoralen with ultraviolet A irradiation. Psoralen intercalates into DNA, and UVA exposure induces cross-linking, leading to apoptosis of malignant T cells in the skin and modulation of local immune responses.
Method of administration	Localised light-based therapy performed in a clinical setting.
Dosing	Typically administered 2 to 3 times per week; treatment frequency adjusted by skin response and tolerance.
Dosing in the health economic model (including relative dose intensity)	Three sessions per week for 14 weeks; mean dose intensity 100%.
Should the medicine be administered with other medicines?	In combination with oral or topical psoralen.
Treatment duration/ criteria for end of treatment	Continue for 14 weeks or until maximal clinical response or intolerance.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	N/A.

Abbreviations: DRG, diagnosis related groups.

Table 24 Description of local radiotherapy

Overview of comparator - local radiotherapy

Generic name	Local radiotherapy
ATC code	N/A (DRG: 27MP03)
Mechanism of action	Ionizing radiation induces DNA damage and apoptosis of malignant T cells within treated skin lesions, leading to local tumour control.
Method of administration	Localized external beam radiotherapy targeted to affected skin areas.
Dosing	Individualized by lesion size and depth; typical total dose 8 to 36 Gy delivered in fractions.



Overview of comparator - local radiotherapy

Dosing in the health economic model (including relative dose intensity)	One treatment course per year; mean dose intensity 100%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	Single annual course or as clinically indicated for local relapse.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	N/A.

Abbreviation: DRG, diagnosis related groups; Gy, gray.

Table 25 Description of total skin electron beam therapy (TSBET)

Overview of comparator - total skin electron beam therapy

Generic name	Total skin electron beam therapy
ATC code	N/A (DRG: 27MP03)
Mechanism of action	High-energy electron radiation delivered to the entire skin surface, inducing DNA damage and apoptosis of malignant T cells, resulting in tumour regression and disease control in MF/SS.
Method of administration	Localised external beam radiotherapy targeting the full skin surface, performed in specialized radiotherapy units.
Dosing	Individualized; typical total dose 30–36 Gy delivered in multiple fractions over 8–10 weeks; low-dose regimens (10–12 Gy) used for palliation.
Dosing in the health economic model (including relative dose intensity)	One treatment course per year; mean dose intensity 100%.
Should the medicine be administered with other medicines?	No.
Treatment duration/ criteria for end of treatment	One full course per year or until maximal response; repeat courses possible after relapse.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.
Package size(s)	N/A.

Abbreviation: DRG, diagnosis related groups; MF, mycosis fungoides; SS, Sézary syndrome; Gy, gray.

3.6 Cost-effectiveness of the comparator(s)

Brentuximab vedotin has been evaluated in Denmark for lymphoma indications, demonstrating clinical benefit in selected hematologic malignancies. However, the Danish Medicines Council (DMC) has issued cautious recommendations due to high cost and uncertain incremental cost-effectiveness (39). Pembrolizumab has undergone multiple cost-effectiveness assessments in oncology and is reimbursed for specific cancers, but not for cutaneous T-cell lymphomas. Agents such as gemcitabine, alemtuzumab, doxorubicin, and



pegylated interferon alfa are supported by clinical guidelines and established practice, though no formal DMC cost-effectiveness evaluations have been published. Retinoids including acitretin and isotretinoin are primarily dermatologic agents with well-characterized safety and cost profiles but lack formal economic assessments in MF/SS. Methotrexate and bexarotene, while not evaluated by the DMC, are long-standing components of European and Danish treatment guidelines. Their continued use reflects a presumed acceptable cost-effectiveness ratio, given their demonstrated clinical efficacy, low acquisition costs, and extensive clinician experience. In Denmark, these agents are considered standard first-line systemic options when topical or phototherapy approaches (e.g., PUVA) are insufficient

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The most relevant efficacy outcomes for this assessment are outlined in Table 26. For the clinical assessment of mogamulizumab, these include PFS, ORR, DOR, OS, and NTFS. For the assessment of the relevant comparator of this analysis (DK SoC), the relevant efficacy outcomes are OS and NTFS (indirectly modelled, see section 8.4).

Table 26 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) by investigator [MAVORIC](5)	7.7 months	Defined as the time in months from randomisation until investigator-assessed disease progression or death due to any cause whichever occurs first.	See Sections 6, 7, 8, and Appendix D
Overall response rate (ORR) [MAVORIC](5)	At the end of cycle 1. Every other cycle in year 1. QW16 weeks in year 2+	Defined as the count of subjects who had a confirmed CR or PR, defined as documented CR or PR per Global Composite Response Score that was confirmed by a subsequent observation at least 4 weeks later.	
Duration of response (DOR) [MAVORIC](5)	14.1 months	Defined as the time in months from first achievement of an overall response to progression or death.	
Overall survival (OS) [MAVORIC (5) and DK SoC(28)]	Max 3 years of max follow up	MAVORIC: Defined as the time in months from randomisation until death or censoring in the mogamulizumab arm. DK SoC: Defined as time in months from initiation of the most recent observed systemic therapy until death or censoring.	
Next treatment-free survival (NTFS) [MAVORIC (5) and DK SoC(28)]	See section 6, 7, and 8	MAVORIC: Defined as the time in months from the initiation of a therapy until the initiation of the next line of therapy or death, whichever occurs first.	



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
-----------------	-------------	------------	--

DK SoC: Estimated indirectly based on cycle specific hazard ratio.

Notes: * Time point for data collection used in analysis (follow up time for time-to-event measures).
Abbreviations: QW, once weekly; CR, complete response; PR, partial response; DK SoC, Danish standard of care.

3.7.1.1 Validity of outcomes

PFS, ORR, DOR, and OS are standard, reliable oncology endpoints and have been used by the DMC in multiple prior assessments. NTFS is a valuable endpoint measuring the duration patients remain free from further treatment or death, reflecting clinical stability and well-being. It captures the durability and tolerability of therapy by incorporating quality of life during remission or low disease activity, key in MF and SS, where disease is often indolent but requires ongoing therapy adjustments for relapses or adverse effects (40, 41).

4. Health economic analysis

A Danish-adapted Excel-based cost-effectiveness model (CEM) was used for a cost-utility analysis assessing mogamulizumab versus DK SoC in adults with MF or SS after ≥ 1 prior systemic therapy. Model outcomes included total and incremental costs and QALYs.

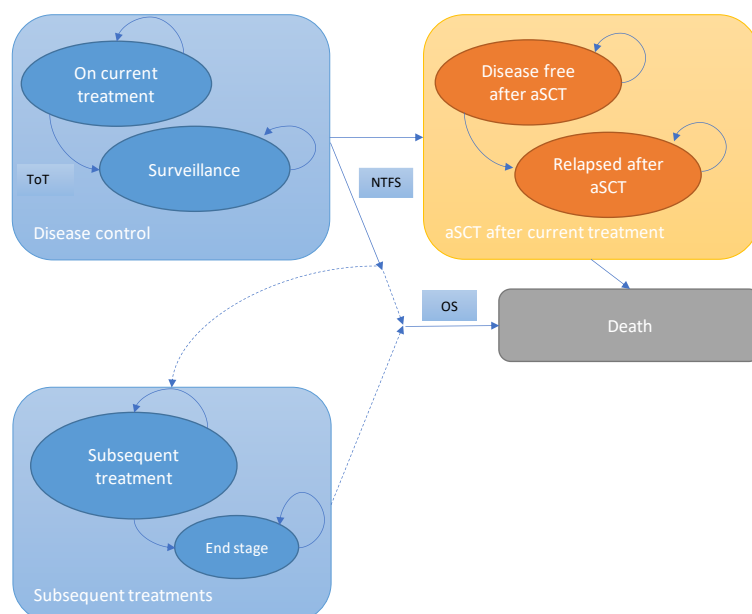
4.1 Model structure

The analysis used a partitioned survival model (PSM), a standard oncology modelling approach suited for progressive, chronic conditions with time-dependent risks such as progression and death. This method is also commonly accepted by the DMC. Two adaptations were made to reflect mogamulizumab's mechanism of action:

- Inclusion of potential aSCT as a curative option, consistent with clinical practice and NICE TA577.
- Use of NTFS instead of PFS to define health states.



Figure 3 Model structure



Abbreviations: ToT, time on treatment; NTFS, next treatment-free survival; aSCT, allogenic stem cell transplantation; OS, overall survival.

As shown in Figure 3, health states were defined by either disease control or the need for new treatment, using NTFS (time to next treatment or death) instead of PFS. All simulated patients started in the Disease control state, receiving mogamulizumab or DK SoC. At any cycle, treatment could stop. If no new therapy was needed, patients entered surveillance within the same state. Eventually, they progressed to the subsequent treatment state and possibly end stage. Death could occur at any time, consistent with the PSM structure. A proportion of patients could also undergo aSCT after their current treatment. Following aSCT, they either entered disease free or relapsed states, with death possibly occurring at any stage.

4.2 Model features

The features of the health economic model are presented in Table 27.

Table 27 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with MF or SS who have received at least one prior systemic therapy	Aligned with this submission
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines
Cycle length	7 days	Allows for inclusion of all treatment schedules



Model features	Description	Justification
Half-cycle correction	No	Cycle is sufficiently short so that half cycle correction does not impact results
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Mogamulizumab	Relevant for this assessment
Comparator(s)	DK SoC	Current clinical practice in Denmark based on local clinician input and observed utilisation in national Danish registers
Outcomes	OS (MAVORIC and IPTW adjusted) NTFS (MAVORIC and indirect estimation)	Needed for the modified partitioned survival model structure

Abbreviations: MF, mycosis fungoides; SS, sézary syndrome; DMC, Danish medicines council; DK SoC, Danish standard of care ; OS, overall survival; IPTW, inverse probability of treatment weighting; NTFS, next treatment-free survival.

5. Overview of literature

5.1 Literature used for the clinical assessment

A clinical systematic literature review (SLR) was conducted for this DMC application to identify interventional and observational studies on the efficacy and safety of mogamulizumab. Full methods and results, including the PRISMA flowchart and search outputs, are presented in Appendix H.



Table 28 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*
Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. <i>Lancet Oncol.</i> 2018;19(9):1192-1204.(5) Kim YH, Ortiz-Romero PL, Pro B, et al. Time to next treatment in patients with previously treated cutaneous T-cell lymphoma (CTCL) receiving mogamulizumab or vorinostat: A MAVORIC post-hoc analysis. <i>Hematol Oncol.</i> 2019; 37(S2):285-286(42) Kim YH, Bagot M, Zinzani PL, et al. Safety of mogamulizumab in mycosis fungoides and Sézary syndrome: final results from the Phase 3 MAVORIC study. <i>Blood.</i> 2019;134(Suppl 1):530(43)	MAVORIC	NCT01728805	Start: 11/12 Completion: 17/02/21 Data cut-off: 02/03/19	Mogamulizumab vs vorinostat in patients with previously treated cutaneous T-cell lymphoma (relapsed or refractory MF or SS). Only mogamulizumab arm is relevant for this submission.
Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. <i>J Clin Oncol.</i> 2012;30(33):4091-4097.	EORTC 21012	NCT00074087	Start: 10/03 Completion: 09/10 Data cut-off: N/A	Liposomal doxorubicin in patients who have stage IIB, stage IVA, or stage IVB recurrent or refractory MF after at least two previous systemic therapies. Used to model overall survival and disease-free survival post aSCT.
Scarisbrick J, Arumainathan A, Cowan R, DeSimone J, Esler C, Geskin LJ, et al. A-201 Patient-reported symptoms and HRQL of MF and SS patients receiving mogamulizumab over 24 weeks: interim results from the PROSPER study. <i>European Journal of Cancer.</i> 2024;211.	PROSPER	NCT05455931	Start: 09/11/22 (estimated) Completion: 07/08/25	Real-world observational study of mogamulizumab in adult patients with MF/SS, collecting quantitative and qualitative data on treatment experience, clinical practice, and patient-reported outcomes Used as supportive clinical evidence on early symptom improvement in patients with



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*
				advanced MF/SS, particularly outcomes related to symptom burden and HRQL are relevant for this submission
Ritzau. Global Registry Data Show Meaningful Overall Survival Benefit in Patients with Advanced Cutaneous T-cell Lymphoma (CTCL) treated with POTELIGEO (mogamulizumab) 2025	PROCLIP	NCT02848274	Start: 10/16 (estimated) Completion: 03/27	Prospective observational study collecting standardized clinical data to identify prognostic factors and develop a prognostic index model for advanced mycosis fungoides and Sézary syndrome (stages IIB–IVB). Used as complementary clinical evidence demonstrating improved overall survival in advanced MF/SS, with survival outcomes across CLIP risk groups relevant for this submission.

Notes: * If there are several publications connected to a trial, include all publications used. Abbreviations: MF, mycosis fungoides; SS, sézary syndrom ; aSCT, allogenic stem cell transplant.

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

Health state utility values (HSUVs) were estimated using MAVORIC trial data and the Danish EQ-5D algorithm (44), in line with DMC guidelines. Additional states, such as post-aSCT, were informed by external validated sources.



Table 29 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
Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. <i>Lancet Oncol.</i> 2018;19(9):1192-1204(5)	HSUVs for the main model states (Disease control and Subsequent treatments)	See section 10.1
Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. <i>Leuk Lymphoma.</i> 2015 Jun;56(6):1839-45. doi: 10.3109/10428194.2014.970542. Epub 2014 Nov 3. PMID: 25284490. (45)	HSUV associated with end-of-life stage	See section 10.3
van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. a prospective randomised trial. <i>Eur J Cancer.</i> 2001 Sep;37(14):1781-9. doi: 10.1016/s0959-8049(01)00198-8. PMID: 11549432. (46)	HSUVs associated with post-SCT stages	See section 10.3

Abbreviations: HSUVs, health state utility values; post-SCT, post stem cell transplant.



5.3 Literature used for inputs for the health economic model

Table 30 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
NICE TA577 (47)	Post aSCT disease modelling	Treatment specific identification (aSCT) and previous use in National health technology assessment.	Section 8.3

Abbreviations: aSCT, allogenic stem cell transplant.



6. Efficacy

6.1 Efficacy of mogamulizumab compared to vorinostat for patients with MF or SS who have received at least one prior systemic therapy

6.1.1 Relevant studies

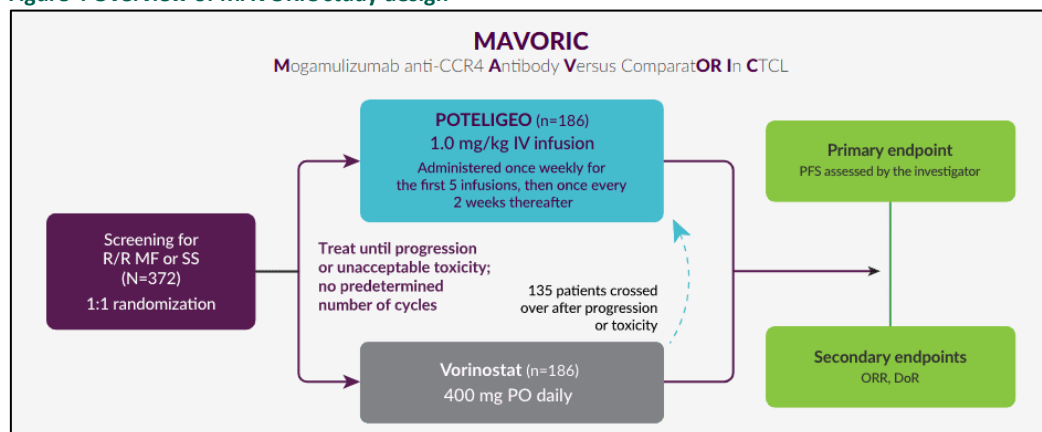
The phase 3 MAVORIC trial, a multinational randomized open-label study, evaluated the efficacy of mogamulizumab against vorinostat in 372 adults with CTCL (MF or SS), randomized 1:1 (186 per arm) (5). While not considered an appropriate comparator in the DMC's original assessment, vorinostat is presented here to comply with the template requirements and to provide background information.

In the MAVORIC trial, mogamulizumab was administered intravenously at 1 mg/kg weekly during the first 28-day cycle and on days 1 and 15 of subsequent cycles. Vorinostat was given orally at 400 mg daily. Patients with disease progression or intolerance to vorinostat could cross over to mogamulizumab. Of the 186 patients randomized to vorinostat, 136 crossed over to mogamulizumab (5). Treatment continued until progression or unacceptable toxicity. Key exclusion criteria were autoimmune disease, central nervous system metastasis, need for systemic immunosuppression, active infections (HIV, HBV, HCV), and ECOG ≥ 2 .

At baseline, 36% had stage IB to II, 12% stage III, and 51% stage IV disease. The study included patients regardless of their baseline level of CCR4 expression in skin biopsy (5). MF and SS diagnoses were histologically confirmed (MF: 56.% vs 53.%; SS: 44% vs 47% in mogamulizumab and vorinostat arms, respectively). Baseline characteristics and prior therapies were well balanced. Median age was 64 years; 47% were ≥ 65 years. Overall, 59% were male and 67% white. Both mogamulizumab and vorinostat arms had a median of 3 previous systemic therapies. Median mogamulizumab exposure was 170 days

Study design, endpoints, and key characteristics are summarized in Figure 4 and Table 31. As the MAVORIC comparator (vorinostat) is not used in Denmark, clinical expert input and Danish register data were used to define DK SoC and conduct an indirect treatment comparison (ITC) (see section 7). Although vorinostat data are also reported in section 6, the focus of this submission and cost-effectiveness analysis is comparing mogamulizumab with DK SoC.

Figure 4 Overview of MAVORIC study design



Abbreviations: CTCL, cutaneous T-cell lymphoma, IV, intravenous; MF, mycosis fungoides; mg, milligrams; kg, kilograms; PFS, progression-free survival; ORR, overall response rate; DoR, duration of response; PO, per os; R/R, relapsed/refractory; SS, Sézary syndrome. Source: Kim et al. (5).



Table 31 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
MAVORIC, NCT01728805 (5)	Open-Label, Multi-Center, Randomized, Active comparator, Phase 3	Up to 36 months	Adult patients with IB to IVB histologically confirmed relapsed or refractory MF or SS who have received at least one previous systemic therapy	Mogamulizumab administered intravenously at a dose of 1.0 mg/kg weekly for the first four weeks, followed by every two weeks thereafter	Vorinostat administered orally at 400 mg daily.	Primary Progression-free survival: Time from randomization to investigator-assessed progression or death from any cause, whichever occurred first, assessed up to 36 months. Secondary Overall response rate: At the end of Cycle 1 (Days 26 to 28), then every other cycle in Year 1 (Cycles 3, 5, 7, 9, 11, 13), and every 16 weeks (Cycles 17, 21, etc.) in Year 2 and beyond, up to 36 months. Duration of response: Time from first documented overall response to progression or death. Quality of life: Skindex-29 Symptoms Scale assessed at Cycles 1, 3, and 5. Exploratory Overall survival: Time from randomization to death from any cause. Time to treatment failure: Time from randomization until treatment failure.

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome; mg, milligrams; kg, kilograms.



6.1.2 Comparability of studies

6.1.2.1 Comparability of patients across studies

Baseline patient characteristics for each arm of the MAVORIC trial and the DK SoC arm are presented in Table 32.

Table 32 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	MAVORIC (5)		DK SoC
	Mogamulizumab (n=186)	Vorinostat (n=186)	Relevant comparator arm
Age, years	64 (54–73)	65 (56–72)	
Age group, years			
<65	99 (53%)	89 (48%)	
≥65	87 (47%)	97 (52%)	
Male	109 (59%)	107 (58%)	
ECOG performance status †			
0	106 (57%)	104 (56%)	N/A
1	78 (42%)	82 (44%)	N/A
2	2 (1%)	0	N/A
Time from initial diagnosis, months	41.0 (17.4–78.8)	35.4 (16.2–68.2)	
Mycosis fungoides	105 (56%)	99 (53%)	
Sézary syndrome	81 (44%)	87 (47%)	
Current clinical stage			
IB–IIA	36 (19%)	49 (26%)	N/A
IIB	32 (17%)	23 (12%)	N/A
IIIA–IIIB	22 (12%)	16 (9%)	N/A
IVA ₁	73 (39%)	82 (44%)	N/A
IVA ₂	19 (10%)	12 (6%)	N/A
IVB §	4 (2%)	4 (2%)	N/A
Previous cutaneous T-cell lymphoma therapies			
No. of previous systemic regimens received	3 (2–5)	3 (2–5)	

Data are median (1st–3rd quartile) or n (%). †Baseline in MAVORIC is defined as the last measurement obtained before the first dose of study drug; 2 patients in the mogamulizumab group had an ECOG performance status <2 at screening but equal to 2 at baseline. ECOG performance status was not available for the DK SoC arm.

§Two patients in MAVORIC (1 in each treatment group) were noted to have stage IVB disease at baseline but did not have measurable visceral disease at baseline. Staging was not available for the DK SoC arm.

Abbreviations: SoC, standard of care; ECOG, Eastern Cooperative Oncology Group.

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

Given the use of National registers to inform the Danish SoC arm, specific characteristics of the Danish population, such as age and proportion of female patients are directly available (aligned with the included DK SoC arm). For values not available in the registers, such as patient weight, an assumption on the equivalence with the mogamulizumab arm is made. Nonetheless, the matching analysis presented in Section 7, is also expected



to partly address these differences. Ultimately, baseline settings in the model were informed with the MAVORIC analysis for consistency with the matching analysis carried out on the efficacy estimates.

Table 33 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (DK SoC)	Value used in health economic model (MAVORIC)
Age		63.04
Females proportion		41.9%
Patient weight	Assumed same as MAVORIC	77kg

Note: Averages presented

Source: MAVORIC: Data cut-off 19th of March

6.1.4 Efficacy – results per MAVORIC trial

6.1.4.1 Primary efficacy endpoint: Investigator-assessed progression-free survival

Mogamulizumab resulted in a statistically significant improvement in investigator-assessed PFS. Median PFS for the mogamulizumab group was 7.7 months (95% CI: 5.67–10.33) vs 3.1 months (95% CI: 2.87–4.07) for the vorinostat group, which resulted in a HR of 0.53 (95% CI: 0.41–0.69), $p < 0.0001$ (2-sided, stratified log rank test) (5, 48). For SS specifically, mogamulizumab conferred a PFS advantage over vorinostat (median PFS 13.3 vs. 3.13 months, respectively, HR 0.32, $p < 0.0001$), and also for MF patients with advanced disease (stage III/IV, median PFS 10.9 vs. 3.0 months, HR 0.36, $p < 0.0001$). In stage IB/II MF patients, a 2.3-month advantage was observed with mogamulizumab vs vorinostat (median PFS 5.4 vs. 3.1 months, HR 0.72, $p = 0.0675$) (5, 48). Table 34 presents a summary of PFS in the ITT population and in the pre-specified subgroups.

Table 34 PFS in ITT population and pre-specified subgroups

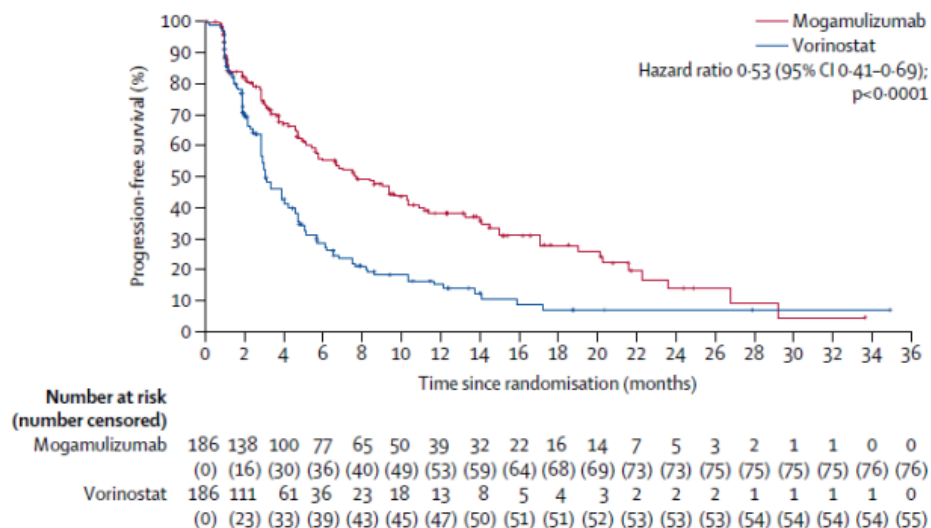
	Mogamulizumab (n=186)	Vorinostat (n=186)
PFS (months) ITT, median (95% CI)	7.70 (5.67–10.33)	3.10 (2.87–4.07)
Hazard ratio (95% CI)	0.53 (0.41–0.69)	
Log rank p-value	0.0001	
PFS (months) SS, median (95% CI)	13.3 (7.70–17.07)	3.13 (2.83–3.87)
Hazard ratio (95% CI)	0.32 (0.21–0.49)	
Log rank p-value	0.0001	
PFS (months) MF, median (95% CI)	5.40 (3.97–7.57)	3.10 (2.87–4.70)
Hazard ratio (95% CI)	0.72 (0.51–1.01)	
Log rank p-value	0.0675	
PFS (months) III/IV, median (95% CI)	10.90 (7.03–15.03)	3.00 (2.83–3.87)
Hazard ratio (95% CI)	0.36 (0.26–0.51)	
Log rank p-value	0.0001	
PFS (months) IB/II, median (95% CI)	4.70 (2.90–7.47)	3.90 (2.87–4.73)
Hazard ratio (95% CI)	0.88 (0.58–1.35)	
Log rank p-value	0.716	

Abbreviations: MF, mycosis fungoides; SS, Sézary syndrome; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival.



Figure 5 presents a Kaplan–Meier (KM) plot of PFS for the ITT population. The curves for the mogamulizumab and vorinostat treatment arms begin to separate within the second cycle of treatment, and the separation is maintained until approximately month 28 (5, 48). For the 136 patients who crossed over from vorinostat to mogamulizumab, median PFS calculated from the first dose of mogamulizumab was 8.87 months (95% CI: 5.37–14.77) (5, 48). The majority of censored observations were due to patients who discontinued randomized treatment without documented disease progression per CTCL response criteria. The percentage of patients who were censored due to discontinuation for AE or intolerance was higher for the vorinostat group than for the mogamulizumab group, while the percentage of patients who were censored due to discontinuation for clinical progression was similar for the two treatment groups.

Figure 5 Kaplan–Meier plot of investigator-assessed PFS for the ITT population



Abbreviations: CI, confidence interval; ITT, intention-to-treat. Source: Kim et al.(5); EMA (48).

6.1.4.2 Secondary efficacy endpoints

6.1.4.2.1 Progression-free survival based on independent review

Results for PFS based on independent review were consistent with the investigator assessment with a HR of 0.64 (95% CI: 0.49–0.84); $p = 0.0007$) in favour of mogamulizumab. Median PFS was 6.70 months (95% CI: 5.63–9.37) for mogamulizumab and 3.83 months (95% CI: 3.00–4.70) for vorinostat (5, 49).

6.1.4.2.2 Overall response rate based on investigator review

In patients randomized to mogamulizumab, the ORR (lasting at least 8 weeks) was 28.0% (95% CI: 21.6–35.0), which was six times greater than in patients treated with vorinostat (4.8%; 95% CI: 2.2–9.0.). Furthermore, mogamulizumab resulted in similar ORR in patients who crossed over from the vorinostat treatment group (30.1% [41 patients], 95% CI: 22.6–38.6) (49). These results suggest that treatment with mogamulizumab offers greater potential for more patients to become eligible for aSCT compared with vorinostat. When assessed by compartment, mogamulizumab had an increased effect in blood, skin and lymph nodes compared to vorinostat (49). Out of the compartments, the response rates in the blood demonstrated the greatest improvement with response observed in 66.9% of



patients treated with mogamulizumab compared to 18.4% with vorinostat (95% CI: 36.8–58.8, $p < 0.0001$). There were no responses in viscera; however, there were very few patients enrolled with visceral involvement ($n = 10$), making interpretation of the results difficult (49).

6.1.4.2.3 Best overall response

Treatment with mogamulizumab led to higher response rates than vorinostat (5, 49). Overall, 35.0% of patients had a complete or partial response (CR and PR) following treatment with mogamulizumab compared to 6.5% of patients treated with vorinostat (5). The responding patients in the mogamulizumab arm included five patients who showed a CR and 60 patients who showed a PR, while all 12 responders in the vorinostat arm showed a PR (49). When the responses were investigated by compartment, treatment with mogamulizumab also led to higher response rates compared to vorinostat (49). Patients with MF or SS and blood, skin or lymph node involvement had higher complete or PR rates following treatment with mogamulizumab than those patients treated with vorinostat therapy. Response rates for patients with visceral involvement were similar between mogamulizumab and vorinostat; however, the small number of patients in each arm ($n=3$ for both) may not be sufficient for a meaningful comparison (49).

6.1.4.2.4 Duration of response

Mogamulizumab demonstrated superior efficacy compared with vorinostat through significantly longer duration of response. For confirmed responders, the global composite response (combined results of all four compartments; skin, lymph nodes, blood and viscera), was 5 months longer in median duration for patients treated with mogamulizumab (14.07 months; 95% CI: 9.43–19.17) compared to patients treated with vorinostat (9.13 months; 95% CI: 4.67–not reported) (49).

6.1.4.3 Exploratory post-hoc endpoint results

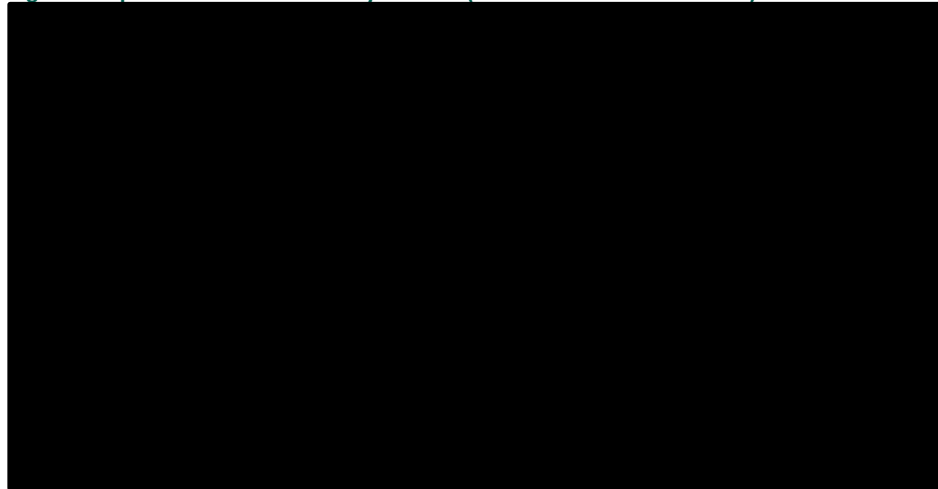
6.1.4.3.1 Overall survival

Effects on OS, at the initial data cut-off of 31 December 2016, showed that patients randomized to mogamulizumab had similar survival rates compared to patients treated with vorinostat, with a HR of 0.93 (95% CI: 0.61–1.43; $p = 0.9439$) (5, 49). The median OS for patients in the mogamulizumab arm was 23.2 months, comparable with the median of 25.4 months in the vorinostat arm. There were several confounding factors affecting the data interpretation including a large proportion of patients crossing over from the vorinostat to the mogamulizumab arm (136/186 patients). Furthermore, the MAVORIC study was not powered to detect differences in OS.

An updated OS analysis was subsequently conducted with a data cut-off of 2nd March 2019 (50). At this data cut-off the median OS in the ITT population was [REDACTED] with mogamulizumab and was [REDACTED] months [REDACTED] with vorinostat, resulting in a HR of [REDACTED]. A Kaplan–Meier curve representing the updated analysis is presented in Figure 6.



Figure 6 Kaplan–Meier survival analysis of OS (data cut-off 2nd March 2019)



Abbreviations: Moga, mogamulizumab; OS, overall survival; Vor, vorinostat.

Several OS analyses were conducted in the following populations:

- Overall population, including patients who had an aSCT.
- Overall population, excluding patients who had an aSCT (because the OS of MAVORIC could not account for the survival of these patients due to their longer survival).
- Advanced population (patients in MAVORIC with Stage IIb disease or higher), including patients who had an aSCT.
- Advanced population excluding patients who had an aSCT.

Importantly, the one-way crossover design of the MAVORIC trial reduced the power to detect differences and confounded initial OS results given that the majority of patients [REDACTED] in the vorinostat arm had switched to the mogamulizumab arm by the data cut-off (switched because they had received ≥ 2 cycles of treatment and showed confirmed disease progression or had intolerable toxicity, despite dose reduction and appropriate management of side effects). Therefore, for each population studied for OS, three analyses were conducted:

- Allowing no adjustment for treatment switching.
- Adjusting for switching by the inverse probability of censoring weights (IPCW) method: patients receiving vorinostat were weighted according to their probability of switching treatment, and patients who switched were censored at time of crossover. Patients receiving mogamulizumab were given a weight of 1. This method increases weights for patients who did not switch but had a high estimated propensity for treatment switching relative to patients with a low estimated propensity for treatment switching.
- Adjusting for switching by the two-stage method: to adjust for switching that occurs after disease progression (i.e. a 'secondary baseline', whilst data for patients receiving vorinostat were treated as an observational dataset). All patients were assumed to be at a similar stage of disease at the point of progression and the effect of mogamulizumab was estimated on extending survival from the point of disease progression to death, specifically for patients switching from vorinostat.



Results for the OS analyses within the populations of interest are presented in Table 35 below.

Table 35 Exploratory analyses of OS results from the MAVORIC trial

Analysis	HR (95% CI) for mogamulizumab vs vorinostat	
	Overall MAVORIC population	Advanced population (Stage ≥IIb disease)
Including patients with aSCT		
Without crossover adjustment	██████████	██████████
Adjusted for crossover using IPCW method	██████████	██████████
Adjusted for crossover using two-stage method	██████████	██████████
Excluding patients with aSCT		
Without crossover adjustment	██████████	██████████
Adjusted for crossover using IPCW method	██████████	██████████
Adjusted for crossover using two-stage method	██████████	██████████

Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weights; OS, overall survival; SCT, stem cell transplant.

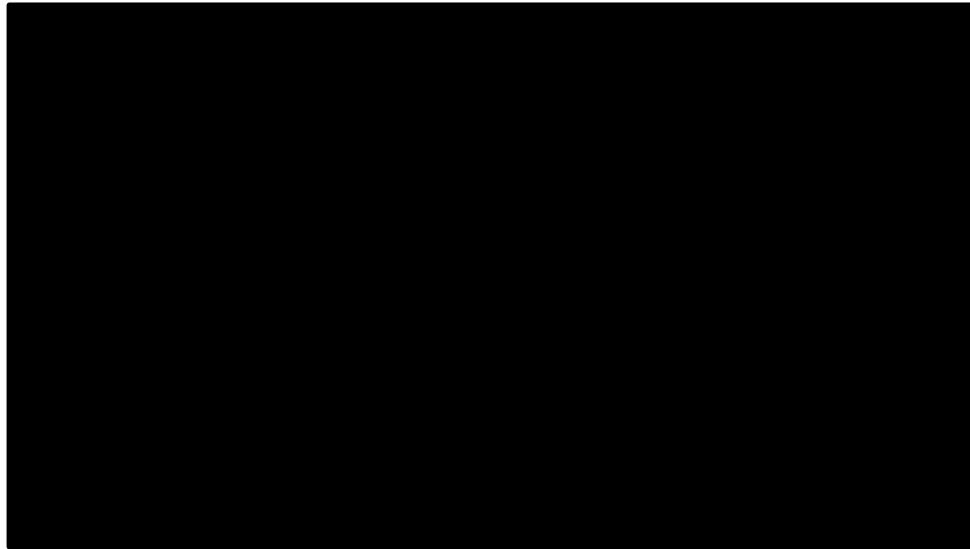
When adjusted for the highly confounded data associated with crossover, all populations studied showed ██████████ in OS with mogamulizumab. In particular, when OS was adjusted using the IPCW method, deemed to be the most appropriate method of crossover adjustment according to clinical experts, assessment of goodness-of fit-statistics, and visual inspection of curves, the HR for mogamulizumab versus vorinostat ranged ██████████; this was also found to be statistically significant for the advanced population when patients with an aSCT were included.

6.1.4.3.2 Time-to-treatment failure and time-to-next treatment

Time-to-treatment failure (TTF) and time-to-next treatment (TTNT) are both measures that reflect the natural course of a disease, capturing the duration of clinical benefit and the time until patients require subsequent therapy. As such, they can provide insight into whether treatment with mogamulizumab has the potential to modify disease progression by extending these intervals. The median TTF for mogamulizumab was ██████████ as observed for patients treated ██████████ (49). Median TTNT was ██████████ for mogamulizumab treatment compared with vorinostat ██████████ (██████████) (42). It should also be noted that due to a possible immunomodulatory effect, the median TTNT for mogamulizumab is more than double than what has been reported historically for systemic treatments including chemotherapy agents ██████████ (51). TTNT closely resembles NTFS, the only difference being that NTFS includes death as an event, making the outcome suitable for partitioned survival modelling. Median NTFS was higher for treatment with mogamulizumab compared with vorinostat ██████████.

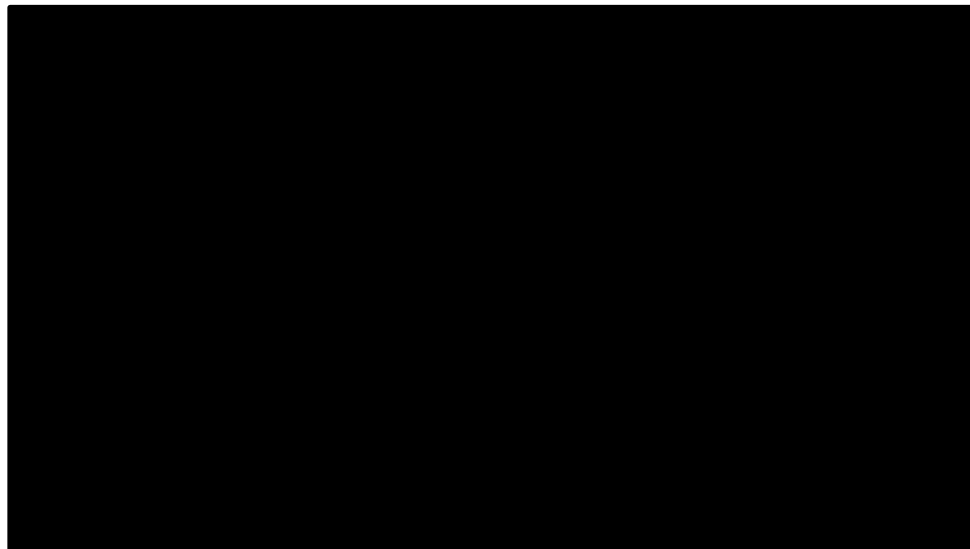


Figure 7 Kaplan–Meier curve of TTNT for the ITT population



Abbreviations: ITT, intention-to-treat; TTNT, time to next treatment. Source: Kim et al. (42).

Figure 8 Kaplan–Meier curve of NTFS for the ITT population



Abbreviations: ITT, intention-to-treat; NTFS, next treatment free survival. Source: Data on file.

6.1.5 Efficacy – results per PROSPER and PROCLIP real-world data studies

Findings from the recent PROSPER study (52) demonstrate meaningful real-world improvements in patient-reported outcomes with mogamulizumab. Among the first 20 patients enrolled (60% with SS, 90% with advanced disease, and 65% with blood involvement), all six skin symptoms improved by week 4 and remained improved through week



24. Fatigue and health-related quality of life (HRQL) scores also improved, shifting from moderate at baseline to mild within 24 weeks.

Complementary evidence from the PROCLIP study (53) supports these findings, showing longer overall survival among patients with advanced-stage mycosis fungoides (MF) and SS treated with mogamulizumab. In a cohort of 371 patients, those who received mogamulizumab (n=72) had a median overall survival of 64 months from treatment initiation compared with 54 months among those not receiving mogamulizumab (n=175; $p<0.01$). Across risk groups defined by the new Cutaneous Lymphoma International Prognostic Index (CLIPi), mogamulizumab was consistently associated with improved survival. Among patients with SS (n=96), median overall survival was approximately 6.5 years for those treated with mogamulizumab (n=46) versus 3 years for those treated with other systemic therapies (n=50; $p<0.01$). When stratified by risk, median overall survival was 67 months for low-risk patients treated with mogamulizumab compared with not reached for those not treated; 64 versus 48 months for intermediate-risk patients; and 26 versus 13 months for high-risk patients.

7. Comparative analyses of efficacy

To support the comparison of mogamulizumab vs DK SoC, an ITC using inverse probability of treatment weighting (IPTW) was conducted between the mogamulizumab arm of the MAVORIC trial and an external control arm constructed from Danish national health register data. In accordance with DMC recommendations (54), an on-file report, following the recommendations for reporting real-world evidence in the HARPER framework (55), that describes the ITC in detail has been submitted alongside this application.

The primary target causal question that was addressed in the ITC was:

What is the potential effect on overall survival if patients with relapsed or refractory mycosis fungoides or Sézary syndrome, defined as having received at least one prior systemic therapy, in Denmark had been treated with mogamulizumab instead of standard of care?

For further rationales, definitions, and assumptions than may justifiably be included in this application template, the report document should be consulted; however, the following outlines excerpts of the most important aspects of the comparison.

7.1.1 DK SoC sample selection

Patients were eligible for inclusion in the DK SoC arm if they:

- Were diagnosed with a primary or secondary diagnosis code for MF (ICD-10 C84.0) and/or SS (ICD-10 C84.1) since 1995 in the Danish National Patient Register (DNPR) (56), and
- had ever been registered with a SNOMED code for MF (M9700*, M970A*, M9625*) or SS (M9701*) since 1995 according to the Danish SNOMED classification in the Danish Pathology Register (57), and



- had undergone at least one prior DK SoC systemic treatment *after* a histologically confirmed MF or SS diagnosis, as registered in the DNPR or Danish National Prescription Register (DNPPR) since 1995, or the National Hospital Medication Register (NHMR) since May 2018.

Based on clinical expert consultation, DK SoC for relapsed or refractory MF and SS closely follows international guidelines and include (16): retinoids (bexarotene, acitretin, isotretinoin, and alitretinoin), chemotherapies (cyclophosphamide, doxorubicin, vincristine, prednisolone, gemcitabine, low and high dose methotrexate, etoposide, chlorambucil, chlormethine, and carmustine), interferon (alpha and pegylated), extracorporeal photopheresis, and targeted therapies (alemtuzumab, brentuximab vedotin, and pembrolizumab). Anatomical Therapeutic Chemical (ATC) codes were used to identify SoC systemic treatments as registered in the DNPR, DNPPR, and NHMR.

As in the MAVORIC trial, patients in the DK SoC arm who had undergone aSCT as per the DNPR and/or had a record of histologically confirmed large cell transformations in the DPR were excluded.

7.1.2 Differences in definitions of exposures and outcomes between studies

To conduct the ITC between the Danish SoC arm and the MAVORIC mogamulizumab arm, temporal alignment of index timepoints between the study arms is imperative. For the Danish SoC arm, we defined the index timepoint (T_0) as the date of initiation of the most recent observable systemic treatment, whereas for the mogamulizumab arm, T_0 corresponded to the date of randomisation. This approach was adopted to enable the inclusion of a larger patient population with varying histories of prior systemic treatments in the Danish SoC arm, thereby improving the overlap with the treatment-experienced population enrolled in the MAVORIC trial. However, while this strategy enhances the potential for matching and increases statistical power, it does so at the risk of introducing immortal time bias in the Danish SoC arm. Specifically, setting T_0 at this timepoint in the Danish SoC arm implicitly required patients to have survived and remained eligible through multiple lines of treatment, whereas the majority of patients in the mogamulizumab arm entered the trial after a median of three previous systemic treatments. This discrepancy can confer a survival advantage to the Danish SoC group, potentially biasing the comparison. At the same time, the approach also risks the opposite distortion, often described as depletion of susceptible or reverse survivor bias, where patients initiating what proves to be their final systemic therapy may represent a subset with rapidly progressing disease or limited remaining survival, leading to potential underestimation of OS compared with the trial population.

To mitigate this bias, the number of prior systemic treatments was included as a covariate in the propensity score model used to derive the IPTW weights alongside other potential effect modifiers and prognostic factors, serving as a control for disease trajectory and prior survival time. Residual confounding may nonetheless persist due to unmeasured or misclassified covariates, including time-dependent factors not captured in the available data.



7.1.3 Method of synthesis

The mogamulizumab and DK SoC arms were compared using an IPTW approach. Since there is no common comparator between the two arms, the comparison was unanchored, meaning that the results of the comparison rely on the assumption of conditional constancy of absolute effect. This assumption states that all variables that influence treatment outcomes have been measured and appropriately adjusted for in the analysis (58). Unlike anchored indirect comparisons where relative effects can be estimated by adjusting only for effect modifiers, unanchored comparisons require adjustment for both effect modifiers and prognostic factors. This is a strong assumption that is rarely fully met. However, including known effect modifiers and prognostic variables allows for the estimation of an approximate relative effect.

In the IPTW approach, weights are derived from propensity scores estimated in a logistic regression model. The propensity score represents the probability of receiving a particular treatment (in this case DK SoC) conditional on the included baseline covariates, expressed as:

$$ps = P(T = 1|X)$$

where ps is the propensity score, T is the treatment indicator ($T = 1$ for DK SoC and $T = 0$ for mogamulizumab), and X is a vector of baseline covariates.

Variable selection for the logistic regression model followed a comprehensive and systematic process. Firstly, candidate variables were identified based on clinical relevance and plausibility, prioritising predictors that aligned with established medical knowledge (50). Secondly, the statistical significance of individual predictors was evaluated to retain only those variables that demonstrated a meaningful association with treatment assignment, unless strong clinical justification warranted their retention. Thirdly, competing model specifications were compared using the Akaike Information Criterion (AIC) to quantitatively assess and balance model fit against complexity, thereby minimising the risk of overfitting. Lastly, a final set of covariates was selected that achieved an optimal trade-off between statistical robustness, clinical utility, and model parsimony. The final model was specified as:

$$\text{logit}(ps) = \beta_0 + \beta_1(\text{sex}) + \beta_2(\text{age}) + \beta_3(\text{disease_type}) + \beta_4(\text{age}^2) + \beta_5(\text{age}^3) + \beta_6(\text{previous_lines}) + \beta_7(\text{previous_lines}^2)$$

Disease type was included as a binary variable indicating MF or SS. Age and number of previous systemic treatment lines were modelled as continuous variables, with higher-order polynomial terms (squared and cubic) to account for potential non-linear relationships with the probability of treatment assignment.

7.1.3.1 Weight estimation for the average treatment effect on the treated

After estimating the propensity scores, IPTW weights were calculated to estimate the average treatment effect on the treated (ATT). Individuals in the DK SoC arm ($T = 1$) were assigned a weight of 1, while individuals in the mogamulizumab arm ($T = 0$) were assigned a weight of $\frac{ps}{1-ps}$ such that:

$$w_1 = 1 \text{ when } T = 1$$



$$w_0 = \frac{ps}{(1 - ps)} \text{ when } T = 0$$

Under the assumptions of no unmeasured confounding and sufficient overlap in covariate distributions (positivity), applying w_1 and w_0 when estimating outcomes generates a pseudo population in which the distribution of important baseline covariates is balanced across treatment groups. In the pseudo population, a reweighted version of the original sample, each individual contributes to the outcome estimation proportionally to their weight.

7.1.3.2 Extreme weights

Inverse probability weights that are too large can inflate variance and produce unstable estimates (59). Therefore, the distribution of the estimated ATT weights was visually inspected to identify extreme values. To reduce their influence, weights were winsorized. Winsorization replaces outlying weights with a defined threshold to stabilize variance (60). Following Crump et al. (59), a propensity score of 0.9 corresponds to an extreme weight of $1 / 0.9 = 9$; to minimize information loss in the relatively small sample, weights were capped at this upper bound. Only two observations exceeded 9 and were replaced accordingly.

After weighting, covariate balance between groups was assessed at two levels: (1) overall balance via the propensity score distribution and (2) individual covariate balance. Balance was examined visually using density plots and histograms and quantitatively using standardized mean differences (SMDs). An absolute SMD < 0.1 (10%) was considered indicative of adequate balance) (61, 62).

7.1.4 Results from the comparative analysis

A total of [REDACTED] patients were identified who had a histologically confirmed diagnosis of MF (C84.0), while [REDACTED] patients had histologically confirmed SS (C84.1). Among these, [REDACTED] MF patients and [REDACTED] SS patients had received at least one prior DK SoC systemic treatment, constituting a total analysis sample of [REDACTED] patients.

Table 36 presents descriptive statistics for key baseline variables across the mogamulizumab and Danish SoC arms. Notable differences were observed, particularly in age distribution and the relative proportions of MF and SS.

Table 36 Descriptive statistics of the compared populations

Variables	[REDACTED]	Mogamulizumab arm	p-value
N	[REDACTED]	186	
Age			
Mean (SD)	[REDACTED]	62.82 (13.34)	<0.001
Median [Min–Max]	[REDACTED]	63.50 (25–101)	
Sex			<0.001
Male, n (%)	[REDACTED]	109 (58.6)	
Female, n (%)	[REDACTED]	77 (41.4)	
Proportion of patients with MF			<0.001



No, n (%)	████	81 (43.5)	
Yes, n (%)	████	105 (56.5)	
Proportion of patients with SS			<0.001
No, n (%)	████	105 (56.5)	
Yes, n (%)	████	81 (43.5)	
Nr. of previous systemic treatments			
Mean (SD)	████	4.06 (3.17)	<0.001
Median [Min–Max]	████	3 (1–18)	

Abbreviations: SD, standard deviation; DK, Denmark; SoC, standard of care; SS, Sézary syndrome; MF, mycosis fungoides.

Table 37 displays the distribution of previous treatments as derived from the Danish registers. The proportions do not sum to 100%, as the same patient may receive multiple therapies. In the model these proportions have been renormalised to add up to 100%

Table 37 Distribution of treatments in the DK SoC arm

Treatment	Proportions of patients for █████
Bexaroten	████
Acitretin	████
Isotretinoin	████
Alitretinoin	████
Interferon alpha-2a or pegylated	████
Methotrexate	████
Cyclophosphamide	████
Doxorubicin	████
Vincristin	████
Prednisolone	████
Gemcitabin	████
Etoposide	████
Chlorambucil	████
Chlormetin	████
Carmustine	████
Alemtuzumab	████
Brentuximab vedotin	████
Pembrolizumab	████
PUVA	████
ECP	████
TSEBT	████
Local radiotherapy	████

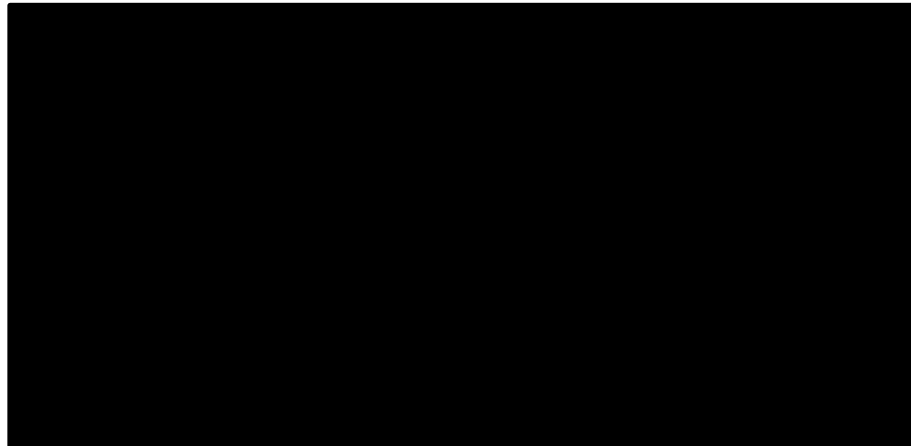
Abbreviations: DK, Denmark; SoC, standard of care.

Figure 9 presents the distribution of the estimated ATT weights following winsorization. Only weights for the mogamulizumab arm are included in the figure, as all patients in the



DK SoC arm were assigned a weight of 1. The horizontal axis represents the weight values, while the vertical axis depicts the corresponding frequency of such values.

Figure 9 Distribution of winsorized ATT weights for the mogamulizumab arm

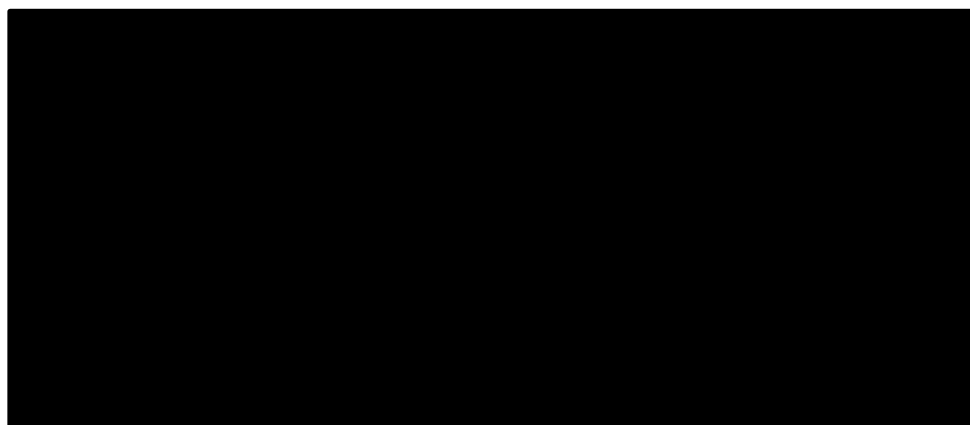


Abbreviations: ATT, average treatment effect on the treated.

7.1.5 Efficacy – results per overall survival

Figure 10 displays the unweighted KM curves, and number at risk, for OS stratified by treatment arm. The curves indicate that the survival probability over time was consistently higher in the mogamulizumab group compared to the DK SoC with median survival of [REDACTED] and [REDACTED], respectively. In the mogamulizumab arm [REDACTED] patients out of [REDACTED] while in the DK SoC [REDACTED] out of [REDACTED]. A Cox proportional hazards regression model, unadjusted for covariates or weights, yielded a HR of [REDACTED] indicating a statistically significant survival benefit for patients treated with mogamulizumab.

Figure 10 Unweighted Kaplan–Meier curves of OS by treatment arm

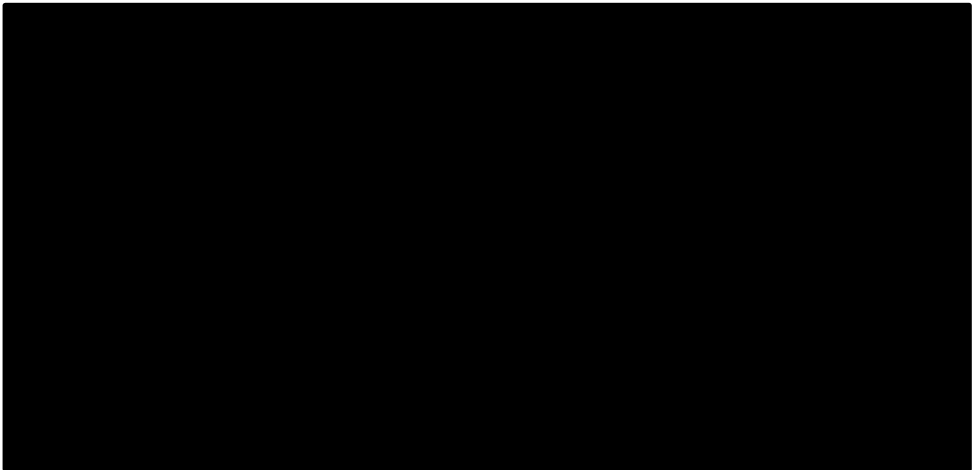


Notes: Shaded areas represent 95% confidence intervals. Abbreviations: OS, overall survival; DK SoC, Danish standard of care.



Figure 11 shows the ATT-weighted KM curves for OS. Following reweighting, mogamulizumab continued to demonstrate a marked survival benefit (■■■■). The weighted Cox regression yielded a ■■■■.

Figure 11 Weighted Kaplan–Meier curves of OS by treatment arm



Notes: Shaded areas represent 95% confidence intervals. Abbreviations: OS, overall survival; DK SoC, Danish standard of care.

Table 38 Results from the comparative analysis of mogamulizumab vs. DK SoC

Outcome measure	[Mogamulizumab] (N=186)	[DK SoC] (N=206)	Result
Weighed OS	Median■■■■	Median: ■■■■	HR: ■■■■
Proportion of patients dying (raw)	■■■■	■■■■	

Abbreviations: DK SoC, Danish standard of care; SS, Sézary syndrome; MF, mycosis fungoides; OS, overall survival; CI, confidence interval.

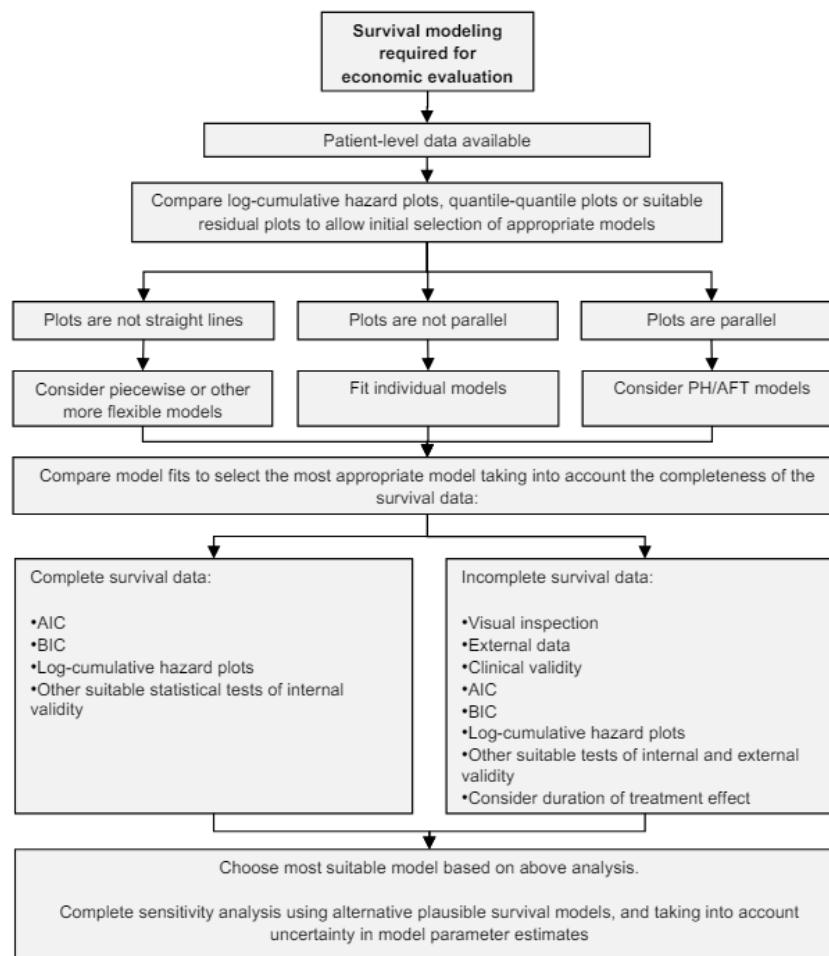
8. Modelling of efficacy in the health economic analysis

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

The MAVORIC study was used to derive clinical efficacy evidence for mogamulizumab. The IPTW approach, presented in Section 7, was used to re-weight the efficacy outcome (i.e., OS) from the trial, to now match the Danish population. The MAVORIC reweighted data, and the DK SoC arm data, were extrapolated based on survival models chosen following the NICE technical support document 14, as seen in Figure 12.



Figure 12 Survival model selection process algorithm



Abbreviations: PH/AFT, proportional hazards/accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion

8.1.1 Extrapolation of efficacy data

For OS, parametric curves could be fitted both independently (i.e., separate models for the mogamulizumab arm and the re-weighted DK SoC arm), and jointly (dependent curves fitted to both mogamulizumab and DK SoC arms, with the calculation of a treatment arm coefficient to capture differences between the two). Each approach has its advantages: the jointly fitted estimates draw on a greater pool of evidence, informed by approximately twice the number of observations, but assumes proportional hazards between the two arms. Independent curve fitting avoids the undue influence of the comparator arm on estimates, and does not rely on the proportional hazard's assumption, but incurs in greater uncertainty associated with sample size. Proportional hazards assessments (log (cumulative hazards) versus log (time)) were conducted for the ITT population of interest. Six parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, and generalised gamma) were fitted to data for each endpoint. Appropriate curve selection was determined according to statistical (AIC and BIC), visual goodness of fit and the clinical plausibility of extrapolations.



8.1.1.1 Extrapolation of OS

The base-case analysis fitted dependent parametric models to extrapolate OS. This choice was based on the assessment of the proportional hazard (PH) assumption (see Figure 37), where the parallel trend suggests that the PH assumption holds. Model selection was based on both visual assessment (see Appendix D) and AIC/BIC values reported in Table 40. Scenario analyses explored other plausible parametric models and unweighted MA-VORIC estimates.

Table 39 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	MAVORIC + weights from IPTW analysis
Model	Fully parameterized models
Assumption of proportional hazards between intervention and comparator	Proportional hazard
Function with best AIC fit	Combined: log-normal
Function with best BIC fit	Combined: log-normal
Function with best visual fit	Combined: log-normal
Function with best fit according to evaluation of smoothed hazard assumptions	Mogamulizumab: multiple options DK SoC: multiple options Smoothed hazard plots are presented in Appendix D
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	Mogamulizumab: N/A DK SoC: N/A
Selected parametric function in base case analysis	Combined: log-normal
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

Abbreviations: IPTW, inverse probability of treatment weighting; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SoC, standard of care.

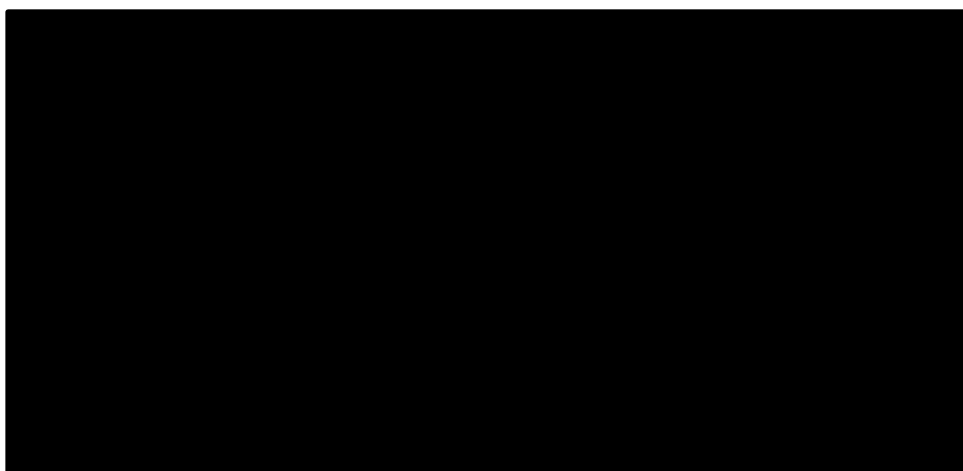
Table 40 Goodness of fit for OS (mogamulizumab and DK SoC combined models)

Model	AIC	BIC
Exponential	1742.30	1750.30
Generalised Gamma	1690.30	1706.20
Gompertz	1704.60	1716.60
Log-logistic	1689.80	1701.70
Log-normal	1688.30	1700.30
Weibull	1706.70	1718.60

Abbreviations: OS, overall survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DK SoC, Danish standard of care.



Figure 13 Base-case model for OS; Log-normal adjusted for general population OS



Abbreviations: OS, overall survival; DK SoC, Danish standard of care.

8.1.1.2 Extrapolation of NTFS

While for the mogamulizumab arm (ITT population) IPD data was available from the MA-VORIC trial. The estimation of NTFS in the DK SoC arm relied on cycle-adjusted hazard ratios as further explained in section 8.4.

For the mogamulizumab arm, 6 parametric models were fit to the data to extrapolate beyond the observed time horizon (Figure 14). Given the close visual fit of all the curves, the optimal selection was based on the best statistical fit (AIC and BIC) reported in Table 42. The base-case considered a log-normal distribution for NTFS.

Table 41 Summary of assumptions associated with extrapolation of next-treatment free survival

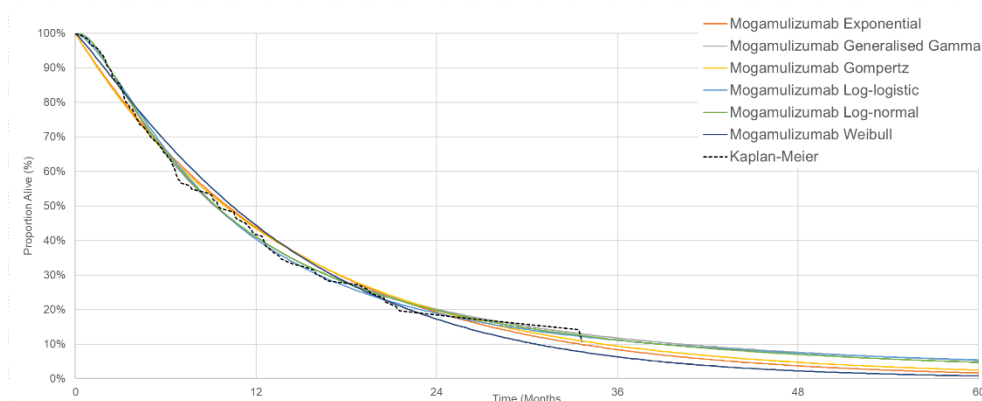
Method/approach	Description/assumption
Data input	MAVORIC
Model	Fully parameterized model for mogamulizumab
Assumption of proportional hazards between intervention and comparator	No PH assumption
Function with best AIC fit	mogamulizumab: log-normal DK SoC: N/A (see section 8.4)
Function with best BIC fit	mogamulizumab: log-normal DK SoC: N/A (see section 8.4)
Function with best visual fit	mogamulizumab: multiple DK SoC: N/A (see section 8.4)
Function with best fit according to evaluation of smoothed hazard assumptions	mogamulizumab: N/A DK SoC: N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	mogamulizumab: N/A DK SoC: N/A
Selected parametric function in base case analysis	mogamulizumab: log-normal DK SoC: N/A (see section 8.4)



Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	N/A, See OS
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: PH, proportional hazards; OS, overall survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DK SoC, Danish standard of care.

Figure 14 NTFS extrapolated curves for mogamulizumab



Abbreviations: NTFS, next treatment-free survival.

Table 42 Goodness of fit for NTFS (mogamulizumab)

Model	AIC	BIC
Exponential	928.60	931.80
Generalised Gamma	917.30	927.00
Gompertz	930.40	936.90
Log-logistic	918.10	924.60
Log-normal	915.40	921.90
Weibull	928.40	934.80

Abbreviations: NTFS, next treatment-free survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

8.1.1.3 Extrapolation of TOT

For the mogamulizumab arm, ITT population, IPD data was available from the MAVORIC trial. The estimation of TOT in the DK SoC arm relied on cycle-adjusted hazard ratios as further explained in section 8.4. For the mogamulizumab arm, 6 parametric models were fit to the data to extrapolate beyond the observed time horizon (Figure 15). Given the close visual fit of all the curves, the optimal selection was based on the best statistical fit (AIC and BIC) reported in Table 44. The base-case considered a generalised gamma distribution for TOT.

Table 43 Summary of assumptions associated with extrapolation of time on treatment

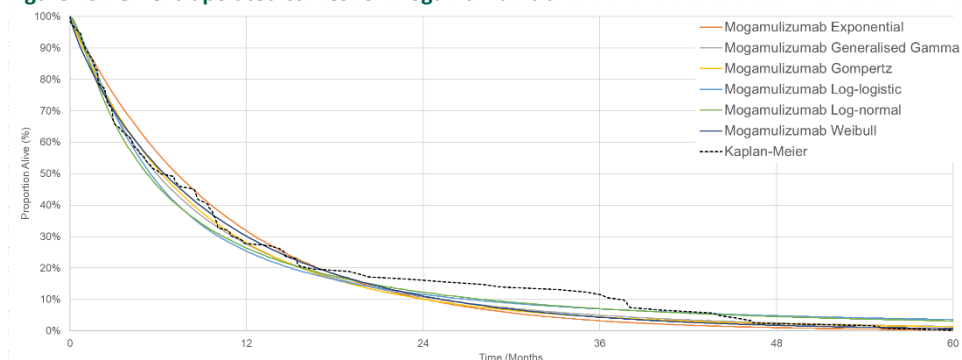
Method/approach	Description/assumption
Data input	MAVORIC
Model	Fully parameterized model for mogamulizumab



Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	No PH assumption
Function with best AIC fit	mogamulizumab: generalised gamma DK SoC: N/A (see section 8.4)
Function with best BIC fit	mogamulizumab: gompertz DK SoC: N/A (see section 8.4)
Function with best visual fit	mogamulizumab: multiple DK SoC: N/A (see section 8.4)
Function with best fit according to evaluation of smoothed hazard assumptions	mogamulizumab: N/A DK SoC: N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	mogamulizumab: N/A DK SoC: N/A
Selected parametric function in base case analysis	mogamulizumab: generalised gamma DK SoC: N/A (see section 8.4)
Adjustment of background mortality with data from Statistics Denmark	N/A, See OS.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: PH, proportional hazards; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SoC, standard of care; OS, overall survival.

Figure 15 TOT extrapolated curves for mogamulizumab



Abbreviations: TOT, time on treatment.

Table 44 Goodness of fit for TOT (mogamulizumab)

Model	AIC	BIC
Exponential	1248.10	1251.30
Generalised Gamma	1239.50	1249.20
Gompertz	1242.10	1248.50
Log-logistic	1243.30	1249.80
Log-normal	1248.50	1255.00
Weibull	1243.80	1250.30

Abbreviations: TOT, time on treatment; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.



8.1.2 Calculation of transition probabilities

N/A. Analysis based on a PSM.

Table 45 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N/A	N/A
	Death	N/A	N/A
Recurrence	Death	N/A	N/A

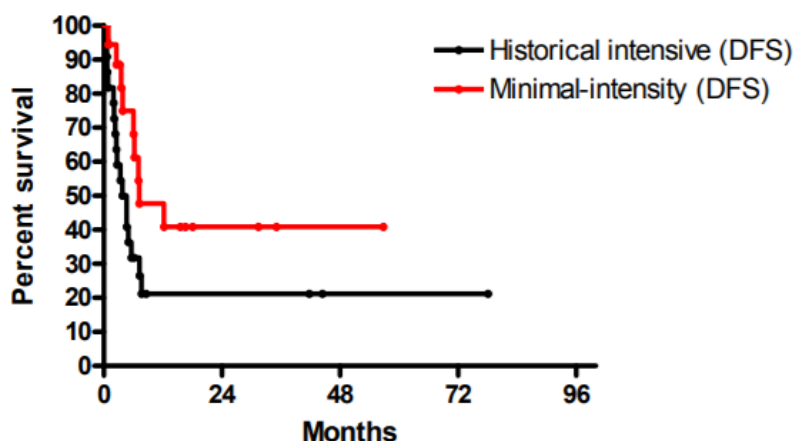
8.2 Presentation of efficacy data from London supra regional centre

Data from the London supra-regional centre was used to model the efficacy (i.e., OS) of patients receiving aSCT and is described in section 8.3 according to the DMC template.

8.3 Modelling effects of subsequent treatments

Both subsequent treatments and aSCT are accounted for as separate model states. Therefore, the OS outcomes presented so far did not include patients who have received aSCT. KM curves from the London supra-regional centre, using the minimal intensity Stanford Protocol in the NICE TA577, were used to inform disease-free survival (DFS) and OS (Figure 16 and Figure 17) of those patients receiving aSCT in the model.

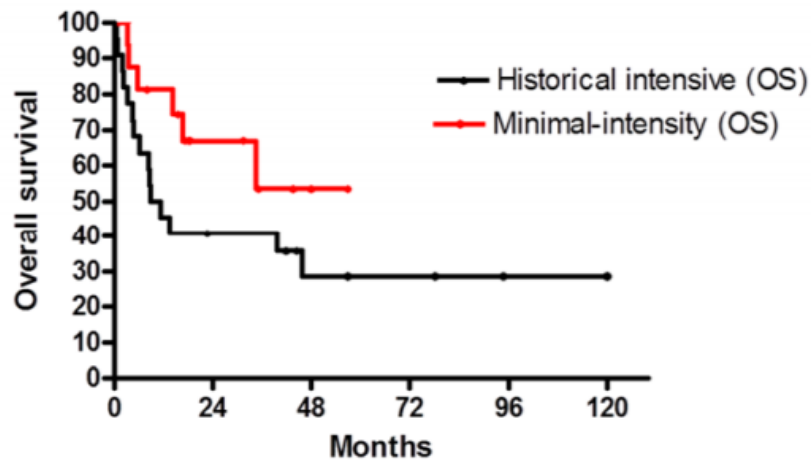
Figure 16 DFS following aSCT KM data, London supra-regional centre



Abbreviations: aSCT, allogenic stem cell transplant; DFS, disease free survival; KM, Kaplan–Meier. Source: (47).



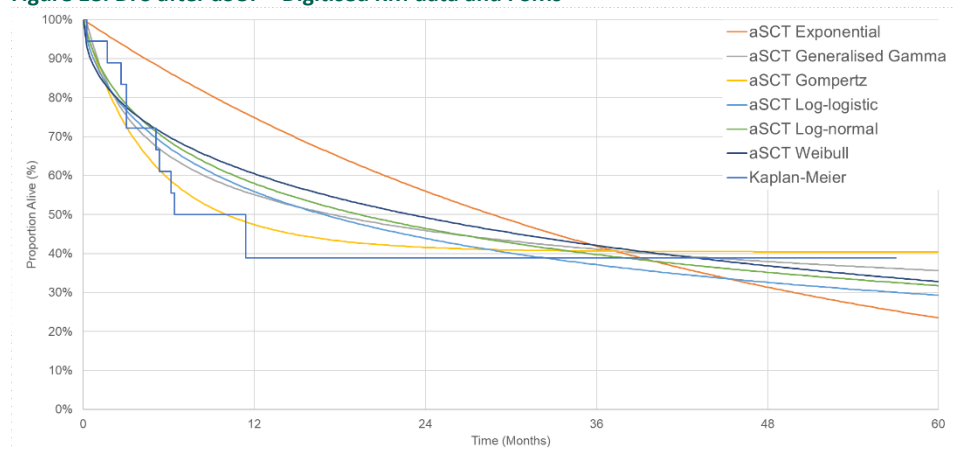
Figure 17 OS following aSCT KM data, London supra-regional centre



Abbreviations: aSCT, allogenic stem cell transplant; OS, overall survival; KM, Kaplan–Meier. Source: (47).

The DFS and OS KM curves were digitalised (using GetData software) (63) and standard parametric survival models were fitted to the derived pseudo-patient-level data (47) (Figure 18 and Figure 19). Based on the statistical fit criteria Table 46 and the visual fit, for DFS Gompertz distribution was the best fit, while for OS the lognormal model fitted the best.

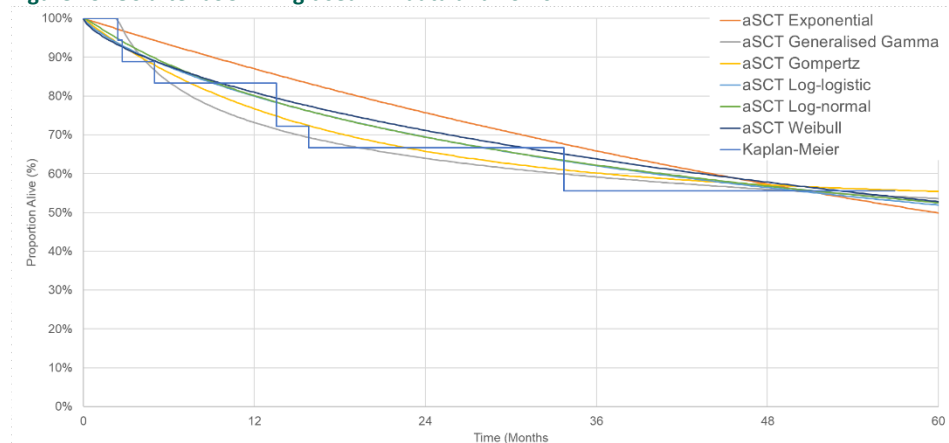
Figure 18: DFS after aSCT – Digitised KM data and PSMs



Abbreviations: aSCT, allogenic stem cell transplant; DFS, disease-free survival; Gen, generalised; KM, Kaplan–Meier; PSM, parametric survival model.



Figure 19: OS after aSCT – Digitised KM data and PSMs



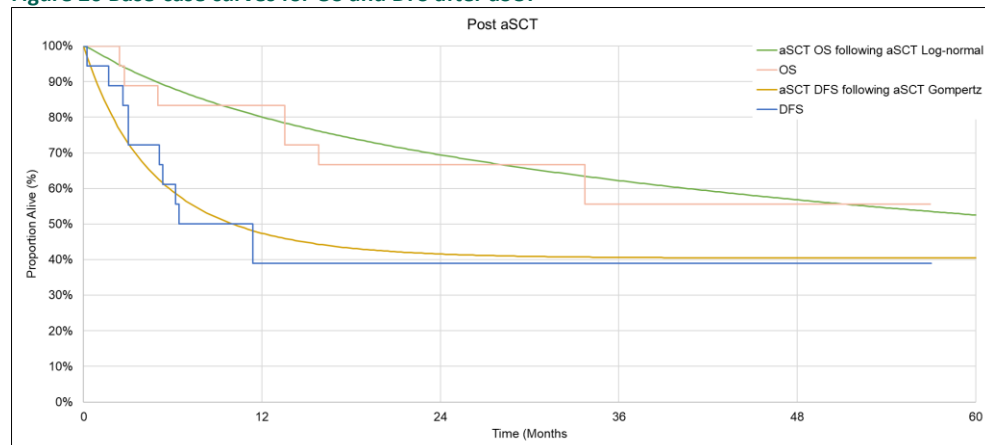
Abbreviations: alloSCT, allogenic stem cell transplant; KM, Kaplan–Meier; OS, overall survival; PSM, parametric survival model.

Table 46 AIC and BIC statistics for PSMs fitted to digitised DFS and OS for aSCT

Model	DFS		OS	
	AIC	BIC	AIC	BIC
Exponential	105.9	106.8	89.3	90.2
Weibull	97.9	99.7	89.8	91.6
Gompertz	87.0	88.8	87.8	89.6
Log-logistic	95.4	97.2	89.1	90.9
Log-normal	94.8	96.6	88.4	90.2
Generalised gamma ^a	94.6	97.3	N/A	N/A

Notes: ^a In NICE TA577 the generalised gamma function did not converge when fitting it to DFS and OS data. However, it did converge when fitted to the pseudo-patient DFS data in this application. Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DFS, disease free survival; N/A, not applicable; OS, overall survival; PSM, parametric survival model; aSCT, allogenic stem cell transplant.

Figure 20 Base-case curves for OS and DFS after aSCT



Abbreviations: aSCT, allogenic stem cell transplant; OS, overall survival; DFS, disease free survival.

In TA577, clinical input was used to support the base case choice of curves to model outcomes after alloSCT (47). The Gompertz distribution was preferred to model DFS as it was the only distribution that reflected the expectation of a decreasing probability of relapse reducing over time to zero (a plateau) (47). This behaviour was validated by clinical experts



who considered that after 12 months of receiving an aSCT, patients would enter a long-term remission where it would be unlikely to observe new relapse events (47). In the TA577 appraisal, the manufacturer also presented a second data cut for the data with results for PFS, but these data were redacted (47). After clinical validation PFS (redacted) was considered more suitable than DFS as the latter is a more stringent endpoint (requiring complete response at or prior to transplant) and would omit patients who would otherwise be considered in remission under a PFS definition (47). By using DFS data in this submission, it is likely that the proportion of patients in remission post-aSCT is underestimated, leading to conservative estimates as higher proportion of patients in the mogamulizumab arm are expected to benefit from aSCT.

For the post-aSCT OS in NICE TA577, the log-normal model fit was selected, based on the timepoint where the DFS curve converged with the OS curve (i.e. the timepoint at which all relapsed patients were implied to have died (47). Although the (redacted) updated London supra-regional centre data-cut used in TA577 also included an update for OS, the final TA577 analysis was based on the first OS data-cut as the OS data were consistent across both datasets (47). Following TA577, the log-normal model was used in the base case.

8.4 Other assumptions regarding efficacy in the model

In the CEM, NTFS for the DK SoC arm is estimated by applying the hazard ratio between the extrapolated OS and NTFS curves from the mogamulizumab arm to the OS of the DK SoC arm. Specifically, at each model cycle, we calculated the cycle-specific hazards for both OS and NTFS in the mogamulizumab arm and derived the corresponding hazard ratio (OS hazard / NTFS hazard). These hazard ratios were then applied exponentially to the conditional survival probabilities of the extrapolated OS curve for the DK SoC arm to derive the corresponding NTFS estimates for DK SoC. This method rests on the assumption that the relationship between OS and NTFS observed in the mogamulizumab arm is consistent across treatment groups. Such consistency is considered plausible, given similarities in clinical progression dynamics, treatment sequencing, and censoring mechanisms across the two arms.

Similarly, TOT for the DK SoC arm is estimated by applying the hazard ratio between the extrapolated NTFS and TOT curves from the mogamulizumab arm. At each model cycle, we calculated the cycle-specific hazards for both NTFS and TOT in the mogamulizumab arm and derived the corresponding hazard ratio (NTFS hazard / TOT hazard). These hazard ratios were then applied exponentially to the conditional survival probabilities of the extrapolated NTFS curve for the DK SoC arm to derive the corresponding TOT estimates for DK SoC. This approach assumes that the relationship between NTFS and TOT observed in the mogamulizumab arm is generalizable to the DK SoC arm. This assumption is reasonable given that both arms are expected to have similar treatment discontinuation patterns, tolerability profiles, and reasons for treatment cessation.



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

Table 47 Estimates in the model

	Modelled average [OS] (reference in Excel)	Modelled median [OS] (reference in Excel)	Observed median from relevant study
Mogamulizumab			Not reached (see section 7.1.4)
DK SoC			

Abbreviations: OS, overall survival; DK SoC, Danish standard of care.

Table 48 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length*[months]	Disease control (on tx)	Disease control (surveillance)	Subsequent tx	aSCT DF	aSCR relapsed	Death
Mogamulizumab	14.22 months	0.85 years	0.51 years	10.26 years	0.71 years	0.11 years	17.58 years
DK SoC	1.42 months	0.11 years	0.18 years	4.44 years	0.38 years	0.06 years	24.87 years

Note: *treatment length based on non aSCT patients, see model for combined estimates. Abbreviations: tx, treatment; surv, surveillance; aSCT, allogenic stem cell transplant; DF, disease free; DK SoC, Danish standard of care.

9. Safety

9.1 Safety data from the clinical documentation

In the MAVORIC study, the median duration of follow-up was 34.5 months (range, 0.13-70.0) in the randomized part of the study for the final safety analysis (43). For patients in the mogamulizumab arm, the median length of exposure was twice as long compared to patients in the vorinostat arm (170 vs 84 days). Despite the duration of mogamulizumab therapy being double that of vorinostat (which increases the time a patient is at risk of experiencing AEs), mogamulizumab demonstrated a comparable safety profile to vorinostat in patients with MF and SS (49). A summary of the AEs in the safety population of the MAVORIC study are presented in Table 49 (64).

Table 49 Overview of safety events in the MAVORIC trial.

	Randomized treatment period		Crossover
	Mogamulizumab (N = 184)	Vorinostat (N = 186)	Mogamulizumab (N = 136)
Number of adverse events, n			
Number and proportion of patients with ≥1 adverse events, n (%)			
Number of serious adverse events*, n			



	Randomized treatment period		Crossover
	Mogamulizumab (N = 184)	Vorinostat (N = 186)	Mogamulizumab (N = 136)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	████	████	████
Number of CTCAE grade ≥ 3 events, n	████	████	████
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events [§] , n (%)	████	████	████
Number of adverse reactions, n	████	████	████
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	████	████	████
Number and proportion of patients who had a dose reduction, n (%)	████	████	████
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	████	████	████
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	████	████	████

Notes: * 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). § CTCAE v. 5.0 must be used if available. Abbreviations: CTCAE, common terminology criteria for adverse events.

The pattern of TEAEs reported by █████ of patients in either treatment arm during the randomized treatment period showed substantial differences between mogamulizumab and vorinostat (64). The most frequently reported TEAEs (reported in █████ of subjects) in the mogamulizumab group for all grades were infusion-related reaction (████), drug eruption (████), diarrhoea (████), and fatigue (████). The most frequently reported TEAEs for patients in the vorinostat group for all grades were diarrhoea (████), nausea (████), fatigue (████), thrombocytopenia (████), dysgeusia (████), blood creatinine increased (████), and decreased appetite (████). AEs that occurred with higher frequency in the mogamulizumab group than in the vorinostat group included infusion-related reaction (████ versus █████) and drug eruption (████ versus █████). The majority of these events were mild or moderate in severity; Grade ≥ 3 infusion-related reactions occurred in █████ (████) subjects, and Grade ≥ 3 drug eruption occurred in █████ (████) subjects in the mogamulizumab group (64). TEAEs of infections and infestations were also more frequent in the mogamulizumab group than in the vorinostat group (████ versus █████) with higher rates of skin infection (████ versus █████), folliculitis (████ versus █████) and oral candidiasis (████ versus █████). All TEAEs of skin infection, folliculitis and oral candidiasis in the mogamulizumab group were Grade 1 or 2 severity. The incidence of pyrexia was also higher in the mogamulizumab group than in the vorinostat group (████ versus █████). Despite nearly twice the exposure time to mogamulizumab compared to vorinostat, the frequency of other TEAEs experienced by patients treated with mogamulizumab was either comparable to or lower than that observed for patients treated with vorinostat (64). A summary of the TEAEs in the safety population of the MAVORIC study are presented in Table 50 (64).



Table 50 Grade ≥ 3 TEAEs reported in the trial, regardless of frequency

	Mogamulizumab (N = 186)	Vorinostat (N = 186)	DK SoC
Aspartate aminotransferase increased	■	■	Assumed equal to mogamulizumab
Asthenia	■	■	Assumed equal to mogamulizumab
Cellulitis	■	■	Assumed equal to mogamulizumab
Constipation	■	■	Assumed equal to mogamulizumab
Decreased appetite	■	■	Assumed equal to mogamulizumab
Diarrhoea	■	■	Assumed equal to mogamulizumab
Drug eruption	■	■	Assumed equal to mogamulizumab
Dysgeusia	■	■	Assumed equal to mogamulizumab
Fatigue	■	■	Assumed equal to mogamulizumab
Headache	■	■	Assumed equal to mogamulizumab
Hypertension	■	■	Assumed equal to mogamulizumab
Infusion-related reaction	■	■	Assumed equal to mogamulizumab
Muscle spasms	■	■	Assumed equal to mogamulizumab
Nausea	■	■	Assumed equal to mogamulizumab
Peripheral oedema	■	■	Assumed equal to mogamulizumab
Pneumonia	■	■	Assumed equal to mogamulizumab
Pulmonary embolism	■	■	Assumed equal to mogamulizumab
Pyrexia	■	■	Assumed equal to mogamulizumab
Sepsis	■	■	Assumed equal to mogamulizumab
Thrombocytopenia	■	■	Assumed equal to mogamulizumab
Upper respiratory tract infection	■	■	Assumed equal to mogamulizumab
Vomiting	■	■	Assumed equal to mogamulizumab
Weight decreased	■	■	Assumed equal to mogamulizumab

Abbreviations: TEAEs, treatment emergent adverse events; DK SoC, Danish standard of care.

The incidence of serious adverse events (SAEs) was higher in the mogamulizumab group (39,7%) than the vorinostat group (24,7%). Treatment-emergent serious adverse events (SAEs) were higher in the mogamulizumab group (37,5%) than the vorinostat group (24,7%); the incidence of drug-related SAEs was 19,6% in the mogamulizumab group compared with 16,1% in the vorinostat group. In the mogamulizumab arm, the most frequently



reported SAEs of any cause were pyrexia in eight (4%) and cellulitis in five (3%) patients. In the vorinostat arm, the most frequently reported SAEs were cellulitis in six (3%), pulmonary embolism in six (3%), and sepsis in five (3%) patients. For mogamulizumab, the most common treatment-related SAEs were pneumonia in four (2%) patients and pyrexia in four (2%) patients and for vorinostat pulmonary embolism in five (3%) patients and thrombocytopenia in three (2%) patients (5, 48).

Table 51 Serious adverse events (Data cutoff, 31 December 2016)

Adverse events	Pre-treatment and randomised treatment period		Crossover portion
	Mogamulizumab (n=184)	Vorinostat (n=186)	Mogamulizumab (n=136)
Number of patients with adverse events			
Any SAEs	73 (39.7)	46 (24.7)	38 (27.9)
Treatment-emergent SAEs	69 (37.5)	46 (24.7)	36 (26.5)
Drug-related Treatment-emergent SAEs	36 (19.6)	30 (16.1)	14 (10.3)

* 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). Abbreviations: SAEs, serious adverse events.

In the health economic model adverse events were accounted for by converting observed event frequencies from the clinical trial data into cycle-specific probabilities using an exponential survival model. The model calculated event rates per patient-month from the total number of events and the total patient months at risk, then transformed these rates into probabilities for each treatment cycle duration. This approach assumed a constant hazard rate over time and enabled the incorporation of adverse event costs at appropriate intervals throughout the model.

The cycle probability was based on the formula $1 - \exp(-\lambda t)$, where λ represents the hazard rate derived from observed event frequencies divided by total patient-time at risk, and t represents the cycle duration. This exponential survival function converts the constant hazard rate into the probability of experiencing each adverse event at each cycle considered.

As previously mentioned in this submission, for the base-case analysis, DK SoC is considered as the relevant comparator. Due to the limited data available, adverse events' frequencies for DK SoC were assumed to be the same as those observed in the mogamulizumab arm. Alternative scenarios, with a 50% reduction (and increase) in AEs frequency for DK SoC were tested.

Table 52 Adverse events used in the health economic model

Adverse events	Intervention mogamulizumab	Comparator DK SoC		
	Frequency used in economic model for inter- vention	Frequency used in eco- nomic model for comparator	Source	Justification



Adverse events	Intervention mogamulizumab	Comparator DK SoC		
Adverse event				
Aspartate aminotransferase increased	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Asthenia	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Cellulitis	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Constipation	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Decreased appetite	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Diarrhoea	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Drug eruption	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Dysgeusia	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Fatigue	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Headache	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Hypertension	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Infusion-related reaction	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Muscle spasms	■	■	Mogamulizumab: MAVORIC	To align with comparator agreed on by



Adverse events	Intervention mogamulizumab	Comparator DK SoC		
			DK SoC: assumption	the DMC for this assessment
Nausea	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Peripheral oedema	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Pneumonia	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Pulmonary embolism	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Pyrexia	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Sepsis	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Thrombocytopenia	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Upper respiratory tract infection	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Vomiting	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment
Weight decreased	■	■	Mogamulizumab: MAVORIC DK SoC: assumption	To align with comparator agreed on by the DMC for this assessment

Abbreviations: DK SoC, Danish standard of care; DMC, Danish medicine council.



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

N/A. No external safety data was included in the model.

Table 53 Grade 3+ adverse events (TEAEs) that appear in more than 5 % of patients

Adverse events	Mogamulizumab (N=184)			DK SoC █████			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
Aspartate aminotransferase increased	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Asthenia	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Cellulitis	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Constipation	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Decreased appetite	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Diarrhoea	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Drug eruption	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Dysgeusia	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A
Fatigue	████	N/A	████	Assumed same as mogamulizumab	N/A	████	N/A	N/A



Headache	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Hypertension	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Infusion-related reaction	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Muscle spasms	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Nausea	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Peripheral oedema	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Pneumonia	■	N/A	N/A	Assumed same as mogamulizumab	N/A	N/A	N/A	N/A
Pulmonary embolism	■	N/A	N/A	Assumed same as mogamulizumab	N/A	N/A	N/A	N/A
Pyrexia	■	N/A	■	Assumed same as mogamulizumab	N/A	N/A	N/A	N/A
Sepsis	■	N/A	N/A	Assumed same as mogamulizumab	N/A	N/A	N/A	N/A
Thrombocytopenia	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Upper respiratory tract infection	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Vomiting	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A
Weight decreased	■	N/A	■	Assumed same as mogamulizumab	N/A	■	N/A	N/A



Alanine ami- notransferase in- creased	■	N/A	N/A	Assumed same as mogamulizumab	N/A	N/A	N/A	N/A
Anaemia	■	N/A	Not modelled	Assumed same as mogamulizumab	N/A	Not modelled	N/A	N/A
Neutropenia	■	N/A	Not modelled	Assumed same as mogamulizumab	N/A	Not modelled	N/A	N/A

Abbreviations: TEAEs, treatment emergent adverse events; SoC, standard of care. Source: GVD (Data on file).



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

Table 54 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	MAVORIC trial	To measure HRQOL with 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Used to estimate HSUVs.
FACT-G		To assess HRQoL in patients with cancer; it consists of 27 items assessing four domains: physical well-being, social/family well-being, emotional well-being and functional well-being
Skindex-29		To measure the effect of skin disease on HRQoL; it consists of 29 items assessing three domains: emotions, symptoms, and functioning
ItchyQoL		Pruritus-specific QoL instrument that includes 22 items covering three domains: symptoms, functioning, and emotions

Abbreviations: EQ-5D-3L, EuroQol Group 5-Dimension 3-Level Self-Report Questionnaire; FACT-G = Functional Assessment of Cancer Therapy-General; HRQoL, health-related quality of life; QoL, quality of life.

10.1 Presentation of the health-related quality of life (EQ-5D)

10.1.1 Study design and measuring instrument

The EuroQol/EQ-5D is a standardized, reliable and validated instrument to measure health-related quality of life. The EQ-5D self-reported questionnaire includes the EQ-5D descriptive system and a visual analog scale (VAS). The EQ-5D 3 level version (EQ-5D-3L) descriptive system comprises the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The EQ-5D self-reported questionnaire also includes a visual analog scale (VAS), which records the respondent's self-rated health status on a graduated (0-100) scale, with 100 = best imaginable health state and 0 = worst imaginable health state. No EQ-5D-5L data from the MAVORIC trial is available, therefore EQ-5D-3L responses were mapped using validated algorithms.

10.1.2 Data collection

The improvement (change from baseline) for each of the QoL measurements was evaluated for each treatment arm on days 26-28 of cycles 1, 3, 5, 7, 9 and 11 up until end of treatment. For EQ-5D-3L, the EQ-5D index score was treated as missing if not all five descriptors were responded. Please note that in this section 1 cycle refers to 4 weeks.



Table 55 Pattern of missing data and completion, mogamulizumab

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	184	1 (0.5%)	184	183 (99.5%)
Cycle 1	184	3 (1.6%)	172	169 (98.3%)
Cycle 3	184	9 (4.9%)	132	123 (93.2%)
Cycle 5	184	3 (1.6%)	104	101 (97.1%)
Cycle 7	184	2 (1.1%)	87	85 (97.7%)
Cycle 9	184	3 (1.6%)	73	70 (95.9%)
Cycle 11	184	2 (1.1%)	52	50 (96.2%)
EOT	184	7 (3.8%)	115	108 (93.9%)

Abbreviations: HRQoL, health-related quality of life

Table 56 Pattern of missing data and completion, vorinostat

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	186	3 (1.6%)	186	183 (98.4%)
Cycle 1	186	4 (2.2%)	178	174 (97.8%)
Cycle 3	186	5 (2.7%)	105	100 (95.2%)
Cycle 5	186	2 (1.1%)	63	61 (96.8%)
Cycle 7	186	0 (0.0%)	41	41 (100.0%)
Cycle 9	186	0 (0.0%)	30	30 (100.0%)
Cycle 11	186	2 (1.1%)	24	22 (91.7%)
EOT	186	2 (1.1%)	23	21 (91.3%)

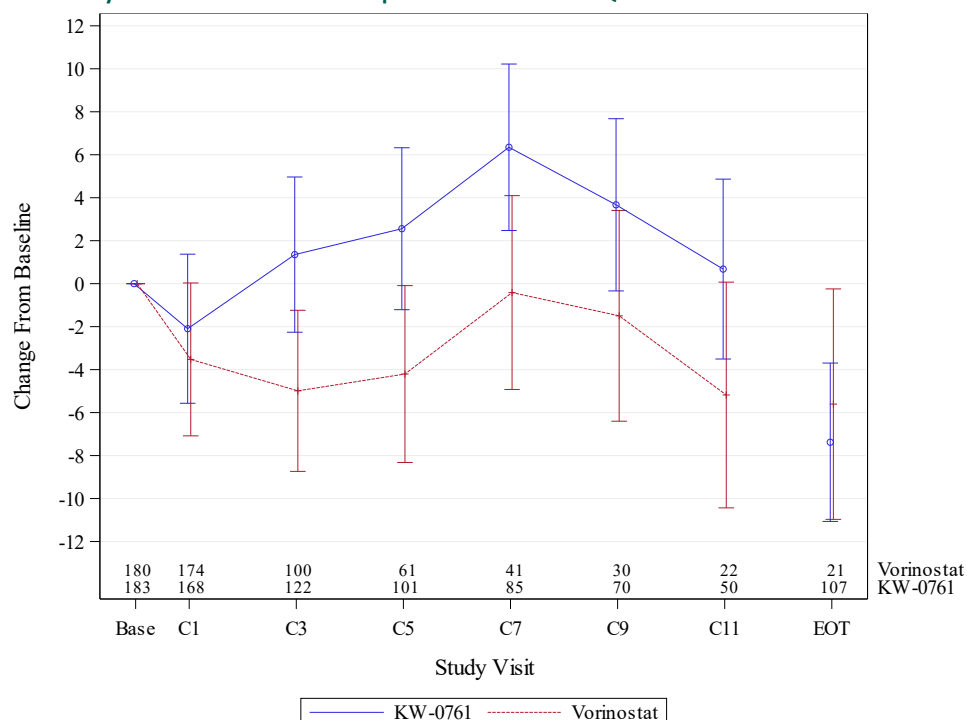
10.1.3 HRQoL results

The change from baseline for the EQ-5D-3L VAS is presented in

Figure 21 (blue=mogamulizumab, red=vorinostat). The PRO analysis set included the longitudinal period population (LPP) which consisted of subjects who had survived and maintained in the study through from Baseline to Day 1 of Cycle 1 to Day 1 of the specified cumulative cycle and have available QoL data for that time point. The summary statistics of both the mogamulizumab and vorinostat arms are presented in Table 57.



Figure 21 Treatment Effect via Adjusted Mixed Model¹ of QoL Symptoms Score Change from Baseline by Visit² and Treatment Group of the LPP³ for the EQ-5D-3L VAS Score⁴



Values displayed are the adjusted means. Notes: [1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement). [2]Subjects were administered the PRO instruments at baseline, on Days 26–28 of every other treatment cycle (odd-numbered cycles), and at the End of Treatment visit. [3]The LPP population consisted of subjects who had survived and maintained in the study through from Baseline to Day 1 of Cycle 1 to Day 1 of the specified cumulative cycle and have available QoL data for that time point. [4]The EQ-5D-3L includes 5 items which address the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scores of the 5 health state domains are scored into a single HUI. The EQ-VAS measures current health status from 0 to 100 where 0 is given the verbal label “worst imaginable health state” and 100 is given the label “best imaginable health state.” Abbreviations: EQ-5D-3L, European Quality of Life 5 dimensions 3 levels; HUI, Health Utility Index; LPP, longitudinal period population; MF, mycosis fungoides; PRO, patient-reported outcome; QoL, quality of life; SS, Sézary syndrome.

Table 57 HRQoL EQ-5D-3L VAS summary statistics

	Mogamalizumab		Vorinostat		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline					NA



	Mogamalizumab		Vorinostat		Intervention vs. comparator
Cycle 1	■	■	■	■	NA
Cycle 3	■	■	■	■	NA
Cycle 5	■	■	■	■	NA
Cycle 7	■	■	■	■	NA
Cycle 9	■	■	■	■	NA
Cycle 11	■	■	■	■	NA
End of treatment	■	■	■	■	NA

Abbreviations: SE, standard error; CI, confidence interval.

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

10.2.1 HSUV calculation

The relationship between health state and patient-reported health utility was evaluated through a longitudinal analysis of adjusted EQ-5D-3L HUI scores by health state. In general, a higher HUI score indicates better health. Mapping from EQ-5D-3L to EQ-5D-5L was performed (See section 10.2.1.1) and Danish weights were applied to the mapped EQ-5D-5L responses based on the study published by Jensen et al. (2021)(44).

For the purpose of health-economic modelling, data was analysed through a mixed-effect model for repeated measures. The model included variables such as baseline utility scores, treatment, cycle, progression status, and histology.

For the disease control state, the pre-progression estimate was used: 0.739 (95% CI 0.711; 0.767). For the subsequent treatment state, the post-progression estimate was used: 0.712 (95% CI 0.674; 0.751).

Mixed Effects Repeated Measures Model:

$$HSUV_{ij} = \beta_0 + \beta_1(BASELINE_i) + \beta_2(TRTPN_i) + \beta_3(HISTDIAG_i) + \beta_4(AVISITN_{ij}) + \beta_5(PROG_{ij}) + u_i + \epsilon_{ij}$$

Where:

- $HSUV_{ij}$ is the health state utility value for patient i at visit j
- β_0 is the intercept
- $\beta_1, \beta_2, \beta_3, \beta_4$ are the fixed effect coefficients
- $BASELINE_i$ is the baseline utility value for patient i
- $TRTPN_i$ is the randomized treatment for patient i
- $HISTDIAG_i$ is the CTCL type (Mycosis fungoides/Sézary syndrome) for patient i
- $AVISITN_{ij}$ is the visit number for patient i at visit j
- $PROG_{ij}$ is the progression status for patient i at visit j
- u_i is the random effect for patient $i \sim N(0, \sigma_u^2)$
- ϵ_{ij} is the residual error term $\sim N(0, \sigma_e^2)$



The model used a compound symmetry covariance structure for the repeated measures, with patient as the subject variable. Both HSUVs selected were indicative of the mogamulizumab arm of the MAVORIC trial and applied to the disease control and subsequent treatments states independently of the treatment assigned in the model. HSUV in the model were age-adjusted following section 7.3 of the methods guide, as outlined by the Danish Medicines Council.

10.2.1.1 Mapping

For the estimation of HSUVs from the trial data, EQ-5D-3L data was mapped to EQ-5D-5L data following the validated crosswalk algorithm developed by van Hout et al. (2021) (65). This algorithm uses indirect mapping, where EQ-5D-3L responses are first converted to EQ-5D-5L health state profiles before utility values are derived using the Danish EQ-5D-5L value set. The mapping algorithm was developed using data from a large general population sample (n=3,885) recruited across seven countries, with utility scores anchored to the EQ-5D-5L value sets of the respective countries. As the algorithm was derived from a general population rather than a disease-specific sample, some caution is warranted when applying it to a CTCL population, and more generally to specific disease, where health state profiles may differ in ways not fully captured by the general population mapping model. However, in the absence of a disease-specific crosswalk, the van Hout et al. algorithm represents a methodologically robust and widely accepted approach.

10.2.2 Disutility calculation

N/A. No disutilities associated with adverse events are included in the health economic model.

10.2.3 HSUV results

Table 58 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Disease control state	0.739 (0.711; 0.767)	EQ-5D-5L	DK	Estimate is based on mogamulizumab arm of the MAVORIC trial
Subsequent treatments state	0.712 (0.674; 0.751)	EQ-5D-5L	DK	Estimate is based on mogamulizumab arm of the MAVORIC trial

Abbreviations: HSUVs, Health state utility values; CI, confidence interval; EQ-5D-3L, European Quality of Life 5 dimensions 3 levels; DK, Danish.

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

No data were available for patients in the end-stage symptom management state (i.e., having exhausted all active systemic therapy). Therefore, it was assumed that quality of life would be similar to relapsed/refractory and end-of-life states of related lymphomas with a larger literature base, such as Hodgkin lymphoma or systemic anaplastic large cell lymphoma.



For the palliative care health state, the progressive disease utility value of 0.38 from Swinburn et al. (2015) (45) was applied. This international utility valuation study used time trade-off methodology across seven countries to elicit health state values for relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. The study is well-recognized and frequently cited as a representative source for highly progressed lymphoma patients, having been previously utilized in multiple health technology appraisals, including NICE TA577.

For post-autologous stem cell transplantation utility values, van Agthoven et al. (2001) (46) was identified within the same NICE TA577 appraisal as an informative evidence source. This prospective randomized trial comparing peripheral blood stem cell transplantation versus bone marrow transplantation in lymphoma patients provided EQ-5D utility trajectories following transplantation, with values of 0.42 at 14 days post-transplant, approximately 0.60 as an intermediate value, and 0.77 at 3 months post-discharge for the transplant patient population.

10.3.1 Swinburn et al. 2015 Study design

An international utility valuation study conducted across seven countries using time trade-off (TTO) methodology. Health state vignettes were developed for relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma through literature review, clinician consultation, and patient interviews. Nine health states were created describing treatment outcomes and adverse events.

10.3.2 Swinburn et al. 2015 Data collection

A total of 601 members of the general public participated across seven countries. Participants were recruited through convenience sampling and underwent face-to-face interviews using standardized TTO exercises. Health state descriptions were translated and culturally adapted for non-English speaking countries.

10.3.3 Swinburn et al. 2015 HRQoL Results

The study focused on utility elicitation rather than direct HRQoL measurement. Health state descriptions incorporated HRQoL impacts based on EQ-5D dimensions. Patient interviews revealed that nausea, fatigue, anxiety, and depression were commonly experienced symptoms that necessitated activity reduction.

10.3.4 Swinburn et al. 2015 HSUV and disutility results

Complete response was valued highest across all countries. For progressive disease, the UK assigned a utility value of 0.38 (SD = 0.28), representing substantial disease burden. Significant cross-country variation was observed, and adverse events substantially reduced utility values across all health states.

Table 59 Overview of health state utility values [and disutilities] in Swinburn et al 2015.

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
End-of-life stage	0.38	Consistent with EQ-5D	UK	Estimate is based on time-trade-off (TTO) methodology



Results [95% CI]	Instrument	Tariff (value set) used	Comments
(0.307, 0.456)			

Abbreviations: EQ-5D, European Quality of Life 5 dimensions; UK, United Kingdom.

10.3.5 Van Agthoven 2001 Study design

This was a prospective randomized multi-center trial comparing autologous peripheral blood stem cell transplantation (PBSCT) versus autologous bone marrow transplantation (ABMT) in patients with refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. The study was conducted in six Dutch centers between 1994-1998, with patients randomized 2:1 to undergo either PBSCT (n=62) or ABMT (n=29) following induction chemotherapy.

10.3.6 Van Agthoven 2001 Data collection

Quality of life was measured using EuroQol (EQ-5D and EQVAS), SF-36, and Rotterdam Symptom Checklist (RSCL) at three time points: day before transplantation, 14 days post-transplantation, and 3 months after hospital discharge. Cost analysis was performed from the institutional perspective covering the period from induction chemotherapy through 3 months post-discharge.

10.3.7 Van Agthoven 2001 HRQoL Results

No significant differences were found between PBSCT and ABMT groups using generic instruments (EuroQol, SF-36). However, the cancer-specific RSCL showed significant differences favoring PBSCT, with ABMT patients reporting more complaints about tiredness, lack of energy, headache, dizziness, hair loss, palpitations, rash, sweating, and shivering at 14 days post-transplant.

10.3.8 Van Agthoven 2001 HSUV and disutility results

For the ABMT group, EQ-5D index scores showed 0.42 at 14 days post-transplantation and 0.77 at 3 months after discharge. An interpolated intermediate value of approximately 0.60 can be derived from these endpoints. These values demonstrate the utility trajectory following stem cell transplantation, with the lowest utility occurring in the immediate post-transplant period and recovery to higher utility levels by 3 months post-discharge.

Table 60 Overview of health state utility values [and disutilities] in Van Agthoven 2001.

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Post-SCT (first two weeks)	0.42 (0.339, 0.503)	EQ-5D index	DK	Based on estimate at 14 days after transplantation
Post-SCT (week 3 to month 4)	0.60 (0.480, 0.714)	EQ-5D index	Dutch	Interpolated from the other two estimates
Post-SCT (3 months onwards)	0.77 (0.603, 0.901)	EQ-5D index	Dutch	Based on estimate at 3 months after hospital discharge

Abbreviations: SCT, stem cell transplant; CI, confidence interval; EQ-5D, European Quality of Life 5 dimensions.



Table 61 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
End-stage care	0.38 (0.307, 0.456)	Consistent with EQ-5D	UK	Estimate is based on time-trade-off (TTO) methodology
Post-SCT (first two weeks)	0.42 (0.339, 0.503)	EQ-5D	DK	Based on estimate at 14 days after transplantation
Post-SCT (week 3 to month 4)	0.60 (0.480, 0.714)	EQ-5D	Dutch	Interpolated from the other two estimates
Post-SCT (3 months onwards)	0.77 (0.603, 0.901)	EQ-5D	Dutch	Based on estimate at 3 months af- ter hospital discharge

Abbreviations: SCT, stem cell transplant; CI, confidence interval; EQ-5D, European Quality of Life 5 dimensions, UK, United Kingdom.

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Mogamulizumab

Mogamulizumab is implemented in the model as per its marketing authorisation. The recommended dose is 1 mg/kg mogamulizumab administered as an intravenous infusion. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on days 1 and 15 of each subsequent 28-day cycle. The cost of a single vial containing 20 mg of mogamulizumab is DKK 10,686.53.

In the base-case mogamulizumab was costed following a dose banding approach in which based on predetermined weight limits, the possible vial usage is calculated.

According to this, weight bands were derived, with each band requiring different numbers of vials (each with their costs). The distribution of patients according to these weight bands from the MAVORIC trial was multiplied by the cost of the vials for each band to generate an average cost per dose of 42,207.95 DKK. This base case price assumed a RDI of 100%.

MAVORIC reported a mean relative dose intensity (RDI) of 94.4%, which was applied throughout the treatment time period in a separate scenario analysis, derivation of RDI from the MAVORIC trial data can be seen in Equation 1 below.

Equation 1: Relative dose intensity of Mogamulizumab

$$RDI \text{ mogamulizumab} = 100 \times \frac{\left(\frac{\text{Total actual dose} / \text{Total duration of treatment}}{7} \right)}{\left(\frac{\text{Total planned dose}}{\text{Total planned weeks}} \right)}$$

Definitions: Actual dose: average dose actually received per patient; Planned dose: average intended dose per patient.

Source: MAVORIC's CSR

**Danish standard of care (DK SoC)**

The DK SoC is a basket composed of several drugs and therapies. Clinical experts (see section 14) validated treatment frequencies and their inclusion in the DK SoC basket. The inclusion of treatments in the basket was further corroborated with data from Danish registries (28). Medicines' pharmacy purchasing prices (AIP) were sourced from medicinpriser.dk and for the base case the lowest price was used, the recommended dosage was obtained from pro.medicin.dk and validated by clinical experts in Denmark (66, 67). The DK SoC therapies can be found in Table 62 along with the intervention, with their respective cost components.



Table 62 Pharmaceutical costs used in the model

Type	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Administration route	Pack Size	Price** per pack (DKK)
Drug	Mogamulizumab	1.00 mg/kg	100%	Days 1, 8, 15, 22 of Cycle 1; Days 1 and 15 of each subsequent 28-day cycle	Yes*	IV	20 ml	10,686.53
	Bexarotene	600.00 mg	100%	Twice daily	Yes*	Oral	100 capsules	DKK 7,412.85
	Acitretin	30.00 mg	100%	Once daily	Yes*	Oral	50 capsules	DKK 690.36
	Isotretinoin	38.38 mg	100%	Once daily	Yes*	Oral	50 capsules	DKK 91.98
	Alitretinoin	30.00 mg	100%	Once daily	Yes*	Oral	30 capsules	DKK 1,473.54
	Interferon alfa-2a	180.00 µg	100%	Once weekly	Yes*	Subcutaneous	1 syringe	DKK 4,996.50
	Methotrexate	30.00 mg	100%	Once weekly	Yes*	Oral or subcutaneous	100 tablets	DKK 250.02
	Cyclophosphamide (CHOP)	1,432.50 mg	100%	Day 1 of 21-day cycle	Yes*	IV	500 mg	DKK 922.53
	Doxorubicin (CHOP)	95.50 mg	100%	Day 1 of 21-day cycle	Yes*	IV	1 ml	DKK 375.03
	Vincristine (CHOP)	2.67 mg	100%	Day 1 of 21-day cycle	Yes*	IV	2 ml	DKK 404.00
	Prednisolone (CHOP)	76.40 mg	100%	Day 1, 2, 3, 4, 5 of 21-day cycle	Yes*	Oral	100 tablets	DKK 207.66
	Gemcitabine	1,910.00 mg	100%	Day 1 and 8 of 21-day cycle	Yes*	IV	10 ml	DKK 420.02
	Etoposide	343.80 mg	100%	Days 1, 2, 3, 4, 5 of 28-day cycle	Yes*	Oral	20 capsules	DKK 278.72



Type	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Administration route	Pack Size	Price** per pack (DKK)
	Chlorambucil	10.00 mg	100%	Daily	Yes*	Oral	25 tablets	DKK 207.13
	Chlormethine	1 g	100%	Once daily to affected skin up to a maximum of 6 x 60g patient per year	Yes*	Gel/cream	60g	DKK 17,800.00
	Carmustine	200.00 mg	100%	Once every 6 weeks	Yes*	IV	100mg	DKK 22,310.87
	Alemtuzumab	10.00 mg	100%	Three times weekly	Yes*	IV	1 piece	0***
	Brentuximab vedotin	138.18 mg	100%	Once every 3 weeks	Yes*	IV	1 piece	DKK 18,322.45
	Pembrolizumab	200.00 mg	100%	Once every 3 weeks	Yes*	IV	4 ml	DKK 21,573.58
Therapy	PUVA	One treatment	100%	Three times a week for 14 weeks	N/A	Topical	N/A	2,136.00
	ECP	One treatment	100%	Twice on consecutive days per 4-week cycle	N/A	Topical	N/A	10,318.00
	TSEBT	One treatment	100%	Once per year	N/A	Topical	N/A	137,049.00
	Local radiotherapy	One treatment	100%	Once per year	N/A	Topical	N/A	5,261

Notes: *No wastage cost assumed; **AIP prices; ***As of June 23rd Alemtuzumab has been discontinued in Denmark. Prior to that it was granted compassionate use. As it was only given to 2% of patients, the impact of this change is marginal. Abbreviations: PUVA, Phototherapy UV-A; ECP, Extracorporeal photopheresis; TSEBT, Total skin electron beam therapy; IV, Intravenous; mg, miligrams; g, grams; ml, millilitre.



The cost components above, where used to calculate the cost per administration for each treatment was calculated by multiplying the dose by its RDI, then dividing this by the result of the price per pack multiplied by the dose strength, divided by the package size. Adjustments were made to account for drug-specific requirements. Table 63 displays the results of these calculations for treatments included in the DK SoC. The patient distribution for each treatment included in the SoC basket was obtained from Danish register data and can be found below (28). These distributions were used in the model to estimate the costs in the comparator arm. This was done by taking a weighted average between the cost per administration for each treatment in the SoC basket, using both their frequency per cycle and patient distribution as weighting factors.

Table 63 Distribution of treatments under DK SoC and cost per administration

Type	Treatment	Patient distribution (%)	Cost per administration (DKK)	Source
Drug	Bexarotene	■	DKK 1,186.06	Danish real-world data (28).
	Acitretin	■	DKK 8.28	
	Isotretinoin	■	DKK 3.53	
	Alitretinoin	■	DKK 49.12	
	Interferon alfa-2a	■	DKK 1,249.13	
	Methotrexate	■	DKK 30.00	
	Cyclophosphamide (CHOP)	■	DKK 264.30	
	Doxorubicin (CHOP)	■	DKK 179.08	
	Vincristine (CHOP)	■	DKK 1,080.30	
	Prednisolone (CHOP)	■	DKK 6.35	
	Gemcitabine	■	DKK 364.65	
	Etoposide	■	DKK 191.65	
	Chlorambucil	■	DKK 41.43	
	Chlormethine	■	DKK 1,854.17	
	Carmustine	■	DKK 44,621.74	
	Alemtuzumab	■	0.00*	
	Brentuximab vedotin	■	DKK 50,614.66	
	Pembrolizumab	■	DKK 43,147.16	
Therapy	PUVA	■	2,136.00	
	ECP	■	10,318.00	
	TSEBT	■	137,049.00	
	Local radiotherapy	■	5,261.00	

Notes: *As of June 23rd Alemtuzumab has been discontinued in Denmark. Prior to that it was granted compassionate use. As it was only given to 2% of patients, the impact of this change is marginal. Abbreviations: PUVA, Phototherapy UV-A; ECP, Extracorporeal photopheresis; TSEBT, Total skin electron beam therapy.



11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Administration costs were considered for both intervention and comparator arms in this cost-effectiveness analysis. For the intervention, the inclusion of administration costs aligns with Mogamulizumab’s EPAR whilst for the comparators it was validated by Danish KOLs. The unit cost for the administration was sourced from local DRG tariffs 2025 (68).

For the intervention arm costs associated with a routine IV infusion administration were included following the intervention’s treatment frequency. For the DK SoC arm, administration costs were considered only for the drugs in the basket which were administered through IV infusion. In the analysis the proportion of patients receiving each of these therapies incurs the administration costs per cycle, taking in consideration the frequency with which the treatments occur per cycle.

Table 64 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion (routine administration)	Mogamulizumab: Days 1, 8, 15, 22 of Cycle 1; Days 1 and 15 of each subsequent	1,543.00	11MA98	DRG 2025 (68)
	DK SoC: Following each SoC treatment’s own frequency			

Abbreviations: IV, intravenous; DRG, diagnosis-related group; DK SoC, Danish standard of care.

11.4 Disease management costs

In both the mogamulizumab and DK SoC arms, disease monitoring and patient follow-up is expected. Disease monitoring whilst on primary or subsequent treatment requires visiting clinical nurses as well as specialists (dermatology and oncology), but with different frequencies. The fees associated with each visit type were sourced from the Værdisætning afenhedsomkostninger manual and the Takstkort for dermatology, whereas the frequencies of the visits were obtained after consultations with Swedish experts (69). The unit costs and frequencies are reported in Table 65. The yearly frequency of visits and the unit cost were used to estimate a weekly cost for each resource, which were incorporated in the model’s cycles.

Table 65 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Cost (DKK/week)	Reference
Clinical nurse visit	Disease control: ■	462	N/A	Disease control: 35.44	Unit cost catalogue (70)
	Subsequent Treatment: ■			Subsequent Treatment: 106.32	



Activity	Frequency	Unit cost [DKK]	DRG code	Cost (DKK/week)	Reference
Physician visit (Dermatology)	Disease control: Subsequent Treatment: 	593	N/A	Disease control: 5.98 Subsequent Treatment: 17.95	Unit cost catalogue (70)
Physician visit (Oncology)	Disease control: Subsequent Treatment: 	739	N/A	Disease control: 31.30 Subsequent Treatment: 93.90	Unit cost catalogue (70)

Abbreviations: DRG, diagnosis-related group.

11.5 Costs associated with management of adverse events

Based on the AEs presented in Section 9, the model accounts for the costs incurred due to these adverse events per cycle and for both arms, as shown on Table 66. The probability of a patient experiencing adverse events for mogamulizumab were taken from the MA-VORIC study, due to limited data availability these were assumed to be the same for the DK SoC arm for the base case.

Event frequencies from the clinical trial's data were used in the model to calculate the event rates per patient-month from the total number of events and the total patient months at risk. A constant hazard rate was assumed and derived from observed event frequencies divided by total patient-time at risk. An exponential survival function was the used to convert these into probabilities for each treatment cycle duration. The calculations behind the cycle probabilities of experiencing each adverse event are further outlined in Section 9.1. Specific AEs' costs were sourced from the published 2025 DRG tariffs (68).

Table 66 Cost associated with management of adverse events

Adverse Event	DRG code	Unit cost/DRG tariff
Aspartate aminotransferase increased	DRG: 07MA98 Action diagnosis: DK769 Secondary diagnosis: DC848	2,072.00
Cellulitis	DRG: 09MA98 Action diagnosis: DL089 Secondary diagnosis: DC848	1,578.00
Constipation	DRG: 06MA11 Action diagnosis: DK590 Secondary diagnosis: DC848	4,977.00
Decreased appetite	DRG: 10MA98 Action diagnosis: DR630 Secondary diagnosis: DC848	1,992.00
Diarrhoea	DRG: 06MA11 Action diagnosis: DK591 Secondary diagnosis: DC848	4,977.00
Drug eruption	DRG: 16MA98 Action diagnosis: DT808	2,208.00



Adverse Event	DRG code	Unit cost/DRG tariff
	Secondary diagnosis: DC848	
Fatigue	DRG: 23MA03 Action diagnosis: DR539A Secondary diagnosis: DC848	5,271.00
Hypertension	DRG: 05MA11 Action diagnosis: DI159 Secondary diagnosis: DC848	18,807.00
Infusion-related reaction	DRG: 16MA98 Action diagnosis: DT808 Secondary diagnosis: DC848	2,208.00
Nausea	DRG: 06MA11 Action diagnosis: DR119B Secondary diagnosis: DC848	4,977.00
Pneumonia	DRG: 04MA14 Action diagnosis: DJ110 Secondary diagnosis: DC848	34,955.00
Pyrexia	DRG: 18MA98 Action diagnosis: DR509 Secondary diagnosis: DC848	2,781.00
Sepsis	DRG: 18MA01 Action diagnosis: DA419 Secondary diagnosis: DC848	53,570.00
Weight decreased	DRG: 10MA98 Action diagnosis: DR634 Secondary diagnosis: DC848	1,992.00

Abbreviations: DRG, diagnosis-related group.

11.6 Subsequent treatment costs

Following initial treatment on either mogamulizumab or DK SoC, a proportion of patients is expected to go on to receiving subsequent treatment (by entering the subsequent treatments state) or aSCT.

Multiple subsequent treatments, excluding aSCT, are available. Data from Danish registers was used to obtain the distribution of patients which, following the DK SoC, receive each subsequent therapy. This distribution was assumed to also apply for patients on mogamulizumab arm, as it perfectly reflects Danish real-world practice.

Subsequent therapies, excluding aSCT, did not carry administration costs. AIP prices for each subsequent treatment were obtained from sundhedsdatastyrelsen.dk and medicinpriser.dk, and their recommended dosages were obtained either through clinical expert elicitation or assumed (66, 68). Subsequent treatment costs per administration were calculated using the elements presented in Table 67 and Table 68. Final state costs were calculated using average days between doses per cycle and time on treatment estimates, with the exception of TSEBT, which due to its comprehensive DRG code, was assumed to be a one-off cost item.



Table 67 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
PUVA	1	100%	Based on average days between doses per cycle and time on treatment	N/A
TSEBT	1	100%	Assumed as a one-off session with DRG 27MP01	N/A
Local radiotherapy	1	100%	Based on average days between doses per cycle and time on treatment	N/A
Clobetason and clobetasol	5 g	100%	Based on average days between doses per cycle and time on treatment	No wastage
Betamethason	6,25 g	100%	Based on average days between doses per cycle and time on treatment	No wastage
Hydrocortison	6,25 g	100%	Based on average days between doses per cycle and time on treatment	No wastage
Mometasone	3,75 g	100%	Based on average days between doses per cycle and time on treatment	No wastage

Abbreviations: PUVA, Phototherapy UV-A; TSEBT = Total skin electron beam therapy.

Table 68 Costs of subsequent treatments

Medicine	Average days between doses per cycle	Time on treatment (days)	Route of Administration	Pack size	Pack cost (DKK)	Percentage of all patients receiving medicine *	Cost per administration (DKK)
PUVA	3,5	98	Localised	N/A	2,136.00	8.83%	2,136.00
TSEBT	N/A	N/A	Localised	N/A	137,049.00	8.48%	137,049.00
Local radiotherapy	7	125	Localised	N/A	2,224.00	16.25%	2,224.00
Clobetason and clobetasol	1	100	Topical	100 g	53.00	28.62%	2.65
Betamethason	1	180	Topical	100 g	50.65	12.01%	3.17
Hydrocortison	1	365	Topical	90 g	72.40	3.89%	5.03
Mometason	1	180	Topical	100 g	65.00	21.91%	2.44

Notes: *The percentage of all patients receiving each subsequent treatment was assumed the same for intervention and comparator arms. Abbreviations: PUVA, Phototherapy UV-A; TSEBT, Total skin electron beam therapy.



11.6.1 Allogenic stem cell transplant

The model was designed to account, after either mogamulizumab or DK SoC, for patients undergoing aSCT. Whilst this is a possible (subsequent) treatment it also constitutes a health state that is modelled separately. The proportion of patients receiving aSCT after current treatment varied between the mogamulizumab and DK SoC arms. In the base case the value for mogamulizumab was set to [REDACTED], derived from a clinician survey (71), and to 4.2% as derived from Danish register data. Using the same sources, in the mogamulizumab arm patients undergo aSCT, on average, [REDACTED] into the treatment, for DK SoC at [REDACTED]. After receiving aSCT a patient, irrespective of the arm, may relapse and further require other subsequent treatments or monitoring, the likelihood of this occurring was derived from direct survival extrapolations as presented in section 8.3. Distributions and cost components associated with aSCT and a relapse can be found on Table 69.

Table 69 Costs of aSCT

Medicine	Percentage of all patients receiving medicine*	Time at which aSCT is given (weeks)	Cost (DKK)
aSCT	Mog amu- li- zum ab: [REDACTED]	[REDACTED]	1,035,036
	DK 4.20% SoC: [REDACTED]	[REDACTED]	
aSCT re- lapse	Based on DFS as presented in Section 8.4	Based on DFS as presented in Section 8.4	Subsequent treatment 117,080 Monitoring post relapse 267

Abbreviations: aSCTC, Allogenic stem cell transplant; DK SoC= Danish Standard of Care; DFS disease free survival.

11.7 Patient costs

Transportation (DKK 140.00 per visit) and patients costs (DKK 188.00 per hour) are included in the economic analysis as indicated in the DMC guidelines with unit cost sourced from the DMC's catalogue of unit costs. The inputs regarding number of trips and time spent in relation to treatment are shown in Table 70. Patient costs were considered in relation to IV administrations and disease management visits.

Table 70 Patient costs used in the model

Activity	Time spent [hours]
IV administration	Assumed 1 hour for the infusion + 0.5 hours observation afterwards + 0.5 hours trips to and from the hospital (total 2 h)
Monitoring visits	Assumed 0.5 hours visit + 0.5 hours trips

Abbreviations: IV, intravenous.



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

N/A. All relevant costs have been presented.

12. Results

12.1 Base case overview

The base-case overview is presented in Table 71.

Table 71 Base case overview

Feature	Description
Comparator	Danish Standard of Care
Type of model	Partitioned survival model
Time horizon	30 years (lifetime)
Treatment line	At least 1 prior systemic treatment. Subsequent treatments modelled as a separate state.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in MAVORIC. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Administration costs Disease management costs Adverse event costs Patient costs
Dosage of medicine	Based on weight, SmPc, or KOL input
Average time on treatment	Intervention: [REDACTED] Comparator: [REDACTED]
Parametric function for NTFS	Intervention: log-normal Comparator: modelled with HR
Parametric function for OS	Combined model: log-normal
Inclusion of waste	No wastage assumed for both arms
Average time in model health state	See Table 48

Abbreviations: EQ-5D-3L, European quality of life 5 dimensions, 3 level; SmPC, summary of product characteristics ;KOL, key opinion leader ; NTFS, next treatment-free survival ; HR, hazard ratio; OS, overall survival.

12.1.1 Base case results

Table 72 presents the discounted base-case results for the treatment of MF and SS with mogamulizumab against DK SoC.

Table 72 Base case results, discounted estimates

	Mogamulizumab	DK SoC	Difference
Drug costs	DKK 994,812	DKK 21,406	DKK 973,406
Administration costs	DKK 36,367	DKK 790	DKK 35,577
Monitoring costs - current treatment	DKK 3,755	DKK 513	DKK 3,241
Monitoring costs - Surveillance	DKK 2,081	DKK 811	DKK 1,271
Monitoring costs - Subsequent treatments	DKK 97,631	DKK 46,763	DKK 50,868



	Mogamulizumab	DK SoC	Difference
Patient costs	DKK 72,329	DKK 29,096	DKK 43,233
Subsequent treatment costs - non aSCT	DKK 20,043	DKK 20,670	-DKK 627
Adverse event costs	DKK 3,398	DKK 465	DKK 2,933
aSCT costs and monitoring DF	DKK 82,311	DKK 43,472	DKK 38,840
Subsequent treatment costs - aSCT	DKK 5,823	DKK 2,898	DKK 2,925
Monitoring aSCT – Relapsed	DKK 902	DKK 520	DKK 381
ESC costs – aSCT	DKK 0	DKK 0	DKK 0
Total	DKK 1,319,452	DKK 167,694	DKK 1,151,759
Disease control - Current treatment	0.83	0.11	0.72
Disease control - Surveillance	0.46	0.18	0.28
Subsequent treatments/ESC	7.21	3.45	3.76
aSCT DF	0.50	0.26	0.24
aSCT Relapsed	0.10	0.05	0.05
Total LY	9.10	4.06	5.04
Disease control - Current treatment	0.61	0.08	0.53
Disease control - Surveillance	0.34	0.13	0.21
Subsequent treatments/ESC	4.91	2.31	2.60
aSCT DF	0.37	0.19	0.18
aSCT Relapsed	0.08	0.04	0.04
Total QALYs	6.32	2.76	3.56
Incremental costs per life year gained		228,554 DKK/LY	
Incremental cost per QALY gained (ICER)		323,961 DKK/QALY	

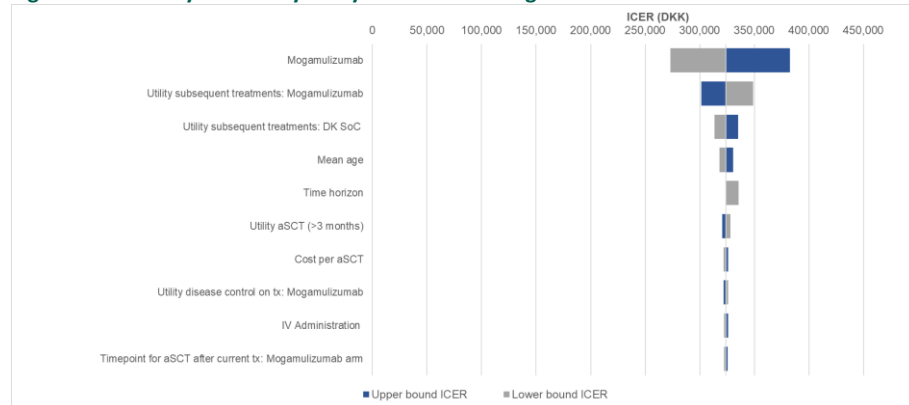
Abbreviations: DK SoC, Danish standard of care; aSCT, allogenic stem cell transplant; DF, disease free; ESC, end stage care; QALYs, quality adjusted life years; LY, liife years; ICER, incremental cost-effectiveness ratio.

12.2 Sensitivity analyses

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available or using standard errors estimated based on $\pm 10\%$ variation around the mean where measures of variance around the base case values were not available. The analysis is reported for the 10 most influential parameters on the ICER. OWSA results for mogamulizumab versus DK SoC are presented in Figure 22 and Table 73. The OWSA showed that the parameters with the greatest influence on the ICER were starting age in the model, the price of mogamulizumab, and the utility associated with the subsequent treatment state.



Figure 22 One way sensitivity analysis – tornado diagram



Abbreviations: ICER, incremental cost-effectiveness ratio; DK SoC, Danish standard of care; SCT, stem cell transplant.

12.2.1 Deterministic sensitivity analyses

Table 73 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			1152048	3.56	323961
Mean age	61	Lower and upper CI	1153503	3.63	318004
	64		1149798	3.48	330674
Mogamulizumab price	34540.22	+/- 10%	971035	3.56	273060
	51067.20		1360565	3.56	382597
Utility subsequent treatments: Mogamulizumab	0.67	Lower and upper CI	1151758.55	3.30	349007.75
	0.75		1151758.55	3.82	301594.48
Utility subsequent treatments: DK SoC	0.67	Lower and upper CI	1151758.55	3.67	313631.36
	0.75		1151758.55	3.44	335118.99
Time horizon	24.12	+/- 10%	1147003	3.42	335,796
	35.88		1151766	3.56	323,862
Utility aSCT (>3 months)	0.60	Lower and upper CI	1151758.55	3.51	328201.92
	0.90		1151758.55	3.59	320552.74
Cost per aSCT	847005.58	+/- 10%	1144702.70	3.56	321895.86
	1252285.26		1159910.85	3.56	326172.47
Utility disease control: Mogamulizumab	0.71	Lower and upper CI	1151758.55	3.53	326014.42
	0.77		1151758.55	3.58	321773.36
IV administration	1262.69	+/- 10%	1,145,295	3.56	322063
	1866.87		1,159,226	3.56	325980
Proportion of patients receiving aSCT after current tx: Mogamulizumab arm	0.06		1147451.97	3.56	322228.55
	0.10	+/- 10%	1156226.41	3.55	325622.61



Abbreviations: ICER, incremental cost-effectiveness ratio; DK SoC, Danish standard of care; CI, confidence interval; QALY, quality adjusted life years; aSCT, allogenic stem cell transplant.

12.2.2 Scenario analyses

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the cost-effectiveness estimates. Table 74 lists the scenarios conducted around the base case analysis presented above.

Table 74 Scenario analyses

Description	ICER (DKK)	Difference from base case (%)
Discount rate 0%	241,989.86	-25%
Discount rate 6%	386,883.29	19%
Time Horizon - 10 years	540,968.08	67%
Time Horizon - 20 years	356,908.49	10%
Unweighted analysis	381,193.11	18%
Increased AEs frequency in DK SoC (50%)	323,814.73	0%
Decreased AEs frequency in DK SoC (-50%)	323,945.31	0%
aSCT proportion moga equal to DK RWD	319,470.87	-1%
Include caregiver utilities	307,218.01	-5%
aSCT timing moga equal to DK RWD	333,291.42	3%
No aSCT	323,534.91	0%
RDI from MAVORIC	314,327.13	-3%

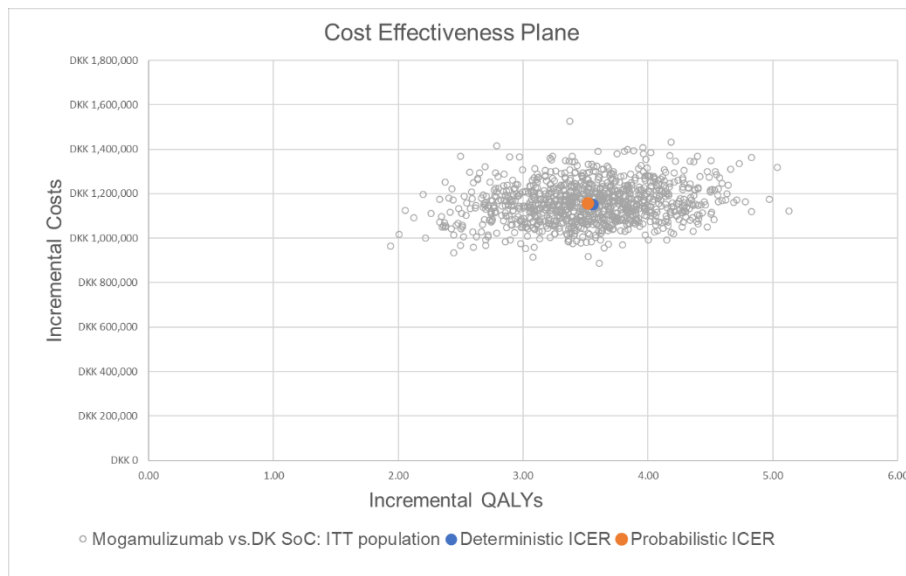
Abbreviations: ICER, incremental cost-effectiveness ratio; DK SoC, Danish standard of care; AE, adverse events; aSCT, allogenic stem cell transplant; RWD, real-world data.

12.2.3 Probabilistic sensitivity analyses

The variables included in the PSA are listed in the “Parameters” sheet in the model. The user can select which variables to include/exclude from the analysis and which distribution to select for each parameter from column “K”. For values not empirically estimated, an arbitrary uncertainty of +/- 10% around the point estimate was applied. The probabilistic ICER was of 328,970 DKK/QALY, well aligned with the deterministic results.

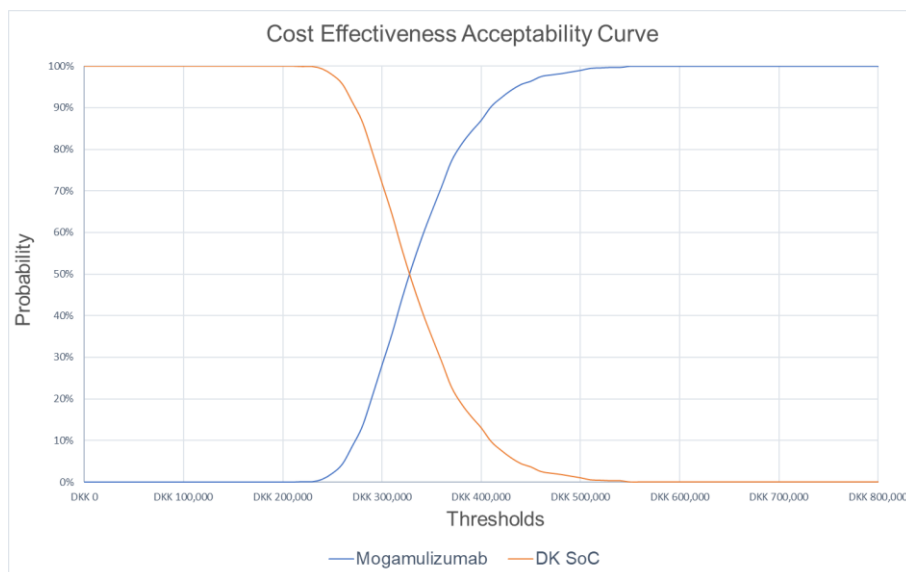
Figure 23 presents the cost effectiveness plane including all the 1000 PSA iterations, which are all located in the north-east quadrant of the plane, indicating that mogamulizumab is associated with higher costs but also higher benefits in 100% of the iterations. Figure 24 shows the cost effectiveness acceptability curve, while the convergence plot in Figure 25 indicates convergency of the ICER at around 100 iterations.

Figure 23 Incremental cost-effectiveness plane



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years: SoC, standard of care.

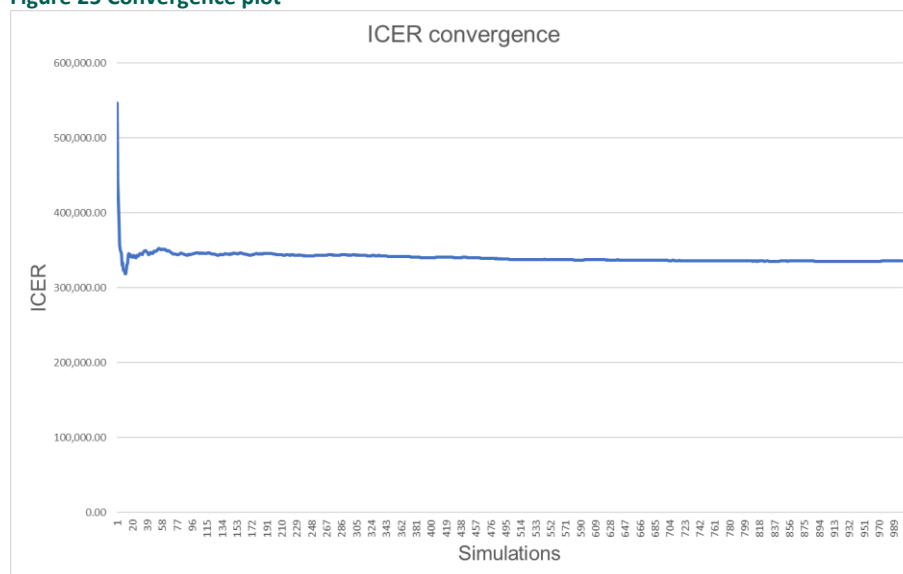
Figure 24 Cost-effectiveness acceptability curve



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years: DK SoC, Danish standard of care.



Figure 25 Convergence plot



Abbreviations: ICER, incremental cost-effectiveness ratio.

13. Budget impact analysis

Number of patients (including assumptions of market share)

The number of patients included in this application and the assumptions taken to calculate them are described in section 3.2, including the expected mogamulizumab uptake in case of recommendation, which was approximately one third for MF patients and 100% for SS patients.

Table 75 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					
Mogamulizumab	11	11	11	11	11
DK SoC	16	16	16	16	16
Non-recommendation					
Mogamulizumab	0	0	0	0	0
DK SoC	27	27	27	27	27

Abbreviations: DK SoC, Danish standard of care.

Budget impact

The budget impact estimates the results of the cost analysis described in Section 11 of this application, with no discounting applied and excluding patient costs.

Table 76 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	10,450,684 DKK	12,704,275 DKK	13,773,628 DKK	14,389,821 DKK	14,783,530 DKK
The medicine under consideration is NOT recommended	2,536,082 DKK	2,724,198 DKK	2,874,792 DKK	3,018,884 DKK	3,139,430 DKK



	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation	7,914,602 DKK	9,980,078 DKK	10,898,837 DKK	11,370,937 DKK	11,644,100 DKK

14. List of experts

[REDACTED]

[REDACTED]

Maria Rørbæk Kamstrup, MD, PhD
Specialist Dermatologist, Department of Dermatology & Venereology, Bispebjerg Hospital / Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark.

[REDACTED]



15. References

1. Lymphoma Research Foundation. Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL) Cutaneous Lymphoma. 2024.
2. Parker SR, Bethaney JV. Cutaneous T cell lymphoma-mycosis fungoides and Sezary syndrome: an update. *G Ital Dermatol Venereol*. 2009;144(4):467-85.
3. Girardi M, Edelson RL. Cutaneous T-cell lymphoma: pathogenesis and treatment. *Oncology (Williston Park)*. 2000;14(7):1061-70; discussion 70-4, 76.
4. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2017;92(10):1085-102.
5. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(9):1192-204.
6. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-85.
7. Mehta-Shah N, Horwitz SM, Ansell S, Ai WZ, Barnes J, Barta SK, et al. NCCN Guidelines Insights: Primary Cutaneous Lymphomas, Version 2.2020. *J Natl Compr Canc Netw*. 2020;18(5):522-36.
8. Haun PL, Scarisbrick JJ, editors. Fast Facts Fast Facts : Diagnosing Cutaneous T-Cell Lymphoma 2017.
9. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. *Br J Dermatol*. 2019;180(3):496-526.
10. Mangold AR, Thompson AK, Davis MD, Saulite I, Cozzio A, Guenova E, et al. Early clinical manifestations of Sezary syndrome: A multicenter retrospective cohort study. *J Am Acad Dermatol*. 2017;77(4):719-27.
11. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(6):1713-22.
12. Scarisbrick J. Staging of Mycosis Fungoides and Sézary Syndrome: Time for an Update? *EMJ Hematology*. 2018:92-100.
13. Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010;28(31):4730-9.
14. Scarisbrick JJ, Prince HM, Vermeer MH, Quaglino P, Horwitz S, Porcu P, et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sezary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. *J Clin Oncol*. 2015;33(32):3766-73.
15. Scarisbrick JJ, Whittaker S, Evans AV, Fraser-Andrews EA, Child FJ, Dean A, et al. Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. *Blood*. 2001;97(3):624-30.
16. Latzka J, Assaf C, Bagot M, Cozzio A, Dummer R, Guenova E, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome - Update 2023. *Eur J Cancer*. 2023;195:113343.
17. Talpur R, Singh L, Daulat S, Liu P, Seyfer S, Trynosky T, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. *Clin Cancer Res*. 2012;18(18):5051-60.



18. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. 2003;139(7):857-66.
19. van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, de Rie M, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. *Arch Dermatol*. 2000;136(4):504-10.
20. Vonderheid EC, Pena J, Nowell P. Sezary cell counts in erythrodermic cutaneous T-cell lymphoma: implications for prognosis and staging. *Leuk Lymphoma*. 2006;47(9):1841-56.
21. Demierre MF, Gan S, Jones J, Miller DR. Significant impact of cutaneous T-cell lymphoma on patients' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. *Cancer*. 2006;107(10):2504-11.
22. Beynon T, Selman L, Radcliffe E, Whittaker S, Child F, Orlowska D, et al. 'We had to change to single beds because I itch in the night': a qualitative study of the experiences, attitudes and approaches to coping of patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2015;173(1):83-92.
23. Orlowska D, Selman LE, Beynon T, Radcliffe E, Whittaker S, Child F, et al. 'It's a traumatic illness, traumatic to witness': a qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2018;179(4):882-8.
24. Tsang Y, Gu T, Sharma G, Raspa S, Drake B, 3rd, Tan H. Healthcare resource utilization, costs of care, and treatment of mycosis fungoides cutaneous T-cell lymphoma patterns in a large managed care population: a retrospective US claims-based analysis. *J Dermatolog Treat*. 2018;29(8):747-53.
25. Braccia D, Nikonova E, Herr FM. Pcn124 Systematic Literature Review of Economic Evidence in Cutaneous T-Cell Lymphoma. *Value in Health*. 2019;22:S79.
26. Polsinelli B, Tsigkos S, Naumann-Winter F, Mariz S, Sepodes B. Evolving prevalence of haematological malignancies in orphan designation procedures in the European Union. *Orphanet J Rare Dis*. 2017;12(1):17.
27. Sundhed. Mycosis fungoides 2024 [Available from: <https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/hud/tilstande-og-sygdomme/skaellende-hudlidelser/mycosis-fungoides/>].
28. Kyowa Kirin. Ad-hoc analysis of Danish register data. Data on file.; 2025.
29. Eklund Y, Aronsson A, Schmidtchen A, Relander T. Mycosis Fungoides: A Retrospective Study of 44 Swedish Cases. *Acta Derm Venereol*. 2016;96(5):669-73.
30. Francesco d'Amore PHN, Peter de Nully Brown, Jakob Madsen, Bodil Mathisen, Jacob Haaber, Pär Lars Josefsson. ANBEFALINGER FOR DIAGNOSTIK OG BEHANDLING AF PERIFERE T-CELLE LYMFOMER (PTCL) 2016.
31. Willemze R, Hodak E, Zinzani PL, Specht L, Ladetto M, Committee EG. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv30-iv40.
32. Medicinrådet. Medicinrådets protokol for vurdering af mogamulizumab til behandling af voksne med mycosis fungoides eller Sézarys syndrom , der har fået mindst to tidligere systemiske behandlinger. . 2020. p. 0-17.
33. Prince HM, Querfeld C. Integrating novel systemic therapies for the treatment of mycosis fungoides and Sezary syndrome. *Best Pract Res Clin Haematol*. 2018;31(3):322-35.
34. Pelcovits A, Ollila TA, Olszewski AJ. Advances in Immunotherapy for the Treatment of Cutaneous T-Cell Lymphoma. *Cancer Manag Res*. 2023;15:989-98.
35. European Medicines Agency. Poteligeo (mogamulizumab) 2018 [Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/poteligeo#authorisation-details-section>].



36. Duvic M, Pinter-Brown LC, Foss FM, Sokol L, Jorgensen JL, Challagundla P, et al. Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. *Blood*. 2015;125(12):1883-9.
37. European Medicines Agency. Summary of Product characteristics of Poteligeo. 2024.
38. Kyowa Kirin. Data on file - Market access slides. 2016.
39. Medicinrådet. Medicinrådets anbefaling vedrørende brentuximab vedotin som mulig standardbehandling til kutant T-celle-lymfom. 2018.
40. Olsen EA, Whittaker S, Willemze R, Pinter-Brown L, Foss F, Geskin L, et al. Primary cutaneous lymphoma: recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC. *Blood*. 2022;140(5):419-37.
41. Palomba ML, Ghione P, Patel AR, Deighton K, Jacobson C, Nahas M, et al. A Comparison of Clinical Outcomes from Updated Zuma-5 (Axicabtagene Ciloleucel) and the International Scholar-5 External Control Cohort in Relapsed/Refractory Follicular Lymphoma (R/R FL). *Blood*. 2021;138(Supplement 1):3543-.
42. Kim YH, Ortiz-Romero PL, Pro B, Sokol L, Scarisbrick J, Musiek A, et al. Time to Next Treatment in Patients with Previously Treated Cutaneous T-Cell Lymphoma (Ctcl) Receiving Mogamulizumab or Vorinostat: A Post-Hoc Analysis of the Mavoric Study. *Hematological Oncology*. 2019;37(S2):285-6.
43. Kim YH, Bagot M, Zinzani PL, Duvic M, Morris S, Kim E, et al. Safety of Mogamulizumab in Mycosis Fungoides and Sézary Syndrome: Final Results from the Phase 3 Mavoric Study. *Blood*. 2019;134(Supplement_1):5300-.
44. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy*. 2021;19(4):579-91.
45. Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. *Leuk Lymphoma*. 2015;56(6):1839-45.
46. van Agthoven M, Vellenga E, Fibbe WE, Kingma T, Uyl-de Groot CA. Cost analysis and quality of life assessment comparing patients undergoing autologous peripheral blood stem cell transplantation or autologous bone marrow transplantation for refractory or relapsed non-Hodgkin's lymphoma or Hodgkin's disease. a prospective randomised trial. *Eur J Cancer*. 2001;37(14):1781-9.
47. National Institute for Health and Care Excellence (NICE). TA577: Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma 2018 [Available from: <https://www.nice.org.uk/guidance/ta577>].
48. European Medicines Agency. Assessment report - POTELIGEO. 2018.
49. Kyowa Kirin. Data on file - Clinical Study Report. 2017.
50. Hawkins N, Muszbek N, Evans R, McNamara L, Jones T. Overall survival in the UK in mycosis fungoides or Sezary syndrome cutaneous T-cell lymphoma: comparative effectiveness of mogamulizumab versus current standard of care. *J Comp Eff Res*. 2023;12(10):e230017.
51. Hughes CF, Khot A, McCormack C, Lade S, Westerman DA, Twigger R, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sezary syndrome: a comparative study of systemic therapy. *Blood*. 2015;125(1):71-81.
52. Scarisbrick J, Arumainathan A, Cowan R, DeSimone J, Esler C, Geskin LJ, et al. A-201 Patient-reported symptoms and HRQL of MF and SS patients receiving mogamulizumab over 24 weeks: interim results from the PROSPER study. *European Journal of Cancer*. 2024;211.
53. Ritzau. Global Registry Data Show Meaningful Overall Survival Benefit in Patients with Advanced Cutaneous T-cell Lymphoma (CTCL) treated with POTELIGEO (mogamulizumab) 2025 [Available from:



<https://via.ritzau.dk/pressemeddelelse/14633576/global-registry-data-show-meaningful-overall-survival-benefit-in-patients-with-advanced-cutaneous-t-cell-lymphoma-ctcl-treated-with-poteligeo-mogamulizumab?publisherId=90456&lang=en>.

54. Medicinrådet. Real-world evidence in applications to the Danish Medicines Council 2023 [Available from: <https://medicinraadet.dk/media/kplh2pge/danish-medicines-council-rwe-guideline-vers-1-0.pdf>].
55. Wang SV, Pottegård A, Crown W, Arlett P, Ashcroft DM, Benchimol EI, et al. HARmonized Protocol Template to Enhance Reproducibility of hypothesis evaluating real-world evidence studies on treatment effects: A good practices report of a joint ISPE/ISPOR task force. *Pharmacoepidemiology and Drug Safety*. 2023;32(1):44-55.
56. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-90.
57. Bjerregaard B, Larsen OB. The Danish Pathology Register. *Scand J Public Health*. 2011;39(7 Suppl):72-4.
58. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for Population-Adjusted Indirect Comparisons in Health Technology Appraisal. *Med Decis Making*. 2018;38(2):200-11.
59. Crump RK, Hotz VJ, Imbens GW, Mitnik OA. Dealing with limited overlap in estimation of average treatment effects. *Biometrika*. 2009;96(1):187-99.
60. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-64.
61. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-79.
62. Zubizarreta JR, Stuart EA, Small DS, Rosenbaum PR, editors. *Handbook of Matching and Weighting Adjustments for Causal Inference*. 1 ed: CRC Press; 2023.
63. GetData Graph Digitizer. GetData Graph Digitizer 2013 [Available from: <http://getdata-graph-digitizer.com/index.php>].
64. Kyowa Kirin. Data on file - Safety Data Addendum. 2017.
65. van Hout BA, Shaw JW. Mapping EQ-5D-3L to EQ-5D-5L. *Value Health*. 2021;24(9):1285-93.
66. Lægemedelstyrelsen. Medicinpriser.DK: Lægemedelstyrelsen; 2025 [updated 24.09.2025. Available from: medicinpriser.dk].
67. Dansk Lægemedel Information A/S Medicin.dk 2025 [Available from: <https://pro.medicin.dk/>].
68. Sundhedsdatastyrelsen. Takstsystem 2025. Sundhedsdatastyrelsen; 2025 April 25,2025.
69. Hans Hagberg AO. Clinicians interview. 2020.
70. Medicinrådet. Værdisætning af enhedsomkostninger. 2024 3 June 2024.
71. Kirin K. NCPE cost-effectiveness analysis mogamulizumab. 2022.
72. Danish Medicines Council. Mogamulizumab (Poteligeo) 2021 [Available from: <https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/m/mogamulizumab-poteligeo-behandling-af-voksne-patienter-med-mycosis-fungoides-mf-eller-sezarys-syndrom-ss-der-har-modtaget-mindst-en-tidligere-systemisk-behandling>].
73. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7 Suppl):12-6.
74. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 Suppl):22-5.
75. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-9.



76. Rosenkrantz O, Wheler J, Westphal Thrane MC, Pedersen L, Sorensen HT. The Danish National Hospital Medication Register: A Resource for Pharmacoepidemiology. *Clin Epidemiol*. 2024;16:783-92.
77. Andersen MA, Jensen TL, Petersen TS. Data Resource Profile: The Danish National Hospital Medicine Register. *Pharmacoepidemiol Drug Saf*. 2024;33(11):e70054.
78. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-f.
79. Thernau J. survival - A Package for Survival Analysis in R. 3.5-7 ed2023.
80. Skoetz N, Goldkuhle M, van Dalen EC, Akl EA, Trivella M, Mustafa RA, et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles. *J Clin Epidemiol*. 2020;118:124-31.
81. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-84.



Appendix A. Main characteristics of studies included

Table 77 Main characteristics of studies included - MAVORIC

Trial name: MAVORIC(5)		NCT01728805
Objective	The purpose of this study is to compare the progression free survival of KW-0761 versus vorinostat for subjects with relapsed or refractory CTCL.	
Publications – title, author, journal, year	Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(9):1192-1204.	
Study type and design	Open-label, multi-center, randomized phase 3 study. Enrolled patients were randomized 1:1 using an interactive voice web response system to receive mogamulizumab or vorinostat and stratified by cutaneous T-cell lymphoma subtype (mycosis fungoides vs Sézary syndrome) and disease stage (IB–II vs III–IV). This was an open-label study. Blinding of treatment groups was not considered appropriate due to different routes of administration (IV vs. oral) and different side effect profiles. Subjects randomized to vorinostat who progress or suffer intolerable toxicities could cross over to the mogamulizumab arm, given that they had 2 cycles of vorinostat treatment.	
Sample size (n)	372	
Main inclusion criteria	• Male and female subjects ≥ 18 years of age at the time of enrollment, except in Japan where subjects must be ≥ 20 years of age at the time of enrollment • Histologically confirmed diagnosis of mycosis fungoides (MF) or Sezary Syndrome (SS) • Stage IB, II-A, II-B, III and IV • Subjects who had failed at least one prior course of systemic therapy. Psoralen plus ultraviolet light therapy (PUVA) is not considered to be a systemic therapy • Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1 at study entry • Resolution of all clinically significant toxic effects of prior cancer therapy to grade ≤ 1 by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE, v.4.0) • Adequate hematological, renal and hepatic function • Subjects previously treated with anti-CD4 antibody or alemtuzumab were eligible provided their CD4+ cell counts were $\geq 200/\text{mm}^3$ • Subjects with mycosis fungoides (MF) and a known history of non-complicated staphylococcus infection/colonization were eligible provided they continued to receive stable doses of prophylactic antibiotics	
Main exclusion criteria	• Prior treatment with KW-0761 or vorinostat.	



Trial name: MAVORIC(5)		NCT01728805
	• Large cell transformation. However, subjects with a history of LCT but without current aggressive disease and no current evidence of LCT on pathology in skin and lymph nodes would be eligible. • Diagnosed with a malignancy in the past two years. However, subjects with non-melanoma skin cancers, melanoma in situ, localized cancer of the prostate with current PSA of <0.1 ng/mL, treated thyroid cancer or cervical carcinoma in situ or ductal/lobular carcinoma in situ of the breast within the past two years could enroll as long as there was no current evidence of disease. • Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins. • Known active autoimmune disease were excluded. (For example, Grave's disease; systemic lupus erythematosus; rheumatoid arthritis; Crohn's disease; psoriasis). • History of allogeneic transplant	
Intervention	186 patients were randomized to receive mogamulizumab 1.0 mg/kg as an IV infusion over at least 1 hour on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles; each treatment cycle was 28 days and treatment were to be continued until progressive disease, drug intolerance or unacceptable toxicity	
Comparator(s)	186 patients were randomized to receive vorinostat 400 mg orally once daily beginning on day 1 for 28-day cycles, administered on an outpatient basis; each treatment cycle was 28 days and treatment were to be continued until progressive disease, drug intolerance or unacceptable toxicity	
Follow-up time	17.0 months (IQR 11.6–26.9)	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	Primary endpoint Progression-free survival (PFS) as assessed by the Investigator based on the global composite response score, i.e. response in each compartment (skin, blood, lymph nodes and viscera). Secondary endpoints: - Overall response rate (ORR: CR or PR) as assessed by the Investigator. - Change in Skindex-29 score from baseline through the 6-month assessment - Change in FACT-G total score from baseline through the 6-month assessment - Change in EQ-5D-3L index score from baseline through the 6-month assessment - PFS as assessed by independent review (IR)	



Trial name: MAVORIC(5)	NCT01728805
	- ORR by IR - Best overall response - Duration of response (DOR; INV and IR based) - Time to response (TTR) - ORR in the crossover portion of the trial - Changes from baseline in Skindex-29, FACT-G, and EQ-5D-3L at other time points - Changes from baseline in Pruritus Evaluation (Likert scale & Itchy QoL) Exploratory efficacy endpoints - Overall survival (OS) - Time to treatment failure (TTF) Response in skin and blood was evaluated every 4 weeks. Response in lymph nodes and viscera was evaluated at 4 weeks, then every 8 weeks in the first year, and then every 16 weeks thereafter.
Method of analysis	<u>Efficacy analysis sets</u> Intent-to-treat (ITT): Includes all patients randomized to a therapy (mogamulizumab or vorinostat) and assigned a study number. Efficacy evaluable set: Includes all patients who received the first cycle of treatment (at least one dose) and who had a baseline tumour assessment and at least one post-baseline assessment for response. The ITT population included 372 patients: 186 in the mogamulizumab arm, and 186 in the vorinostat arm. The Efficacy Evaluable Set included 361 patients. <u>Primary endpoint analysis</u> The primary efficacy variable was PFS based upon the assessment by the Investigator, defined as the time from the day of randomization to a treatment arm until documented PD or death due to any cause. The primary comparison of PFS between mogamulizumab and vorinostat was performed on the ITT set based upon the results of the on-site investigator's assessment using a stratified Log-rank test at the one-sided 2.5% significance level. A Cox proportional hazard model with treatment, disease type, disease stage, and region (U.S., Japan, and Rest of World) as covariates was used to assess the magnitude of the treatment difference in PFS. The median PFS and the 2-sided 95% CI for each treatment was estimated using the Kaplan–Meier survival analysis methods.
Subgroup analyses	Pre-planned subgroup analyses were performed within the following patient populations: - Disease type (MF, SS) - Disease stage (IB/II, III/ IV)



Trial name: MAVORIC(5)		NCT01728805
	- Blood involvement (yes, no) - Region (US, Japan, Rest of World) - Age group (<65 years, ≥65 years) - Gender (male, female) - Race category (Black or African American, White, Other) - Lactate dehydrogenase (LDH) (normal, elevated) Of which the most relevant for this submission are the analyses of PFS, ORR and TTNT in patients with advanced disease (≥Stage IIB MF and all SS patients)	

Other relevant information N/A

Abbreviations: CTCL, cutaneous T-cell lymphoma; LCT, large cell transformation; PSA, ; mg, miligrams; kg, kilorams; IV, intravenous; IQR, interquartile range; CR, complete response; PR, partial response; EQ5D-3L, European quality of life 5 dimensions 3 level ; QoL, quality of life; CI, confidence interval.

Table 78. Main characteristics of studies included - EORTC 21012

Trial name: EORTC 21012		NCT00074087
Objective	To evaluate the effectiveness of liposomal doxorubicin in treating patients who have stage IIB, stage IVA, or stage IVB recurrent or refractory MF.	
Publications – title, author, journal, year	Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. J Clin Oncol. 2012;30(33):4091-4097.	
Study type and design	Single-arm open label phase II study	
Sample size (n)	49	
Main inclusion criteria	• Histologically confirmed mycosis fungoides ○ Stage IIB, IVA, or IVB • Refractory or recurrent disease after at least 2 of the following prior therapies: ○ Local and/or systemic steroids ○ Retinoids ○ Interferon alfa ○ Local carmustine ○ Systemic chemotherapy	



Trial name: EORTC 21012		NCT00074087
	○ Psoralen and ultraviolet A (PUVA) light therapy • Karnofsky Performance status 60-100% • Prior systemic chemotherapy allowed provided all of the following conditions are met: ○ Cumulative anthracycline dose is less than 200 mg/m² ○ No allergy to anthracyclines ○ Prior methotrexate is low dose (i.e., weekly dose less than 30 mg)	
Main exclusion criteria	• No CNS involvement • No erythroderma (T4)	
Intervention	49 patients received 20 mg/m ² pegylated liposomal doxorubicin hydrochloride IV over 1 hour on days 1 and 15. Treatment repeats every 28 days for up to 6 courses.	
Comparator(s)	N/A	
Follow-up time	Median follow-up of 10.6 months (range not reported).	
Is the study used in the health economic model?	No. Study design and comparator not aligned	
Primary, secondary and exploratory endpoints	Primary endpoint ORR4 is the proportion of patients who achieved an objective response (CR or PR) that lasted at least 4 months, as determined by an independent review facility (IRF). Objective responses will be based on a Global Response Score (GRS), which consists of skin evaluation (mSWAT assessment) by investigator, nodal and visceral radiographic assessment by IRF, and detection of circulating Sézary cells (MF only) by IRF. - Skin evaluation (mSWAT) performed at screening, before dosing on Day 1 of Cycles 1, -3 and at the end of every cycle beginning at Cycle 3, EOT, and at post treatment follow-up visits - CT scans for patients without nodal or visceral involvement were performed at screening and during the cycle following the first skin response and 6 cycles (or ≥ 4 months) after that or in case of suspected new/progressive disease in the LN/viscera - CT scans for patients with baseline nodal/visceral disease, were performed at screening and at the end of Cycles 3, 6, 9, 12, and 15, and per the follow-up schedule until PD or suspected new/progressive disease in the LN/viscera and at EOT	



Trial name: EORTC 21012

NCT00074087

- Blood sample for Sézary cell enumeration in patients with MF performed at screening; at the end of Cycles 3, 6, 9, 12, and 15, at EOT, and per the follow-up schedule until PD or study closure

Secondary endpoints:

- CR - proportion of patients who achieved a CR as their best response on study as determined by an IRF by GRS criteria
- PFS- time from randomisation until PD per IRF or death due to any cause, whichever occurs first
- Changes in symptom domain (7 items) according to Skindex-29 questionnaire (administered on Day 1 of Cycles 1 and subsequent even number cycles)
- DOR- analysed for patients in the ITT population with a confirmed response per IRF
- DOR in skin- analysed for patients in the ITT population with skin response (CR or PR in skin) per investigator
- EFS- time from randomisation until any cause of treatment failure per IRF: PD, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first.
- Concentrations of brentuximab vedotin (serum) and MMAE (plasma)
- Immunogenicity assessment
- QoL assessments according to Skindex-29 and FACT-G questionnaires
- AEs and SAEs, according to NCI CTCAE version 4.03 and assessments of clinical laboratory values

Exploratory endpoints

- Qualitative and quantitative measures of CD30 expression in biopsied tumour assessed before and after brentuximab vedotin treatment. The Quest clinical trial assay was initially used for screening to determine CD30 expression in tissue samples from skin biopsies. This assay was later replaced by the Ventana anti-CD30 (Ber-H2) assay.
- Serum concentration of PD markers such as sCD30
- Presence or absence of gene or protein variation associated with CTCL or brentuximab vedotin mechanism of action
- Utilisation of health resources

Method of analysis

The ITT population included all patients who were identified as CD30+ by the Ventana anti- CD30 (Ber-H2) assay and were randomised to treatment; analysed according to randomisation treatment. The ITT population was used for the primary efficacy analysis and for all other efficacy analyses unless specified otherwise. The Per-Protocol (PP) population included a subset of ITT patients who received study drug and did not have major protocol violations as determined by the project clinician; analysed according to received treatment. The PP population was used for supplemental analysis of the primary endpoint ORR4.



Trial name: EORTC 21012		NCT00074087
	The Safety population included patients who received at least 1 dose of study drug. All patients were analysed according to the actual treatment received. Stratified log-rank test statistics will be used to compare PFS between the 2 treatment arms. The HRs and 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of the time-to event endpoints for each treatment. An alpha level of 0.01 (2-sided) was specified per the weighted Holm procedure.	
Subgroup analyses	Pre-specified subgroups analyses were performed for the following subgroups: baseline disease diagnosis, ECOG PS, sex, age (<65, ≥65), region, race and physician's choice. Baseline disease involvement and baseline skin tumour involvement were not pre-specified.	
Other relevant information	N/A	

Abbreviations; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; mg, miligram; m², squared meter; IV, intravenous; CR, complete response ; PR, partial response ; LN, lymph nodes ; EOT, end of treatment ; PD, progressive disease; CT, computed tomography; PFS, progression-free survival; DOR, duration of response ; EFS, event free survival ; ITT,intention-to-treat ; MMAE, Monomethyl auristatin E ; CTCL, cutaneous T-cell lymphoma; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.



Appendix B. Efficacy results per study

Results per study

Table 79 Results per study - MAVORIC

Results of MAVORIC (NCT01728805)(5)										
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
				Difference	95% CI	P value	Difference	95% CI	P value	
Median OS	Mogamulizumab	186	Not reached	N/A	N/A	N/A	HR: 0.93	0.61–1.43	0.9439	Exploratory endpoint. Time from the date of randomization until the date of death due to any cause.
	Vorinostat	186	43.93 (43.57- NR)							
Median OS crossover adjusted IPCW	Mogamulizumab	173	51.7 (40.7-NE)	24.63	N/A	N/A	HR: 0.57	0.26–1.25	0.16	Exploratory endpoint. Time from the date of randomization until the date of death due to any cause. Crossover adjusted via IPCW method models
	Vorinostat	177	27.07 (28.37-NE)							
Median PFS	Mogamulizumab	186	7.7 (5.67–10.33) months	4.6	N/A	N/A	HR: 0.53	0.41–0.69	<0.0001	Investigator based on the ITT set, with a stratified log rank test at the one-sided 2,5% significance level, adjusted for stratification factors disease type (MF or SS, disease stage (IB/II or III/IV) and region (U.S., Japan, and rest of the world). The median PFS and the 2-sided 95% CI for each treatment was estimated using the
	Vorinostat	186	3.1 (2.87– 4.07) months							



Results of MAVORIC (NCT01728805)(5)											
				Estimated absolute difference in ef- fect			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		
Kaplan–Meier survival analysis methods											

Abbreviations: CI, confidence intervals; OS, overall survival; HR, hazard ratio; IPCW, inverse probability of censoring weights; PFS, progression free survival; ITT, intention- to-treat; MF, mycosis fungoides; SS, Sézary syndrome; NR, not reached

Table 80. Results per study – EORTC 21012

Results of EORTC 21012 (NCT00074087)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	
Median PFS	Doxorubicin	49	7.4 (4.5-8.6)	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: EORTC,European Organisation for Research and Treatment of Cancer; PFS, progression free survival; CI, confidence interval



Appendix C. Comparative analysis of efficacy

Table 81 is not applicable since no NMA was carried out.

Table 81 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

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

Abbreviations: NMA, network meta-analysis; CI, confidence intervals; HR, hazard ratio; HRQoL, health related quality of life



C.1 Introduction

Cutaneous T-cell lymphoma (CTCL) is a rare form of non-Hodgkin lymphoma that primarily affects the skin. It is characterised by erythematous, rash-like lesions, scaly or raised plaques, and in more advanced stages, the development of skin tumours. CTCL encompasses several distinct subtypes, the most common of which is mycosis fungoides (MF), followed by the rarer and more aggressive Sézary syndrome (SS). Both MF and SS are chronic, relapsing diseases with a highly variable clinical course and a limited array of effective therapeutic options. To date, allogeneic stem cell transplantation (aSCT) remains the only curative treatment; however, this option is feasible for only a small subset of patients due to age, comorbidities, and disease stage at diagnosis (16).

In recent years, novel treatments have emerged with the goal of delaying disease progression and improving patient outcomes. One such treatment is mogamulizumab, a humanised IgG1 kappa monoclonal antibody (marketed as Poteligeo® by Kyowa Kirin), which received marketing authorisation from the European Medicines Agency (EMA) in 2018 (35). Mogamulizumab targets CCR4, a chemokine receptor expressed at high levels on malignant T cells which is implicated in lymphocyte trafficking to the skin and other tissues. The efficacy of mogamulizumab was demonstrated in the MAVORIC trial, a pivotal phase III, multinational, open label, randomised controlled trial (5). The trial enrolled patients with relapsed or refractory (R/R) MF or SS who had received at least one prior systemic treatment and compared clinical outcomes of mogamulizumab to vorinostat, a histone deacetylase inhibitor. The study found that mogamulizumab significantly improved progression-free survival (PFS) compared to vorinostat, establishing its clinical potential as an effective treatment in this patient population; however, no statistically significant difference was detected in overall survival (OS) and median OS was not reached in the mogamulizumab arm (5).

Following these results, Kyowa Kirin applied to the Danish Medicines Council (DMC) to have mogamulizumab recommended for patients with MF or SS who had received at least one prior systemic treatment. However, the DMC declined to recommend the drug, citing concerns that the MAVORIC trial's comparator arm – vorinostat – did not reflect the Danish standard of care (SoC), thereby limiting the generalisability of the trial results to the Danish context (72). In its original assessment of mogamulizumab, the DMC defined the SoC for advanced R/R MF and SS as including the immunotherapies alemtuzumab, brentuximab vedotin, pembrolizumab, and romidepsin, in addition to systemic chemotherapy regimens involving high-dose methotrexate, doxorubicin, and gemcitabine.

In contrast to the DMC's decision, the Swedish Dental and Pharmaceutical Benefits Agency accepted vorinostat as a reasonable proxy for the Swedish SoC, which includes the same treatments as the Danish SoC. Eventually, mogamulizumab was approved in Sweden for patients who had received at least one prior systemic treatment. This decision was partially supported by a naïve indirect survival comparison between the MAVORIC control arm – vorinostat – and real-world data on SoC from the UK Hospital Episode Statistics (HES) database, which demonstrated comparable survival trajectories between the two. Building on this, an indirect treatment comparison conducted by Hawkins et al. reweighted individual patient data from the MAVORIC mogamulizumab arm to align with baseline characteristics of patients in the UK HES cohort, seeking to provide a more robust comparative estimate of mogamulizumab's effectiveness relative to the UK SoC (50). Based on that analysis and the Swedish recommendation, mogamulizumab was since also recommend in Norway by Nye Metoder.

C.2 Study aim

As vorinostat is not considered an appropriate comparator by the DMC, any future recommendation of mogamulizumab in Denmark for treating R/R MF and SS depend on the generation of robust comparative

evidence demonstrating its effectiveness against established Danish SoC. This study aims to uncover such evidence, providing both new insights into the real-world treatment effect of mogamulizumab and enabling a more accurate comparison for inclusion in cost-effectiveness models.

Therefore, the primary target causal question to be answered in this study is:

What is the potential effect on overall survival if patients with relapsed or refractory mycosis fungoides or Sézary syndrome, defined as having received at least one prior systemic therapy, in Denmark had been treated with mogamulizumab instead of standard of care?

C.3 Methods

To address the overall study objective, an indirect treatment comparison was performed using an inverse probability of treatment weighting (IPTW) approach. In the primary analysis, individual patient-level data (IPD) from the mogamulizumab arm of the MAVORIC trial were reweighted to reflect the demographic and clinical characteristics of the Danish real-world patient population. This approach enabled estimation of comparative treatment effects while adjusting for cross-population differences in prognostic variables and potential effect modifiers. Two analysis datasets were independently constructed and subsequently merged for comparative evaluation: one comprising IPD from the MAVORIC trial's mogamulizumab treatment arm (the "treatment group"), and the other comprising real-world IPD derived from Danish national health registers (the "external control group").

C.4 MAVORIC trial data

In MAVORIC, 186 patients with R/R MF or SS were randomised to receive 1.0 mg/kg of mogamulizumab weekly for a first cycle of 28 days. In the subsequent cycles, mogamulizumab was administered on days 1 and 15. The primary outcome of the MAVORIC trial was PFS defined as time from randomisation to progression or death, compared with patients randomised to treatment with vorinostat. Secondary outcomes included overall response rate and quality of life. Exploratory outcomes included OS and exposure-response relationship. Importantly, the MAVORIC trials was not powered to detect differences in OS.

C.4.1 Patient eligibility MAVORIC

The main inclusion and exclusion criteria from the MAVORIC trial are presented in Table 2.

Table 82: MAVORIC inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Male and female subjects ≥ 18 years of age at the time of enrolment, except in Japan where subjects had to be ≥ 20 years of age at the time of enrolment. - Histologically confirmed diagnosis of MF or SS. - MF or SS stage IB, II-A, II-B, III or IV. - Had failed at least one prior course of systemic treatment. Psoralen plus ultraviolet light therapy (PUVA) was not considered to be a systemic treatment. - An ECOG performance status score of ≤ 1 at study entry. - Resolution of all clinically significant toxic effects of prior cancer therapy to grade ≤ 1 by the National Cancer Institute Common	- Prior treatment with mogamulizumab or vorinostat. - Large cell transformation (LCT). However, subjects with a history of LCT but without current aggressive disease and no current evidence of LCT on pathology in skin and lymph nodes were eligible. - Diagnosed with a malignancy in the past two years. However, subjects with non-melanoma skin cancers, melanoma in situ, localised cancer of the prostate with current PSA of <0.1 ng/mL, treated thyroid cancer or cervical carcinoma in situ, or ductal/lobular carcinoma in situ of the breast within the past two years could enrol as long as there was no current evidence of disease. - Clinical evidence of central nervous system metastasis. - Psychiatric illness, disability, or social situation that would have compromised the subject's safety or ability to provide consent, or limited compliance with study requirements.

Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE, v.4.0). • Adequate haematological, renal, and hepatic function. • Previously treated with anti-CD4 antibody or alemtuzumab provided that CD4+ cell counts were $\geq 200/\text{mm}^3$. • Patients with MF and a known history of non-complicated staphylococcus infection/colonization were eligible provided they continued to receive stable doses of prophylactic antibiotics. • Women of childbearing potential (WOCBP) had to have had a negative pregnancy test within seven days of receiving study medication. • WOCBP and male subjects as well as their female partners of childbearing potential had to have had agreed to use effective contraception throughout the study and for 3 months after the last dose of mogamulizumab (KW-0761).	• Significant uncontrolled intercurrent illness. • Known or tested positive for human immunodeficiency virus, human T-cell leukaemia virus hepatitis B, or hepatitis C. • Active herpes simplex or herpes zoster. Subjects on prophylaxis for herpes who started taking medication at least 30 days prior to study entry, and had no active signs of active infection, and whose last active infection was more than 6 months ago, could enter the study, and had to continue to take the prescribed medication for the duration of the study. • Experienced allergic reactions to monoclonal antibodies or other therapeutic proteins. • Known active autoimmune diseases were excluded (e.g., Grave's disease, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, and psoriasis). • Was pregnant (confirmed by beta human chorionic gonadotrophin) or lactating. • History of allogeneic haemopoietic stem cell transplantation.
--	--

C.4.2 Observation period MAVORIC

The observation period for the MAVORIC trial, starting in November 2012, has been reported through multiple data cuts over time. These data cuts reflect different durations of follow-up, allowing for updated analyses of efficacy and safety outcomes as additional patient data accrued. Interim and earlier analyses were published at various stages of the trial's progression (e.g., Kim et al. (5)), but subsequent data cuts have provided extended follow-up on, e.g., PFS and OS. In this analysis, we relied on the most recent and comprehensive data cut available from March 2nd 2019.

C.4.3 Data preparation MAVORIC

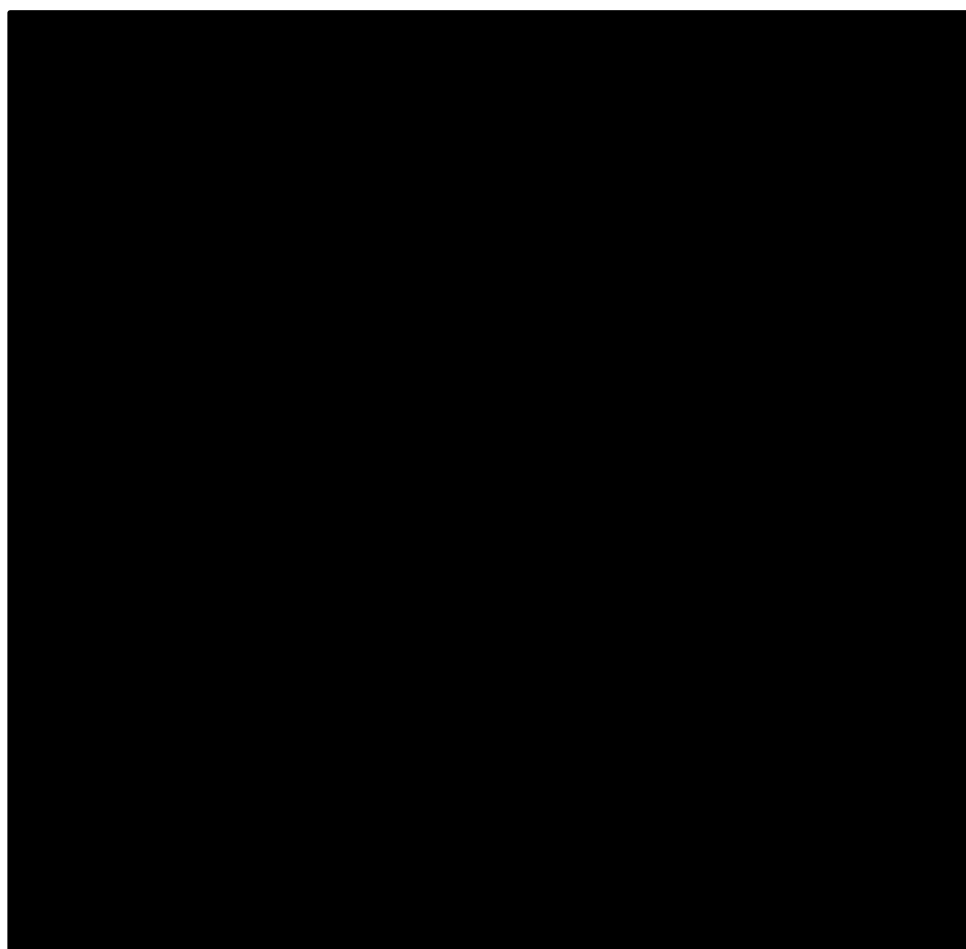
Data from the MAVORIC trial were structured according to the Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) standard. Key ADaM datasets used in this study included the subject level (ADSL) dataset and time-to-event (ADTTE) dataset.

C.5 Danish real-world data

In Denmark, there is a long-standing tradition of collecting IPD on the population's health and storing these in national registers (73). IPD are collected routinely by health care professionals as part of all patients' treatment in the Danish healthcare system. Because no individual with a CPR-number is exempt from data collection, the national registers include data on virtually all individuals in Denmark. Data can be combined across registers at the individual level via CPR-numbers that are unique to any individual with a permanent address or tax paying obligation in Denmark (74).

This study utilised data from several high-quality Danish national health registers (Figure 26) enabling comprehensive identification, characterisation, and longitudinal follow-up of patients diagnosed with MF or SS, including the Danish Civil Registration System (CPR) register (74, 75), the Danish National Patient Register (DNPR) (56), the Danish Pathology Register (DPR) (57), the National Hospital Medication Register (NHMR) (76, 77), and the Danish National Prescription Register (DNPPR) (78).

Figure 26. National Danish registers used to define the Danish real-world population



The CPR register was used to identify the study population and ensure valid follow-up. It includes encrypted personal identification numbers (CPR numbers) and provides essential demographic and vital status information, including sex, date of birth, and dates of death or migration. The DNPR contains data on all in- and outpatient hospital contacts in Denmark, including primary, secondary, and supplementary diagnoses coded using the ICD-10 system, as well as surgical procedures and treatment codes. These data were used to identify MF and SS diagnoses and systemic treatments received during in or out-patient hospital-based care. The DPR captures data from all pathology investigations performed in Denmark and includes details on the performed pathology tests, macro- and microscopic descriptions, and the final pathological diagnosis. Diagnoses are recorded using the Danish adaptation of the Systematized Nomenclature of Medicine (SNOMED), which in combination with clinician-recorded diagnoses from the DNPR facilitates precise identification of MF and SS cases based on histopathological criteria. The NHMR and the DNPPR contain product-level information on medications administered or dispensed during in- and outpatient hospital care and prescriptions dispensed from pharmacies, respectively, allowing for – in conjunction with treatment data from the DNPR – a highly granular level of systemic treatment trajectories.

C.5.1 Patient eligibility Danish SoC

Patients were eligible for inclusion in the Danish SoC arm if they:

- 1) were diagnosed with a primary or secondary diagnosis code for MF (C84.0) and/or SS (C84.1) since 1995 in the DNPR, and

- 2) had ever been registered with a SNOMED code for MF (M9700*, M970A*, M9625*) or SS (M9701*) since 1995 according to the Danish SNOMED classification in the DPR, and
- 3) had undergone at least one prior SoC systemic treatment after diagnosis, as registered in the DNPR or DNPPR since 1995, or the NHMR since May 2018.

Based on clinical expert input, Danish SoC treatments for R/R MF and SS were defined in accordance with international guidelines as (16): retinoids (bexarotene, acitretin, isotretinoin, and alitretinoin), chemotherapies (cyclophosphamide, doxorubicin, vincristine, prednisolone, gemcitabine, low and high dose methotrexate, etoposide, chlorambucil, chlormethine, and carmustine), interferon (alpha and pegylated), extracorporeal photopheresis, and immunotherapies (alemtuzumab, brentuximab vedotin, and pembrolizumab). Anatomical Therapeutic Chemical (ATC) codes were used to identify SoC systemic treatments as registered in the DNPR, DNPPR, and NHMR.

As in the MAVORIC trial, patients in the Danish SoC arm who had undergone aSCT as per the DNPR and/or had a record of histologically confirmed large cell transformations in the DPR were excluded.

C.5.2 Observation period Danish SoC

A one-year washout period was implemented to ensure that included patients were observed from the time of their primary diagnosis. Thus, the Danish SoC arm included all MF and SS patients registered in Denmark from 1996 to April 15th, 2024, as identified by the outlined eligibility criteria. The latest available data extraction for this cohort allowed for follow-up until March 1st, 2025.

C.5.3 Data preparation Danish SoC

The data obtained from the national registers were combined at the individual patient level and organised as a time-to-event dataset using the “Tidy” concept. In tidy data, 1) each variable is placed in a separate column, 2) each observation is placed in a separate row, and 3) each type of observational unit is placed in a separate dataset. Table 83 details the steps involved in the data cleaning process.

Table 83: Data cleaning procedures.

Step	Description
Data merging	Raw data from multiple registers were merged at the individual patient level using unique patient identifiers to ensure that each record corresponds to a single patient across all data sources.
Missing data	Missing data were not imputed, regardless of the nature and extent of the missingness.
Data normalisation and transformation	Variables were assessed for consistency in units and scales (e.g., days, months, and years). Normalisation or standardisation was applied where necessary to ensure comparability across observations.
Data tidying	Following the tidy data principles: each variable in a separate column, each observation in a separate row, and different observational units in separate datasets. Because the unit of observation was always the patient level, separation into datasets was based on outcomes (e.g., one dataset for OS, another for NTF5).
Time-to-event data structuring	The dataset was organised as a time-to-event (survival) dataset, generating variables indicating time from treatment initiation (T_0) to an event or censoring.
Consistency checks	Performed to ensure data adhered to expected formats and relationships between variables were logical. Verified that event dates followed chronological order.
Final dataset verification	The final dataset was reviewed for completeness and accuracy before locking the dataset.

C.6 Comparative study design

C.6.1 Outcomes

The primary outcome of interest in this study was OS. In the Danish SoC arm, OS was defined as the time (in months) from the arm-specific T_0 to the date of death (section C.6.2 contains details on T_0). Patients were censored at the date of emigration, disappearance, or administratively on March 1st, 2025. In the mogamulizumab arm, OS was defined analogously, with censoring at the study end date.

The secondary outcome was PFS, which was approximated by NTFS¹. Because the index date by definition cannot be set to the most recent observable treatment as for OS, as this would result in zero events, NTFS results were using an indirect estimation approach to ensure structural consistency of model inputs (OS and NTFS) for cost-effectiveness modelling. In this approach, we extracted survival curves for both OS and NTFS from the IPTW-weighted mogamulizumab arm. Then, at each model cycle, we calculated the hazard ratio between the OS and NTFS and applied it to the extrapolated OS curves of the Danish SoC arm to derive corresponding NTFS estimates. This method rests on the assumption that the relationship between OS and NTFS observed in the mogamulizumab arm is consistent across treatment groups. Such consistency is considered plausible, given similarities in clinical progression dynamics, treatment sequencing, and censoring mechanisms across the two arms. It is important to acknowledge that the validity of this approach depends on the stability of the OS–NTFS relationship over time. For the mogamulizumab arm, a progression event was investigator-assessed.

C.6.2 Exposure alignment

To conduct the indirect treatment comparison between the Danish SoC arm and the MAVORIC mogamulizumab arm, temporal alignment of index timepoints between the study arms is imperative. For the Danish SoC arm, we defined the index timepoint (T_0) as the date of initiation of the most recent observable systemic treatment, whereas for the mogamulizumab arm, T_0 corresponded to the date of randomisation. This approach was adopted to enable the inclusion of a larger patient population with varying histories of prior systemic treatments in the Danish SoC arm, thereby improving the overlap with the treatment-experienced population enrolled in the MAVORIC trial. However, while this strategy enhances the potential for matching and increases statistical power, it does so at the risk of introducing immortal time bias in the Danish SoC arm. Specifically, setting T_0 at this timepoint in the Danish SoC arm implicitly required patients to have survived and remained eligible through multiple lines of treatment, whereas the majority of patients in the mogamulizumab arm entered the trial after a median of three previous systemic treatments. This discrepancy can confer a survival advantage to the Danish SoC group, potentially biasing the comparison. At the same time, the approach also risks

¹ NTFS reflects the duration during which a patient remains alive without initiating a subsequent systemic treatment, serving as a pragmatic proxy for a period of clinical disease control in the absence of direct progression data. Specifically, NTFS is defined analogously to the more conventional time-to-next-treatment as the time from index treatment initiation until the start of a new systemic treatment but also accounts for death from any cause as an event, whichever occurs first. Given that information on histologically and radiologically confirmed disease progression is not systematically captured in the Danish registers, NTFS functions as an indirect measure of progression by leveraging treatment patterns, which are often initiated in response to histological, radiological, or symptomatic-indicated progression in routine practice. This approach has been previously validated in real-world oncology research as a reasonable surrogate for PFS in administrative data sources lacking progression information (14).

the opposite distortion, often described as depletion of susceptible or reverse survivor bias, where patients initiating what proves to be their final systemic therapy may represent a subset with rapidly progressing disease or limited remaining survival, leading to potential underestimation of OS compared with the trial population. To mitigate this bias, the number of prior systemic treatments was included as a covariate in the propensity score model used to derive the IPTW weights alongside other potential effect modifiers and prognostic factors (see section C.7 for details), serving as a control for disease trajectory and prior survival time. Residual confounding may nonetheless persist due to unmeasured or misclassified covariates, including time-dependent factors not captured in the available data.

C.7 Statistical methods

The mogamulizumab and Danish SoC arms were compared using an IPTW approach. Since there is no common comparator between the two arms, the comparison was ‘unanchored’, meaning that the results of the comparison rely on the assumption of conditional constancy of absolute effect. This assumption states that all variables that influence treatment outcomes have been measured and appropriately adjusted for in the analysis (58). Unlike anchored indirect comparisons where relative effects can be estimated by adjusting only for effect modifiers, unanchored comparisons require adjustment for both effect modifiers and prognostic factors. This is a strong assumption that is rarely fully met. However, including the most important known effect modifiers and prognostic variables allows for the estimation of an approximate relative effect.

C.7.1 Primary analysis

C.7.1.1 Propensity score estimation

In the IPTW approach, weights are derived from propensity scores estimated in a logistic regression model. The propensity score represents the probability of receiving a particular treatment (in this case Danish SoC) conditional on the included baseline covariates, expressed as:

$$ps = P(T = 1|X)$$

where ps is the propensity score, T is the treatment indicator ($T = 1$ for Danish SoC and $T = 0$ for mogamulizumab), and X is a vector of baseline covariates.

Variable selection for the logistic regression model followed a comprehensive and systematic process. Firstly, candidate variables were identified based on clinical relevance and plausibility, prioritising predictors that aligned with established medical knowledge (50). Candidate variables that were available in the included registers were age, sex (male vs female), disease type (MF vs SS), large cell transformation (yes vs no), number of previous systemic treatments, and disease duration. Secondly, the statistical significance of individual predictors was evaluated to retain only those variables that demonstrated a meaningful association with treatment assignment, unless strong clinical justification warranted their retention. Thirdly, competing model specifications were compared using the Akaike Information Criterion (AIC) to quantitatively assess and balance model fit against complexity, thereby minimising the risk of overfitting. Lastly, a final set of covariates was selected that achieved an optimal trade-off between statistical robustness, clinical utility, and model parsimony.

The covariates included in the final model are presented in Table 84. To align with the MAVORIC trial exclusion criteria, large cell transformation was used as an exclusion criterion in the Danish SoC arm rather than as a covariate in the propensity score model; disease duration, defined as time from initial diagnosis to index, did not provide any improvement in statistical fit and was removed.

Table 84: Covariates included in the estimation of propensity scores

Variables	Variable type	Definition	Source
Age*	Continuous	Years	CPR
Sex	Dichotomous	Male / female	CPR
Disease type	Dichotomous	MF / SS	DNPR, DPR
Nr. of previous systemic treatments**	Continuous	Nr. of previous systemic treatments	DNPR, NHMR, DNPPR

Notes: *The model also included squared and cubic terms for the age variable. **The model also included a squared term for the number of previous systemic treatments variable. Abbreviations: DK, Denmark; SoC, standard of care; SS, Sézary syndrome; MF, mycosis fungoides.

Specifically, the logistic model used to estimate the propensity scores was specified as:

$$\text{logit}(ps) = \beta_0 + \beta_1(\text{sex}) + \beta_2(\text{age}) + \beta_3(\text{disease_type}) + \beta_4(\text{age}^2) + \beta_5(\text{age}^3) + \beta_6(\text{previous_lines}) + \beta_7(\text{previous_lines}^2)$$

C.7.1.2 Weight estimation for the average treatment effect on the treated

After estimating the propensity scores, IPTW weights were calculated to estimate the average treatment effect on the treated (ATT). Individuals in the treated group ($T = 1$; Danish SoC) were assigned a weight of 1, while individuals in the control group ($T = 0$; mogamulizumab arm) were assigned a weight of $\frac{ps}{1-ps}$ such that:

$$w_1 = 1 \text{ when } T = 1$$

$$w_0 = \frac{ps}{(1-ps)} \text{ when } T = 0$$

Under the assumptions of no unmeasured confounding and sufficient overlap in covariate distributions (positivity), applying w_1 and w_0 when estimating outcomes generates a pseudo population in which the distribution of important baseline covariates is balanced across treatment groups. In the pseudo population, a reweighted version of the original sample, each individual contributes to the outcome estimation proportionally to their weight.

C.7.1.3 Extreme weights

Using histograms, we assessed the distribution of the estimated weights to identify potential issues with extreme values. Inverse probability weights that are too large can destabilise estimates, increase variance, and lead to unreliable results. Crump et al. (59) recommend excluding observations with propensity scores outside the range [0.1, 0.9] when estimating treatment effects, as both low and high scores can produce extreme weights. However, such guidance primarily applies to estimation of average treatment effect (ATE) weighting schemes where both treated and control units can yield large weights when propensity scores approach 0 or 1. In contrast, our primary analysis used ATT weighting, where only individuals in the mogamulizumab arm ($T = 0$)

were reweighted. As weights in this group are defined as $\frac{ps}{1-ps}$, large values occur only when the propensity score is close to 1, i.e., when patients in the mogamulizumab arm closely resemble those in the Danish SoC arm. Consequently, the risk of unstable weights is more limited in scope compared to ATE weighting but still warrants assessment.

We used a winsorization procedure to limit the influence of extreme weights. Following the rule of thumb proposed by Crump et al. (59), the most extreme inverse probability weight expected under a trimming threshold of 0.9 is approximately 9 (i.e., $1/0.9$). To avoid potential loss of information in our relatively small sample, we opted not to trim observations, but instead winsorized the weights at an upper bound of 9. Winsorization is a variance-stabilizing technique that replaces extreme values with a specified threshold, thereby reducing the influence of outliers at the cost of introducing a small amount of bias (60). In our case, only two observations had weights exceeding 9, and these were replaced with the value 9. All primary analyses were based on these winsorized ATT weights.

C.7.1.4 Assessing balance

After estimating the inverse probability weights, covariate balance between the treatment groups should be evaluated to assess the adequacy of the weighting procedure. Balance can be examined at two levels: (1) at the propensity score level, to assess face validity and ensure adequate overlap between groups; and (2) at the covariate level, to evaluate whether the distribution of individual covariates is comparable across groups after weighting. This assessment may be conducted visually, for example by comparing the distribution of covariates before and after weighting using density plots or histograms. Alternatively, balance can be evaluated quantitatively by calculating standardized mean differences (SMDs) for each covariate. A commonly used threshold is an absolute SMD of 0.1 (or 10%), above which residual imbalance is considered potentially meaningful and indicative of inadequate covariate adjustment (61, 62). In this study, we assessed covariate balance both visually and quantitatively.

C.7.2 Outcome analyses

The final analysis dataset included the following elements for each patient: 1) survival time from T_0 to event or censoring, 2) event indicator (1 = death, 0 = censored), 3) treatment indicator (1 = Danish SoC, 0 = mogamulizumab), and 4) an IPTW weight.

C.7.2.1 Overall survival

OS was first analysed using unweighted Kaplan-Meier estimates, followed by a weighted analysis incorporating the weights derived from the IPTW (see section 7.1.3.1). The weighted Kaplan-Meier analysis was implemented using the *survfit* function from the *survival* package in R (79), with the following syntax:

$$\text{survfit}(\text{Surv}(\text{time}, \text{event}) \sim \text{treatment}, \quad \text{weights} = \text{weights})$$

Subsequently, a weighted Cox proportional hazards model was fitted to the OS data using the *coxph* function from the same package (79):

$$\text{coxph}(\text{Surv}(\text{time}, \text{event}) \sim \text{treatment}, \quad \text{weights} = \text{weights})$$

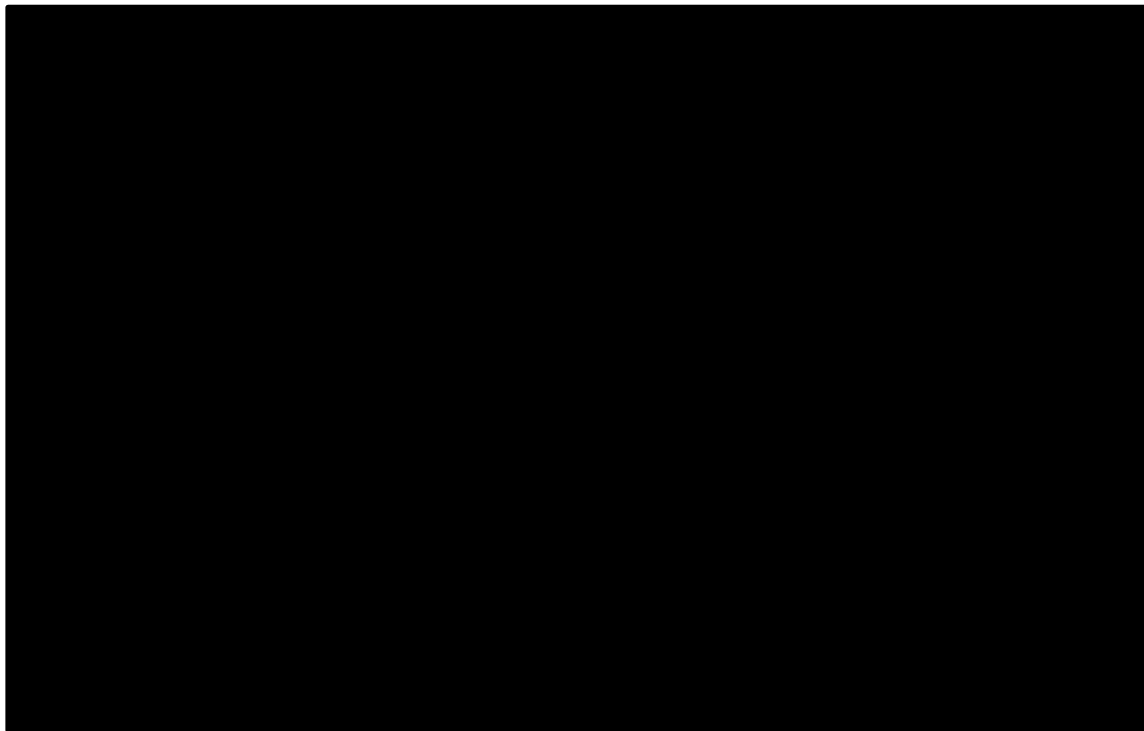
The function returned estimates of the hazard ratio (HR), standard errors, p-values, and 95% confidence intervals, in addition to residual diagnostics and model fit statistics, such as AIC. The proportional hazard (PH) assumption was visually assessed using plots of the log cumulative hazard against the log of time, where approximately parallel curves are indicative of proportionality of hazards.

C.8 Results

C.8.1 Descriptive statistics

Overall, [REDACTED] patients were identified that had been treated in the Danish secondary healthcare system for CTCL as defined by the ICD-10 diagnosis code C84 (Figure 27).

Figure 27: Flowchart of selected patients from the Danish registers



Notes: *The year 1995 was excluded to allow one year of washout. **Retinoids (bexarotene, acitretin, isotretinoin, and alitretinoin), chemotherapies (cyclophosphamide, doxorubicin, vincristine, prednisolone, gemcitabine, low and high dose methotrexate, etoposide, chlorambucil, chlormethine, and carmustine), interferon (alpha and pegylated), extracorporeal photopheresis, and immunotherapies (alemtuzumab, brentuximab vedotin, and pembrolizumab). *** Patients who are seen in the secondary health care sector and have undergone one prior systemic treatment are assumed to be advanced patients.

Out of this population, [REDACTED] patients had a histologically confirmed MF diagnosis (ICD-10 code C84.0) and [REDACTED] patients had a histologically confirmed SS diagnosis (ICD-10 code C84.1). In the MF population, [REDACTED] patients had undergone at least one prior systemic treatment; in the SS population, [REDACTED] patients had undergone at least one prior systemic treatment. Thus, the total analysis sample in the Danish SoC arm consisted of [REDACTED] patients with histologically confirmed R/R MF or SS.

Table 85 compares descriptive statistics of key variables between the mogamulizumab and the Danish SoC arms. The distributions clearly show that there are large differences between the two study arms, particularly with regards to age and the proportion of patients with MF and SS, necessitating statistical alignment.

Table 85: Descriptive statistics

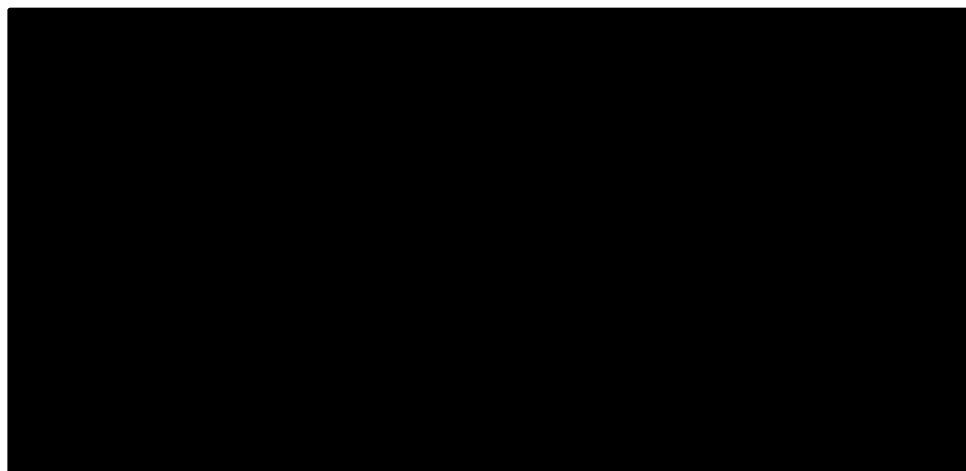
Variables	Danish SoC arm	Mogamulizumab arm	p-value
N		186	
Age			
Mean (SD)		62.82 (13.34)	<0.001
Median [Min, Max]		63.50 (25;101)	
Sex			<0.001
Female, n (%)		109 (58.6)	
Male, n (%)		77 (41.4)	
Proportion of patients with MF			<0.001
No, n (%)		81 (43.5)	
Yes, n (%)		105 (56.5)	
Proportion of patients with SS			<0.001
No, n (%)		105 (56.5)	
Yes, n (%)		81 (43.5)	
Nr. of previous systemic treatments			
Mean (SD)		4.06 (3.17)	<0.001
Median [Min, Max]		3 (1; 18)	

Abbreviations: SD, standard deviation; DK, Denmark; SoC, standard of care; SS, Sézary syndrome; MF, mycosis fungoides.

C.8.2 ATT weights

Figure 9 presents the distribution of the estimated ATT weights following winsorization. The horizontal axis represents the weight values, while the vertical axis depicts the corresponding frequency of patients. The distribution illustrates a right-skewed pattern, with a large proportion of patients receiving weights close to zero, and a long tail extending towards higher values, indicating the presence of a small number of treated individuals with relatively high weights even after winsorization.

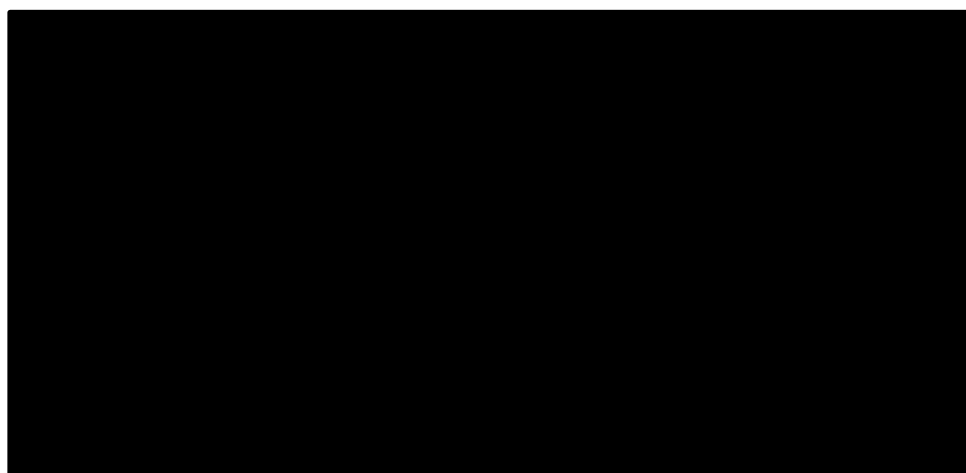
Figure 28: Distribution of winsorized ATT weights for the mogamulizumab arm



C.8.3 Balance assessment

Figure 29 illustrates the distribution of the age covariate across treatment arms before and after adjustment using ATT weights (additional figures showing the distribution of covariates (unadjusted and adjusted) are available in Appendix A in section C.9).

Figure 29: Distributional balance of age



The left panel presents the unadjusted sample, showing clear discrepancies in age distributions between the two treatment groups, indicating covariate imbalance. The right panel shows the adjusted sample, where ATT weights have been applied.

Table 86 presents a summary of the covariates included in the propensity score model, reporting their distributions before and after the application of ATT weights. The table displays unadjusted and adjusted means for both treatment arms, along with the post-adjustment standardized mean differences (SMDs) for continuous variables and raw differences in proportions for dichotomous variables. The results indicate that weighting substantially reduced imbalances across all covariates. For instance, the SMD for age decreased from [REDACTED] (unadjusted) [REDACTED] (adjusted), while similar reductions were observed for sex and number of previous systemic treatments. The small absolute differences observed post-weighting support the effectiveness of the ATT weighting procedure in achieving a better covariate balance.

Table 86: Balance table for model covariates pre and post weighting

Variables	Variable type	Mogamulizumab unadjusted mean*	Danish SoC unadjusted mean*	Mogamulizumab adjusted mean*	Danish SoC adjusted mean*	SMD**
Age	Continuous	62.82	██████	██████	██████	██████
Sex	Dichotomous	0.41	██████	██████	██████	██████
Disease type	Dichotomous	0.44	██████	██████	██████	██████
Previous systemic treatments	Continuous	4.06	██████	██████	██████	██████

Notes: *Proportions are reported for dichotomous variables. **Standardized mean difference reported for continuous variables; raw difference in proportions reported for dichotomous variables. Abbreviations: SMD, Standardized mean difference.

Unweighted efficacy outcomes results

Figure 30 displays the unweighted Kaplan–Meier (KM) curves for OS stratified by treatment arm. The curves indicate that the survival probability over time was consistently higher in the mogamulizumab group compared to the Danish SoC with median survival of ██████████ respectively. In the mogamulizumab arm ██████ patients out of ████████, while in the Danish SoC ██████. A Cox proportional hazards regression model, unadjusted for covariates or weights, yielded a HR of ██████████, indicating a statistically significant survival benefit for patients treated with mogamulizumab. Figure 31 presents a log-log plot used to visually assess the PH assumption. The approximately parallel curves suggest that the PH assumption holds.

Figure 30: Unweighted KM curves of OS by treatment arm

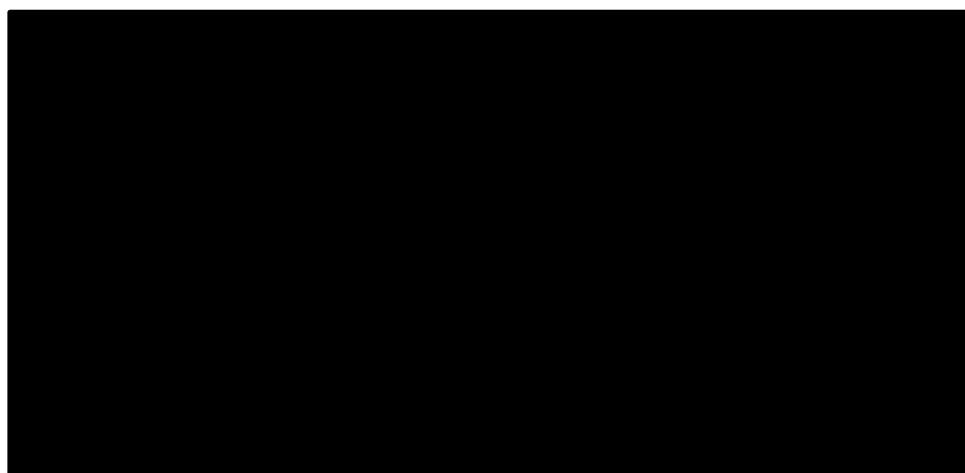
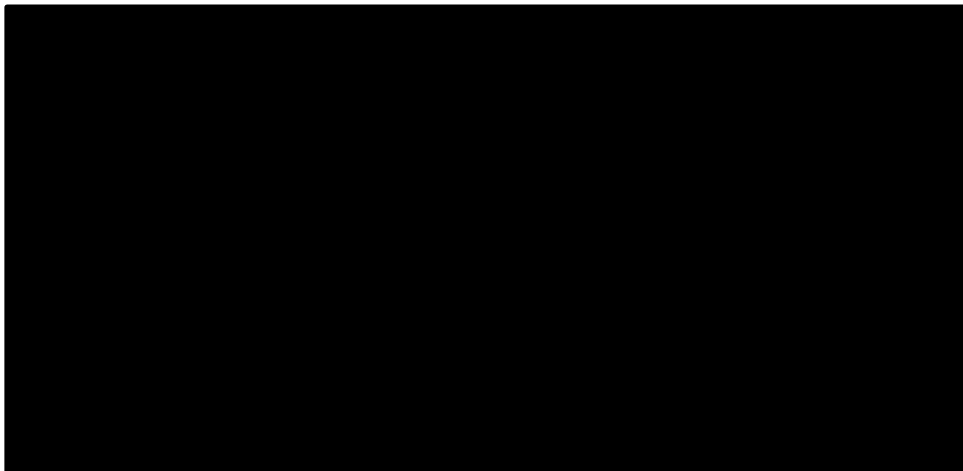


Figure note: Shaded areas represent 95% confidence intervals.



Figure 31: Log hazard over log time by treatment arm, unweighted



C.8.4 Weighted efficacy outcomes results

Figure 32 shows the ATT-weighted KM curves for OS. Following reweighting, mogamulizumab continued to demonstrate a marked survival benefit (median survival not reached). The weighted Cox regression yielded an HR of [REDACTED], suggesting an even stronger treatment effect under covariate adjustment. As in the unweighted analysis, the Cox regression relied on the PH assumption (Figure 33), and similarly, the approximately parallel lines suggest that the assumption holds.

Figure 32: Weighted KM curves of OS by treatment arm

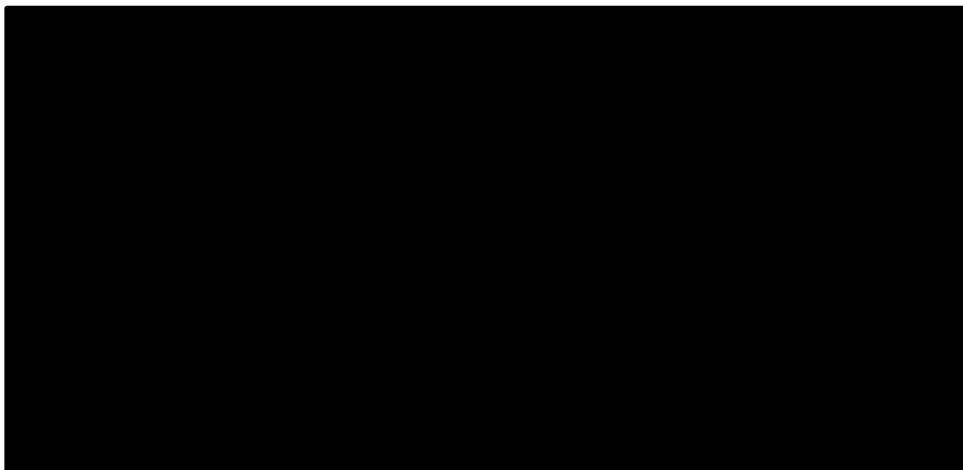
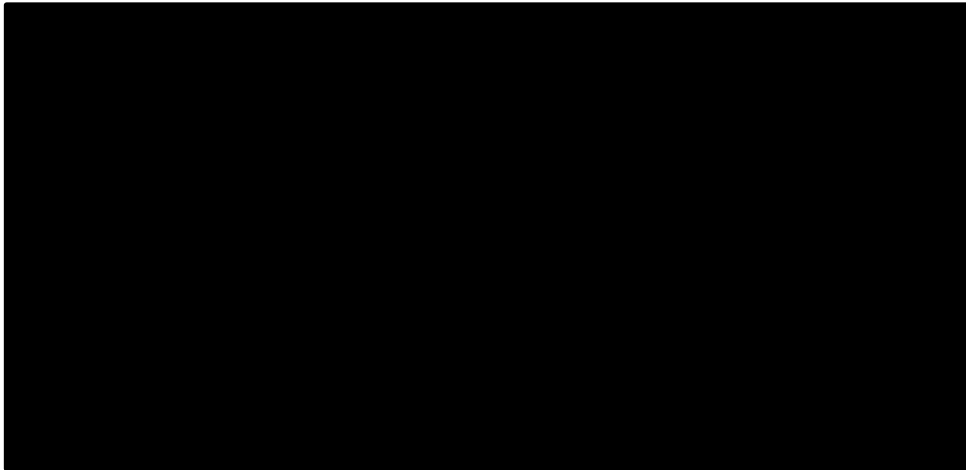


Figure note: Shaded areas represent 95% confidence intervals

Figure 33: Log hazard over log time by treatment arm, weighted

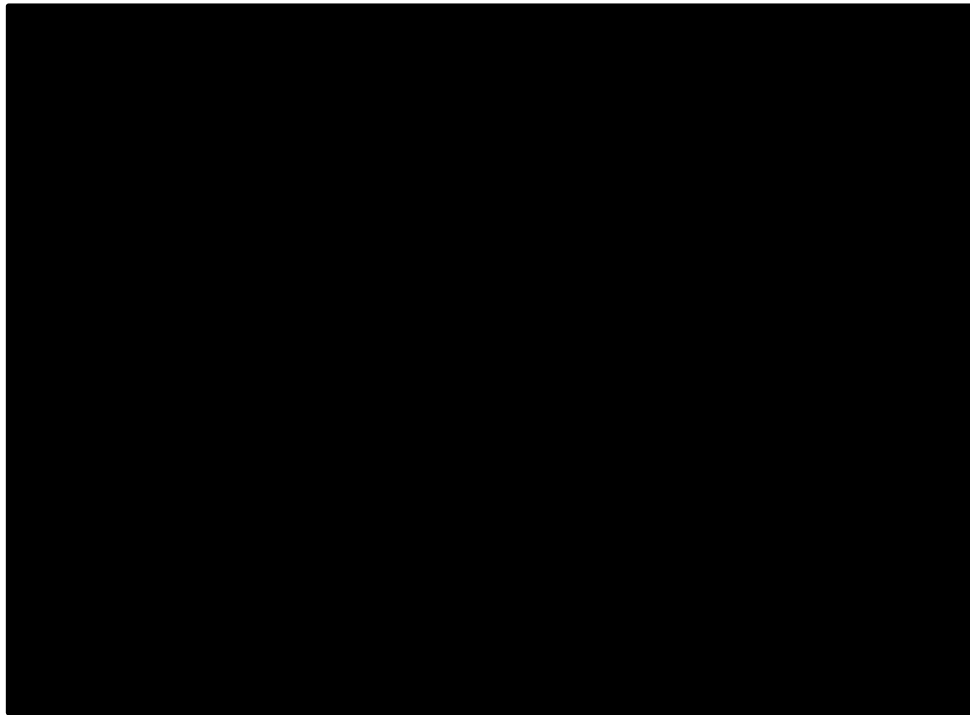


C.8.5 Concluding remarks

In the primary analysis, across both unweighted and ATT-weighted analyses, mogamulizumab was consistently associated with improved OS compared to the Danish SoC. The divergence of the KM curves, particularly following covariate adjustment via ATT weights, supports the robustness of the treatment effect in a population comparable to DK SoC patients.

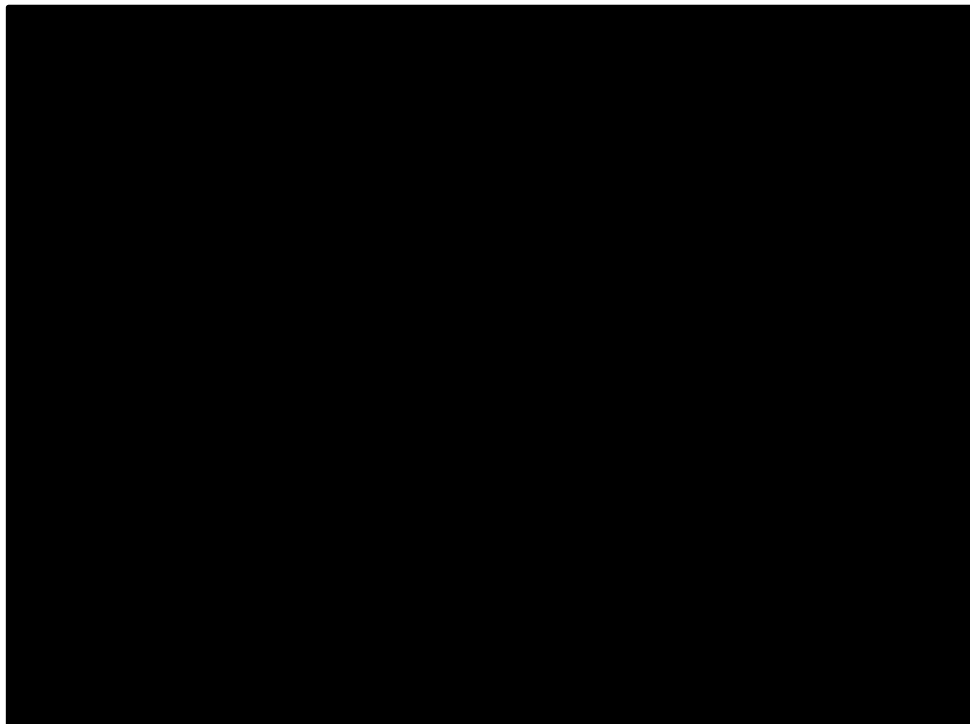
C.9 Appendix A: Balance assessment

Figure 34: Distributional balance of number of previous systemic treatments



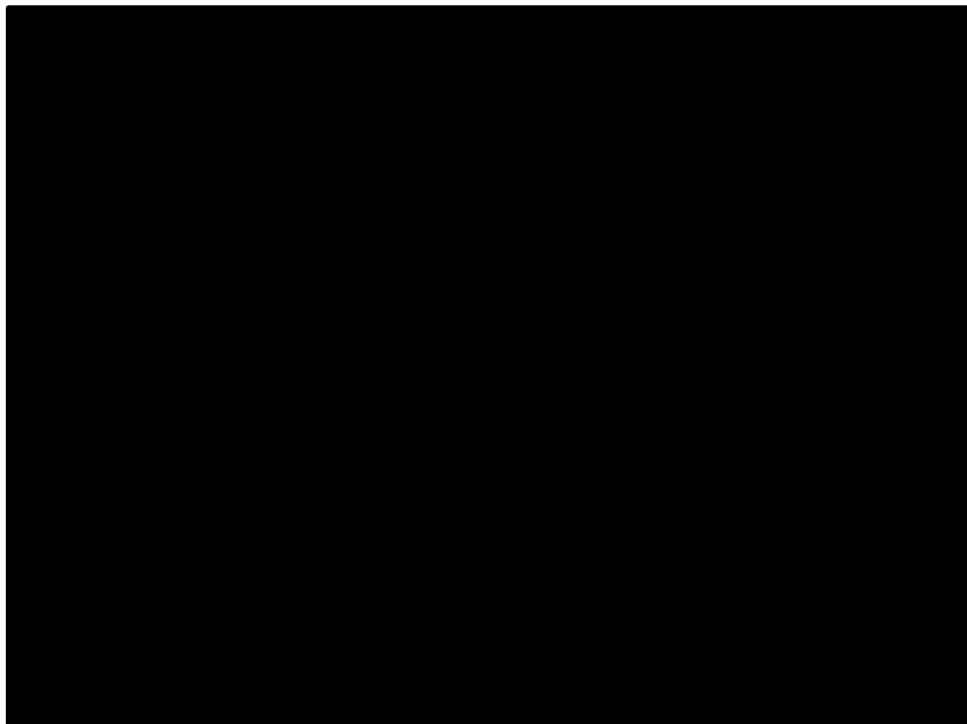
Abbreviations: SS, Sezary syndrome; MF, Mycosis fungoides; DK, Denmark; SoC, standard of care.

Figure 35: Distributional balance of type of diagnosis



Abbreviations: SS, Sezary syndrome; MF, Mycosis fungoides; DK, Denmark; SoC, standard of care.

Figure 36: Distributional balance of sex



Abbreviations: SS, Sezary syndrome; MF, Mycosis fungoides; DK, Denmark; SoC, standard of care.

Appendix D. Extrapolation

D.1 Extrapolation of OS

D.1.1 Data input

OS was based on the MAVORIC study and the IPTW analysis presented in Section 7. OS was extrapolated beyond the follow-up of the study to assess the CE of mogamulizumab vs DK SoC over a lifetime horizon.

D.1.2 Model

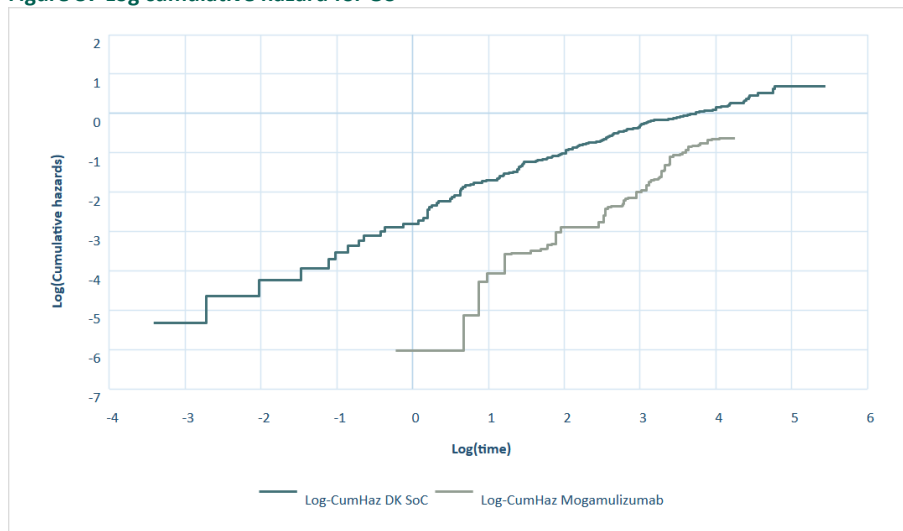
A treatment effect model was chosen as the most appropriate as described in Section 8. Standard parametric models were used to extrapolate OS, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.1.3 Proportional hazards

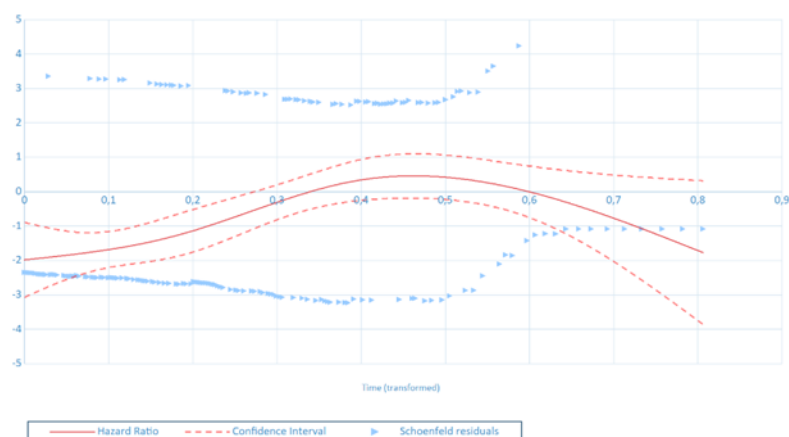
To assess proportional hazards two plots are presented, see log cumulative hazards in Figure 37 and Schoenfeld residuals plot in Figure 38 below. Due to the parallel trends in log cumulative hazards, a treatment effect model was chosen in the base case.

Figure 37 Log cumulative hazard for OS



Abbreviations: OS, overall survival; Log-CumHaz, log cumulative hazards; DK SoC, Danish standard of care.

Figure 38 Schoenfeld residuals



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

AIC and BIC values for the combined models are reported in Section 8.

Below the AIC and BIC for the separate fits of overall survival.

Table 87 Goodness of fit for OS (mogamulizumab separate models)

Model	AIC	BIC
Exponential	539.70	542.90
Generalised Gamma	540.00	549.70
Gompertz	540.50	547.70
Log-logistic	537.70	544.10
Log-normal	539.20	545.70
Weibull	538.50	545.00

Abbreviations: OS, overall survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Table 88 Goodness of fit for OS (DK SoC separate models)

Model	AIC	BIC
Exponential	1742.30	1748.90
Generalised Gamma	1683.90	1703.50
Gompertz	1696.60	1709.70
Log-logistic	1680.60	1693.70
Log-normal	1681.50	1694.60
Weibull	1688.90	1702.00

Abbreviations: OS, overall survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DK SoC, Danish standard of care.

D.1.5 Evaluation of visual fit

The visual fit was evaluated for mogamulizumab and DK SoC. For mogamulizumab, all extrapolations seem to fit the KM data reasonably well. The Gompertz curve, due to its

asymptotic behaviour was not chosen, as it predicted that about 50% of patients would remain alive indefinitely.

For DK SoC, all extrapolations seem to fit the KM data reasonably well, with only the exponential curve being heavily misaligned (i.e., overestimates up to around month 50, and underestimates after month 50).

Figure 39 Extrapolated mogamulizumab curves (dependent fit, weighted)

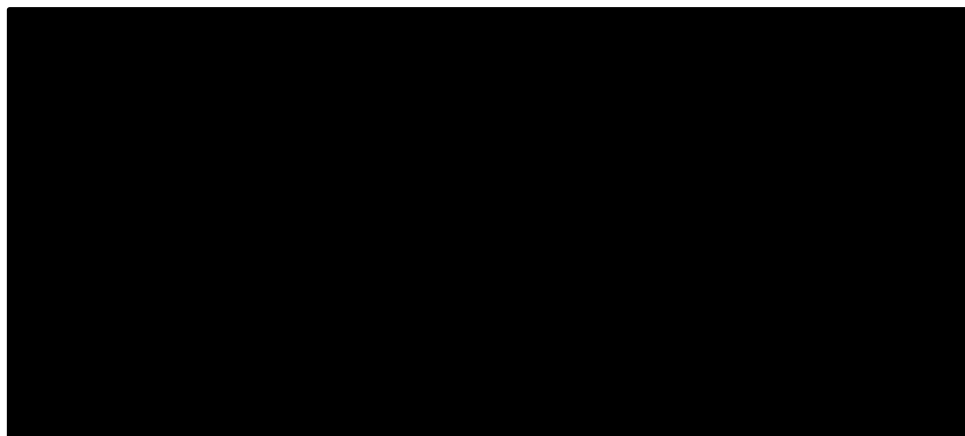
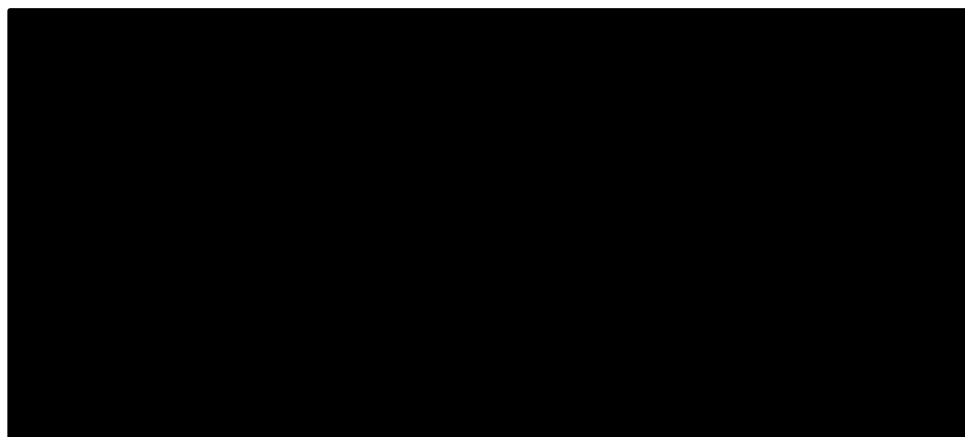


Figure 40 Extrapolated DK SoC curves (dependent fit, weighted)



Abbreviation: DK SoC, Danish standard of care.

Figure 41 Extrapolated mogamulizumab curves (independent fit, weighted)

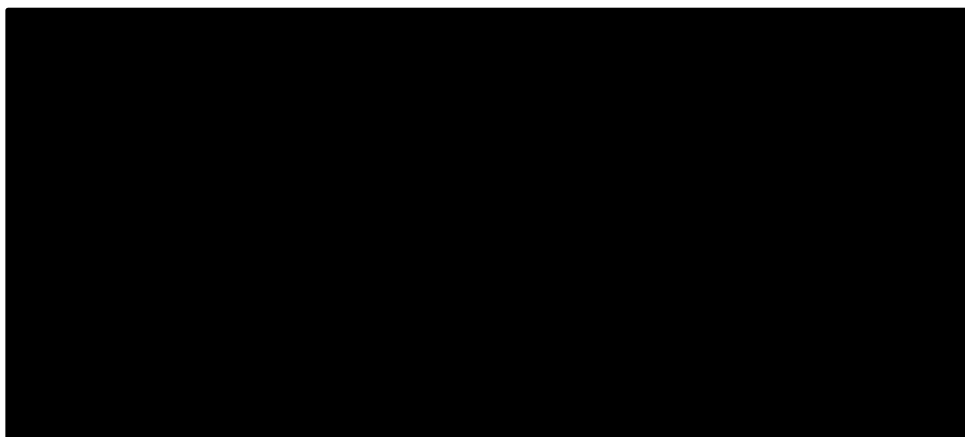
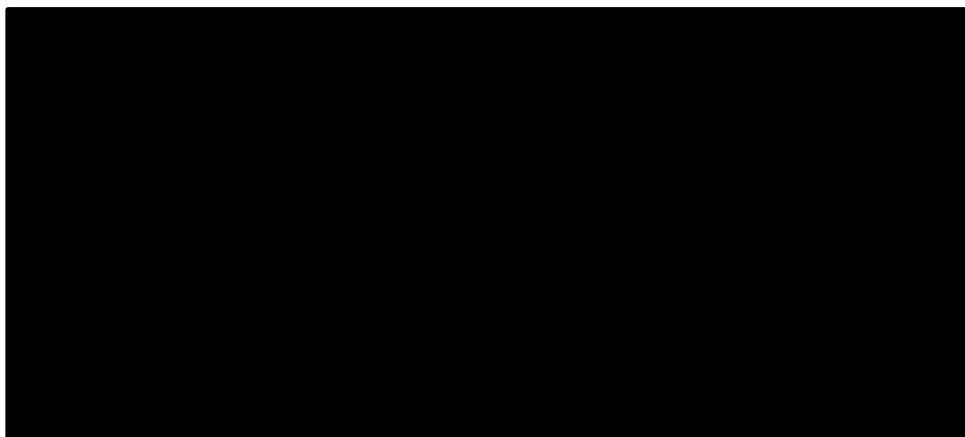


Figure 42 Extrapolated DK SoC curves (independent fit, weighted)



D.1.6 Evaluation of hazard functions

For Mogamulizumab none of the extrapolated hazard functions seems to provide a perfect fit. The generalized gamma shows an increasing and then decreasing hazard also observed in the smoothed mogamulizumab data (although delayed).

For DK SoC none of the extrapolated hazard functions seems to provide a perfect fit. However, with the exclusion of the exponential hazard, the remaining models seem to capture the decreasing nature of the smoothed DK SoC data in the long term.

Figure 43 Extrapolated and observed hazard functions mogamulizumab (combined)

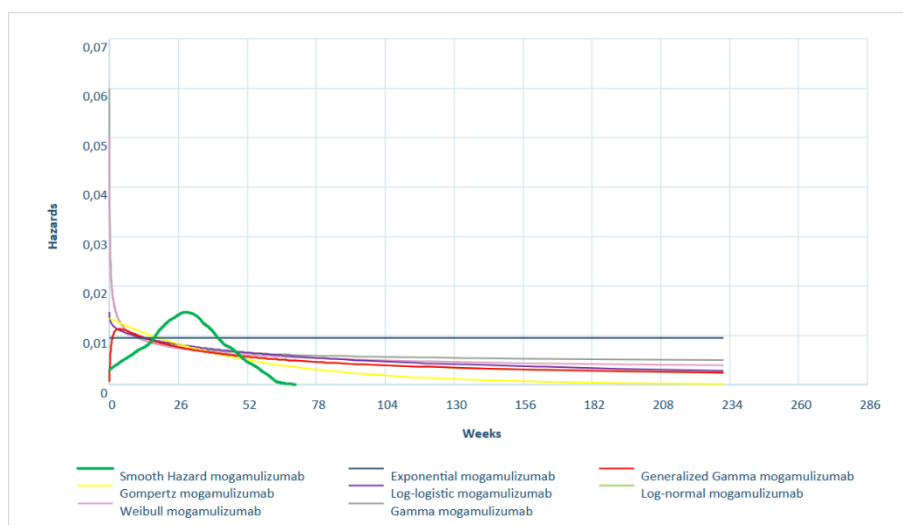


Figure 44 Extrapolated and observed hazard functions DK SoC (combined)

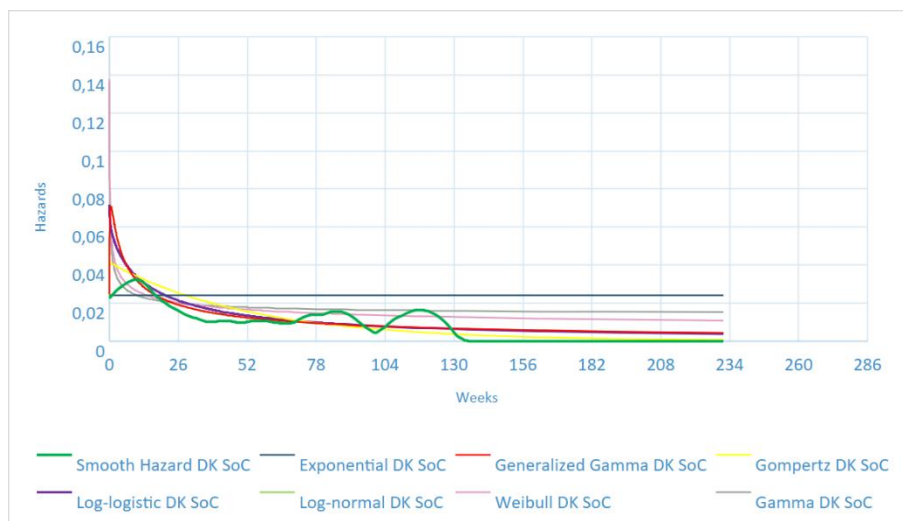


Figure 45 Extrapolated and observed hazard functions mogamulizumab (separate)

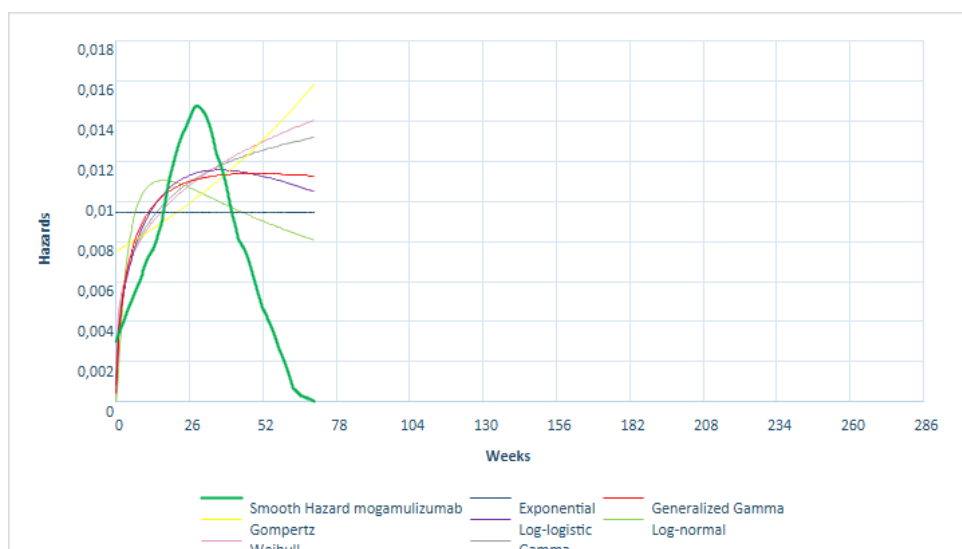
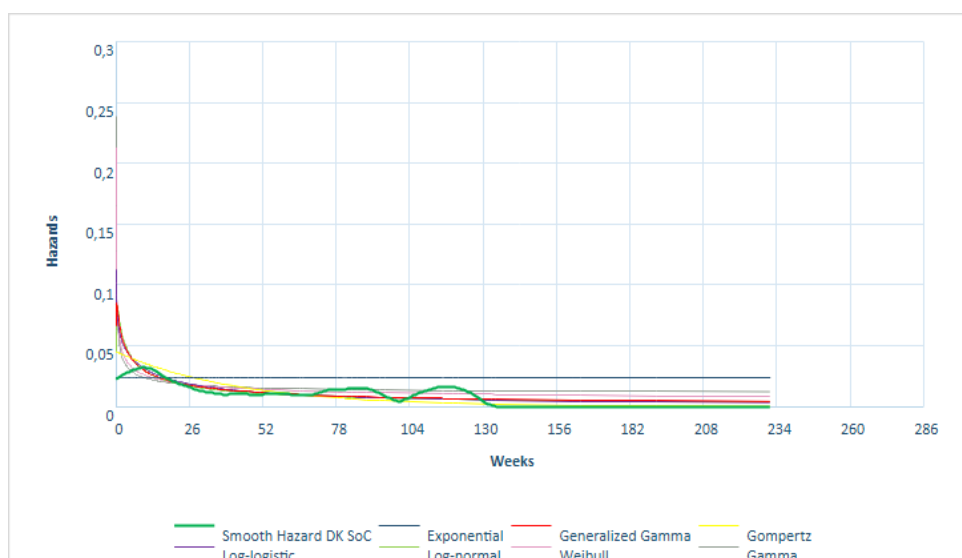


Figure 46 Extrapolated and observed hazard functions mogamulizumab (separate)



D.1.7 Validation and discussion of extrapolated curves

Beyond hazard considerations, all extrapolated curves, in both arms, seem to provide reasonable estimates of survival, with the exclusion of the Gompertz curve in the mogamulizumab arm.

D.1.8 Adjustment of background mortality

Background mortality was incorporated into the CEM following the DMC guidelines.

D.1.9 Adjustment for treatment switching/cross-over

N/A.

D.1.10 Waning effect

N/A.

D.1.11 Cure-point

N/A.

Appendix E. Serious adverse events

Please see section 9.1

Appendix F. Health-related quality of life

Overall, the baseline scores prior to treatment for all domains in the Skindex-29, Pruritus ItchyQoL and Likert Scale, FACT-G, and EQ-5D-3L were similar between the mogamulizumab and vorinostat treatment groups. A simple comparative analysis on the PRO score changes from Baseline between cycles and treatment group was performed at each subsequent treatment cycle. Over the course of the study, results become less interpretable due to study size attrition. As the number of subjects declined, the variability observed for each of the PRO measures' domains increased, reducing the interpretability of the results. Therefore, only the results at Cycles 1, 3, 5, 7, 9, and 11 are summarized.

15.1.1.1 Skindex-29

Overall, both treatment groups reported an improvement in emotions, symptoms, and functioning associated with their skin condition, with a higher improvement reported in subjects treated with mogamulizumab compared to subjects treated with vorinostat at most time points. Specifically, in the Emotions domain, a statistically significant difference observed in favor of the mogamulizumab treatment group compared to the vorinostat treatment group was reported at Cycle 1

[REDACTED]. Similar results were observed at Cycle 3 [REDACTED]
[REDACTED], and Cycle 11 [REDACTED]). Comparable results were reported in regard to the Functioning domain (statistically significant differences favoring the mogamulizumab treatment group over the vorinostat group were observed at Cycle 3 [REDACTED] Cycle 5: [REDACTED] and Cycle 11 [REDACTED]) and the Symptoms domain (Cycle 3: [REDACTED] Cycle 5 [REDACTED], and Cycle 11 [REDACTED]
[REDACTED]

15.1.1.2 FACT-G

A higher improvement in cancer-specific QoL based on a subject's physical, emotional, and functional well-being was reported in subjects treated with mogamulizumab compared to subjects treated with vorinostat at most time points. Specifically, in the Physical Well-being domain, a statistically significant difference was observed in favor of the mogamulizumab treatment group compared to the vorinostat treatment group at Cycle 1 ([REDACTED]), Cycle 3 ([REDACTED]) and at Cycle 5 ([REDACTED]). Similar results were reported for the Emotional Well-being domain (statistically significant differences favoring the mogamulizumab treatment group over the vorinostat group were observed at Cycle 3: [REDACTED] and Cycle 5: [REDACTED])

[REDACTED] and the Functional Well-being domain (Cycle 3: [REDACTED] and Cycle 5: 1.7 versus [REDACTED]). No statistically significant differences were observed for the Social/Family Well-being domain.

In addition, an improvement in overall QoL (based on the total score) was reported in subjects treated with mogamulizumab compared to a decline in the QoL of subjects treated with vorinostat. Specifically, statistically significant differences in favor of the mogamulizumab treatment group compared to the vorinostat treatment group were reported at Cycle 1 ([REDACTED]), Cycle 3 ([REDACTED]), Cycle 5 ([REDACTED]), and Cycle 7 ([REDACTED]).

15.1.1.3 EQ-5D-3L

Overall, subjects in the mogamulizumab group reported a greater improvement in overall mobility, self-care, usual activities, pain or discomfort, and anxiety (based on the index score) and current health status (based on the VAS score) compared to subjects treated with vorinostat most time points.

Specifically, based on the index score, a statistically significant difference was observed in favor of the mogamulizumab treatment group compared to the vorinostat treatment group at Cycle 3 ([REDACTED]) and Cycle 5 ([REDACTED]). Similar results were reported for the VAS score, with statistically significant differences favoring the mogamulizumab treatment group over the vorinostat group at Cycle 3 ([REDACTED]), Cycle 5 ([REDACTED]), Cycle 7 ([REDACTED]), Cycle 9 ([REDACTED]), and Cycle 11 ([REDACTED]).

15.1.1.4 Pruritus ItchyQoL and Likert Scale

Overall, subjects in the mogamulizumab group compared to the vorinostat reported a greater improvement in QoL in regard to their emotional experiences associated with having itchy skin. Specifically, in the Emotions domain, a statistically significant difference observed in favor of the mogamulizumab treatment group compared to the vorinostat treatment group was reported at Cycle 3 ([REDACTED])

[REDACTED], Cycle 5 [REDACTED]

[REDACTED] In addition, a sporadic instance of a statistically significant difference in the Functioning domain was observed in favor of the mogamulizumab treatment group compared to the vorinostat group at Cycle 11 [REDACTED]

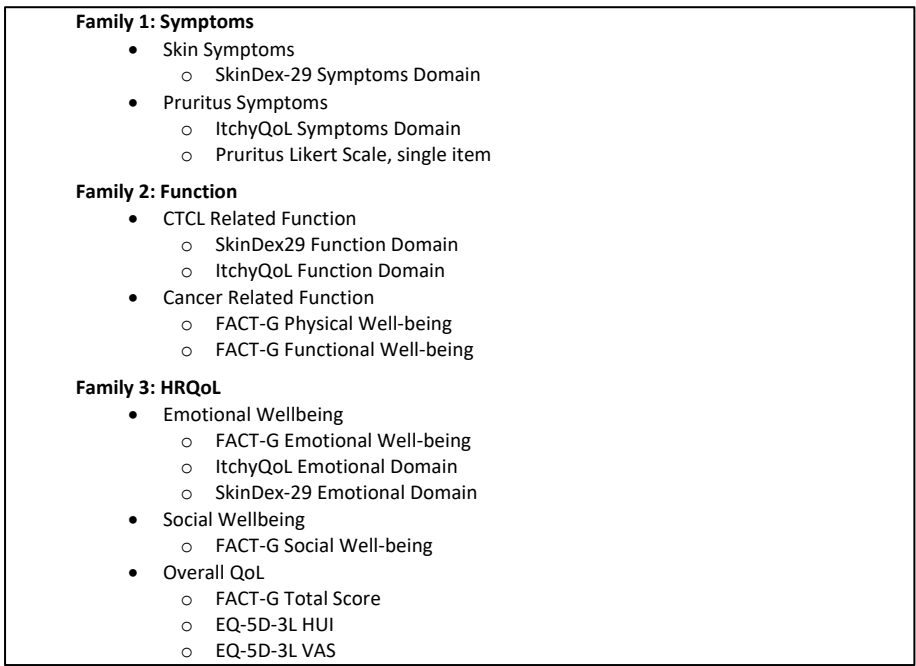
[REDACTED], although these results were not considered clinically meaningful. No statistically significant

differences were observed between treatment groups for the Symptoms Scale domain or Likert Scale score.

15.2 Longitudinal Mixed Model to Examine the Changes in QoL Endpoints Due to Treatment

The QoL measures were grouped into hierarchically ordered families of HRQoL domains so that the first family corresponded to the most important objective (see [Figure 47](#)). Families were tested hierarchically at $p \leq 0.05$.

Figure 47: Families for Hierarchically Testing HRQoL Domains Related to CTCL



Abbreviations: CTCL = cutaneous t-cell lymphoma; EQ-5D-3L = European Quality of Life 5 dimensions 3 levels; FACT-G = Functional Assessment of Cancer Therapy-General; HRQoL = health-related quality of life; HUI = Health Utility Index; QoL = quality of life; VAS = Visual Analogue Scale

Longitudinal modeling of the continuous subdomains within the families in see [Figure 47](#) was conducted to estimate the effect difference on repeated responses over a selected period and between the treatment arms. Mixed models were conducted on a set of covariates for a fully exhaustive model including treatment group, baseline value of outcome, region (US, Japan, Rest of World), age group (< 65 or ≥ 65 years), gender (males or females), and race category (Black or African American, White, other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

A parsimonious model was also used, which included treatment group, age, and region. For each evaluated model, a covariate was only retained in the model if the significance associated with the main effect of the variable was ≤ 0.10 in a univariate analysis.

15.2.1 Family 1 of Hierarchical Models

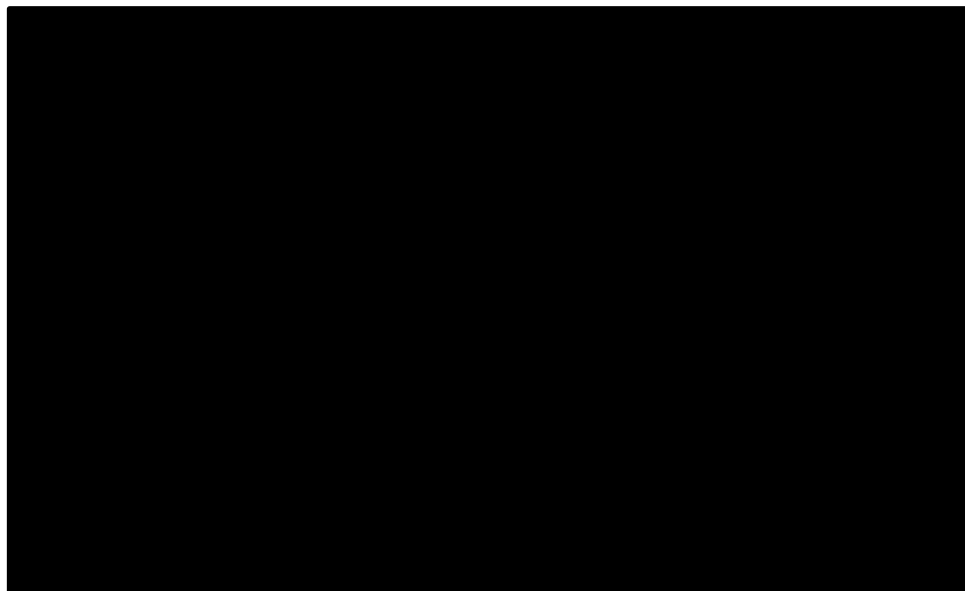
In the Skindex-29 Symptoms Scale domain, vorinostat subjects reported worsening symptoms associated with their skin condition at the beginning of the study (based on questions which included how frequent their skin condition itched, burned or stung, hurt, bled, was irritated, etc.). Statistically significant lower LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle 3

[REDACTED], Cycle 5 (-12.0 versus -5.0, respectively; $p = 0.0307$), and Cycle 7 [REDACTED]; [Figure 48](#)).

Minimal differences between treatment groups were observed in both the Pruritus ItchyQoL Symptoms domain and Pruritus Likert Scale score, and these results were not considered statistically significant at any prespecified time point (odd Cycles 1 through 11). Specifically, the LS mean scores for the Pruritus ItchyQoL Symptoms domain ranged from [REDACTED] for the mogamulizumab group and [REDACTED] (Figure 49). In the Pruritus Likert Scale Score, adjusted LS mean scores ranged [REDACTED] for the mogamulizumab group and [REDACTED] for the vorinostat group (Figure 50).

Overall, these data suggest that subjects treated with mogamulizumab had an improvement in the symptoms associated with their skin condition compared to subjects treated with vorinostat.

Figure 48: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Skindex-29 Symptom Scale Score

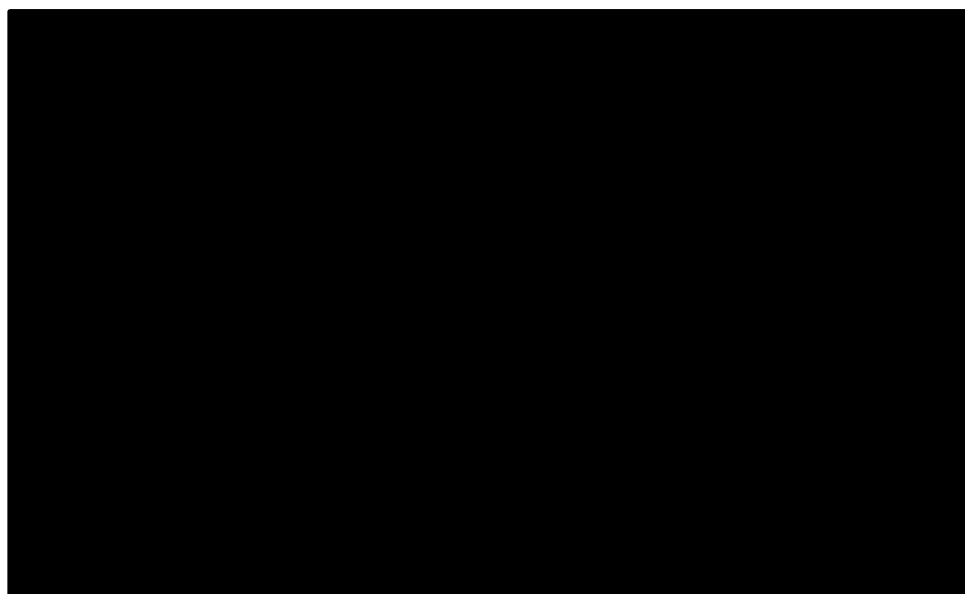


Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 49: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus Itchy QoL Symptom Score

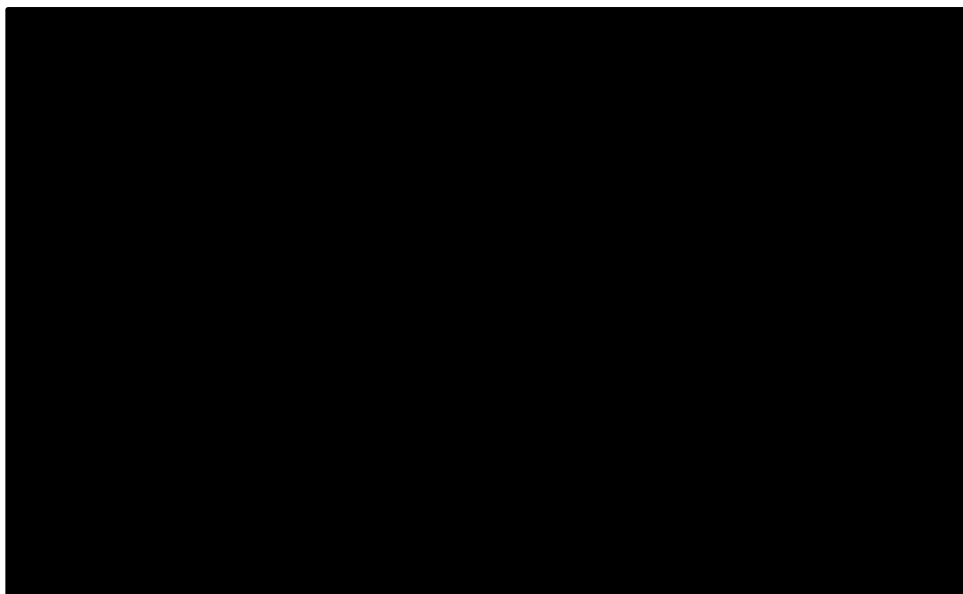


Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 50: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus Likert Scale Score



Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

15.2.2 Family 2 of Hierarchical Models

In the Skindex-29 Functioning domain, vorinostat subjects reported a worsening ability to function because of their skin condition at the beginning of the study (based on questions which included how often their skin condition affected their interaction with others, the desire to be with other people, difficulty in showing affection, affect on social life, and difficulty doing work or hobbies, etc.). Statistically significant lower LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle 3 [REDACTED]

[REDACTED] and Cycle 5 ([REDACTED]; [Figure 51](#)).

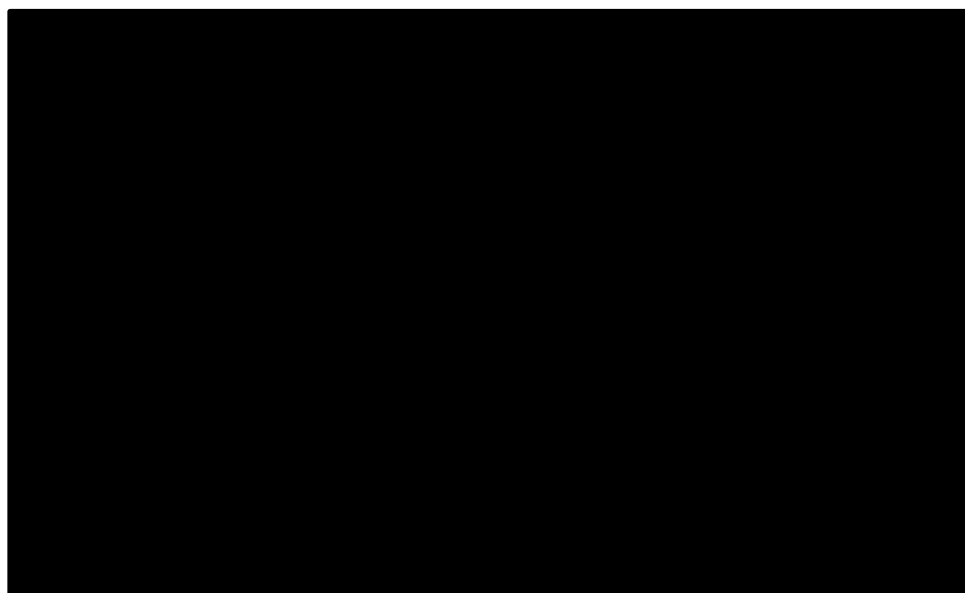
Minimal differences between treatment groups were observed in the Pruritus ItchyQoL Functioning domain and these results were not considered statistically significant at any prespecified time point (odd Cycles 1 through 11; [Figure 52](#)).

In the FACT-G Physical Well-being domain, vorinostat subjects reported an overall worsening in their physical well-being (cancer-specific) at the beginning of the study (based on questions which included how often their cancer affected how often they had lack of energy, nausea, pain, feeling bothered by their side effects of treatment, felt ill, etc.). Statistically significant higher LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle 1 ([REDACTED]), Cycle [REDACTED]; Figure 53).

Similar results were observed for the FACT-G Functional Well-being domain (based on the questions which included how often their cancer affected their ability to work, ability to enjoy life, sleeping well, and ability to enjoy doing fun things, etc.). Statistically significant higher LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle 3 ([REDACTED]), Cycle 5 ([REDACTED]), and Cycle 9 ([REDACTED]; Figure 54).

Overall, these data suggest that subjects treated with mogamulizumab had an improvement in their functional ability associated with their skin condition and cancer-specific physical and functional well-being compared to subjects treated with vorinostat.

Figure 51: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Skindex-29 Functioning Score

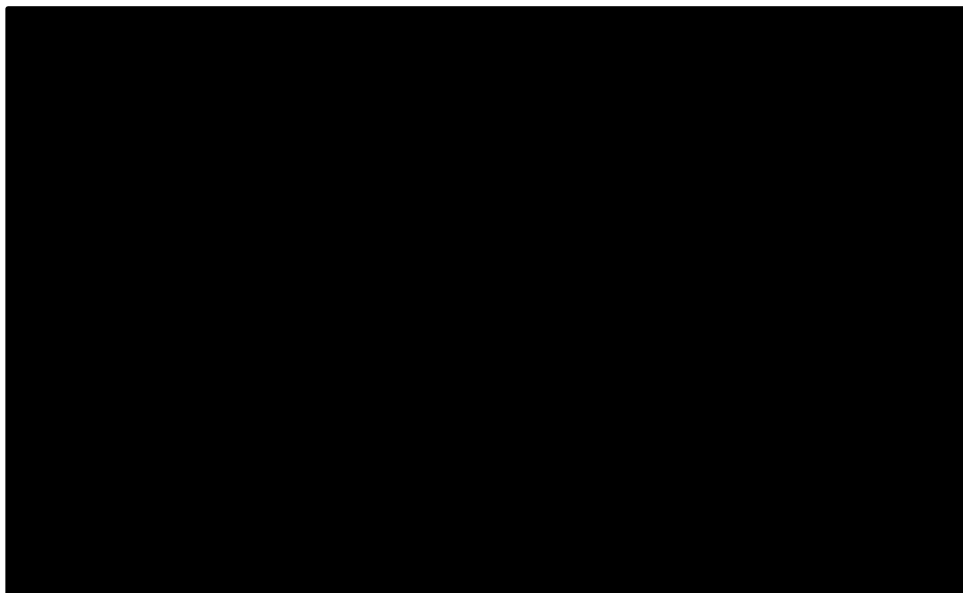


Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome
Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB

and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

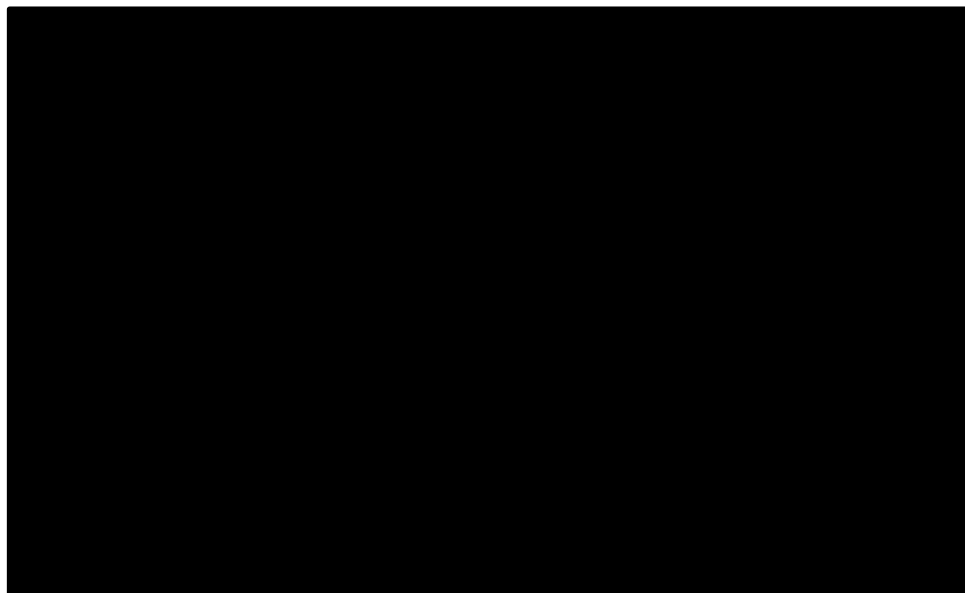
Figure 52: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus ItchyQoL Functioning Score



Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome
Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 53: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Physical Well-Being Score

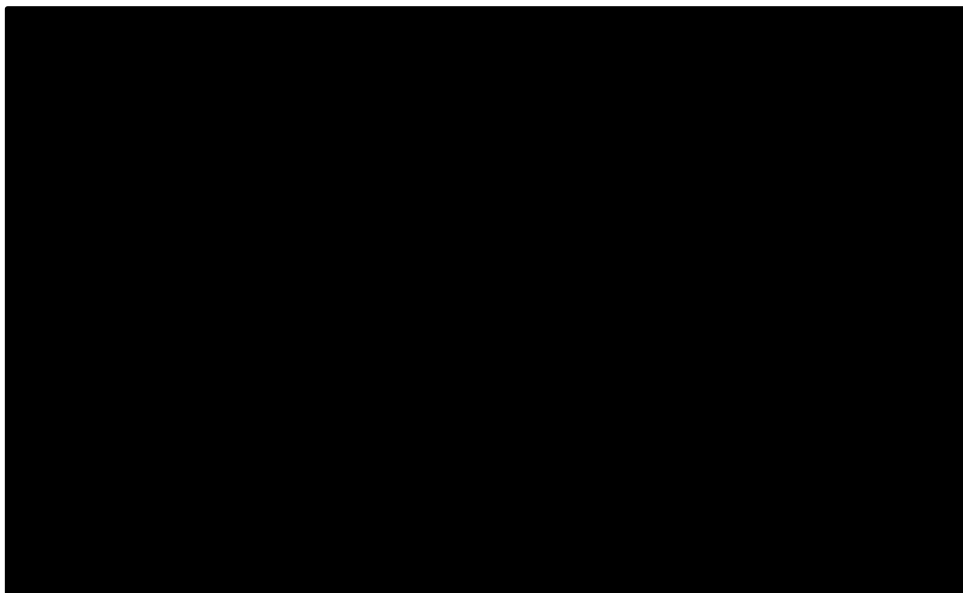


Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 54: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Functional Well-Being Score



Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

15.2.3 Family 3 of Hierarchical Models

In the FACT-G Emotional Well-being domain, vorinostat subjects reported worsening of their overall emotional well-being (cancer-specific) at the beginning of the study (based on the questions which included how often their cancer affected how sad they were, feeling satisfied with how they are coping with their illness, feeling nervous, worrying about dying, etc.). Statistically significant higher LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle

(), Cycle 3 (), Cycle 5 (), Cycle 9 (), and Cycle 11 ().

Similar results were observed for the Pruritus ItchyQoL Emotions domain (based on the questions which included how often their itchy skin makes them feel frustrated, embarrassed, angry or irritable, depressed or sad, etc.), with statistically significant lower LS mean scores in favor of the mogamulizumab group reported at most time points

including Cycle 3 [REDACTED]
[REDACTED]), Cycle 5
[REDACTED]
[REDACTED]

Figure 56) and in the Skindex-29 Emotions Scale domain (based on the questions which included how often their skin condition made them worry that their skin condition will get worse, be frustrated, embarrassed, annoyed, or depressed about their skin condition, etc.). Specifically, statistically significant lower LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle 3 [REDACTED]
[REDACTED], Cycle 5 [REDACTED]), Cycle 7
[REDACTED]), Cycle 9
[REDACTED]), and Cycle 11 [REDACTED]
[REDACTED]; Figure 57).

In the FACT-G Social Well-being domain, vorinostat subjects reported worsening of their overall social well-being (cancer-specific) at the beginning of the study (based on the questions which included how often they received emotional support from their family, acceptance of their illness from their family, feeling satisfied with family communication regarding their illness, etc.). Statistically significant higher LS mean scores in favor of the mogamulizumab group were reported at most time points including Cycle 3 [REDACTED]
[REDACTED] and Cycle 5 [REDACTED] Figure 58). Similar results were observed for the FACT-G Total Score (based on the total individual subscale scores), with statistically significant higher LS mean scores in favor of the mogamulizumab group reported at most time points including Cycle 1 ([REDACTED]
[REDACTED] Cycle 3
[REDACTED]), Cycle 7
[REDACTED] and Cycle 9
[REDACTED];

Figure 59).

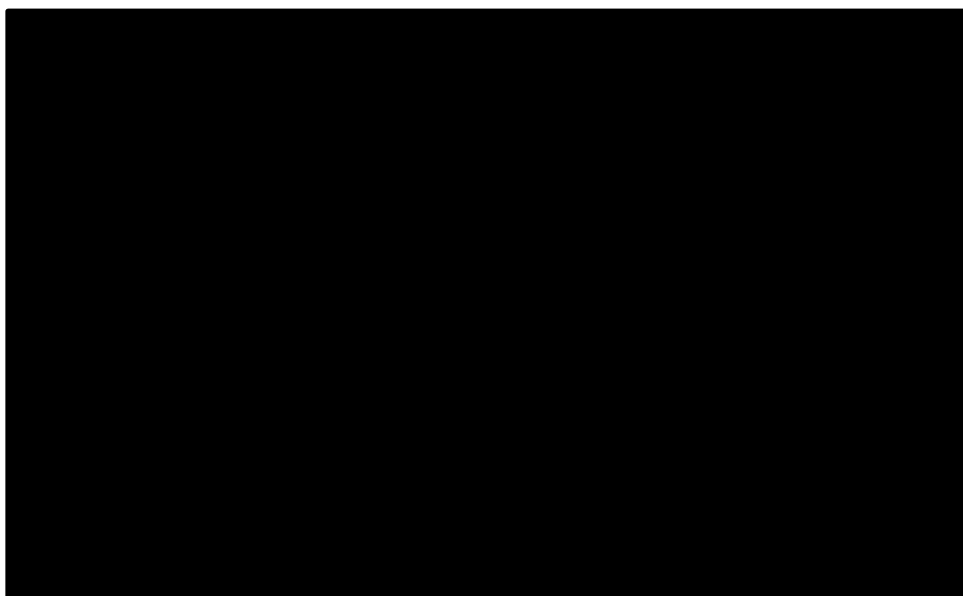
In addition, a sporadic instance of a statistically significant difference in favor of the mogamulizumab group for the EQ-5D-3L HUI score (based on the scores of the 5 health state domains: Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) was observed at Cycle 3 ([REDACTED]).

[REDACTED] Statistically significant differences in favor of the mogamulizumab group was also observed for the EQ-5D-3L VAS score (based on the measurement of current health status) at Cycle 3 ([REDACTED]).

[REDACTED] and Cycle 5 ([REDACTED]).

Overall, these data suggest that subjects treated with mogamulizumab had improved emotional feelings associated with their cancer and skin condition (including itchiness associated with their skin condition), improved social well-being associated with their cancer, overall well-being associated with their cancer (based on the FACT-G total score), and current health status compared to subjects treated with vorinostat.

Figure 55: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Emotional Well-Being Score



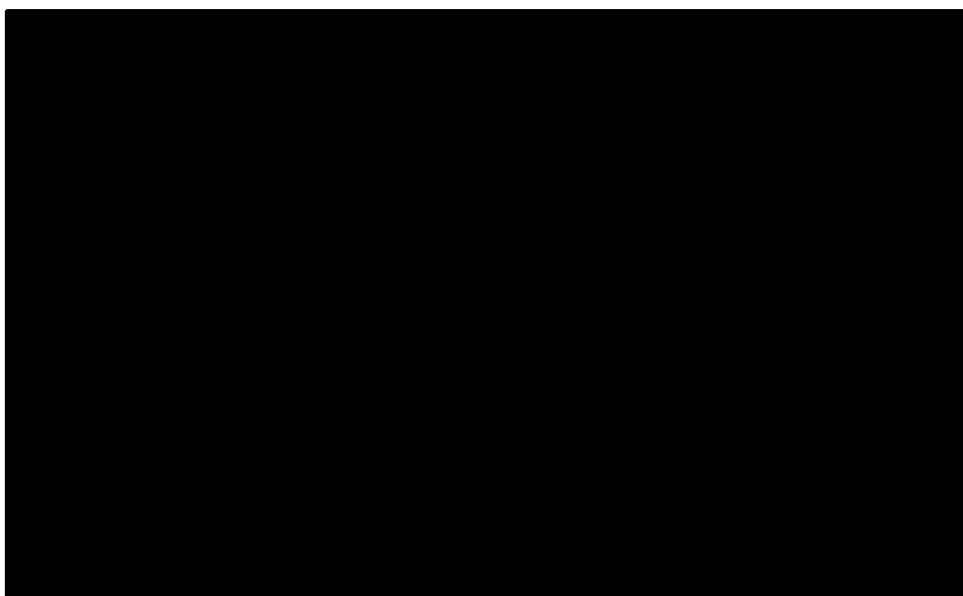
Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB

and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

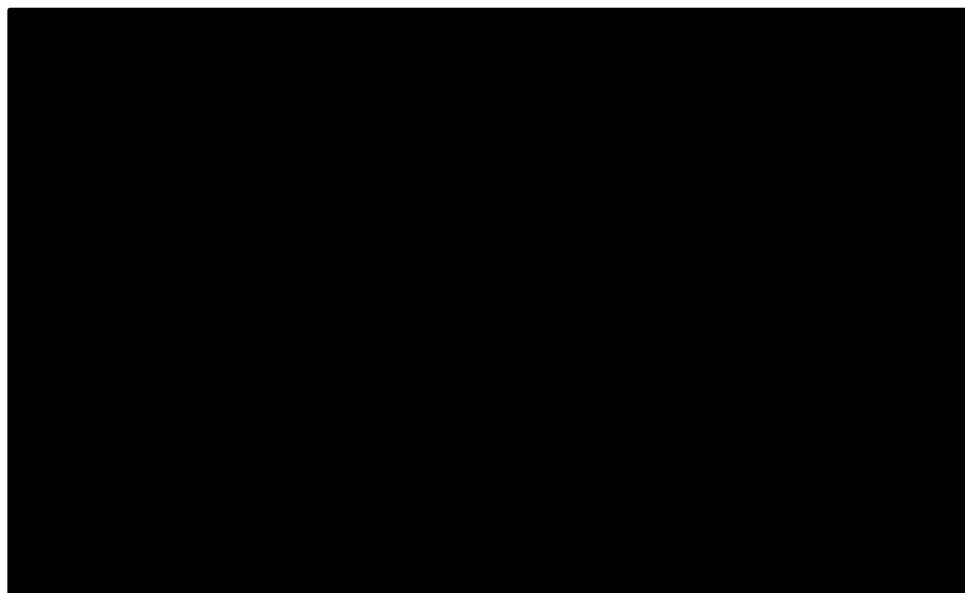
Figure S6: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Pruritus ItchyQoL Emotion Score



Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome
Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

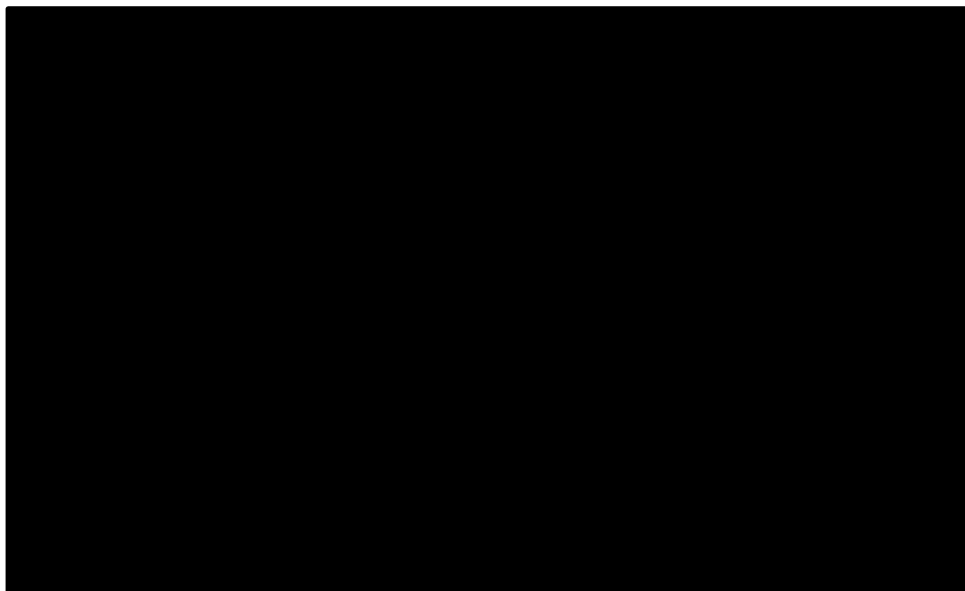
Figure 57: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the Skindex-29 Emotion Score



Abbreviations: LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome
Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 58: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Social Well-Being Score

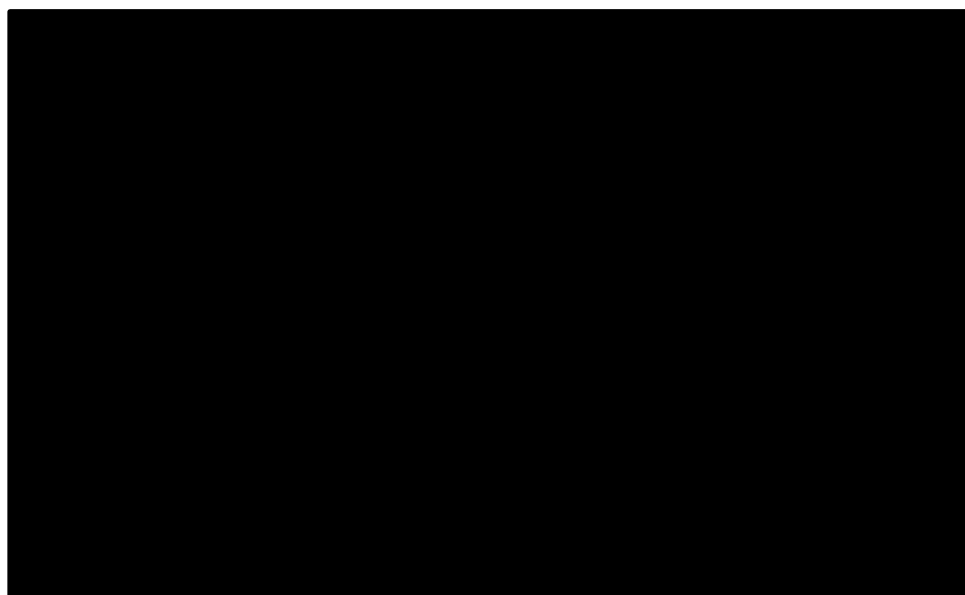


Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 59: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the FACT-G Total Score

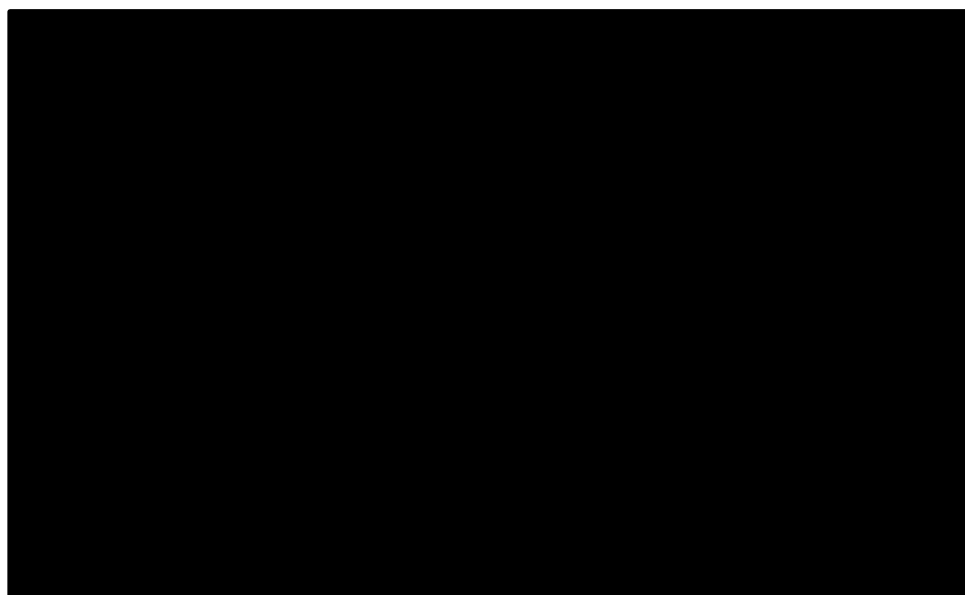


Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome

Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

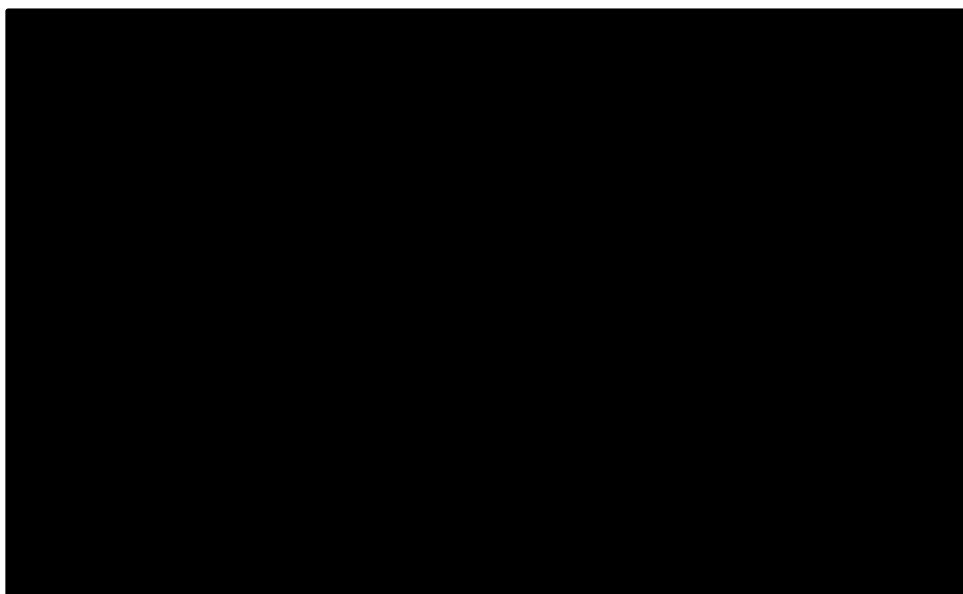
Figure 60: Treatment Effect via Adjusted Mixed Model^[1] of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the EQ-5D-3L Index Score



Abbreviations: EQ-5D-3L = European Quality of Life 5 dimensions 3 levels; HUI = Health Utility Index; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome
Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Figure 61: Treatment Effect via Adjusted Mixed Model of QoL Symptoms Score Change from Baseline by Visit and Treatment Group of the LPP for the EQ-5D-3L VAS Score



Abbreviations: EQ-5D-3L = European Quality of Life 5 dimensions 3 levels; HUI = Health Utility Index; LPP = longitudinal period population; MF = mycosis fungoides; PRO = patient-reported outcome; QoL = quality of life; SS = Sézary syndrome
Values displayed are the adjusted means.

^[1]The adjusted model contained the treatment group, visits, treatment*visit interaction, baseline value of outcome, age group (< 65 or ≥ 65 years), gender, region, race category (Black or African American, White, Other), CCR4 expression status, disease subtypes (MF or SS), disease stage (IB and II versus III or IV), and compartment involvement (blood involvement or no blood involvement).

Appendix G. Probabilistic sensitivity analyses

Table 89. Overview of parameters in the PSA

Parameter	Point estimate	Lower bound	Upper bound	Distribution
Time horizon	30	24.120 10805	35.879 89195	Normal
Mean age	63.04	61.724 02879	64.355 97121	Normal
Mean body surface area (BSA)	1.91	1.8845 9515	1.9354 0485	Normal
Mean body weight	76.7344 2029	74.049 25839	79.490 93288	Log-normal
Proportion of patient female	0.41935 4839	0.3384 07884	0.5025 25197	Beta
Mogamulizumab relative dose intensity	1	0	0	Beta
Comparator relative dose intensity	1	0	0	Beta
Sunsequent treatment relative dose intensity	1	0	0	Beta
Proportion of patients receiving aSCT after current tx: Mogamulizumab arm	0.07952 509	0.0646 41048	0.0957 85856	Beta
Timepoint for aSCT after current tx: Mogamulizumab arm	18	14.472 06483	21.527 93517	Normal
Proportion of patients receiving aSCT after current tx: DK SoC arm	0.042	0.0341 55789	0.0506 04789	Beta
Timepoint for aSCT after current tx: DK SoC arm	40	32.160 14406	47.839 85594	Normal
Patient distribution for compTX1 (Bexarotene)	0.01941 7476	0.0194 17476	0.0204 46097	Dirichlet
Patient distribution for compTX2 (Acitretin)	0.18640 7767	0.1864 07767	0.1802 97398	Dirichlet
Patient distribution for compTX3 (Isotretinoin)	0.00776 699	0.0077 6699	0.0092 9368	Dirichlet
Patient distribution for compTX4 (Alitretinoin)	0.00194 1748	0.0019 41748	0.0037 17472	Dirichlet
Patient distribution for compTX5 (Interferon alfa-2a)	0.13203 8835	0.1320 38835	0.1282 52788	Dirichlet
Patient distribution for compTX6 (Methotrexate)	0.10679 6117	0.1067 96117	0.1040 89219	Dirichlet
Patient distribution for compTX7 (Cyclophosphamide)	0	0	0.0018 58736	Dirichlet
Patient distribution for compTX8 (Doxorubicin)	0.01165 0485	0.0116 50485	0.0130 11152	Dirichlet
Patient distribution for compTX9 (Vincristine)	0	0	0.0018 58736	Dirichlet

Patient distribution for compTX10 (Prednisolone)	0.16504 8544	0.1650 48544	0.1598 51301	Dirichlet
Patient distribution for compTX11 (CHOP)	0	0	0.0018 58736	Dirichlet
Patient distribution for compTX12 (Gemcitabine)	0.00776 699	0.0077 6699	0.0092 9368	Dirichlet
Patient distribution for compTX13 (Etoposide)	0.00388 3495	0.0038 83495	0.0055 76208	Dirichlet
Patient distribution for compTX14 (Chlorambucil)	0.00194 1748	0.0019 41748	0.0037 17472	Dirichlet
Patient distribution for compTX15 (Chlormethine)	0.04854 3689	0.0485 43689	0.0483 27138	Dirichlet
Patient distribution for compTX16 (Carmustine)	0	0	0.0018 58736	Dirichlet
Patient distribution for compTX17 (Alemtuzumab)	0.02135 9223	0.0737 86408	0.0724 90706	Dirichlet
Patient distribution for compTX18 (Brentuximab vedotin)	0.01941 7476	0.0388 34951	0.0390 33457	Dirichlet
Patient distribution for compTX19 (Pembrolizumab)	0.00970 8738	0.0427 18447	0.0427 50929	Dirichlet
Patient distribution for compTX20 (PUVA)	0.07378 6408	0.0213 59223	0.0223 04833	Dirichlet
Patient distribution for compTX21 (ECP)	0.03883 4951	0.0194 17476	0.0204 46097	Dirichlet
Patient distribution for compTX22 (TSEBT)	0.04271 8447	0.0097 08738	0.0111 52416	Dirichlet
Patient distribution for compTX23 (Local radiotherapy)	0.10097 0874	0.1009 70874	0.0985 13011	Dirichlet
IV Administration	1543	1262.6 89998	1866.8 68544	Log-Normal
Time on treatment (in days) for subTX1 (PUVA)	98	80.196 77238	118.56 97455	Log-Normal
Time on treatment (in days) for subTX3 (local radiotherapy)	125	102.29 18015	151.23 69203	Log-Normal
Time on treatment (in days) for subTX4 (clobetasol and clobetasol)	100	81.833 4412	120.98 95362	Log-Normal
Time on treatment (in days) for subTX5 (betamethasone)	180	147.30 01942	217.78 11652	Log-Normal
Time on treatment (in days) for subTX6 (hydrocortison)	365	298.69 20604	441.61 18072	Log-Normal
Time on treatment (in days) for subTX7 (mometasone)	180	147.30 01942	217.78 11652	Log-Normal
Mogamulizumab: Patient distribution for subTX1 (PUVA)	0.0883	0.1625 4417	0.1620 68966	Dirichlet
Mogamulizumab: Patient distribution for subTX2 (TSEBT)	0.0848	0.0883 39223	0.0896 55172	Dirichlet

Mogamulizumab: Patient distribution for subTX3 (local radiotherapy)	0.1625	0.0848 05654	0.0862 06897	Dirichlet
Mogamulizumab: Patient distribution for subTX4 (clobetasol and clobetasol)	0.2862	0.2862 19081	0.2827 58621	Dirichlet
Mogamulizumab: Patient distribution for subTX5 (betamethason)	0.1201	0.1201 41343	0.1206 89655	Dirichlet
Mogamulizumab: Patient distribution for subTX6 (hydrocortison)	0.0389	0.0388 69258	0.0413 7931	Dirichlet
Mogamulizumab: Patient distribution for subTX7 (moemetasone)	0.2191	0.2190 81272	0.2172 41379	Dirichlet
SoC: Patient distribution for subTX1 (PUVA)	0.0883	0.1625 4417	0.1620 68966	Dirichlet
SoC: Patient distribution for subTX2 (TSEBT)	0.0848	0.0883 39223	0.0896 55172	Dirichlet
SoC: Patient distribution for subTX3 (local radiotherapy)	0.1625	0.0848 05654	0.0862 06897	Dirichlet
SoC: Patient distribution for subTX4 (clobetasol and clobetasol)	0.2862	0.2862 19081	0.2827 58621	Dirichlet
SoC: Patient distribution for subTX5 (betamethason)	0.1201	0.1201 41343	0.1206 89655	Dirichlet
SoC: Patient distribution for subTX6 (hydrocortison)	0.0389	0.0388 69258	0.0413 7931	Dirichlet
SoC: Patient distribution for subTX7 (moemetasone)	0.2191	0.2190 81272	0.2172 41379	Dirichlet
Cost of subsequent treatment after aSCT	10789.8 2459	8829.6 8476	13054. 55873	Log-Normal
Monitoring post aSCT relapse	259.615 0195	212.45 19043	314.10 70081	Log-Normal
Time spent (in hours) on a IV administration	2	1.6366 68824	2.4197 90725	Log-normal
Time spent (in hours) on a monitoring visit	1	0.8183 34412	1.2098 95362	Log-normal
Yearly frequency of visits to a clinical nurse during disease control	4	3.2160 14406	4.7839 85594	Normal
Yearly frequency of visits to a dermatologist during disease control	2	1.6080 07203	2.3919 92797	Normal
Yearly frequency of visits to a oncologist during disease control	2	1.6080 07203	2.3919 92797	Normal
Yearly frequency of visits to a clinical nurse during subsequent treatment	12	9.6480 43219	14.351 95678	Normal
Yearly frequency of visits to a dermatologist during subsequent treatment	6	4.8240 21609	7.1759 78391	Normal
Yearly frequency of visits to a oncologist during subsequent treatment	6	4.8240 21609	7.1759 78391	Normal
Frequency of AE1 Mogamulizumab	2	1.6080 07203	2.3919 92797	Normal

Frequency of AE2 Mogamulizumab	0	0	0	Normal
Frequency of AE3 Mogamulizumab	4	3.2160 14406	4.7839 85594	Normal
Frequency of AE4 Mogamulizumab	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE5 Mogamulizumab	2	1.6080 07203	2.3919 92797	Normal
Frequency of AE6 Mogamulizumab	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE7 Mogamulizumab	8	6.4320 28812	9.5679 71188	Normal
Frequency of AE8 Mogamulizumab	0	0	0	Normal
Frequency of AE9 Mogamulizumab	3	2.4120 10805	3.5879 89195	Normal
Frequency of AE10 Mogamulizumab	0	0	0	Normal
Frequency of AE11 Mogamulizumab	8	6.4320 28812	9.5679 71188	Normal
Frequency of AE12 Mogamulizumab	3	2.4120 10805	3.5879 89195	Normal
Frequency of AE13 Mogamulizumab	0	0	0	Normal
Frequency of AE14 Mogamulizumab	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE15 Mogamulizumab	0	0	0	Normal
Frequency of AE16 Mogamulizumab	7	5.6280 25211	8.3719 74789	Normal
Frequency of AE17 Mogamulizumab	0	0	0	Normal
Frequency of AE18 Mogamulizumab	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE19 Mogamulizumab	2	1.6080 07203	2.3919 92797	Normal
Frequency of AE20 Mogamulizumab	0	0	0	Normal
Frequency of AE21 Mogamulizumab	0	0	0	Normal
Frequency of AE22 Mogamulizumab	0	0	0	Normal
Frequency of AE23 Mogamulizumab	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE1 DK SoC	2	1.6080 07203	2.3919 92797	Normal
Frequency of AE2 DK SoC	0	0	0	Normal
Frequency of AE3 DK SoC	4	3.2160 14406	4.7839 85594	Normal
Frequency of AE4 DK SoC	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE5 DK SoC	2	1.6080 07203	2.3919 92797	Normal

Frequency of AE6 DK SoC	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE7 DK SoC	8	6.4320 28812	9.5679 71188	Normal
Frequency of AE8 DK SoC	0	0	0	Normal
Frequency of AE9 DK SoC	3	2.4120 10805	3.5879 89195	Normal
Frequency of AE10 DK SoC	0	0	0	Normal
Frequency of AE11 DK SoC	8	6.4320 28812	9.5679 71188	Normal
Frequency of AE12 DK SoC	3	2.4120 10805	3.5879 89195	Normal
Frequency of AE13 DK SoC	0	0	0	Normal
Frequency of AE14 DK SoC	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE15 DK SoC	0	0	0	Normal
Frequency of AE16 DK SoC	7	5.6280 25211	8.3719 74789	Normal
Frequency of AE17 DK SoC	0	0	0	Normal
Frequency of AE18 DK SoC	1	0.8040 03602	1.1959 96398	Normal
Frequency of AE19 DK SoC	2	1.6080 07203	2.3919 92797	Normal
Frequency of AE20 DK SoC	0	0	0	Normal
Frequency of AE21 DK SoC	0	0	0	Normal
Frequency of AE22 DK SoC	0	0	0	Normal
Frequency of AE23 DK SoC	1	0.8040 03602	1.1959 96398	Normal
Utility cycle 1-2: Mogamulizumab	0.753	0.727	0.78	Beta
Utility cycle 3-4: Mogamulizumab	0.795	0.765	0.825	Beta
Utility cycle 5-6: Mogamulizumab	0.808	0.744	0.842	Beta
Utility cycle 7-8: Mogamulizumab	0.796	0.759	0.833	Beta
Utility cycle 9-10: Mogamulizumab	0.827	0.787	0.868	Beta
Utility cycle 11-12: Mogamulizumab	0.85	0.804	0.897	Beta
Utility cycle 1-2: DK SoC	0.753	0.727	0.78	Beta
Utility cycle 3-4: DK SoC	0.795	0.765	0.825	Beta
Utility cycle 5-6: DK SoC	0.808	0.744	0.842	Beta
Utility cycle 7-8: DK SoC	0.796	0.759	0.833	Beta
Utility cycle 9-10: DK SoC	0.827	0.787	0.868	Beta
Utility cycle 11-12: DK SoC	0.85	0.804	0.897	Beta
Utility disease control on tx: Mogamulizumab	0.739	0.711	0.767	Beta
Utility disease control on tx: DK SoC	0.739	0.711	0.767	Beta

Utility disease control surveillance: Mogamulizumab	0.739	0.711	0.767	Beta
Utility disease control surveillance: DK SoC	0.739	0.711	0.767	Beta
Utility subsequent treatments: Mogamulizumab	0.712	0.674	0.751	Beta
Utility subsequent treatments: DK SoC	0.712	0.674	0.751	Beta
Utility End of life stage	0.38	0.3070 31202	0.4557 73059	Beta
Utility aSCT (0-14 days)	0.42	0.3389 21128	0.5032 90385	Beta
Utility aSCT (14 days - 3 months)	0.6	0.4799 30984	0.7142 96654	Beta
Utility aSCT (>3 months)	0.77	0.6033 05828	0.9013 93466	Beta
Mogamulizumab OS Log-normal param 1	2.89232 1113			Multivariate Normal
Mogamulizumab OS Log-normal param 2	0.63149 3784			Multivariate Normal
Mogamulizumab OS Log-normal param 3	1.84218 7243			Multivariate Normal
Mogamulizumab OS Log-normal param 4	0			Multivariate Normal
Mogamulizumab ToT Generalised Gamma param 1	1.99543 5695			Multivariate Normal
Mogamulizumab ToT Generalised Gamma param 2	0.19411 9198			Multivariate Normal
Mogamulizumab ToT Generalised Gamma param 3	0.53490 6282			Multivariate Normal
Mogamulizumab ToT Generalised Gamma param 4	0			Multivariate Normal
Mogamulizumab NTFS Log-normal param 1	2.23329 3884			Multivariate Normal
Mogamulizumab NTFS Log-normal param 2	0.10408 0229			Multivariate Normal
Mogamulizumab NTFS Log-normal param 3	0			Multivariate Normal
Mogamulizumab NTFS Log-normal param 4	0.10828 9076			Multivariate Normal
DK SoC OS Log-normal param 1	2.89232 1113			Multivariate Normal
DK SoC OS Log-normal param 2	0.63149 3784			Multivariate Normal
DK SoC OS Log-normal param 3	1.84218 7243			Multivariate Normal
DK SoC OS Log-normal param 4	0			Multivariate Normal

Mogamulizumab NTFS vs OS HR	0.09	0.0541 4	0.1469	Log-Normal
-----------------------------	------	-------------	--------	------------

Abbreviations: PSA, probabilistic sensitivity analysis; HSUV, health state utility value.

Appendix H. Literature searches for the clinical assessment

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

Objective

To identify relevant clinical evidence for mogamulizumab in relapsed/refractory CTCL including MF and SS.

Method

The original database searches for the SLR were performed on 2 July 2019. Updated searches were performed on the 15 September 2020, 31 May 2021 and 3 February 2025.

Searches for the clinical SLR were designed with a combination of sensitivity and specificity, and to meet the requirements of European HTA agencies. The following electronic databases were searched (i.e. standard evidence sources used in HTA assessments):

- MEDLINE® In-Process (using Pubmed.com)
- Embase® and MEDLINE (using Embase.com)
- The Cochrane Library, including the following:
 - The Cochrane Database of Systematic Reviews (CDSR)
 - Cochrane Central Register of Controlled Trials (CENTRAL)
 - Database of Abstracts of Reviews of Effectiveness (DARE)
 - Health Technology Assessment Database (HTAD)

Searches for grey literature included searching conference proceedings from 2017-February 2025 to identify abstracts of interest. These included:

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- European Society for Medical Oncology (ESMO)
- International Conference on Malignant Lymphoma (ICML)
- International Society of Cutaneous Lymphomas (ISCL) / World Congress of Cutaneous Lymphomas
- EORTC (European Organisation for Research and Treatment of Cancer) Cutaneous Lymphoma Meeting
- Word Congress of Dermatology
- United States Cutaneous Lymphoma Consortium (USCLC)
- UK Cutaneous Lymphoma Group (UKCLG) Annual Meeting
- European Medicines Agency (EMA)

An overview of the searched databases and conference proceedings is presented in Table 90 and Table 91.

Table 90 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Medline & EMBASE	EMBASE.com	No limit	02.07.2019
		2019-2020	15.09.2020

Database	Platform/source	Relevant period for the search	Date of search completion
		2020-2021	31.05.2021
		2021-2025	03.02.2025
Medline-in-process	Pubmed.com	No limit	02.07.2019
		2019-2020	15.09.2020
		2020-2021	31.05.2021
		2021-2025	03.02.2025
DARE	Onlinelibrary.wiley.com	No limit	02.07.2019
CENTRAL	Onlinelibrary.wiley.com	No limit	02.07.2019
		2019-2020	15.09.2020
		2020-2021	31.05.2021
		2021-2025	03.02.2025

Abbreviations: Embase, Excerpta Medica database; MEDLINE, Medical Literature Analysis and Retrieval System Online; DARE, Database of Abstracts of Reviews of Effect; CENTRAL, Cochrane Central Register of Controlled Trials.

Table 91 Conference material included in the literature search

Conference	Source of abstracts	Words/terms searched	Relevant period for the search	Date of search
American Society of Clinical Oncology	Conference program	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2018-2024	03.03.2025
European Society for Medical Oncology	Abstract books	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2017-2024	03.03.2025
International Conference on Malignant Lymphoma	Abstract books	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2017-2024	03.03.2025
International Conference on Malignant Lymphoma	Abstract books	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2017-2024	03.03.2025
International Society of Cutaneous Lymphomas	Meeting abstracts	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous,	2018-2024	03.03.2025

Conference	Source of abstracts	Words/terms searched	Relevant period for the search	Date of search
		Pagetoid reticulosis, Lymphomatoid Papulosis		
World Congress of Cutaneous Lymphomas	Conference program	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2016	03.03.2021
International Society for Pharmacoeconomics and Outcomes Research: European	Conference website	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2017-2024	03.03.2025
International Society for Pharmacoeconomics and Outcomes Research: Annual	Conference website	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2018-2024	03.03.2025
American Society of Haematology	Conference website	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2017-2024	03.03.2025
EORTC Cutaneous Lymphoma Meeting	Abstract collection	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	2018	03.03.2025
European Medicines Council	Website	Cutaneous T-Cell Lymphoma, CTCL, Cutaneous lymphoma, Mycosis, Sézary, Primary cutaneous, Pagetoid reticulosis, Lymphomatoid Papulosis	N/A	03.03.2025

Abbreviations: CTCL, Cutaneous T-Cell Lymphoma; EORTC, European Organisation For Research And Treatment Of Cancer; N/A, Not available.

H.1.1 Search strategies

The search strings for the July 2019, September 2020, May 2021 and February 2025 SLRs are reported in the tables below.

H.1.1.1 July 2019

Table 92 of Search strategy for Medline & EMBASE (conducted on 2 July 2019)

No.	Searches	Results
#1	'cutaneous t cell lymphoma'/exp OR 'sezary syndrome'/exp OR 'mycosis fungoides'/exp	14130

No.	Searches	Results
#2	'cutaneous t cell lymphoma':ab,ti,kw OR 'sezary syndrome':ab,ti,kw OR 'mycosis fungoides':ab,ti,kw OR 'alibert bazin':ab,ti,kw OR 'granuloma fungoides':ab,ti,kw OR 'skin t-cell lymphoma':ab,ti,kw OR 'granuloma sarcomatodes':ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR 'lymphomatoid papulosis':ab,ti,kw OR 'pagetoid reticulosis':ab,ti,kw OR 'woringer-kolopp disease':ab,ti,kw OR 'woringer kolopp*':ab,ti,kw OR 'granulomatous slack skin':ab,ti,kw	13349
#3	'woringer kolopp disease'/exp OR 'granulomatous slack skin'/exp OR 'lymphomatoid papulosis'/exp	1428
#4	#1 OR #2 OR #3	17562
#5	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	2083039
#6	'clinical study'/de OR 'clinical article'/mj OR 'clinical trial'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR 'intervention study'/exp OR 'major clinical study'/de OR 'open study'/exp OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'case control study'/exp OR 'retrospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR retrospectiv*:ab,ti OR 'medical record review'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'observational study'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	9548523
#7	#5 OR #6	11417308
#8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	4369440
#9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	4804215
#10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	2391444
#11	#8 OR #9 OR #10	11983179

No.	Searches	Results
#12	#4 AND #7	6754
#13	#12 NOT #11	3862

Table 93 Search strategy for Medline In-Process (conducted on 2 July 2019)

No.	Searches	Results
#1	Search cutaneous t cell lymphoma	11984
#2	Search (sezary syndrome OR mycosis fungoides)	8090
#3	Search (alibert bazin OR granuloma fungoides OR skin t-cell lymphoma OR granuloma sarcomatodes OR wucherflechte OR ctcl)	10604
#4	Search (lymphomatoid papulosis OR pagetoid reticulosis OR woringer-kolopp disease OR woringer kolopp OR granulomatous slack skin)	12257
#5	Search (#1 OR #2 OR #3 OR #4)	14814
#6	Search ((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))	437136
#7	Search (#5 AND #6)	139

Table 94 Search strategy for Cochrane (CENTRAL) (conducted on 2 July 2019)

No.	Searches	Results
#1	MeSH descriptor: [Lymphoma, T-Cell, Cutaneous] explode all trees	82
#2	MeSH descriptor: [Sezary Syndrome] explode all trees	15
#3	MeSH descriptor: [Mycosis Fungoides] explode all trees	51
#4	MeSH descriptor: [Pagetoid Reticulosis] explode all trees	0
#5	MeSH descriptor: [Lymphomatoid Granulomatosis] explode all trees	4
#6	MeSH descriptor: [Lymphomatoid Papulosis] explode all trees	2
#7	"cutaneous t cell lymphoma":ab,ti,kw OR "sezary syndrome":ab,ti,kw OR "mycosis fungoides":ab,ti,kw OR "alibert bazin":ab,ti,kw OR "granuloma fungoides":ab,ti,kw OR "skin t-cell lymphoma":ab,ti,kw OR "granuloma sarcomatodes":ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR "lymphomatoid papulosis":ab,ti,kw OR "pagetoid reticulosis":ab,ti,kw OR "woringe-kolopp disease":ab,ti,kw OR "woringe kolopp*":ab,ti,kw OR "granulomatous slack skin":ab,ti,kw	447
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	448
#9	#8 in Cochrane Reviews, Trials	446

Abbreviations: MeSH, Medical Subject Headings.

Table 95 Search strategy for DARE (conducted on 2 July 2019)

No.	Searches	Results
#1	MeSH DESCRIPTOR Lymphoma, T-Cell, Cutaneous EXPLODE ALL TREES	11

No.	Searches	Results
#2	MeSH DESCRIPTOR Sezary Syndrome EXPLODE ALL TREES	3
#3	MeSH DESCRIPTOR Mycosis Fungoides EXPLODE ALL TREES	4
#4	MeSH DESCRIPTOR Lymphomatoid Papulosis EXPLODE ALL TREES	0
#5	MeSH DESCRIPTOR Pagetoid Reticulosis EXPLODE ALL TREES	0
#6	(cutaneous t cell lymphoma OR sezary syndrome OR mycosis fungoides OR alibert bazin OR granuloma fungoides OR skin t-cell lymphoma OR granuloma sarcomatodes OR wucherflechte OR ctcl)	15
#7	(lymphomatoid papulosis OR pagetoid reticulosis OR woringer-kolopp disease OR woringer OR granulomatous slack skin)	0
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)	16
#9	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) IN DARE	10

Abbreviations: MeSH, Medical Subject Headings.

H.1.1.2 September 2020

Table 96 Search strategy for Medline & EMBASE (conducted on 15 September 2020)

No.	Searches	Results
#1	'cutaneous t cell lymphoma'/exp OR 'sezary syndrome'/exp OR 'mycosis fungoides'/exp	15081
#2	'cutaneous t cell lymphoma':ab,ti,kw OR 'sezary syndrome':ab,ti,kw OR 'mycosis fungoides':ab,ti,kw OR 'alibert bazin':ab,ti,kw OR 'granuloma fungoides':ab,ti,kw OR 'skin t-cell lymphoma':ab,ti,kw OR 'granuloma sarcomatodes':ab,ti,kw OR 'wucherflechte':ab,ti,kw OR 'ctcl':ab,ti,kw OR 'lymphomatoid papulosis':ab,ti,kw OR 'pagetoid reticulosis':ab,ti,kw OR 'woringe-kolopp disease':ab,ti,kw OR 'woringe kolopp*':ab,ti,kw OR 'granulomatous slack skin':ab,ti,kw	14203
#3	'woringe kolopp disease'/exp OR 'granulomatous slack skin'/exp OR 'lymphomatoid papulosis'/exp	1504
#4	#1 OR #2 OR #3	18649
#5	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR 'rct':ab,ti OR ((random NEAR/2 (alloca* OR assign*))ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*))ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	2226479
#6	'clinical study'/de OR 'clinical article'/mj OR 'clinical trial'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR (('follow up' NEAR/1	8221919

No.	Searches	Results
	(study OR studies OR trial*):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR 'intervention study'/exp OR 'major clinical study'/de OR 'open study'/exp OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'case control study'/exp OR 'retrospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR retrospectiv*:ab,ti OR 'medical record review'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'observational study'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	
#7	#5 OR #6	8714074
#8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	4900643
#9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5434445
#10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	2501708
#11	#8 OR #9 OR #10	12548894
#12	#4 AND #7	5995
#13	#12 NOT #11	4183
#14	#13 AND [2019-2020]/py	475

Table 97 Search strategy for Medline In-Process (conducted on 15 September 2020)

No.	Searches	Results
#1	cutaneous t cell lymphoma	12597
#2	(sezary syndrome OR mycosis fungoides)	8539
#3	(alibert bazin OR granuloma fungoides OR skin t-cell lymphoma OR granuloma sarcomatodes OR wucherflechte OR ctcl)	13329
#4	(lymphomatoid papulosis OR pagetoid reticulosis OR woringer-kolopp disease OR woringer kolopp OR granulomatous slack skin)	12876
#5	(#1 OR #2 OR #3 OR #4)	15,535
#6	((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmc-book) OR (pubstatusaheadofprint))	367885
#7	(#5 AND #6)	154

No.	Searches	Results
#8	("2019/07/01"[Date - Create] : "3000"[Date - Create])	1645113
#9	#7 AND #8	129

Table 98 Search strategy for Cochrane (CENTRAL) (conducted on 15 September 2020)

No.	Searches	Results
#1	MeSH descriptor: [Lymphoma, T-Cell, Cutaneous] explode all trees	94
#2	MeSH descriptor: [Sezary Syndrome] explode all trees	19
#3	MeSH descriptor: [Mycosis Fungoides] explode all trees	59
#4	MeSH descriptor: [Pagetoid Reticulosis] explode all trees	0
#5	MeSH descriptor: [Lymphomatoid Granulomatosis] explode all trees	4
#6	MeSH descriptor: [Lymphomatoid Papulosis] explode all trees	2
#7	"cutaneous t cell lymphoma":ab,ti,kw OR "sezary syndrome":ab,ti,kw OR "mycosis fungoides":ab,ti,kw OR "alibert bazin":ab,ti,kw OR "granuloma fungoides":ab,ti,kw OR "skin t-cell lymphoma":ab,ti,kw OR "granuloma sarcomatodes":ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR "lymphomatoid papulosis":ab,ti,kw OR "pagetoid reticulosis":ab,ti,kw OR "woringer-kolopp disease":ab,ti,kw OR "woringer kolopp*":ab,ti,kw OR "granulomatous slack skin":ab,ti,kw	1164
#8	(47-#7)	1165
#9	#8 in Cochrane Reviews, Trials	1139
#10	#9 with Cochrane Library publication date Between Jul 2019 and Sep 2020	146

Abbreviations: MeSH, Medical Subject Headings.

H.1.1.3 May 2021

Table 99 Search strategy for Medline & EMBASE (conducted on 31 May 2021)

No.	Searches	Results
#1	'cutaneous t cell lymphoma'/exp OR 'sezary syndrome'/exp OR 'mycosis fungoides'/exp	15081
#2	'cutaneous t cell lymphoma':ab,ti,kw OR 'sezary syndrome':ab,ti,kw OR 'mycosis fungoides':ab,ti,kw OR 'alibert bazin':ab,ti,kw OR 'granuloma fungoides':ab,ti,kw OR 'skin t-cell lymphoma':ab,ti,kw OR 'granuloma sarcomatodes':ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR 'lymphomatoid papulosis':ab,ti,kw OR 'pagetoid reticulosis':ab,ti,kw OR 'woringer-kolopp disease':ab,ti,kw OR 'woringer kolopp*':ab,ti,kw OR 'granulomatous slack skin':ab,ti,kw	14203
#3	'woringer kolopp disease'/exp OR 'granulomatous slack skin'/exp OR 'lymphomatoid papulosis'/exp	1504

No.	Searches	Results
#4	#1 OR #2 OR #3	18649
#5	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomised controlled trial*':ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	2226479
#6	'clinical study'/de OR 'clinical article'/mj OR 'clinical trial'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR 'intervention study'/exp OR 'major clinical study'/de OR 'open study'/exp OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'case control study'/exp OR 'retrospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR retrospectiv*:ab,ti OR 'medical record review'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'observational study'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	8221919
#7	#5 OR #6	8714074
#8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	4900643
#9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5434445
#10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	2501708
#11	#8 OR #9 OR #10	12548894
#12	#4 AND #7	5995
#13	#12 NOT #11	4649
#14	#13 AND [15-9-2020]/sd NOT [1-6-2021]/sd	286

Table 100 Search strategy for Cochrane (CENTRAL) (conducted on 31 May 2021)

No.	Searches	Results
#1	MeSH descriptor: [Lymphoma, T-Cell, Cutaneous] explode all trees	97
#2	MeSH descriptor: [Sezary Syndrome] explode all trees	21
#3	MeSH descriptor: [Mycosis Fungoides] explode all trees	61
#4	MeSH descriptor: [Pagetoid Reticulosis] explode all trees	0
#5	MeSH descriptor: [Lymphomatoid Granulomatosis] explode all trees	4
#6	MeSH descriptor: [Lymphomatoid Papulosis] explode all trees	2
#7	"cutaneous t cell lymphoma":ab,ti,kw OR "sezary syndrome":ab,ti,kw OR "mycosis fungoides":ab,ti,kw OR "alibert bazin":ab,ti,kw OR "granuloma fungoides":ab,ti,kw OR "skin t-cell lymphoma":ab,ti,kw OR "granuloma sarcomatodes":ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR "lymphomatoid papulosis":ab,ti,kw OR "pagetoid reticulosis":ab,ti,kw OR "woringer-kolopp disease":ab,ti,kw OR "woringer kolopp*":ab,ti,kw OR "granulomatous slack skin":ab,ti,kw	1219
#8	(47-#7)	1220
#9	#8 in Cochrane Reviews, Trials	1197
#10	#9 with Cochrane Library publication date Between Sep 2020 and Apr 2021	56

Abbreviations: MeSH, Medical Subject Headings.

H.1.1.4 February 2025

Table 101 Search strategy table for Medline & EMBASE (conducted on 03 February 2025)

No.	Searches	Results
#1	'cutaneous t cell lymphoma'/exp OR 'sezary syndrome'/exp OR 'mycosis fungoides'/exp	26084
#2	'cutaneous t cell lymphoma':ab,ti,kw OR 'sezary syndrome':ab,ti,kw OR 'mycosis fungoides':ab,ti,kw OR 'alibert bazin':ab,ti,kw OR 'granuloma fungoides':ab,ti,kw OR 'skin t-cell lymphoma':ab,ti,kw OR 'granuloma sarcomatodes':ab,ti,kw OR wucherflechte:ab,ti,kw OR ctcl:ab,ti,kw OR 'lymphomatoid papulosis':ab,ti,kw OR 'pagetoid reticulosis':ab,ti,kw OR 'woringer-kolopp disease':ab,ti,kw OR 'woringer kolopp*':ab,ti,kw OR 'granulomatous slack skin':ab,ti,kw	18090
#3	'woringer kolopp disease'/exp OR 'granulomatous slack skin'/exp OR 'lymphomatoid papulosis'/exp	1890
#4	#1 OR #2 OR #3	29182
#5	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR	2943557

No.	Searches	Results
	'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR ((random NEAR/2 (alloca* OR assign*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp	
#6	'clinical study'/de OR 'clinical article'/mj OR 'clinical trial'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR 'intervention study'/exp OR 'major clinical study'/de OR 'open study'/exp OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'case control study'/exp OR 'retrospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR retrospectiv*:ab,ti OR 'medical record review'/exp OR registry:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'observational study'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti	11545592
#7	#5 OR #6	12164868
#8	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	6110805
#9	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	6246055
#10	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti OR 'meta analysis':ab,ti)	3161847
#11	#8 OR #9 OR #10	15183888
#12	#4 AND #7	10853
#13	#12 NOT #11	7872
#14	#13 AND [2021-2025]/py	2147

Table 102 Search strategy for Cochrane (CENTRAL) (conducted on 03 February 2025)

No.	Searches	Results
#1	MeSH descriptor: [Lymphoma, T-Cell, Cutaneous] explode all trees	146
#2	MeSH descriptor: [Sezary Syndrome] explode all trees	32
#3	MeSH descriptor: [Mycosis Fungoides] explode all trees	95
#4	MeSH descriptor: [Pagetoid Reticulosis] explode all trees	0

No.	Searches	Results
#5	MeSH descriptor: [Lymphomatoid Granulomatosis] explode all trees	4
#6	MeSH descriptor: [Lymphomatoid Papulosis] explode all trees	2
#7	"cutaneous t cell lymphoma":ab,ti,kw	333
#8	"sezary syndrome":ab,ti,kw	139
#9	"mycosis fungoides":ab,ti,kw	278
#10	"alibert bazin":ab,ti,kw	1
#11	"granuloma fungoides":ab,ti,kw	5
#12	"skin t-cell lymphoma":ab,ti,kw	260
#13	"granuloma sarcomatodes":ab,ti,kw	0
#14	wucherflechte:ab,ti,kw	0
#15	ctcl:ab,ti,kw	177
#16	"lymphomatoid papulosis":ab,ti,kw	2
#17	"pagetoid reticulosis":ab,ti,kw	0
#18	"woringer-kolopp disease":ab,ti,kw	0
#19	"woringer kolopp*":ab,ti,kw	0
#20	"granulomatous slack skin":ab,ti,kw	0
#21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	556
#22	#21 in Cochrane Reviews, Trials	555
#23	#22 with Cochrane Library publication date Between Jan 2021 and May 2025	119

Abbreviations: MeSH, Medical Subject Headings.

H.1.2 Systematic selection of studies

H.1.2.1 Study selection criteria

The inclusion and exclusion criteria presented in Table 103 were applied to the literature search results to identify the final set of studies which formed the clinical evidence.

Table 103 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult patients with any stage R/R CTCL, including the subtypes MF and SS, who have been previously	- Healthy volunteers - Paediatric population	N/A

	- treated with at least one systemic therapy - Adult patients with any stage MF and SS who have been previously treated with at least one systemic therapy	- Disease other than R/R CTCL - Frontline therapy
Intervention	All pharmacological interventions and phototherapies <u>Extractions for studies of interventions based on Irish, UK and Nordic clinical practice:</u> - Mogamulizumab - Brentuximab vedotin - Bexarotene - Methotrexate - Gemcitabine - Vorinostat - Interferon - CHOP regimen - Alemtuzumab - Pembrolizumab - Acitretin Extracorporeal photopheresis	Interventions not included in the list
Comparators	- Placebo - Best supportive care (author defined) - Any other pharmacological intervention - No comparator limit for single-arm trials - Standard of care	None
Outcomes	- Response rate - Global composite response - Progression-free survival - Treatment free survival - Overall survival - Time to treatment discontinuation - Mortality - Health-related quality of life - Incidence of adverse events - Study/treatment discontinuation etc	Not reporting any of the outcomes included in the list

Study design/ publication type	• Randomized controlled trials • Non-randomized controlled trials • Single-arm trials • Retrospective and prospective cohort studies • Real-world evidence studies • Systematic reviews	• Letters, comments and editorials • Case studies or case reports
Language restrictions	• English language only	• Non-English language

Abbreviations: CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; R/R, relapsed/refractory; SLR, systematic literature review; SS, Sézary syndrome.

H.1.2.2 Study selection methodology

All retrieved studies were assessed against the eligibility criteria detailed in Table 103. Primary (Level 1) screening was performed by two independent reviewers who reviewed each reference (title and abstract) identified in the literature search, apply basic study selection criteria (population, intervention, study design) and decide whether to include or exclude the study reference at this stage. Any discrepancy regarding the inclusion of studies was checked by a third reviewer.

For secondary (Level 2) screening of potentially relevant articles, the full articles were obtained. These were independently reviewed by two independent reviewers against each eligibility criterion. Again, any discrepancy regarding the inclusion of a study was checked by a third reviewer.

Articles obtained free of charge were initially checked, all remaining references were obtained through the Kyowa Kirin in-house library or the RightFind® service. During screening, a record of all included and excluded articles and the reasons for these decisions was kept. This is summarized in the PRISMA flowchart of this SLR report, and an overview of the excluded articles is presented in Table 106.

H.1.2.3 Data extraction

The data extraction process was performed by a single reviewer in the pre-agreed data extraction template; it was quality checked by a senior reviewer against the source paper. Included randomized controlled trials (RCTs) were subject to a quality appraisal using the standard NICE checklist (Table 107). The quality assessment of the included non-RCTs were performed using a checklist by Downs and Black (Table 110).

H.1.2.4 Results

H.1.2.4.1 July 2019

The original database searches for the SLR were performed on 2 July 2019. A total of 4,241 studies were identified using electronic searches. After deduplication, a total of 4,238 were evaluated for relevance based on the predefined eligibility criteria (Table 103). After preliminary screening of 4,238 abstracts, 3,372 records were excluded. The remaining 866 studies were further screened based on information reported in the full-text articles. After secondary screening of full-text articles, 642 studies were excluded. In addition, 14 studies were identified from the grey literature searches. Consequently, 238 studies were included. Furthermore, restricting the patient population and interventions to focus on the treatments most frequently used in Irish and UK clinical practice, 142 studies were kept outside of the purview.

H.1.2.4.2 September 2020 update

Updated searches were performed on the 15 September 2020. Following deduplication of a total of 567 abstracts were screened for eligibility and 545 articles were excluded. The remaining 22 studies were further screened based on information in the full-text articles. After secondary screening, no additional articles were identified for inclusion in the SLR. From the grey literature searches, the final safety follow-up for the previously identified MAVORIC trial was identified.

H.1.2.4.3 May 2021 update

Searches were further updated on the 31 May 2021 in MEDLINE, Embase and PubMed and up to April 2021 in the Cochrane Library. Following deduplication, a total of 428 abstracts were screened for eligibility and 394 articles were excluded. The remaining 34 studies were further screened based on information in the full-text articles. After secondary screening, 3 additional articles were included in the SLR—restricting the scope to routine Irish and UK clinical practice—and a further 31 full-texts excluded. All 3 publications were post-hoc sub-analyses of the 2 previously identified RCTs MAVORIC and ALCANZA. From the updated grey literature searches, 1 additional conference abstract was identified describing characterization and outcomes in patients with mogamulizumab-associated skin reactions in the MAVORIC trial.

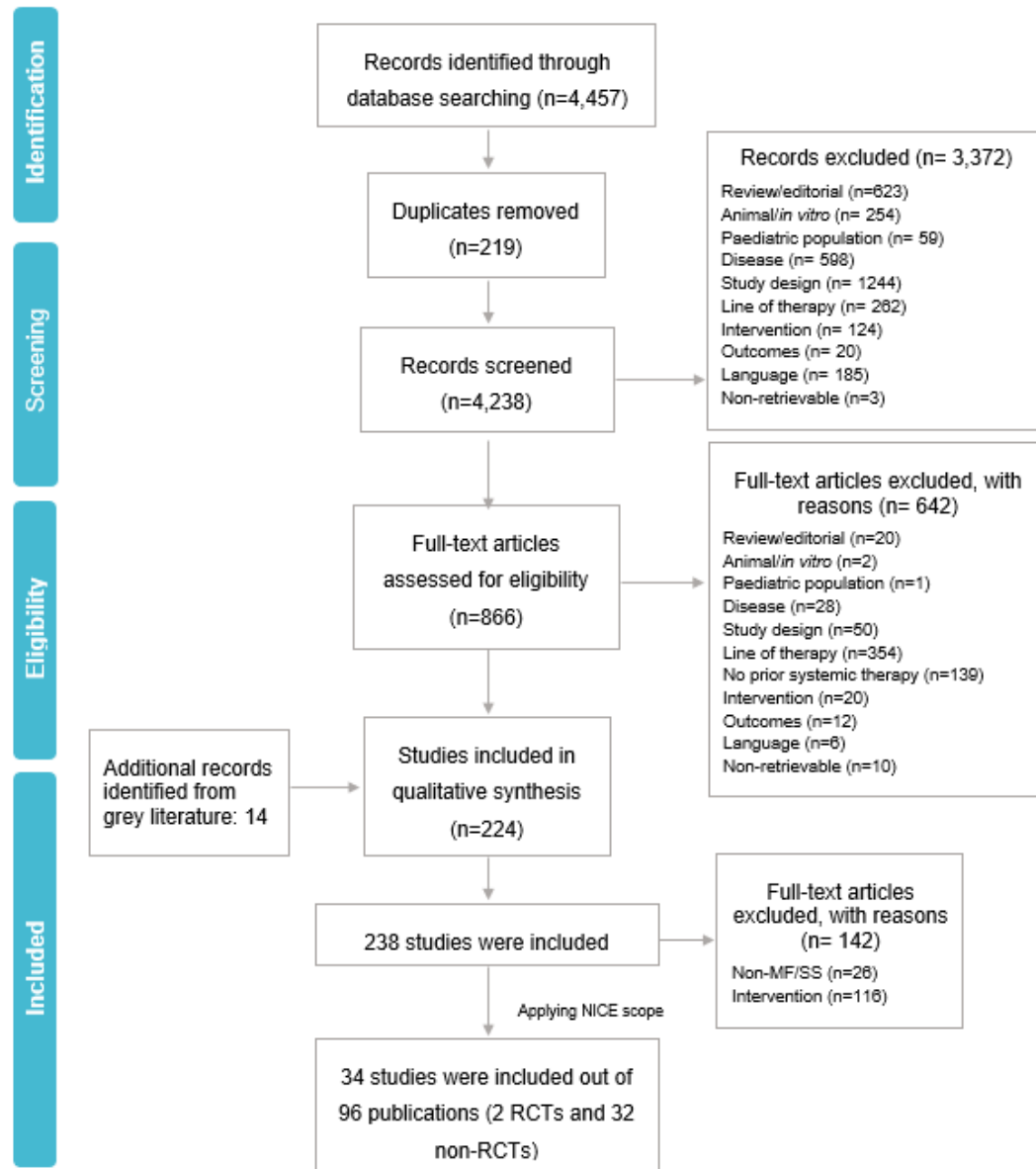
H.1.2.4.4 February 2025 update

An additional update was conducted on 3 February 2025 in MEDLINE (including PubMed not Medline), Embase and the Cochrane Library. Following deduplication, a total of 2233 abstracts were screened for eligibility and 2083 references were excluded. The remaining 150 articles were screened based on information in the full-text articles. Following this, 39 additional articles were included in the SLR.

The limitations applied to the previous iterations of the SLR to focus on treatments most frequently used in Irish and UK clinical practice were expanded for this update to include treatments also frequently used in the Nordics (namely the addition of alemtuzumab, pembrolizumab, acitretin and extracorporeal photopheresis [ECP]) to the scope. As such, studies previously excluded because of the interventions explored were re-reviewed identifying an additional two studies for inclusion in the SLR. Further, a study previously included in the SLR was excluded as upon reflection only 28% of patients had received prior systemic therapy.

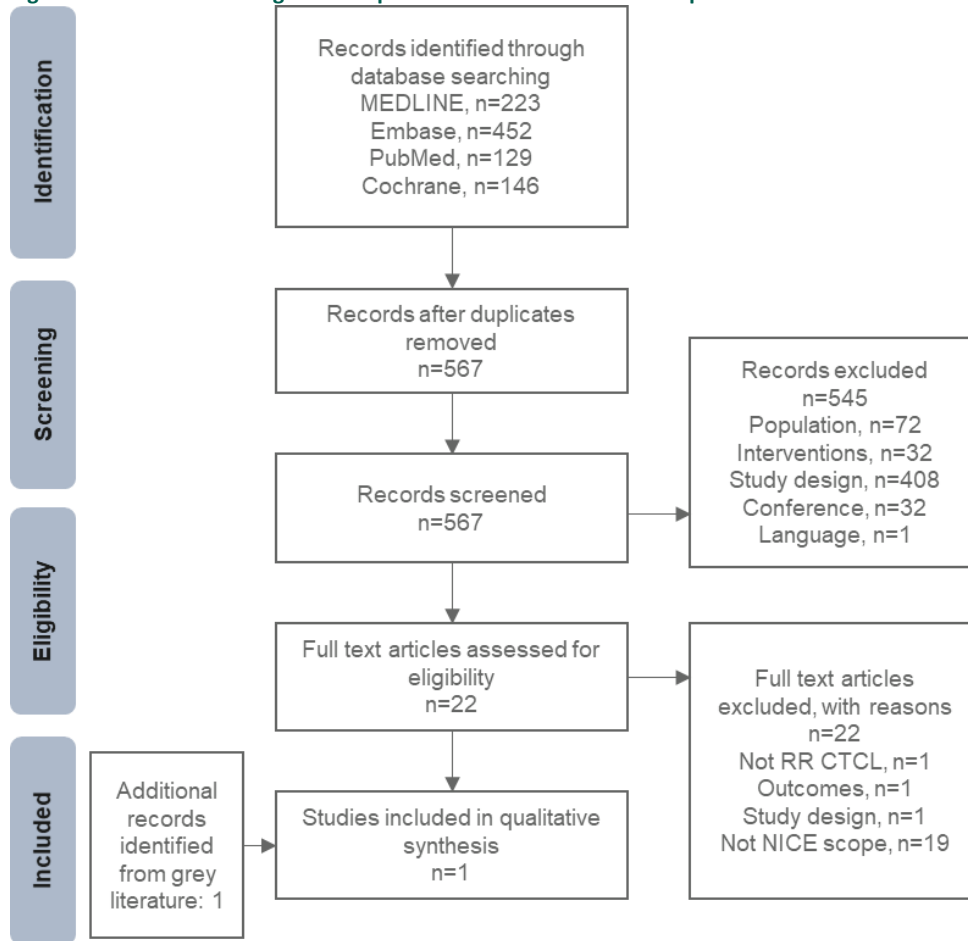
Finally, 54 unique studies were identified from 139 publications. PRISMA flow diagrams for each SLR are provided in Figure 62-20 (Figure 62: original SLR; Figure 63: updated SLR September 2020; Figure 64: updated SLR May 2021; Figure 65: updated SLR February 2025).

Figure 62 PRISMA flow diagram for SLR conducted on 2 July 2019



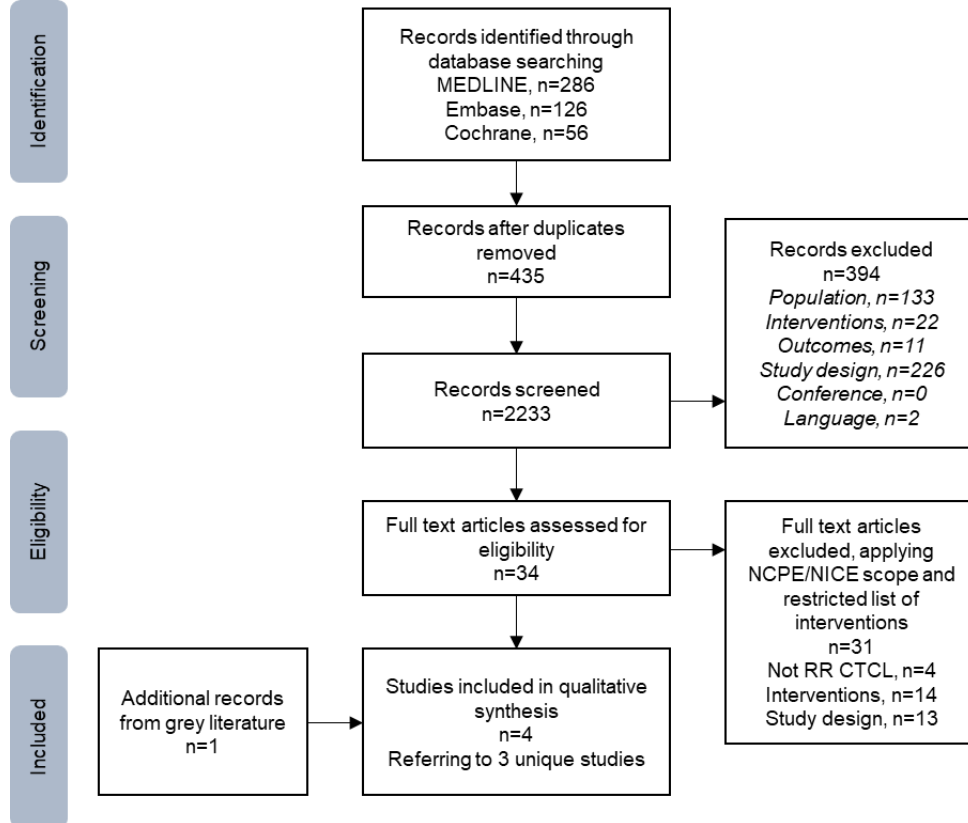
Abbreviations: NICE, National Institute for Health and Care Excellence; RCT, Randomised controlled trial; MF, mycosis fungoides; SS, Sezary syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 63 PRISMA flow diagram for updated SLR conducted on 15 September 2020



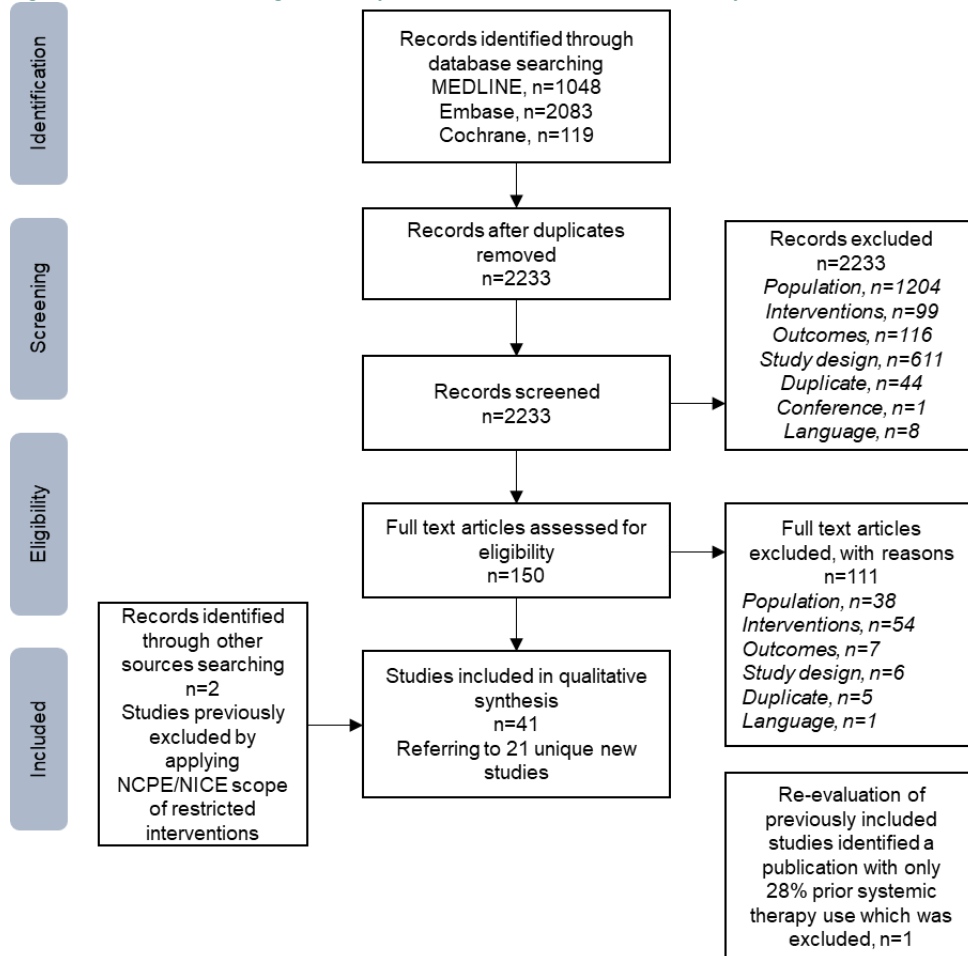
Abbreviations: NICE, National Institute for Health and Care Excellence; RR CTCL, Relapsed or refractory Cutaneous T-Cell Lymphoma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 64 PRISMA flow diagram for updated SLR conducted on 31 May 2021



Abbreviations: NICE, National Institute for Health and Care Excellence; NCPE: National Centre for Pharmacoeconomics; RR CTCL, Relapsed or refractory Cutaneous T-Cell Lymphoma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Figure 65 PRISMA flow diagram for updated SLR conducted on 3 February 2025



Note: This SLR was done with a wider scope but finally studies were included and extracted focusing on NCPE, NICE and SMC submission criteria applying further limit on intervention and disease. The scope was expanded to include additional interventions used in the Nordics for the 2025 update, this included re-reviewing studies previously excluded based on interventions only. Abbreviations: NICE, National Institute for Health and Care Excellence; NCPE: National Centre for Pharmacoeconomics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review Source: Hutton et al., 2015.

H.1.2.4.5 Overview of studies

This systematic review identified 55 primary studies for the treatment of relapsed or refractory MF/SS patients previously treated with at least one systemic therapy. Of all included studies, two were RCTs and the remaining 54 studies were non-RCTs or observational.

Table 104 Overview of study design for studies included in the SLR

Study name	Study phase Study design Blinding Study centre Study country	List of endpoints • Primary • Secondary	Treatment /comparator	Number of patients	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Prior therapy: Me- dian (min–max)	Stages: n (%)
Mogamulizumab based study								
Kim 2018 (MA-VORIC Trial/NCT01728 805) ¹¹	- Phase III - RCT - Open label - Multicentres (61) - USA, Denmark, France, Italy, Germany, the Netherlands, Spain, Switzerland, UK, Japan and Australia	- PFS by investigator - Response rates, TTR, Skindex-29, FACT-G, and EQ-5D-3L, safety and tolerability	Mogamulizumab	186	105 (56) 81 (44) 0	64 (IQR: 54–73)	3 (1–18)	IB–IIA: 36 (19) IIB: 32 (17) IIIA–IIIB: 22 (12) IVA1: 73 (29) IVA2: 19 (10) IVB: 4 (2)
Kim 2018 (MA-VORIC Trial/NCT01728 805) ¹¹	- Phase III - RCT - Open label - Multicentres (61) - USA, Denmark, France, Italy,	- PFS by investigator - Response rates, TTR, Skindex-29, FACT-G, and EQ-5D-3L, safety and tolerability	Vorinostat	186	99 (53) 87 (47) 0	65 (IQR: 56–72)	3 (0–14) &	IB–IIA: 49 (26) IIB: 23 (12) IIIA–IIIB: 16 (9) IVA1: 82 (44) IVA2: 12 (6) IVB: 4 (2)

	Germany, the Netherlands, Spain, Switzerland, UK, Japan and Australia								
Ogura 2014 ²⁷	- Phase II - nRCT non-comparative - Open label - Multicentre (15) - Japan	- Best RR - Assessments of the best RR according to disease site, PFS, OS	Mogamulizumab	8	7 (88) 1 (12)	50 (36–70)	3 (1-6)	NR	
Duvic 2015 ²⁸	- Phase I/II - nRCT non-comparative - Open label - Multicentres (5) - USA	- RR - DoR, TTP	Mogamulizumab	41	22 (53.7) 19 (46.3)	66 (35–85)	3 (1-17)	IB: 3 (7.3) II: 1 (2.4) IIB: 9 (22.0) III: 1(2.4) IIIA: 1 (2.4) IVA: 22 (53.7) IVB: 4 (9.8)	
Zhang 2022 ²⁹	- NR - Retrospective observational - Single center (Moffitt cancer center) - USA	- RR - TTNT	Mogamulizumab	22	0 22 (100)	Mean (min-max): 69 (29-91)	4	NR	
Assaf 2023 ³⁰	- NR - Retrospective/prospective observational	- RR - TTNT - PFS	Mogamulizumab	40	23 (57.5) 17 (42.5)	Mean (SD): 68.2 (11.0)	NR	≥IIB: 35 (87.5) ≥IVA: 26 (65)	

	- Multi-centres - Germany								
Beylot-Barry 2023 ³¹	- NR - Retrospective observational - Multicentres (14) - France	- RR - Safety	Mogamulizumab	122	53 (43.4) 69 (56.6)	Mean (SD) 66.6 (12.1)	3 (Q1, Q3: 2-5)	IA-IB-IIA: 26 (22.2) IIB: 7 (6) IIIA-IIIB: 15 (12.8) IVA1-IVA2-IVB: 69 (58.9)	
Scarisbrick 2023 ³²	- NR - Retrospective observational - Single centre (University Hospital Birmingham) - UK	- PFS - TTNT - Safety	Mogamulizumab	26	17 (65) 6 (23)	57 (9-84)	2.8 (1-6)	I: 4 (24) II: 4 (24) III: 7 (41) IV: 2 (12)	
Ninosu 2024 ³³	- NR - Retrospective observational - Multi centres (4) - Germany	- mSWAT - RR	Mogamulizumab + Extracorporeal photopheresis	11	1 (9) 10 (91)	Mean (SD): 72 (9.2)	NR	IIIA: 1 (9) IVA1: 8 (73) IVB2: 2 (18)	
Brentuximab vedotin based study									
Dumont 2019 ³⁴	- Phase II - nRCT non-comparative - Open label - Multicentre - France	RR*	Brentuximab vedotin + bendamustine	9	2 (22.22) 6 (66.67)	59 (29–84)	NR	NR	

Prince 2017 (AL-CANZA/NCT01578499) ²¹	- Phase III - RCT - Open label - Multicentres (52) - USA, Australia, Austria, Belgium, Brazil, France, Germany, Italy, Poland, Spain, Switzerland and the UK	Objective global response lasting at least 4 months per independent review (ORR4)	Brentuximab vedotin	64	48 (75) 0 16 (25)	NR*	NR*	IA–IIA: 15 (31) IIB: 19 (40) IIIA–IIIB: 4 (8) IVA1: 0 (0) IVA2: 2 (4) IVB: 7 (15)
Prince 2017 (AL-CANZA/NCT01578499) ²¹	- Phase III - RCT - Open label - Multicentres (52) - USA, Australia, Austria, Belgium, Brazil, France, Germany, Italy, Poland, Spain, Switzerland and the UK	- Objective global response lasting at least 4 months per independent review (ORR4) - ORR, PFS, DOR, EFS, Skindex-29, FACT-G, safety and tolerability	Methotrexate or Bexarotene physician's choice treatment)	64	49 (77) 0 15 (23)	NR*	NR*	IA–IIA: 18 (37) IIB: 19 (39) III: 2 (4) IVA1: 1 (2) IVA2: 8 (16) IVB: 0 (0)
Kim 2015 ³⁵	- Phase II - nRCT non-comparative - Open label - Multicentre (Stanford) - USA	- RR - TTR, DoR, PFS, EFS, safety	Brentuximab vedotin	32	29 (91) 3 (9.4)	62 (20–87)	3 (1–13)	IB: 4 (13) IIB: 18 (56) IV: 10 (31)
Duvic 2015 ³⁶	Phase II	RR and safety*	Brentuximab vedotin	28	28 (100) 0 (0)	NR	5 (1-10)	NR

	• nRCT non-comparative • Open label • Single centre (MD Anderson Cancer Center) • USA							
William 2019 ^{37,38}	• Phase II • nRCT non-comparative • Open label • Single centre (Ohio State University) • USA	Safety and RR*	Brentuximab vedotin + lenalidomide	14	• 10 (71.42) • 2 (14.28)	60 (49–74)	5.5 (1-9)	IB: 2 (15) IIB: 7 (54) IVA: 4 (31)
Lewis 2021 ³⁹	• NR • Retrospective observational • Single centre (University of Pennsylvania) • USA	RR TTNT DoR	Brentuximab vedotin	13	• 0 • 13 (100)	Mean (SD): 68.2 (8.6)	6 (0-11)	IVA1: 8 (62) IVA2: 4 (31) IVB: 1 (8)
Sureda 2022 ⁴⁰	• NR • Retrospective observational • Multicentre (30) • Spain	Safety and discontinuation	Brentuximab vedotin	12	• 12 (100) • 0	51.5	NR	IA-IB-IIA: 1 (11.1) IIB: 3 (33.3) III-IV: 5 (55)
Kim 2023 ⁴¹	• Prospective observational	PFS	Brentuximab vedotin	12	• 12 (100) • 0	62 (32-84)	NR	I: 1 (8) II: 6 (50)

	- Multicentre (12) - Korea	OS RR						III/IV: 5 (42)
Muniesa 2023 ⁴²	- NR - Prospective observational - NR - Spain	RR PFS Tolerability	Brentuximab vedotin	55	48 (72) 7 (10)	MF, mean (range): 58 (24-92) SS, mean (range): 65 (43-80)	MF, Mean (range): 4 (2-9) SS, mean (range): 5 (2-11)	MF: IIB: 35 (73) IIIA: 3 (6) IIIB: 1 (2) IVA1: 6 (12) IVA2: 3 (6) SS IVA1: 5 (71) IVA2: 2 (29)
Munayirji 2023 ⁴³	- Phase II - nRCT Single arm study - Multicentre - USA	RR safety	Brentuximab vedotin	33	- Cohort A: MF 19 (100) - Cohort B: MF 12 (86) - Cohort B: SS 2 (14)	Cohort A: 60 (38-85) Cohort B: 62 (39-83)	Cohort A: 2 (0-9) Cohort B: 1.5 (0-4)	Cohort A IB: 6 (32) IIA: 3 (16) IIB: 7 (37) III: 1 (5) IV: 2(11) Cohort B IB: 5 (36) IIB: 6 (43) IV: 3 (21)
Vorinostat based study								
Duvic 2007 ⁴⁴	- Phase II - nRCT non-comparative - Open label	- RR - DoR, safety, tolerability	Vorinostat	37	22 (66.66) 11 (33)	67 (26-82)	5 (1-15)	IA: 1 (3) IB: 3 (9) IIA: 1 (3) IIB: 5 (15)

	• Single centre • USA							III: 5 (15) IVA: 10 (30) IVB: 8 (24)
Olsen 2007 ⁴⁵	• Phase II • nRCT non-comparative • Open label • Multicentre • USA and Canada	RR, TTR, TTP, DoR, safety, tolerability*	Vorinostat	74	• 44 (59.5) • 30 (40.5)	60 (39–83)	3 (1–12)	IB: 11 (14.9) IIA: 2 (2.7) IIB: 19 (25.7) III: 20 (27) IVA: 18 (24.3) IVB: 4 (5.4)
Geskin 2010 ⁴⁶	• NR • Observational non-comparative • NR • Single centre • USA	RR, DoR, DOT, Safety and tolerability*	Vorinostat (200–400 mg) based regimens	14	• 9 (64.2) • 5 (35.7)	Mean: 56.35	NR	IA: 1 (7.14) IB: 2 (14.28) IIA: 4 (28.5) IIB: 1 (7.14) III: 3 (21.4) IVA: 2 (14.28) IVB: 1 (7.14)
Wada 2012 ⁴⁷	• Phase I • nRCT non-comparative • Open label • Multicentre • Japan	RR, TTP, safety, tolerability*	Vorinostat	6	• 6 (100) • 0 (0)	53.5 (34–75)	2.5 (1–5)	IIB: 4 (66.7) IVA1: 2 (33.3)
Kogge 2015 ⁴⁸	• NR • Observational non-comparative • NR • Single centre	RR, TTR, DoR, Safety and tolerability*	Vorinostat	15	• 6 (40) • 9 (60)	64 (36–76)	3 (1–7)	IB: 2 (13.3) IIB: 2 (13.3) IIIA: 2 (13.3) IVA: 9 (60)

- France

Bexarotene based studies

Sokolowska-Wojdylo 2016 ⁴⁹	• NR • Observational non-comparative • NR • Multicentre • Poland	RR, TTR, DoR*	Bexarotene	21	• 19 (90.47) • 2 (9.52)	58.6 (19–84)	NR	IA: 1 IB: 1 IIA: 1 IIB: 4 III: 4 IIIA: 5 IVA1: 3 IVB: 2
Duvic 2017 ⁵⁰	• Phase I/II • nRCT non-comparative • Open label • Multi-centre • US, Italy	RR*	Bexarotene + pralatrexate	34	• 30 (88) • 3 (9)	66 (39–85)	NR	NR
Papadavid 2008 ⁵¹	• NR • Observational comparative • NR • Single centre • Greece	RR, safety and tolerability*	Bexarotene 300 mg/day oral + PUVA	9	• 9 (100) • 0 (0)	NR	NR	IA: 1 (11.1) IB: 6 (66.1) IIA: 1 (11.1) III: 1 (11.1)
			Bexarotene 150 mg/day oral + PUVA	5	• 5 (100) • 0 (0)	NR	NR	IB: 3 (60) IIB: 1 (20) III: 1 (20)
Hughes 2015 ⁵²	• NR	• TTNT • NR	Low dose methotrexate	52	• NR • NR	NR	NR	NR

	- Observational comparative - NR - Multicentre - Australia		Interferon-alpha	41	- NR - NR	NR	NR	NR	NR
Talpur 2014 ⁵³	- Phase II - Observational comparative - NR	RR, safety and tolerability*	Bexarotene 300 mg + pralatrexate	3	3 (100) 0 (0)	Mean: 57.6 (range: 41-77)	NR		NR
			Bexarotene 150 mg + pralatrexate	11	11 (100) 0 (0)	Mean: 62.27 (range: 42-82)	NR		NR
Talpur 2002 ⁵⁴	- NR - Observational non-comparative - NA^{&} - Single centre - USA	RR, safety and tolerability*	Bexarotene based regimen	16	14 (87.5) 2 (12.5)	65 (43–79)	NR		IIB: 1 (6.25) III: 9 (56.25) IVA: 4 (25) IVB: 2 (12.5)
Rupoli 2016 ⁵⁵	Phase II nRCT non-comparative Multicentre Italy	- RR - EFS and safety	Bexarotene + PUVA	15	- NR - NR	NR	NR		IB–IVA
Illidge 2013 ⁵⁶	Phase II nRCT non-comparative NR Multicentre UK	- ORR at 24 weeks - RR, PFS, OS, safety, change in mSWAT and QoL	Gemcitabine + bexarotene	36	- NR - NR	65 (38–83)	NR		IB: 5 (13.9) IIA: 2 (5.6) IIB: 8 (22.2) III: 8 (22.2) IVA: 13 (36.1)
Elsayad 2022 ⁵⁷	NR Prospective observational	- RR - PFS, DOR, OS	TSEBT ± bexarotene	27	24 (89) 3 (11)	64 (25-81)	NR		IB: 8 (30) IIB: 14 (52)

	Single centre Germany							III: 2 (7%) IV: 3 (11%)
Hamada 2022 ⁵⁸	NR Retrospective observational Multicentre Japan	- mSWAT - Physician global assessment, RR, TTR, DoR	Bexarotene	267	139 (79.3) 12 (6.9)	68 (25-91)	NR	IA: 4 (2.9) IB: 34 (24.5) IIA: 8 (5.8) IIB: 67 (48.2) IIIA: 20 (14.4) IVA1: 2 (1.4) IVA2: 4 (2.9)
Teoli 2023 ⁵⁹	NR Retrospective observational NR Italy	- mSWAT - RR, DoR	Chlormethine gel + acitretin or bexarotene	15	15 (100) 0	(48-70)	NR	I: 2 (13) II: 13 (87)
Rey 2023 ⁶⁰	NR Retrospective observational NR Argentina	RR	Bexarotene + extracorporeal photopheresis	8	3 (37.5) 5 (62.5)	63 (57-67)	2 (1-3)	MF IIB: 2 IIIA: 1 SS IVA1: 5
Roccuzzo 2023 ⁶¹	NR Retrospective observational Single centre (University of Turin) Italy	RR	Acitretin, Bexarotene, extracorporeal photopheresis	51	41 (80) 7 (14)	NR	NR	NR
Quaglino 2011 ⁶²	NR nRCT single arm Multi-centre	RR, relapse free survival, safety	Bexarotene	NR	NR	NR	NR	NR

Gemcitabine based studies

Duvic 2006 ⁶³	- Phase II - nRCT non-comparative - Open label - Single centre - USA	RR, OS, DOR, safety*	Gemcitabine	33	20 (60.6) 11 (33.3)	NR	5 (2-13)	IB: 2 (6.1) IIA: 1 (3.0) IIB: 13 (39.4) IVA: 7 (21.2) IVB: 8 (24.2)
Jidar 2009 ⁶⁴	- NR - Observational non-comparative - NR - Multicentre - France	RR, safety*	Gemcitabine	23	14 (60.9) 6 (26.1)	Mean: 64 (range: 26–82)	Mean: 2 (0–5)	IIB/III: 18 (88.2) IV: 5 (21.7)
Braunstein 2024 ⁶⁵	- NR - Retrospective observational - NR - Single centre - USA	RR, PFS, OS, Safety	Gemcitabine + liposomal doxorubicin	18	12 (85) 1 (8)	NR	NR	NR

Interferon based studies

Bunn Jr 1987 ⁶⁶	- NR - nRCT non-comparative - NR - NR	RR, safety*	Recombinant interferon -alfa	20	- NR - NR	NR	NR	II: 5 (25) III: 2 (10) IV: 13 (65)
----------------------------	--	-------------	------------------------------	----	--	----	----	--

- NR

Aviles 2015 ⁶⁷	• NR • nRCT comparative • Open label • NR • NR	OS, safety RR, DOR, PFS	Interferon + metho- trexate	201	• 201 (100) • 0 (0)	64.5 (36–71)	NR	II B: 73 (36) IIIB: 57 (28) IV A: 40 (20) IV B: 29 (14)
			Interferon + retin- oids	176	• 176 (100) • 0 (0)	62.9 (43–75)	NR	II B: 76 (42) IIIB: 36 (20) IV A: 35 (19) IV B: 31 (17)
Roenigk Jr 1990 ⁶⁸	• Phase I • nRCT non-compara- tive • NR • Multicentre • NR • NR	RR, DoR, TTR, safety*	Interferon alpha-2a + PUVA	15	• NR • NR	NR	NR	IB: 7 (63.6) IIB: 2 (18.2) III: 1 (9.1) IVB: 1 (9.1)
Foss 1992 ⁶⁹	• Phase II • nRCT non-compara- tive • NR • NR • NR	RR, OS*	Pentostatin + inter- feron alfa-2a	29	• NR • NR	NR	NR	IV A: 8 (80) IVB: 2 (20)

Kuzel 1995 ⁷⁰	- Phase I/II - nRCT non-comparative - NR - NR - USA	RR, DoR, safety*	Interferon alfa-2a + phototherapy	8	- NR - NR	NR	NR	NR
Foss 1994 ⁷¹	- Phase II - nRCT non-comparative - NR - NR - NR	RR, TTP*	Fludarabine + interferon Alfa-2a	21	- NR - NR	NR	NR	NR
Kohn 1990 ⁷²	- Phase II - nRCT non-comparative - NR - NR - NR	RR, RR (blood, skin, lymph node, viscera), DoR, TTR, safety*	Recombinant interferon -alfa	24	- NR - NR	60 (25–70)	NR	NR
Zhang 2022 ²⁹	- NR - Retrospective observational - Moffitt cancer center - USA	- RR - TTNT	Extracorporeal photopheresis + interferon	13	0 (0) 13 (100)	NR	NR	NR
Mitsunaga 2024 ⁷³	- NR - Retrospective observational	TTNT, RR, DoR, PFS, Safety	Pegylated interferon- α -2a	105	80 (76.2) 25 (23.8)	61 (22-86)	NR	IA-IIA: 42 (40) IIB: 30 (28.6) IIIA-IIIB: 8 (7.6) IVA1: 18 (17.1)

- Multicentre
- 10 countries: Spain, France, Switzerland, Israel, Greece, Austria, UK, Germany, Italy, Brazil

IVA2= 7 (7.6)

Methotrexate based studies

McDonald 1978 ⁷⁴	• NR • nRCT non-comparative • NR • Multicentre • USA	RR, DOR, safety*	Methotrexate + Citrovorum factor	11	• 6 (100) • 0 (0)	Mean: 58.5 (range: 41–78)	NR	II: 3 (50) III: 3 (50)
-----------------------------	--	------------------	----------------------------------	----	--	---------------------------	----	---------------------------

CHOP regimen-based studies

Akpek 1999 ⁷⁵	• Phase II • nRCT non-comparative • NR • NR • NR	RR*	EPOCH regimen	6	• 0 (0) • 6 (100)	NR	NR	IIB–IVB
Wilson 1995 ⁷⁶	• NR • nRCT non-comparative • NR • NR • NR	RR, safety*	EPOCH regimen	8	• 8 (100) • 0 (0)	NR	NR	NR
			Dexverapamil + EPOCH	5	• 5 (100) • 0 (0)	NR	NR	NR

Pembrolizumab based studies

Khodadoust 2019 ⁷⁷	Phase 2 nRCT single arm Multi-centre USA	RR, DOR, PFS, OS	Pembrolizumab	24	• 9 (38) • 15 (62)	66.9 (44-85)	4 (1-6)	IB: 1(4) IIB: 2 (8) IIIA: 2 (8) IIIB: 3 (12) IVA: 16 (67)
Elghawy 2024 ⁷⁸	NR Retrospective observational Single centre (University of Pennsylvania) USA	OS, PFS, RR, safety	Pembrolizumab	29	• 19 (66) • 10 (34)	66 (40-85)	3 (1-8)	Early: 6 (21) Advanced: 23 (79)
Alemtuzumab based studies								
Zhang 2022 ²⁹	NR Retrospective observational Single centre (Moffitt cancer center) USA	RR, TTNT	Alemtuzumab	14	• 0 • 14 (100)	NR	3.5	NR
ECP based studies								
Baquero Rey 2021 ⁷⁹	NR Retrospective observational Single centre Argentina	RR, mSWAT	Extracorporeal photopheresis + multi-modality therapy	28	11 (39.3)	63 (Q1, Q3: 52, 69)	3 (Q1, Q3: 1, 3)	IVA1: 16 (94) IVA2: 1 (6) IVB: 0
					17 (60.7)	63 (Q1, Q3: 57, 68)	1 (Q1. Q3: 1, 4)	IB: 5 (45) IIB: 1 (10) IIIA: 5 (45)
Key: DoR, duration of response; EFS, event-free survival; EQ-5D, EuroQol 5-Dimension; EPOCH, etoposide, prednisone, vincristine (Oncovin®), cyclophosphamide and doxorubicin hydrochloride (hydroxydaunorubicin hydrochloride); FACT-G, Functional Assessment of Cancer Therapy - General; ORR: overall response rate; PFS: progression-free survival; PUVA, psoralen plus ultraviolet A therapy, TTNT, time to next treatment; TTR, time to response.								

Note: *, no separate primary and secondary outcomes were specified; and retrospective study.

Table 105 Overview of study design for studies included in the analyses

Study name	Study phase Study design Blinding Study centre Study country	List of endpoints • Primary • Secondary	Treatment /comparator	Number of patients	Primary diagnosis • MF • SS	Age (years) Median (min–max)	Prior therapy: Me- dian (min–max)	Stages: n (%)
Mogamulizumab based study								
Kim 2018 (MA- VORIC Trial/NCT01728 805) ¹¹	- Phase III - RCT - Open label - Multicentres (61) USA, Denmark, France, Italy, Germany, the Netherlands, Spain, Switzerland, UK, Japan and Australia	- PFS by investigator - Response rates, TTR, Skindex-29, FACT-G, and EQ-5D-3L, safety and tolerabil- ity	Mogamulizumab	186	105 (56) 81 (44) 0	64 (IQR: 54–73)	3 (1–18)	IB–IIA: 36 (19) IIB: 32 (17) IIIA–IIIB: 22 (12) IVA1: 73 (29) IVA2: 19 (10) IVB: 4 (2)

H.1.3 Excluded full-text references

Table 106 provides an overview of the publications excluded at full-text screening and the reason for exclusion.

Table 106 Overview of publications excluded at full-text screening from the SLR

No.	Publication year	Author	Title	Exclusion reason
#1	2019	Ai, W.; Vu, K.; Porcu, P.; Pincus, L.; Wieduwilt, M.; Kaplan, L.; Andreadis, B.; Brammer, J.	Phase I study of romidepsin and liposomal doxorubicin in relapsed or refractory T-cell lymphoma	Comparators

No.	Publication year	Author	Title	Exclusion reason
#2	2019	Bagot, M.; Porcu, P.; Marie-Cardine, A.; Battistella, M.; William, B.M.; Vermeer, M.; Whittaker, S.; Rotolo, F.; Ram-Wolff, C.; Khodadoust, M.S.; Bensussan, A.; Paturel, C.; Bonnafous, C.; Sicard, H.; Azim, H.A.; Kim, Y.H.	IPH4102, a first-in-class anti-KIR3DL2 monoclonal antibody, in patients with relapsed or refractory cutaneous T-cell lymphoma: an international, first-in-human, open-label, phase 1 trial	Comparators
#3	2019	Campbell, B.A.; Ryan, G.; McCormack, C.; Tangas, E.; Bressel, M.; Twigger, R.; Buelens, O.; van der Weyden, C.; Prince, H.M.	Lack of durable remission with conventional-dose total skin electron therapy for the management of sezary syndrome and multiply relapsed mycosis fungoides	Comparators
#4	2020	Dummer, R.; Prince, H.M.; Whittaker, S.; Horwitz, S.M.; Kim, Y.H.; Scarisbrick, J.; Quaglino, P.; Zinzani, P.L.; Wolter, P.; Eradat, H.; Pinter-Brown, L.; Sanches, J.A.; Ortiz-Romero, P.L.; Akilov, O.E.; Geskin, L.; Huen, A.; Walewski, J.; Wang, Y.; Lisano, J.; Richhariya, A.; Feliciano, J.; Zhu, Y.; Bunn, V.; Little, M.; Zagadailov, E.; Dalal, M.R.; Duvic, M.	Patient-reported quality of life in patients with relapsed/refractory cutaneous T-cell lymphoma: Results from the randomised phase III ALCANZA study	Outcomes
#5	2020	Fujimura, Taku; Kambayashi, Yumi; Ohuchi, Kentaro; Amagai, Ryo; Muto, Yusuke; Aiba, Setsuya	Successful treatment of CCR4+ mycosis fungoides palmaris et plantaris with mogamulizumab monotherapy.	Study design
#6	2019	Greko, E.V.; Olisova, O.Y.; Smirnov, K.V.	Puva and interferon α2b combined therapy for patients with mycosis fungoides: A seven-year retrospective study in Russia	Comparators
#7	2019	Hamada, T.; Tokura, Y.; Sugaya, M.; Ohtsuka, M.; Tsuboi, R.; Nagatani, T.; Kiyohara, E.; Tani, M.; Setoyama, M.; Matsushita, S.; Kawai, K.; Yonekura, K.; Saida, T.; Iwatsuki, K.	Long-term efficacy and safety of bexarotene for Japanese patients with cutaneous T-cell lymphoma: The results of a phase 2 study (B-1201)	Population
#8	2020	Huen, A.; Haverkos, B.M.; Zain, J.; Radhakrishnan, R.; Lechowicz, M.J.; Devata, S.; Korman, N.J.; Pinter-Brown, L.; Oki, Y.; Barde, P.J.; Nair, A.; Routhu, K.V.; Viswanadha, S.; Vakkalanka, S.; Iyer, S.P.	Phase i/ib study of tenalisib (Rp6530), a dual pi3k δ/γ inhibitor in patients with relapsed/refractory t-cell lymphoma	Comparators
#9	2019	James, A.M.; Ruckman, J.; Pestano, L.A.; Hopkins, R.D.; Rodgers, R.C.; Marshall, W.S.; Rubin, P.; Escobar, D.	SOLAR: A phase 2, global, randomized, active comparator study to investigate the efficacy and safety of cobomarsen in subjects with mycosis fungoides (MF)	Comparators
#10	2020	Jeans, E.B.; Hu, Y.-H.; Stish, B.J.; King, B.; Davis, M.; Harmsen, W.S.; Fruth, K.M.; Locher, S.E.; Deufel, C.L.; Evans, J.D.; Martenson, J.A.; Lester, S.C.	Low-dose Hypofractionated Total Skin Electron Beam Therapy for Adult Cutaneous T-cell Lymphoma	Comparators

No.	Publication year	Author	Title	Exclusion reason
#11	2020	Kartan, S.; Shalabi, D.; O'Donnell, M.; Alpdogan, S.O.; Sahu, J.; Shi, W.; Porcu, P.; Cha, J.; Nikbakht, N.	Response to Topical Corticosteroid Monotherapy in Mycosis Fungoides	Comparators
#12	2020	Kattner, A.-S.; Holler, E.; Holler, B.; Klobuch, S.; Weber, D.; Martinovic, D.; Edinger, M.; Herr, W.; Wolff, D.	IL6-receptor antibody tocilizumab as salvage therapy in severe chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation: a retrospective analysis	Comparators
#13	2020	Khodadoust, M.S.; Rook, A.H.; Porcu, P.; Foss, F.; Moskowitz, A.J.; Shustov, A.; Shanbhag, S.; Sokol, L.; Fling, S.P.; Ramchurren, N.; Pierce, R.; Davis, A.; Shine, R.; Li, S.; Fong, S.; Kim, J.; Yang, Y.; Blumenschein, W.M.; Yearley, J.H.; Das, B.; Patidar, R.; Datta, V.; Cantu, E.; McCutcheon, J.N.; Karlovich, C.; Mickey Williams, P.; Subrahmanyam, P.B.; Maecker, H.T.; Horwitz, S.M.; Sharon, E.; Kohrt, H.E.; Cheever, M.A.; Kim, Y.H.	Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: A multicenter phase II study	Comparators (later included when eligibility criteria changed)
#14	2019	Kieu, V.; Jhangiani, K.; Dadwal, S.; Nakamura, R.; Pon, D.	Effect of isavuconazole on tacrolimus and sirolimus serum concentrations in allogeneic hematopoietic stem cell transplant patients: A drug-drug interaction study	Comparators
#15	2020	Kim, E.J.; Geskin, L.; Guitart, J.; Querfeld, C.; Girardi, M.; Musiek, A.; Mink, D.R.; Williams, M.J.; Angello, J.T.; Bailey, W.L.	Real-world experience with mechlorethamine gel in patients with mycosis fungoides-cutaneous lymphoma: Preliminary findings from a prospective observational study	Comparators
#16	2020	Ling, Y.-L.; Huang, X.; Mitri, G.; Lovelace, B.; Pham, A.; Knobler, R.; Li, X.; Gao, X.	Real-world use of extracorporeal photopheresis for patients with cutaneous T-cell lymphoma in the United States: 2010–2015	Comparators
#17	2019	Makita, N.; Manaka, K.; Sato, J.; Mitani, K.; Nangaku, M.; Iiri, T.	Bexarotene-induced hypothyroidism: Characteristics and therapeutic strategies	Outcomes
#18	2019	Moskowitz, A.J.; Ghione, P.; Jacobsen, E.D.; Ruan, J.; Schatz, J.H.; Noor, S.; Myskowski, P.; Hancock, H.; Davey, T.; Obadi, O.; Onwasigwe, C.; Ganesan, N.; Pomerantz, L.; Jarjes, C.; Kumar, P.; Sigler, A.; Geyer, M.B.; Noy, A.; Straus, D.J.; Hollmann, T.; Dogan, A.; Galasso, N.; Inghirami, G.; Weinstock, D.M.; Horwitz, S.M.	Final results of a phase II biomarker-driven study of ruxolitinib in relapsed and refractory T-cell lymphoma	Comparators

No.	Publication year	Author	Title	Exclusion reason
#19	2020	Mourad, A.; Gniadecki, R.	Overall Survival in Mycosis Fungoides: A Systematic Review and Meta-Analysis	Comparators
#20	2020	Mukai, M.; Mould, D.; Maeda, H.; Narushima, K.; Greene, D.	Exposure-Response Analysis for Mogamulizumab in Adults With Cutaneous T-Cell Lymphoma	Study design
#21	2019	Scarisbrick, J.; Geskin, L.J.; Bagot, M.; Fisher, D.C.; Elmets, C.; Duvic, M.; Beylot-Barry, M.; Kim, E.J.; Moriya, J.; Leoni, M.; Zinzani, P.L.	Efficacy of mogamulizumab in previously treated patients with less advanced mycosis fungoides: Results from the mavoric study	Comparators
#22	2019	Shimony, S.; Horowitz, N.; Ribakovsky, E.; Rozovski, U.; Avigdor, A.; Zloto, K.; Berger, T.; Avivi, I.; Perry, C.; Abadi, U.; Raanani, P.; Gafter-Gvili, A.; Gurion, R.	Romidepsin treatment for relapsed or refractory peripheral and cutaneous T-cell lymphoma: Real-life data from a national multicenter observational study	Comparators
#23	2019	Sukakul, T.; Nitayavardhana, S.; Janyong, N.; Silpa-Archa, N.; Wongpraparut, C.	Phototherapy for early-stage mycosis fungoides in thais	Comparators
#24	2019	William, B.M.; Abbasi, A.; Huang, Y.; Larbi, R.; Giali, R.; Yang, L.; Brammer, J.; Grantier, C.; Hoffman, C.; Ayyappan, S.; Baiocchi, R.; Epperla, N.; Christian, B.; Alinari, L.; Maddocks, K.; Chung, C.	A phase II trial of brentuximab vedotin (BV) and lenalidomide (LEN) in relapsed and refractory (R/R) cutaneous (CTCL) and peripheral (PTCL) T-cell lymphomas: Preliminary results of a phase II trial	Comparators
#25	2021	Alenezi, F.; Girard, C.; Bessis, D.; Guillot, B.; Du-Thanh, A.; Dereure, O.	Benefit/risk Ratio of Low-dose Methotrexate in Cutaneous Lesions of Mycosis Fungoides and Sézary Syndrome	Population
#26	2021	Alhusayen, R.; Vu, T.T.; Almuhan, N.; Wohlmuth-Wieser, I.; Hardin, J.; Hughes, J.-D.M.; Chia, J.; Street, L.; Shear, N.H.; Walsh, S.R.; Gniadecki, R.	Evaluation of Alitretinoin for the Treatment of Mycosis Fungoides and Sézary Syndrome	Comparators
#27	2021	Bhurani, M.; Admojo, L.; Van Der Weyden, C.; Twigger, R.; Bazargan, A.; Quach, H.; Zimet, A.; Coyle, L.; Lindsay, J.; Radeski, D.; Hawkes, E.; Kennedy, G.; Irving, I.; Gutta, N.; Trotman, J.; Yeung, J.; Dunlop, L.; Hua, M.; Giri, P.; Yuen, S.; Panicker, S.; Moreton, S.; Khoo, L.; Scott, A.; Kipp, D.; McQuillan, A.; McCormack, C.; Dickinson, M.; Prince, H.M.	Pralatrexate in relapsed/refractory T-cell lymphoma: a retrospective multicenter study	Comparators
#28	2021	Cieza-Díaz, Deyss Elizabeth; Machan, Salma; Prieto-Torres, Lucía; Requena, Luis; Córdoba, Raúl	Romidepsin in combination with low-dose methotrexate in advanced-stage mycosis fungoides and Sézary syndrome.	Comparators

No.	Publication year	Author	Title	Exclusion reason
#29	2020	De Brito, M.; Rooke, B.; Clark, F.; Shah, F.; Stevens, A.; Chaganti, S.; Scarisbrick, J.	Interferon alpha-2 is an effective anticutaneous T-cell lymphoma, but drug production has been discontinued	Population
#30	2021	Domingo-Domenech, E.; Duarte, R. F.; Boumedil, A.; Onida, F.; Gabriel, I.; Finel, H.; Arcese, W.; Browne, P.; Beelen, D.; Kobbe, G.; Veelken, H.; Arranz, R.; Greinix, H.; Lenhoff, S.; Poiré, X.; Ribera, J. M.; Thompson, J.; Zuckerman, T.; Mufti, G. J.; Cortelezzi, A.; Olavarria, E.; Dreger, P.; Sureda, A.; Montoto, S.	Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sézary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation.	Comparators
#31	2020	Hamada, T.; Tokura, Y.; Sugaya, M.; Ohtsuka, M.; Tsuboi, R.; Nagatani, T.; Kiyohara, E.; Tani, M.; Setoyama, M.; Matsushita, S.; Kawai, K.; Yonekura, K.; Saida, T.; Iwatsuki, K.	Long-term efficacy and safety of bexarotene for japanese patients with ctcl	Study design
#32	2018	Huen, A.; Porcu, P.; Hudgens, S.; Quaglino, P.; Cowan, R.; Floden, L.; Tsianakas, A.; Leoni, M.; Dale, S.; Duvic, M.	Quality of Life in Cutaneous T-cell Lymphoma Patients Treated with the Anti-CCR4 Monoclonal Antibody Mogamulizumab versus Vorinostat: Results from MAVORIC	Study design
#33	2020	Iyer, S.P.; Huen, A.; Haverkos, B.; Ai, W.Z.; Okada, C.; Kuzel, T.M.; Lechowicz, M.J.; Alderuccio, J.P.; Mohrbacher, A.; Stevens, D.A.; Wilcox, R.A.; Feldman, T.A.; Sundaram, S.; Jagadeesh, D.; Reddy, N.; Routhu, K.V.; Barde, P.; Nair, A.M.	A multi-center, open label, phase I/II study to assess the safety and efficacy of tenalisib given in combination with romidepsin inpatients with relapsed/refractory T-cell lymphoma	Comparators
#34	2020	Karadag, F.K.; Arslan, A.; Pashayev, T.; Soyer, N.A.; Sahin, F.; Vural, F.; TöBü, M.; Saydam, G.	Real experience of brentuximab vedotin for cutaneous T cell lymphomas	Study design
#35	2020	Kim, Y.H.; Khodadoust, M.S.; De Masson, A.; Moins-Teisserenc, H.; Ito, T.; Dwyer, K.; Herr, F.; Bagot, M.	Patient characteristics of long-term responders tomogamulizumab: Results from the mavoric study	Study design
#36	2018	Molloy, K.; Evison, F.; Peng, C.; Guenova, E.; Cowan, R.; Busschots, A.; Woei-A-Jin, S.H.; Bervoets, A.; Hauben, E.; Beylot-Barry, M.; Jonak, C.; Knobler, R.; Pokert, S.; Papadavid, E.; Vakeva, L.; Matin, R.; Bates, A.; Estrach, T.; Prince, M.; Twigger, R.; Berti, E.; Violetti, S.A.; Bayne, M.; McKay, P.; Wachsmuch, R.; Akilov, O.; McCann, S.; Damasco, F.; Sanches, J.A.;	Quality of life in patients with mycosis fungoides and Sezary syndrome is significantly worse in female patients, Sézary syndrome and those with more extensive skin involvement	Study design

No.	Publication year	Author	Title	Exclusion reason
		Miyashiro, D.; Cury-Martins, J.; Turner, D.; Wobser, M.; Benstead, K.; Yoo, J.; Scarisbrick, J.		
#37	2021	Molloy, K.; Vico, C.; Ortiz-Romero, P.L.; Scarisbrick, J.J.	Real-world experience of using mogamulizumab in relapsed/refractory mycosis fungoides/Sézary syndrome	Study design
#38	2020	Musiek, A.C.M.; Whittaker, S.; Horwitz, S.M.; Bagot, M.; Huen, A.; Fisher, D.C.; Haun, P.; Vermeer, M.H.; Ito, T.; Dwyer, K.; Herr, F.; Kim, Y.H.	Characterization and outcomes in patients with mogamulizumab-associated skin reactions in the mavoric trial	Study design
#40	2021	Newman, N.B.; Patel, C.G.; Ding, G.X.; Zic, J.A.; Zwerner, J.; Osmundson, E.C.; Kirschner, A.N.	Prospective observational trial of low-dose skin electron beam therapy in mycosis fungoides using a rotational technique	Study design
#41	2020	Novelli, S.; Martín, A.; Sánchez, J.J.; Espeso, M.; Mozos, A.; Briones, J.	Management experience of advanced-stage mycosis fungoides/Sézary syndrome: a retrospective study from Spanish haematology referral units	Comparators
#42	2020	Oberic, Lucie; Delzor, Faustine; Protin, Caroline; Perriat, Sophie; Laurent, Camille; Grand, Anaïs; Canonge, Jean Marie; Borel, Cécile; Gauthier, Martin; Ysebaert, Loïc; Puisset, Florent	Brentuximab vedotin in real life, a seven year experience in patients with refractory/relapsed CD30+ T cell lymphoma.	Population
#43	2020	Pileri, A.; Fava, P.; Gunnella, S.; Guglielmo, A.; Astrua, C.; Grandi, V.; Simontacchi, G.; Patrizi, A.; Quaglino, P.; Pimpinelli, N.	Bexarotene as maintenance treatment after other than skin-directed therapy in advanced stage mycosis fungoides: A pilot study	Population
#44	2015	Polansky, M.; Talpur, R.; Daulat, S.; Hosing, C.; Dabaja, B.; Duvic, M.	Long-term complete responses to combination therapies and allogeneic stem cell transplants in patients with Sézary syndrome	Comparators
#45	2018	Porcu, P.; Hudgens, S.; Quaglino, P.; Cowan, R.; Floden, L.; Tsianakas, A.; Leoni, M.; Dale, S.; Duvic, M.	Quality of life in cutaneous T cell lymphoma patients treated with the anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat: Results from MAVORIC	Study design
#46	2020	Puchinskaya, M.; Dziamidava, S.; Baranau, Y.	T-cell lymphomas (TCL): Real-world experience analysis from cancer registry	Study design
#47	2020	Querfeld, C.; Tsai, N.-C.; Palmer, J.; Martinez, X.U.; Abdulla, F.; Wu, X.; Rosen, S.T.; Zain, J.	Phase 1 results of anti-PD-ligand 1 (Durvalumab) & lenalidomide in patients with cutaneous T cell lymphoma and correlation with programmed death ligand 1 expression and gene expression profile	Comparators

No.	Publication year	Author	Title	Exclusion reason
#48	2020	Querfeld, C.; William, B.M.; Sokol, L.; Akilov, O.; Poligone, B.; Zain, J.; Tagaya, Y.; Azimi, N.	Co-inhibition of IL-2, IL-9 and IL-15 by the novel immunomodulator, BNZ-1, provides clinical efficacy in patients with refractory cutaneous t cell lymphoma in a phase 1/2 clinical trial	Comparators
#49	2019	Samie, Faramarz H.	Acute toxicity and risk of infection during total skin electron beam therapy for mycosis fungoides.	Comparators
#50	2021	Thompson, L.L.; Pan, C.X.; Chang, M.S.; Molina, G.E.; Chen, Y.B.; Barnes, J.A.; Chen, S.T.	Alemtuzumab, total skin electron beam, and non-myeloablative allogeneic haematopoietic stem-cell transplantation in advanced sezary syndrome: a retrospective cohort study	Comparators
#51	2021	Walker, C.J.; Espinosa, M.L.; Mehta-Shah, N.; Pro, B.; Guitart, J.; Kuzel, T.	Clinical Trial of High-Dose Pegylated-Interferon-Alfa-2b Combined With Phototherapy in Advanced Stage Mycosis Fungoides	Comparators
#52	2020	Zinzani, P.L.; Horwitz, S.M.; Kim, Y.H.; Moskowitz, A.J.; Porcu, P.; Scarisbrick, J.; Leoni, M.; Dwyer, K.; Sun, W.; Nikonova, E.; Bagot, M.	Efficacy of mogamulizumab by prior systemic therapy in patients with previously treated cutaneous T-cell lymphoma in the phase 3 mavoric study	Study design
#53	2021	Cariti, C.; Quaglino, P.; Lupia, T.; Novelli, M.; Marra, E.; Fava, P.; Caliendo, V.; Tonella, L.; De Rosa, F.G.; Fierro, M.T.; Ribero, S.	Infections in Sézary syndrome: A retrospective cohort study of 113 patients	Study design
#54	2021	Huang, X.; Shamseddine, N.; Boing, E.; Fahim, M.; Zhou, H.; Covassin, L.	Real-world use of extracorporeal photopheresis among patients with mycosis fungoides or sezary syndrome: Analysis of a large us commercial claims database	Comparators
#55	2021	Nguyen, M.; LeWitt, T.; Pang, Y.; Espinosa, M.; Pontes, D.; Guitart, J.; Liszewski, W.; Zhou, X.	282 Lifestyle and demographic risk factors in mycosis fungoides and Sezary syndrome: A single institution cohort study	Study design
#56	2021	Severson, K.J.; Cumsy, H.J.L.; Brumfiel, C.M.; Janeczek, M.C.; Ginos, B.F.; Kosiorek, H.E.; Besch-Stokes, J.; Patel, M.H.; Rule, W.G.; DiCaudo, D.J.; Rosenthal, A.C.; Pittelkow, M.R.; Mangold, A.R.	Blue light photodynamic therapy with 5-aminolevulinic acid in refractory mycosis fungoides: A prospective, open-label study	Comparators
#57	2022	Alexander-Savino, C. V.; Chung, C. G.; Gilmore, E. S.; Carroll, S. M.; Poligone, B.	Randomized Mechlorethamine/Chlormethine Induced Dermatitis Assessment Study (MIDAS) Establishes Benefit of Topical Triamcinolone 0.1% Ointment Cotreatment in Mycosis Fungoides	Comparators

No.	Publication year	Author	Title	Exclusion reason
#58	2023	Alghubaywi, F. A.; Alharthi, S. A.; Aldharman, S. S.; Najjar, R. H.; Aleissa, M. Y.; Aljarbou, O. Z.; AlJasser, M. I.; Almohideb, M. A.	Clinicopathologic characteristics and outcomes of patients with mycosis fungoides	Comparators
#59	2022	Amagai, R.; Kambayashi, Y.; Ohuchi, K.; Furudate, S.; Hashimoto, A.; Asano, Y.; Fujimura, T.	Cutaneous T cell lymphoma treated with mogamulizumab monotherapy and mogamulizumab plus etoposide combined therapy: A real-world case series	Study design
#60	2023	Amitay-Laish, I.; Naveh, H. P.; Holzman, R.; Baker, A. A.; Raviv, A.; Friedland, R.; Amitai, D. B.; Reiter, O.; David, M.; Hodak, E.	Ultraviolet A Combined with Narrow-Band Ultraviolet B is an Effective Treatment Modality for Early Folliculotropic Mycosis Fungoides and Early Mycosis Fungoides Refractory to Narrow-Band Ultraviolet B: A Retrospective Cohort Study	Comparators
#61	2023	Assaf, C.; Illidge, T. M.; Waser, N.; He, M.; Li, T.; Zomas, A.; Bent-Ennakhil, N.; Little, M.; Ortiz-Romero, P. L.; Pimpinelli, N.; Dalal, M.; Bagot, M.	A Retrospective Chart Review of Treatment Patterns and Overall Survival among a Cohort of Patients with Relapsed/Refractory Mycosis Fungoides in France, Germany, Italy, Spain and the United Kingdom	Comparators
#62	2022	Assaf, C.; Waser, N.; Bagot, M.; He, M.; Li, T.; Dalal, M.; Gavini, F.; Trinchese, F.; Zomas, A.; Little, M.; Pimpinelli, N.; Ortiz-Romero, P. L.; Illidge, T. M.	Contemporary treatment patterns and response in relapsed/refractory cutaneous T-cell lymphoma (CTCL) across five european countries	Comparators
#63	2021	Aubrais, R.; Chartier, L.; Herbaux, C.; Banos, A.; Brice, P.; Ochmann, M.; Sibon, D.; De Colella, J. M. S.; Cluzeau, T.; Laribi, K.; Calloch, R. L.; Bellal, M.; Daguindau, N.; Amorim, S.; Agbetiafa, K.; Chauchet, A.; Hammami, M.; Durot, E.; Bonnet, C.; Robles, M.; Fouillet, L.; Bijou, F.; Tournilhac, O.; Gaulard, P.; Parrens, M.; Milpied, N. J.; Damaj, G. L.	Salvage therapy with brentuximab-vedotin and bendamustine for patients with relapsed/refractory T cell lymphoma. A multicenter and retrospective study krmo bouabdallah	Population
#64	2023	Awh, K.; Jfri, A.; Fay, C.; Virgen, C.; Tawa, M.; Giobbie-Hurder, A.; Kupper, T.; Fisher, D.; LeBoeuf, N.; Larocca, C.	PREVALENCE and IMPLICATIONS of MOGAMULIZUMAB-INDUCED IMMUNE-RELATED ADVERSE EVENTS in CUTANEOUS T-CELL LYMPHOMA: A SINGLE CENTER EXPERIENCE	Outcomes
#65	2021	Bagot, M.; Kim, Y.; Zinzani, P. L.; Dalle, S.; Beylot-barry, M.; L Ortiz-Romero, P.; Cambalia, A.; Dereure, O.; Mortier, L.; Jacobsen, E.; Rotolo, F.; Azim, H. A.; Porcu, P.	Lacutamab in patients (PTS) with advanced mycosis fungoides (MF) according to KIR3DL2 expression: Early results from the tellomak phase 2 trial	Comparators

No.	Publication year	Author	Title	Exclusion reason
#66	2021	Bagot, M.; Kim, Y.; Zinzani, P. L.; Dalle, S.; Beylot-Barry, M.; Ortiz-Romero, P. L.; Cambalia, A.; Dereure, O.; Mortier, L.; Jacobsen, E.; Battistella, M.; Gru, A.; Moins-Teisserenc, H.; Paiva, C.; Boyer-Chammard, A.; Rotolo, F.; Azim, H. A.; Porcu, P.	Lacutamab in patients (pts) with advanced mycosis fungoides (MF) according to KIR3DL2 expression: early results from the TELLOMAK phase 2 trial	Comparators
#67	2023	Bagot, M.; Kim, Y. H.; Geskin, L. J.; Ortiz-Romero, P. L.; Kim, E.; Mehta-Shah, N.; Dereure, O.; Oro, S.; Beylot-Barry, M.; Dalle, S.; Jacobsen, E.; Lansigan, F.; Ram-Wolff, C.; Khodadoust, M. S.; Battistella, M.; Gru, A. A.; Moins-Teisserenc, H.; Zinzani, P. L.; Viotti, J.; Paiva, C.; Muller, M.; Porcu, P.	Lacutamab in Patients with Relapsed and Refractory Sèzary Syndrome: Results from the Tellomak Phase 2 Trial	Comparators
#68	2023	Bagot, M.; Kim, Y. H.; Ortiz-Romero, P. L.; Zinzani, P. L.; Beylot-Barry, M.; Dalle, S.; Jacobsen, E.; Combalia, A.; Huen, A.; Mehta-Shah, N.; Khodadoust, M.; Mehta, A.; Dereure, O.; Battistella, M.; Gru, A.; Moins-Teisserenc, H.; Viotti, J.; Paiva, C.; Boyer-Chammard, A.; Porcu, P.	Lacutamab in patients with mycosis fungoides: efficacy results according to updated lymph node classification in the TELLOMAK study	Comparators
#69	2022	Bagot, M.; Kim, Y. H.; Ortiz-Romero, P. L.; Zinzani, P. L.; Mehta-Shah, N.; Dereure, O.; Beylot-Barry, M.; Dalle, S.; Jacobsen, E. D.; Huen, A.; Combalia, A.; Battistella, M.; Gru, A. A.; Moins-Teisserenc, H.; Khodadoust, M. S.; Viotti, J.; Paiva, C.; Muller, M.; Porcu, P.	Lacutamab in Patients with Advanced Sezary Syndrome: Results from an Interim Analysis of the Tellomak Phase 2 Trial	Comparators
#70	2022	Barta, S. K.; Feldman, T. A.; DeSimone, J. A.; Kim, E.; Devajaran, K.; Yang, Y.; Fung, H. C.; Mahvish, T.; Nakhoda, S.; Khan, N.	A Phase I Trial Assessing the Feasibility of Romidepsin Combined with Brentuximab Vedotin for Patients Requiring Systemic Therapy for Cutaneous T-Cell Lymphoma	Population
#77	2024	Barta, S. K.; Liu, N.; DerSarkissian, M.; Chang, R.; Ye, M.; Duh, M. S.; Surinach, A.; Fanale, M.; Yu, K. S.	Real-World Treatment Patterns and Clinical Outcomes With Brentuximab Vedotin or Other Standard Therapies in Patients With Previously Treated Cutaneous T-Cell Lymphoma in the United States	Population
#78	2022	Barta, S. K.; Liu, N.; DerSarkissian, M.; Chang, R.; Ye, M.; Duh, M. S.; Surinach, A.; Fanale, M. A.; Yu, K. S.	Real-World Treatment Patterns and Clinical Outcomes with Brentuximab Vedotin or Other Standard Therapies in Patients with Previously Treated Cutaneous T-Cell Lymphoma (CTCL): A Retrospective Chart Review Study in the United States	Duplicate

No.	Publication year	Author	Title	Exclusion reason
#79	2024	Bazewicz, C.; Verardi, N.; Akilov, O.	Utility of Low-Dose Duvelisib for Advanced Mycosis Fungoides: A Single-Institution Study	Comparators
#80	2023	Behkami, N.; Altan Ferhatoğlu, Z.	Evaluation of the Effect of Phototherapy Treatment on Dermatology Quality of Life Index	Comparators
#81	2023	Bennani, N. N.; Cook, J.; Peng, K. W.; Geyer, S. M.; Ginos, B. F.; Zhang, L.; Macapagal, S. C.; Witzig, T. E.; Munoz, J.; Broski, S. M.; Russell, S. J.; Lacy, M.	Systemic VSV-IFN β -NIS oncolytic virotherapy in patients with relapsed refractory T-cell lymphoma	Comparators
#82	2021	Beylot-Barry, M.; Booken, N.; Weishaupt, C.; Medley, M.; Sun, W.; Rosen, J. P.	Efficacy of mogamulizumab in mycosis fungoides by patient blood involvement and time to response analysis in mycosis fungoides and Sézary syndrome: a post hoc analysis of the MAVORIC study	Outcomes
#83	2022	Beylot-Barry, M.; Booken, N.; Weishaupt, C.; Medley, M.; Sun, W.; Rosen, J. P.	Efficacy of Mogamulizumab in Mycosis Fungoides by Patient Blood Involvement and Time to Response Analysis in Mycosis Fungoides and Sézary Syndrome: A post hoc analysis of the MAVORIC Study	Outcomes
#84	2023	Beylot-Barry, M.; Booken, N.; Weishaupt, C.; Scarisbrick, J.; Wu, W.; Rosen, J. P.; Medley, M. C.	Impact of blood involvement on efficacy and time to response with mogamulizumab in mycosis fungoides and Sézary syndrome	Outcomes
#85	2023	Beylot-Barry, M.; Quereux, G.; Nardin, C.; Duval-Modeste, A. B.; Dereure, O.; Dalac-Rat, S.; Dobis, G.; Pham-Ledard, A.; Ram-Wolff, C.; D'Incan, M.; Grange, F.; Braniste, V.; Bagot, M.	Efficacy and tolerability of mogamulizumab in patients with mycosis fungoides or Sézary syndrome: retrospective and real-world data from centres of the French Study Group of Cutaneous Lymphoma	Duplicate
#86	2021	Beylot-Barry, M.; Quereux, G.; Nardin, C.; Duval-Modeste, A. B.; Dereure, O.; Dalac-Rat, S.; Dobos, G.; Pham-Ledard, A.; Ram-Wolff, C.; D'Incan, M.; Grange, F.; Braniste, V.; Bagot, M.	French real-life retrospective study in patients with mycosis fungoides and Sezary syndrome treated by mogamulizumab	Duplicate
#87	2022	Blazejak, C.; Stranzenbach, R.; Gosman, J.; Gambichler, T.; Wehkamp, U.; Stendel, S.; Klemke, C. D.; Wobser, M.; Olk, J.; Nicolay, J. P.; Weyermann, M.; Stadler, R.; Assaf, C.	Clinical Outcomes of Advanced-Stage Cutaneous Lymphoma under Low-Dose Gemcitabine Treatment: Real-Life Data from the German Cutaneous Lymphoma Network	Population

No.	Publication year	Author	Title	Exclusion reason
#88	2021	Bouabdallah, K.; Aubrais, R.; Chartier, L.; Herbaux, C.; Banos, A.; Brice, P.; Ochmann, M.; Sibon, D.; Schiano De Colella, J. M.; Cluzeau, T.; Laribi, K.; Le Calloch, R.; Bellal, M.; Daguindau, N.; Amorim, S.; Agbetiafa, K.; Chauchet, A.; Hammami, M.; Durot, E.; Bonnet, C.; Robles, M.; Fouillet, L.; Bijou, F.; Tournilhac, O.; Gaulard, P.; Parrens, M.; Milpied, N. J.; Damaj, G. L.	Salvage Therapy with Brentuximab-Vedotin and Bendamustine for Patients with Relapsed/Refractory T Cell Lymphoma. a Multicenter and Retrospective Study	Population
#89	2023	Braunstein, Z.; Waller, A.; Dotson, E.; McLaughlin, E.; Hanel, W.; Reneau, J. C.; Addison, D.; Porcu, P.; Brammer, J. E.	Gemcitabine and Liposomal Doxorubicin (GemDox) for the Treatment of Relapsed and Refractory T-Cell Lymphomas	Duplicate
#90	2023	Campbell, B. A.; Dobos, G.; Haider, Z.; Prince, H. M.; Bagot, M.; Evison, F.; van der Weyden, C.; McCormack, C.; Ram-Wolff, C.; Miladi, M.; Scarisbrick, J. J.	International study of treatment efficacy in SS shows superiority of combination therapy and heterogeneity of treatment strategies	Population
#91	2024	Chang, C.; Ristuccia, R.; Zheng, Z.; Takahashi, T.; Nomura, T.; Dennis, E.	Real-world Use of Mogamulizumab Among Patients With Mycosis Fungoides and Sézary Syndrome Before and During COVID-19 in the United States	Outcomes
#92	2024	Christensen, E.; Foss, O. A.; Holien, T.; Juzenas, P.; Peng, Q.	Application of Photodynamic Therapy with 5-Aminolevulinic Acid to Extracorporeal Photopheresis in the Treatment of Cutaneous T-Cell Lymphoma: A First-in-Human Phase I/II Study †	Study design
#93	2023	D'Onghia, M.; Cartocci, A.; Calabrese, L.; Maio, D.; Sirchio, A.; Erasti, M.; Tognetti, L.; Rubegni, P.; Bocchia, M.; Cencini, E.; Fabbri, A.; Cinotti, E.	Characteristics of Primary Cutaneous Lymphoma in Italy: A Tertiary Care, Single-Center Study	Outcomes
#94	2023	Dawson, M. A.; Borthakur, G.; Huntly, B. J. P.; Karadimitris, A.; Alegre, A.; Chaidos, A.; Vogl, D. T.; Pollyea, D. A.; Davies, F. E.; Morgan, G. J.; Glass, J. L.; Kamdar, M.; Mateos, M. V.; Tovar, N.; Yeh, P.; Delgado, R. G.; Basheer, F.; Marando, L.; Gallipoli, P.; Wyce, A.; Krishnatry, A. S.; Barbash, O.; Baskirtzi, E.; Ferron-Brady, G.; Karpnich, N. O.; McCabe, M. T.; Foley, S. W.; Horner, T.; Dhar, A.; Kremer, B. E.; Dickinson, M.	A Phase I/II Open-Label Study of Molibresib for the Treatment of Relapsed/Refractory Hematologic Malignancies	Comparators
#95	2021	de Masson, A.; Dangien, A.; Ram-Wolff, C.; Battistella, M.; Moins-Teissier, H.; Bagot, M.	Ifosfamide and etoposide in advanced-stage, relapsed or refractory primary cutaneous T-cell lymphomas	Comparators

No.	Publication year	Author	Title	Exclusion reason
#96	2021	de Vos, S.; Leonard, J. P.; Friedberg, J. W.; Zain, J.; Dunleavy, K.; Humerick-house, R.; Hayslip, J.; Pesko, J.; Wilson, W. H.	Safety and efficacy of navitoclax, a BCL-2 and BCL-XL inhibitor, in patients with relapsed or refractory lymphoid malignancies: results from a phase 2a study	Comparators
#97	2024	Desai, P.; Lonial, S.; Cashen, A.; Kamdar, M.; Flinn, I.; O'Brien, S.; Garcia, J. S.; Korde, N.; Moslehi, J.; Wey, M.; Cheung, P.; Sharma, S.; Olabode, D.; Chen, H.; Syed, F. A.; Liu, M.; Saeh, J.; Andrade-Campos, M.; Kadia, T. M.; Blachly, J. S.	A Phase 1 First-in-Human Study of the MCL-1 Inhibitor AZD5991 in Patients with Relapsed/Refractory Hematologic Malignancies	Comparators
#98	2022	Di Raimondo, C.; Vaccarini, S.; Nunzi, A.; Rapisarda, V.; Zizzari, A.; Meconi, F.; Monopoli, A.; Narducci, M. G.; Scala, E.; Bianchi, L.; Tesei, C.; Cantonetti, M.	Continuous low-dose gemcitabine in primary cutaneous T cell lymphoma: A retrospective study	Comparators
#99	2023	Dong, N.; Jaiswal, S.; Khadka, S.; Francisque, C.; Zhang, Y.; Glass, L.; Benson, K.; Liu, H.; Sokol, L.	A Retrospective Study of Extracorporeal Photopheresis (ECP) in Treatment of Cutaneous T-Cell Lymphoma (CTCL) Evaluating Global, Skin and Blood Responses	Population
#100	2021	Dwyer, K.; Meier, R.; Hruska, M.; Fox, F.; Ito, T.	Open-label, phase 2 study to assess the safety of mogamulizumab at 2 mg/kg Q4W maintenance dosing in patients with relapsed/ refractory MF/SS subtypes of CTCL	Outcomes
#101	2024	Elghawy, O.; Yang, A. G.; Sussman, J. H.; Thomas, C. J.; Carter, J. S.; Landsburg, D. J.; Svoboda, J.; Kim, E.; Rook, A. H.; Chung, J.; Villasenor-Park, J.; Plataras, J. P.; LaRiviere, M.; Hubbeling, H.; Chelius, M.; Nasta, S. D.; Chong, E. A.; Schuster, S. J.; Barta, S. K.	Retrospective cohort study of novel oral agents lenalidomide and duvelisib for relapsed or refractory mycosis fungoides and Sézary syndrome	Comparators
#102	2023	Elsayad, K.; Weishaupt, C.; Moustakis, C.; Danzer, M. F.; Müller, E. C.; Rolf, D.; Stranzenbach, R.; Livingstone, E.; Booken, N.; Stadler, R.; Eich, H. T.	Ultrahypofractionated Low-Dose Total Skin Electron Beam in Advanced-Stage Mycosis Fungoides and Sézary Syndrome	Population
#103	2022	Falkenhain-López, D.; Puerta-Peña, M.; Fulgencio-Barbarin, J.; Sánchez-Velázquez, A.; Vico-Alonso, C.; Postigo-Llorente, C.; Ortiz-Romero, P. L.	Real-life experience of using pegylated liposomal doxorubicin in primary cutaneous T-cell lymphomas	Comparators
#104	2024	Fleischli, A.; Pierog, O.; Rozati, S.	Dupilumab and other biologic therapies may influence the course and prognosis of cutaneous-T cell lymphoma	Comparators

No.	Publication year	Author	Title	Exclusion reason
#105	2023	Foley, N.; Minor, C.; Musiek, A.; Mehta-Shah, N.	Mogamulizumab-Associated Rash in Patients With Mycosis Fungoides and Sézary Syndrome	Comparators
#106	2024	Garfinkel, V.; Reisch, J. S.; Goff, H. W.	A Retrospective Comparison Between Home and in-Office NB-UVB Efficacy for Patients With Mycosis Fungoides	Comparators
#107	2021	Geskin, L. J.; Kim, E. J.; Angello, J. T.; Kim, Y. H.	Evaluating the Treatment Patterns of Chloromethine/Mechlorethamine Gel in Patients With Stage I-IIA Mycosis Fungoides: By-time Reanalysis of a Randomized Controlled Phase 2 Study	Comparators
#108	2024	Girardi, M.; Carlson, K.; Huang, X.; Corman, S. L.; Edmundson, P.; Schmier, J.; Kale, H. P.; Raina, R.; Foss, F.	Chart review study of real-world clinical outcomes in patients with cutaneous T-cell lymphoma treated with extracorporeal photopheresis in the US in 2017–2019	Population
#109	2022	Gökşin, Ş.; İmren, I. G.; Cenk, H.; Kaçar, N.; Duygulu, Ş.	The use of interferon-α2a as monotherapy in stage IB patients with mycosis fungoides: A retrospective chart review of patient outcomes	Comparators
#110	2024	Gordon, M.; Miljkovic, M.; Ng, S.; Lakhota, R.; Melani, C.; Conlon, K.; Phe-lan, J.; Bryant, B.; Pittaluga, S.; Jaffe, E.; Staudt, L.; Wilson, W.; Roschewski, M.	A phase 1 study of romidepsin, azacitidine, dexamethasone, and lenalidomide (RADR) for relapsed/refractory Tcell malignancies	Comparators
#111	2024	Gorenkova, L. G.; Zvonkov, E. E.; Mangasarova, Y. K.; Chabaeva, Y. A.; Kuli-kov, S. M.; Kovrigina, A. M.; Kuzmina, L. A.; Sidorova, Y. V.; Mozdon, M. A.	Clinical profile and therapeutic aspects of mycosis fungoides: a retrospective analysis of 210 cases in Russia	Language
#112	2023	Grandi, V.; Morsia, E.; Zizzari, A.; Loseto, G.; Fava, P.; Macagno, N.; Violetti, S. A.; Cavallaro, F.; Pileri, A.; Broccoli, A.; Vitiello, P.; Sica, A.; Palazzo, M.; Nassi, L.; Quaglino, P.; Rupoli, S.; Berti, E.; Onida, F.; Zinzani, P. L.; Pimpinelli, N.	Standard brentuximab vedotin schedule vs early discontinuation on clinician's decision in patients with CTCL: a multicenter, retrospective study from the FIL Cutaneous Lymphomas Task Force	Population
#113	2022	Grandi, V.; Simontacchi, G.; Grassi, T.; Pileri, A.; Pimpinelli, N.	Short-term efficacy and safety of total skin electron beam therapy in mycosis fungoides: Systematic review and meta-analysis	Study design
#114	2023	Hamada, T.	594 Relevant factors for dosing period of bexarotene treatment in Japanese patients with mycosis fungoides: A post-hoc analysis from accumulated post-marketing surveillance data	Study design

No.	Publication year	Author	Title	Exclusion reason
#115	2023	Hamed, R.; Hamadah, A.; Alshemmari, S.; Abdulazez, O.; Nanda, A.; Pinto, K.; Lafi, A. A.; Rajy, J.; Al-Sabah, H.	Treatment of relapsed/refractory, and advanced stage of mycosis fungoides with brentuximab vedotin (BV): an experience from Kuwait	Population
#116	2024	Hansen-Abeck, I.; Geidel, G.; Abeck, F.; Kött, J.; Cankaya, R.; Dobos, G.; Mitteldorf, C.; Nicolay, J. P.; Albrecht, J. D.; Menzer, C.; Livingstone, E.; Mengoni, M.; Braun, A. D.; Wobser, M.; Klemke, C. D.; Tratzmiller, S.; Assaf, C.; Terheyden, P.; Klespe, K. C.; Schneider, S. W.; Booken, N.	Pegylated interferon-α2a in cutaneous T-cell lymphoma – a multicenter retrospective data analysis with 70 patients	Population
#117	2024	Hirai, Y.; Sakurai, J.; Yoshida, S.; Kikuchi, T.; Mitsunashi, T.; Miyake, T.; Fujimura, T.; Abe, R.; Fujikawa, H.; Boki, H.; Suga, H.; Shibata, S.; Miyagaki, T.; Shimauchi, T.; Kiyohara, E.; Kawakami, Y.; Morizane, S.	Phase I/II clinical trial of brentuximab vedotin for pretreated Japanese patients with CD30-positive cutaneous T-cell lymphoma	Population
#118	2021	Horwitz, S. M.; Foran, J. M.; Maris, M.; Lue, J. K.; Sawas, A.; Okada, C.; Feldman, T. A.; Sokol, L.; Mei, M.; Flinn, I. W.; Villa, D.; Percival, M. E. M.; Jagadeesh, D.; Savage, K. J.; Akilov, O.; Diefenbach, C. S.; Kim, Y. H.; Lin, G. H. Y.; Catalano, T.; Petrova, P. S.; Uger, B.; Molloy, N.; Large, K.; Bruns, I.; Ansell, S. M.	Updates from ongoing, first-in-human phase 1 dose escalation and expansion study of TTI-621, a novel biologic targeting CD47, in patients with relapsed or refractory hematologic malignancies	Comparators
#119	2022	Hu, B.; Atrash, S.; Cohen, L.; Barta, S. K.; Zhang, Y.; Sokol, L.; Ayers, A.; Malpica Castillo, L. E.; Hwang, S. R.; Bennani, N. N.; Wada, D.; Tun, A. M.; Moyo, T. K.; Ghosh, N.; Shinohara, M. M.	Mogamulizumab-Associated Rash (MAR) Correlates with Longer Progression Free Survival in Cutaneous T Cell Lymphoma (CTCL)	Population
#120	2021	Iyer, S. P.; Huen, A.; Ai, W. Z.; Jagadeesh, D.; Lechowicz, M. J.; Okada, C.; Feldman, T. A.; Sundaram, S.; Alderuccio, J. P.; Reddy, N.; Stevens, D.; Kuzel, T. M.; Mohrbacher, A.; Routhu, K. V.; Barde, P.; Nair, A. M.; Haverkos, B. M.	Safety and efficacy of tenalisib given in combination with romidepsin in patients with relapsed/refractory T-cell lymphoma: Final results from a phase I/II open label multi-center study	Comparators
#121	2024	Izu-Belloso, R.; Gainza-Apraiz, I.; Ortiz-Romero, P.; Servitje-Bedate, O.; Fernández de Misa-Cabrera, R.; Peñate, Y.; Hernandez-Machin, B.; Estrach-Panella, T.; Llamas-Velasco, M.; Yanguas-Bayona, J. I.; Morillo-Andujar, M.; Acebo-Mariñas, E.; Perez-Gala, S.; Armario-Hita, J. C.; Sanchez-Sambucety, P.; Ortiz-Brugues, A.; Eguren-Michelena, C.; Bielsa-Marsol, I.; Lopez-Pestaña, A.; Blanes-Martinez, M.; Fernandez-Guarino, M.; Lopez-Lerma, I.	Experience With Bexarotene to Treat Cutaneous T-Cell Lymphomas: A Study of the Spanish Working Group of Cutaneous Lymphomas	Population

No.	Publication year	Author	Title	Exclusion reason
#122	2022	Jagadeesh, D.; Horwitz, S.; Bartlett, N. L.; Kim, Y.; Jacobsen, E.; Duvic, M.; Little, M.; Trepicchio, W.; Fenton, K.; Onsum, M.; Lisano, J.; Advani, R.	Response to Brentuximab Vedotin by CD30 Expression in Non-Hodgkin Lymphoma	Study design
#123	2021	Kaemmerer, T.; Stadler, P. C.; Helene Frommherz, L.; Guertler, A.; Einar French, L.; Reinholz, M.	Alitretinoin in the treatment of cutaneous T-cell lymphoma	Population
#124	2021	Khan, N.; Noor, S.; Geller, S.; Khodadoust, M. S.; Kheterpal, M.; Hancock, H.; Davey, T.; Ryu, S.; Perez, L.; Lares, A.; Ganesan, N.; Sohail, S.; Santarosa, A.; Galasso, N.; Kim, E.; Myskowski, P.; Kim, Y. H.; Horwitz, S.; Moskowitz, A.	A phase II trial of reduced dose brentuximab vedotin for cutaneous t-cell lymphomas	Population
#125	2021	Kim, E. J.; Guitart, J.; Querfeld, C.; Girardi, M.; Musiek, A.; Akilov, O. E.; Angello, J. T.; Bailey, W. L.; Geskin, L. J.	The PROVe Study: US Real-World Experience with Chlormethine/Mechlorethamine Gel in Combination with Other Therapies for Patients with Mycosis Fungoides Cutaneous T-Cell Lymphoma	Comparators
#126	2022	Kim, Y.; Bagot, M.; Luigi Zinzani, P.; Morris, S.; Ortiz-Romero, P.; Magnolo, N.; Scarisbrick, J.; Dalle, S.; Quaglino, P.; Dréno, B.; Beylot-Barry, M.; Caballero, D.; Cowan, R.; Dummer, R.; Iversen, L.; Vermeer, M.; Nicolay, J.	SAFETY OF MOGAMULIZUMAB IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME: FINAL RESULTS FROM THE PHASE 3 MAVORIC STUDY	Duplicate
#127	2022	Laghi, A.; Franceschini, C.; Mandel, V. D.; Teoli, M.; Musicco, F.; Sansone, M.; La Malfa, A. M.; Ardigò, M.	Topical chlormethine gel in the treatment of mycosis fungoides: A single-center real-life experience and systematic review of the literature	Comparators
#128	2025	Lavin, L.; Dusza, S.; Geller, S.	Cutaneous T-Cell Lymphoma after Dupilumab Use: A Real-World Pharmacovigilance Study of the FDA Adverse Event Reporting System	Comparators
#129	2022	Leupin, N.; Zinzani, P. L.; Morschhauser, F.; Dalle, S.; Maerevoet, M.; Michot, J. M.; Ribrag, V.; Offner, F.; Beylot-Barry, M.; Moins-Teisserenc, H.; Zwaenepoel, K.; de Winne, K.; Battistella, M.; Hultberg, A.; Gandini, D.; Moshir, M.; Jacobs, J.; Delahaye, T.; Khan, A.; Zabrocki, P.; Silence, K.; van Rompaey, L.; Borg, C.; Motta, G.; Melle, F.; Calleri, A.; Pauwels, P.; de Haard, H.; Pileri, S.; Bagot, M.	Cusatuzumab for treatment of CD70-positive relapsed or refractory cutaneous T-cell lymphoma	Comparators
#130	2023	Melchers, S.; Albrecht, J. D.; Zhao, J.; Gülow, G.; Schürch, C. M.; Krammer, P. H.; Nicolay, J. P.	Translational data from a multicenter phase II study on dimethyl fumarate treatment in relapsed and refractory cutaneous T cell lymphoma	Comparators

No.	Publication year	Author	Title	Exclusion reason
#131	2022	Michot, J. M.; Mehta, A.; Samaniego, F.; Bachy, E.; Zinzani, P. L.; Prica, A.; Colins, G. P.; Ribrag, V.; Wagner-Johnston, N.; El-Sharkawi, D.; O'Connor, O. A.; Wilcox, R.; Wang, L.; Wilson, L.; Sims, M.; Taylor, J. A.; Keer, H. N.; Foss, F.	PRELIMINARY ANALYSIS OF THE PHASE II STUDY USING TOLINAPANT (ASTX660) MONOTHERAPY IN 98 PERIPHERAL T-CELL LYMPHOMA AND 51 CUTANEOUS T-CELL LYMPHOMA SUBJECTS WITH RELAPSED REFRACTORY DISEASE	Comparators
#132	2023	Morsia, E.; Grandi, V.; Zizzari, A.; Loseto, G.; Fava, P.; Alberti Violetti, S.; Pileri, A.; Broccoli, A.; Vitiello, P.; Sica, A.; Nassi, L.; Di Riamondo, C.; Quaglino, P.; Pimpinelli, N.; Berti, E.; Zinzani, P. L.; Rupoli, S.	Brentuximab Vedotin in the Treatment of Cutaneous T Cell Lymphomas: A Multicenter, Retrospective, Case-Control Study from Italy	Population
#133	2023	Morsia, E.; Torre, E.; Molinelli, E.; Marrara, F.; Campanati, A.; Offidani, A. M.; Oliveri, A.; Rupoli, S.	Chlormethine gel is an effective “add-on” agent for the treatment of skin lesions in patients with mycosis fungoides in clinical practice	Comparators
#134	2022	Mou, E.; Fernandez-Pol, S.; Li, S.; Kim, Y. H.; Khodadoust, M. S.	Clinical Characteristics, Treatment Patterns, and Outcomes of Cytotoxic Cutaneous T-Cell Lymphomas	Population
#135	2022	Nawar, T.; Elsayad, K.; Müller, E. C.; Rolf, D.; Moritz, R. K. C.; Bormann, E.; Weishaupt, C.; Stranzenbach, R.; Stadler, R.; Moustakis, C.; Assaf, C.; Livingstone, E.; Sunderkötter, C.; Steinbrink, K.; Eich, H. T.	Quality of life in patients with mycosis fungoides and Sézary syndrome undergoing low-dose total skin electron beam therapy with or without maintenance therapy	Comparators
#136	2023	Nicolay, J. P.; Melchers, S.; Albrecht, J. D.; Assaf, C.; Dippel, E.; Stadler, R.; Wehkamp, U.; Wobser, M.; Zhao, J.; Burghaus, I.; Schneider, S.; Gülow, K.; Goerdt, S.; Schürch, C. M.; Utikal, J. S.; Krammer, P. H.	Dimethyl fumarate treatment in relapsed and refractory cutaneous T-cell lymphoma: a multicenter phase 2 study	Comparators
#137	2024	Nikolaou, V.; Panou, E.; Tsimpidakis, A.; Koumprentziotis, I. A.; Patsatsi, A.; Siakantaris, M.; Kruger-Krasagakis, S. E.; Marinos, L.; Georgiou, E.; Lampadaki, K.; Velissari, A.; Daponte, A. I.; Doxastaki, A.; Kaliampou, S.; Vaiopoulos, A.; Konstandinou, I.; Koumourtzis, M.; Lakiotaki, E.; Pappa, V.; Tsamaldoupi, A.; Stratigos, A.; Papadavid, E.	Effectiveness and safety of methotrexate in the treatment of mycosis fungoides: Real-world data from a multicentre study	Population
#138	2022	Papadavid, E.; Koumourtzis, M.; Nikolaou, V.; Lampadaki, K.; Marinos, L.; Patsatsi, A.; Georgiou, E.; Dalamaga, M.; Stratigos, A.	Chlormethine gel is effective for the treatment of skin lesions in patients with early- and late-stage mycosis fungoides in clinical practice	Population

No.	Publication year	Author	Title	Exclusion reason
#139	2021	Patsatsi, A.; Papadavid, E.; Georgiou, E.; Kyriakou, A.; Koletsa, T.; Avgeros, C.; Koumourtzis, M.; Lampadaki, K.; Tsamaldoupis, A.; Lazaridou, E.; Stratis, A.; Nikolaou, V.	The use of pegylated interferon a-2a in a cohort of Greek patients with mycosis fungoides	Population
#140	2022	Polgárová, K.; Polívka, J.; Kodet, O.; Klener, P.; Trněný, M.	Retrospective Analysis of 118 Patients With Cutaneous T-Cell Lymphomas: A Single-Center Experience	Population
#141	2024	Porcu, P.; Bagot, M.; Ram-Wolff, C.; Kim, Y. H.; Huen, A.; Dalle, S.; Poligone, B.; Mehta-Shah, N.; Modeste, A. B. D.; Zinzani, P. L.; Woei-A-Jin, F. J. S. H.; Eigentler, T.; Combalia, A.; Sokol, L.; Battistella, M.; Gru, A.; Teisserenc, H. M.; Viotti, J.; Paiva, C.; Chammard, A. B.	Lacutamab in patients with relapsed and/or refractory mycosis fungoides: Results from the TELLOMAK phase 2 trial	Comparators
#142	2024	Porkert, S.; Griss, J.; Hudelist-Venz, M.; Steiner, I.; Valencak, J.; Weninger, W.; Brunner, P. M.; Jonak, C.	Evaluation of mortality, prognostic parameters, and treatment efficacy in mycosis fungoides	Population
#143	2022	Prince, H. M. M.; Geskin, L. J.; Akilov, O. E.; Kuzel, T. M.; Querfeld, C.; Ooi, C. E.; Xing, D.; Sauter, N.; Singh, P.; Czuczman, M.; Foss, F. M.	Safety and Tolerability of E7777 (improved purity Denileukin diftitox [ONTAK]) in Patients with Relapsed or Refractory Cutaneous T-Cell Lymphoma: Results from Pivotal Study 302	Comparators
#144	2021	Quaglino, P.; Ortiz-Romero, P.; Bagot, M.; Cozzio, A.; Evison, F.; Geskin, L.; Guenova, E.; Hodak, E.; Horwitz, S.; Papadavid, E.; Porcu, P.; Prince, M.; Stadler, R.; Vermeer, M.; Willemze, R.; Zinzani, P.; Whittaker, S.; Cowan, R.; Kim, Y. J.; Scarisbrick, J. J.	Time-to-next-treatment and time-to-next-systemic treatment in patients included in the PROCLIP registry	Population
#145	2023	Querfeld, C.; Chen, L.; Wu, X.; Han, Z.; Su, C.; Banez, M.; Quach, J.; Barnhizer, T.; Crisan, L.; Rosen, S. T.; Zain, J. M.	Preliminary Analysis Demonstrates Durvalumab (Anti-PD-L1) & Lenalidomide Is Superior to Single-Agent Durvalumab (anti-PD-L1) in Refractory/Advanced Cutaneous T Cell Lymphoma in a Randomized Phase 2 Trial	Comparators
#146	2021	Querfeld, C.; Thompson, J. A.; Taylor, M. H.; DeSimone, J. A.; Zain, J. M.; Shustov, A. R.; Johns, C.; McCann, S.; Lin, G. H. Y.; Petrova, P. S.; Uger, R. A.; Molloy, N.; Shou, Y.; Akilov, O. E.	Intralesional TTI-621, a novel biologic targeting the innate immune checkpoint CD47, in patients with relapsed or refractory mycosis fungoides or Sézary syndrome: a multicentre, phase 1 study	Comparators
#147	2021	Querfeld, C. S.; Tsai, N. C.; Palmer, J.; Martinez, X.; Abdulla, F.; Wu, X.; Rosen, S. T.; Zain, J.	Phase 1 results of anti-PD-ligand 1 (DURVALUMAB) & lenalidomide in patients with cutaneous T cell lymphoma and correlation with gene expression profile	Comparators

No.	Publication year	Author	Title	Exclusion reason
#148	2021	Remák, E.; Hawkins, N.; Jones, T.; Otley, M.; Twigger, R.; Prince, M.	Understanding relative survival outcomes for patients with cutaneous T-cell lymphoma (CTCL) subtypes mycosis fungoides and Sézary syndrome treated with mogamulizumab or vorinostat: combining Australian real-world evidence and MAVORIC phase 3 trial data	Study design
#149	2023	Romero, P. O.; Vallverdú, R. P.; Cravo, M.; Cuba, I. Q.; Escudero, A. C.; Núñez, R. M. R.; Montserrat, C. M.; Fernández-de-Misa, R.; Mascuñano, R. C.; Rodríguez, D. N.; Velasco, M. L.; Cabral, R.; Redondo, C. U.; Martitegui, X. M.; Garnelo, J. B.; Villar, A. M.	Real-world effectiveness of mogamulizumab in patients with Sézary syndrome or mycosis fungoides in Spain and Portugal: The MIBERIC study	Population
#150	2021	Rouce, R. H.; Hill, L. C.; Smith, T. S.; Yang, L.; Boriskie, B.; Srinivasan, M.; Zhang, H.; Perconti, S.; Mehta, B.; Dakhova, O.; Grilley, B. J.; Heslop, H. E.; Brenner, M. K.; Mamonkin, M.	Early Signals of Anti-Tumor Efficacy and Safety with Autologous CD5.CAR T-Cells in Patients with Refractory/Relapsed T-Cell Lymphoma	Comparators
#151	2021	Sethi, T.; Gerstein, R.; Schiffer, M.; Amin, K.; Agarwal, S.; Foss, F. M.	EPOCH Is a Safe and Effective Treatment Option for Aggressive T-Cell Lymphomas	Population
#152	2021	Shafagati, N.; Stuver, R. N.; Boussi, L.; Koh, M. J.; Park, A.; Bain, P.; Foss, F. M.; Shen, C.; Jain, S.	Novel Single Agents Are Equivalent to Conventional Chemotherapy Inpatients with Relapsed and Refractory Mature T-Cell Lymphomas: A Meta-Analysis	Comparators
#153	2023	Shastri, A.; Feldman, E. J.; Starodub, A. N.; Feldman, T.; Rodriguez, C. P.; Epstein-Peterson, Z. D.; Stevens, D. A.; Olszewski, A. J.; Huen, A. O.; Porcu, P.; Reneau, J. C.; Barta, S. K.; Marchi, E.; Mattour, A. H.; Pinter-Brown, L. C.; Perea, R.; Donohue, S.; Dey, J.; Agarwal, S.; Karnik, R.; Gollerkeri, A.; Gollob, J.; Smith, S. D.	Preliminary Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of KT-333, a Targeted Protein Degradator of STAT3, in Patients with Relapsed or Refractory Lymphomas, Large Granular Lymphocytic Leukemia, and Solid Tumors	Comparators
#154	2021	Sidiropoulou, P.; Marinos, L.; Gerochristou, M.; Economaki, E.; Papanikolaou, A.; Voudouri, D.; Kalliambou, S.; Stratigos, A.; Nikolaou, V.	Topical mechlorethamine in mycosis fungoides: a prospective clinical, histopathological, and molecular analysis of 13 cases	Population
#155	2023	Simontacchi, G.; Mattioli, C.; Onida, F.; Marrazzo, L.; Cela, D.; Vagge, S.; Schiavone, C.; Grandi, V.; Pimpinelli, N.; Mangoni, M.; Olmetto, E.; Chilà, D.; Livi, L.	Role of total skin electron beam radiotherapy at relapse after allogeneic transplant in mycosis fungoides and Sézary syndrome	Comparators

No.	Publication year	Author	Title	Exclusion reason
#156	2022	Smits, K.; Quint, K. D.; Vermeer, M. H.; Daniëls, L. A.; Willemze, R.; Jansen, P. M.; Jansen, W. P. A.; Neelis, K. J.	Total skin electron beam therapy for cutaneous T-cell lymphomas in the Netherlands: A retrospective analysis of treatment outcomes and selection for high or low dose schedule	Population
#157	2021	Stadler, R.; Romero, P. O.; Bagot, M.; Quaglino, P.; Guenova, E.; Jonak, C.; Papadavid, E.; Stranzenbach, R.; Sartori, D.; Musoro, J. Z.; Falato, C.; Marreaud, S.; Scarisbrick, J. J.; Knobler, R.	Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIb–IVB mycosis fungoides/Sézary syndrome patients relapsed/refractory after a previous systemic treatment (PARCT)	Comparators
#158	2021	Stadler, R.; Scarisbrick, J. J.; Knobler, R.; Quaglino, P.; Borgmann, M.; Orlovius, M.; Danhauser-Ried, S.	Phase II trial evaluating resminostat for maintenance treatment of patients with advanced stage (stage IIb–IVB) mycosis fungoides (MF) or Sézary syndrome (SS): RESMAIN study	Comparators
#159	2023	Stadler, R.; Woei-A-Jin, S.; Dummer, R.; Mitteldorf, C.; Papadavid, E.; Quaglino, P.; Ortiz-Romero, P. L.; Guenova, E.; Abe, R.; Ramelyte, E.; Busschots, A. M.; Knobler, R.; Suzuki, K.; Danhauser-Riedl, S.; Scarisbrick, J.	RESMAIN: results of a multicenter, randomized, double blind, placebocontrolled trial to evaluate resminostat for maintenance treatment in advanced stage mycosis fungoides or Sézary syndrome	Comparators
#160	2025	Straining, R.; Foss, F.; Schiffer, M.; Amin, K.; Agarwal, S.; Isufi, I.; Huntington, S.; Kothari, S.; Seropian, S.; Girardi, M.; Sethi, T.	Real World Data on Efficacy and Safety of EPOCH in T-Cell Lymphoma	Comparators
#161	2021	Strati, P.; Chraniuk, D.; González-Barca, E.; Taszner, M.; Pillai, R.; Chien, C.; Nanda, S.; Rudinski, M.; Jayaprakash, V.; Hahka-Kemppinen, M.; Kania, M.	Preliminary Results from a Phase I Study of HMPL-523, a Selective Oral Syk Inhibitor, in Patients with Relapsed or Refractory Lymphoma	Comparators
#162	2022	Trum, N. A.; Zain, J.; Martinez, X. U.; Parekh, V.; Afkhami, M.; Abdulla, F.; Carson, K. R.; Rosen, S. T.; Bennett, C. L.; Querfeld, C.	Mogamulizumab efficacy is underscored by its associated rash that mimics cutaneous T-cell lymphoma: a retrospective single-centre case series*	Population
#163	2023	Weiner, D.; Pierog, O.; Munjal, A.; Periyapatna, N.; Verardi, N.; Paulino, D.; Allen, P.; Akilov, O.; Rozati, S.	Real-world outcomes and tolerability of mogamulizumab monotherapy and multimodality therapy for cutaneous T-cell lymphoma: results from a multicenter retrospective cohort study	Population
#164	2021	Wilding, S.; Molloy, K.; Scarisbrick, J.; Farquharson, N.; Parry, E.; Cowan, R.	Assessing the efficacy of mogamulizumab: a novel tool for the management of mycosis fungoides and Sézary syndrome	Population
#165	2022	Wojewoda, K.; Gillstedt, M.; Englund, H.; Ali, S.; Lewerin, C.; Osmanovic, A.	Diagnostic Outcomes and Treatment Modalities in Patients with Mycosis Fungoides in West Sweden—A Retrospective Register-Based Study	Population

No.	Publication year	Author	Title	Exclusion reason
#166	2024	Wojewoda, K.; Gillstedt, M.; Lewerin, C.; Osmancevic, A.	Sézary Syndrome in West Sweden: Exploring Epidemiology, Clinical Features, and Treatment Patterns in a Registry-Based Retrospective Analysis	Population
#167	2021	Wu, S. Y.; Fang, P.; Huen, A. O.; Iyer, S. P.; Nair, R.; Steiner, R.; Castillo, L. E. M.; Duvic, M.; Ahmed, S.; Jain, P.; Fayad, L.; Strati, P.; Westin, J.; Neelapu, S. S.; Nastoupil, L.; Pinnix, C. C.; Dabaja, B.; Gunther, J. R.	Concurrent Radiation Therapy With the Antibody-Drug Conjugates Brentuximab Vedotin and Polatuzumab Vedotin	Population
#168	2022	Zhuang, T. Z.; McCook, A. A.; Switchenko, J. M.; Niyogusaba, T.; Tarabadkar, E. S.; Baird, K.; O'Leary, C. B.; Paulino, D.; Lechowicz, M. J.; Allen, P. B.	Characterizing Outcomes in Visceral Cutaneous T-Cell Lymphoma: A Real-World Retrospective Study	Population
#169	2023	Zhuang, T. Z.; McCook-Veal, A.; Switchenko, J.; Niyogusaba, T.; Tarabadkar, E. S.; Baird, K.; O'Leary, C.; Paulino, D.; Lechowicz, M. J.; Allen, P. B.	Characterizing Outcomes in Visceral Cutaneous T-Cell Lymphoma: A Single Center Retrospective Study	Population
#170	2023	Zinzani, P. L.; Morschhauser, F.; Janik, T.; Manamley, N.; Hilgier, K.; Sureda Balari, A. M.	Results from the Cohort Expansion Stage of a Phase I Trial of Tinostamustine Monotherapy in Advanced Haematological Malignancies (NCT02576496): Findings from a Subset of Patients with Cutaneous T-Cell Lymphoma (CTCL)	Comparators
#171	2015	Shi, Y.; Dong, M.; Zhu, J.; Zhou, D.; Huang, H.; Tu, P.; Zhang, W.; Hong, X.; Zhao, X.; Sun, J.; et al.	Phase II Study of Chidamide, a New Subtype-Selective Oral Histone Deacetylase Inhibitor, in Patients with Relapsed or Refractory Cutaneous T-Cell Lymphoma	Comparators
#172	2021	Stadler, R.; Romero, P. O.; Bagot, M.; Quaglino, P.; Guenova, E.; Jonak, C.; Papadavid, E.; Stranzenbach, R.; Sartori, D.; Musoro, J. Z.; et al.	Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIB-IVB mycosis fungoides/Sézary syndrome patients relapsed/refractory after a previous systemic treatment (PARCT)	Comparators
#173	2021	Stadler, R.; Scarisbrick, J. J.; Knobler, R.; Quaglino, P.; Borgmann, M.; Orlovius, M.; Danhauser-Ried, S.	Tre-P-16 - Phase II trial evaluating resminostat for maintenance treatment of patients with advanced stage (stage IIB-IVB) mycosis fungoides (MF) or Sézary syndrome (SS): RESMAIN study...EORTC CL Group 20-21 meeting on Cutaneous Lymphoma: translating Science into Patient Care, 14-16 October, 2021, Marseille, France	Population

H.1.4 Quality assessment

H.1.4.1 Quality assessment of included RCT's

A summary of qualitative assessment and assessment of study limitation (risk of bias) using the NICE recommended checklist is provided in Table 107. The checklist consists of a seven-item questionnaire based on four key criteria: selection bias (allocation concealment and lack of blinding), performance and detection bias, attrition bias, and reporting bias.

Both RCTs were of good quality with respect to randomization methods, baseline comparability between the randomized groups, imbalances in withdrawals between the randomized groups, selective outcome reporting and appropriate use of statistical analysis methods. Both studies were open label as blinding of treatment groups was not possible due to the different routes of administration (intravenous versus oral). However, a blinded independent review of outcomes was carried out to account for any potential bias.

In addition, for the two RCTs identified in the SLR, the evidence for the key outcomes considered in the cost-effectiveness model was evaluated and presented using the "Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox" developed by the international GRADE working group (<https://www.gradeworkinggroup.org/>). The software developed by this group was used to assess and record the quality of each outcome, considering individual study quality factors. Meta-analysis was not performed as the evidence identified in the SLR was related to two different treatment comparisons.

The main criteria considered in the rating of these elements followed the GRADE guidance. These were the following: study limitations (risk of bias) to assess the internal validity of the evidence, inconsistency (heterogeneity or variability in the estimates of treatment effects if meta-analysis was performed), indirectness (extent of differences in PICO characteristics between studies), imprecision (the extent to which confidence in effect estimate is adequate to support a particular decision) and other considerations such as publication bias. Footnotes were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each quality component were then summed to obtain an overall assessment for each outcome (Table 108 and Table 109).

As the two included RCTs have considered different types of treatment comparisons and no meta-analysis was performed, only study limitations, imprecision and other considerations were relevant GRADE domains for their assessment. In addition, due to specific considerations of these two RCTs such as treatment switching, and the impact on Kaplan-Meier analyses, and the lack of individual patient data from one trial (i.e. ALCANZA) which are the focus of coming guidance from GRADE working group(80), absolute effect estimates were not calculated.

Table 107 Study quality assessment of RCT's using the NICE checklist

Study name	Randomization	Allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	ITT analysis
Kim 2018 (MAVORIC Trial)	LR	LR	LR	HR	LR	LR	LR
Prince 2017 (ALCANZA)	LR	LR	LR	HR	LR	LR	HR

Note:

Randomization: was randomization carried out appropriately?

Allocation concealment: was the concealment of treatment allocation adequate?

Baseline characteristics: were the groups similar at the outset of the study in terms of prognostic factors?

Blinding: were the care providers, participants and outcome assessors blind to treatment allocation?

Withdrawals: were there any unexpected imbalances in dropouts between groups?

Outcome selection and reporting: is there any evidence to suggest that the authors measured more outcomes than they reported?

ITT analysis: did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Abbreviations: HR, high risk; ITT, intention-to-treat; LR, low risk.

Table 108 Quality assessment of outcomes used in the included RCT studies – GRADE (Comparison of Mogamulizumab vs. Vorinostat for Relapsed/Refractory Cutaneous T-Cell Lymphoma)

Table 105. Quality assessment of outcomes used in the included RCT studies												
Certainty assessment							No of patients		Effect		Certainty	Im- portance
No of studies	Study design	Risk of bias	Incon- sistency	Indirect- ness	Impreci- sion	Other consid- erations	Mogamuli- zumab	vorinostat	Relative (95% CI)	Absolute (95% CI)		
Survival												
1 MAVORIC Trial	randomised trials	not seri- ous	not serious	not seri- ous	serious a	none	186 partici- pants	186 partici- pants	HR 0.93 (0.61 to 1.43) [Survival]	-- per 1,000 (from -- to --)	⊕⊕⊕○ MODERATE	High
							-	0.0%		-- per 1,000 (from -- to --)		
Progression-free survival (investigator assessed)												
1 MAVORIC Trial	randomised trials	serious b	not serious	not seri- ous	not seri- ous	none	-/186	-/186	HR 0.53 (0.41 to 0.69)	-- per 1,000 (from -- to --)	⊕⊕⊕○ MODERATE	High
Progression-free survival (independent review)												
1 MAVORIC Trial	randomised trials	serious b	not serious	not seri- ous	not seri- ous	none	-/186	-/186	HR 0.64 (0.49 to 0.84)	-- per 1,000 (from -- to --)	⊕⊕⊕○ MODERATE	High
Overall response rate												
1 MAVORIC Trial	randomised trials	serious b	not serious	not seri- ous	not seri- ous	none	52/186 (28.0%)	9/186 (4.8%) 4.8%	RR 23.1 (12.8 to 33.1)	1,000 more per 1,000 (from 571 more to 1,000 more)	⊕⊕⊕○ MODERATE	Moderate
Change in EQ5D-3L												
1 MAVORIC Trial	randomised trials	serious b	not serious	not seri- ous	not seri- ous	none	169	174	-	MD 0.03 higher (0.005 higher to 0.064 higher)	⊕⊕⊕○ MODERATE	High

Note: ^a CI includes null effect size and sample size over 300 patients, ^b Study was unblinded.

Abbreviations: CI, Confidence interval; HR, Hazard Ratio; RR, Risk ratio; MD, Mean difference; EQ5D3L, European quality of life 5 dimensions 3 level; RCT, randomized controlled trial.

Table 109 Quality assessment of outcomes used in the included RCT studies – GRADE (Comparison of Brentuximab vedotin vs. Physician’s Choice for Previously treated CD-30-positive Cutaneous T-Cell Lymphoma)

			Certainty assessment				№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consid- erations	Brentuximab	physician's choice	Relative (95% CI)	Absolute (95% CI)		
Event-free survival												
1 (AL-CANZA)	randomised trials	not serious	not serious	not serious	serious ^a	none	64 partici- pants	64 partici- pants	HR 0.285 (0.189 to 0.429) [Event-free sur- vival]	-- per 1,000 (from -- to --)	⊕⊕⊕○ MODERATE	High
Progression-free survival (EMA criteria)												
1 (AL-CANZA)	randomised trials	serious ^b	not serious	not serious	serious ^a	none	64 partici- pants	64 partici- pants	HR 0.270 (0.169 to 0.430) [death]	-- per 1,000 (from -- to --)	⊕⊕○○ LOW	High
Progression-free survival (FDA criteria)												
1 (AL-CANZA)	randomised trials	serious ^b	not serious	not serious	serious ^a	none	64 partici- pants	64 partici- pants	HR 0.181 (0.101 to 0.324) [death]	-- per 1,000 (from -- to --)	⊕⊕○○ LOW	High
Objective Response Rate (4 months)												
1 (AL-CANZA)	randomised trials	serious ^b	not serious	not serious	not serious	none	36/64 (56.3%)	8/64 (12.5%)	MD 43.8 (29.1 to 58.4)	-- per 1,000 (from -- to --)	⊕⊕⊕○ MODERATE	Moderate

Note: ^a Unclear if optimal information size requirements are met, ^b Study was unblinded.

Abbreviations: CI, Confidence interval; HR, Hazard Ratio; MD, Mean difference; RCT, randomized controlled trials; EMA, European medicines agency; FDA, food and drug administration.

H.1.4.2 Quality assessment of included non-RCT’s

A summary of qualitative assessment and assessment of risk of bias is provided in Table 110. The quality of the non-RCTs was evaluated using the Downs and Black checklist.(81) Each item in this checklist is checked as “yes”, “no”, or “unable to determine”, scored as 1, 0, and 0, respectively. Each item is stated positively; that is, it represents a desired design or reporting feature. A higher score indicates the higher quality of the study.

Across the 53 studies, the total score was between 15 and 20 in 18 studies, and between 9 and 14 in 29 studies. Five studies scored less than 9 all of which were a conference abstract and data reported was limited.

Table 110 Quality assessment of non-RCT's using Downs and Black checklist

Question No.	Duvic 2017	Foss 1992	Foss 1994	Bunn Jr 1987	Illidge 2013	Aviles 2015	Kohn 1990	Ogura 2014	Talpur 2002	Duvic 2006	Jidar 2009	Wada 2012	McDonald 1978	Roenigk Jr 1990	Olsen 2007	Wilson 1995	Sokolowska-Wojdylo 2016	Dumont 2019	William 2019	Papadavid 2008	Larisa 2010	Akpek 1999	Duvic 2015	Talpur 2014	Kim 2015
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	U	Y	N	N	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	U	N	N	N	Y	N	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Y	N	Y	Y	U	N	N	N	Y	N	Y
8	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	N	N	N	Y	N	Y	N	N	N	N	Y	N	N	Y	N	Y	U	N	N	N	N	Y	Y	N
10	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	U	U	N	N	N	N	N
11	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	X	N	U	Y	Y	Y	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	X	N	U	Y	Y	Y	Y	Y	U
13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	X	N	U	Y	Y	U	U	Y	U
14	X	X	X	X	X	N	X	N	X	X	X	X	X	X	X	X	X	X	Y	X	X	X	X	N	X
15	X	X	X	X	X	N	X	N	X	X	X	X	X	X	X	X	X	X	Y	X	X	X	X	N	X
16	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
17	N	N	N	N	Y	Y	N	U	Y	Y	U	U	U	Y	Y	U	Y	X	U	Y	N	N	X	U	N
18	N	N	N	N	Y	N	N	Y	Y	Y	N	Y	N	N	Y	N	N	N	U	N	N	Y	Y	N	Y
19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	U
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
21	X	X	X	X	X	Y	X	Y	X	X	X	X	X	X	X	X	X	X	X	Y	Y	Y	X	Y	X

22	X	X	X	X	X	Y	X	U	X	X	X	X	X	X	X	X	X	X	X	Y	Y	Y	X	U	X
23	X	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24	X	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
25	N	N	N	N	N	N	N	Y	N	Y	Y	N	N	Y	Y	N	N	N	U	Y	U	Y	Y	Y	Y
26	N	N	N	N	Y	N	N	N	U	Y	N	N	Y	N	Y	N	Y	N	U	U	U	Y	Y	Y	N
Score	14	12	13	13	17	14	14	16	14	16	13	14	11	14	19	9	12	9	6	15	12	14	16	15	12
Question No.	Duvic 2007	Kogge 2015	Rupoli 2016	Kuzel 1995	Hughes 2015	Baquero Rey 2021	Beylot-Barry 2023	Braunstein 2024	Elghawy 2024	Elsayad 2022	Hamada 2022	Kim 2023	Lewis 2021	Sureda 2022	Muniesa 2023	Munayirji 2023	Teoli 2023	Zhang 2022	Ninosu 2024	Rey 2023	Scarisbrick 2023	Mitsunaga 2024	Roccuzzo 2023	Quaglino 2011	Khodadoust 2019
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	N	N	Y	U	N	Y
4	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	N	Y	Y	N	N	N
8	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	Y	Y
9	Y	Y	N	Y	Y	Y	U	U	N	Y	U	U	U	U	U	U	U	U	U	U	U	Y	U	N	U
10	N	N	Y	N	Y	Y	N	Y	N	Y	Y	Y	U	N	Y	U	N	Y	N	U	U	Y	U	N	Y
11	Y	Y	Y	Y	Y	U	U	U	N	N	U	U	U	U	U	U	U	U	U	U	U	Y	U	U	Y
12	Y	Y	Y	Y	Y	N	Y	N	N	Y	U	Y	U	Y	Y	U	U	Y	Y	U	U	U	U	U	Y
13	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	U	Y	Y	U	U	Y	Y	U	U	U	U	U	Y
14	X	X	N	N	X	N	N	N	N	N	N	N	N	N	N	U	N	N	N	N	N	N	N	N	N
15	X	X	N	N	X	N	N	N	N	N	N	N	N	N	N	U	N	N	N	N	N	N	N	N	N
16	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	U	N	N	N	N	N	N	N	N	N

17	N	N	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	U	Y	U	U	Y	Y	N	N	Y	N	Y	Y
18	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	U	U	Y	Y	U	U	Y	U	Y	Y
19	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	U	Y	U	U	N	N	U	U	N	U	U	Y
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
21	Y	Y	Y	Y	Y	U	Y	U	U	U	U	U	N	U	U	U	U	Y	U	U	Y	U	Y	U	N
22	Y	Y	Y	Y	Y	U	Y	U	U	Y	U	U	N	U	U	U	U	Y	Y	U	U	Y	U	U	N
23	X	X	X	X	X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
24	X	X	X	X	X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
25	Y	U	Y	Y	Y	N	N	N	N	N	Y	Y	N	N	Y	N	U	N	N	N	N	N	N	N	U
26	Y	U	N	Y	Y	Y	U	Y	U	U	U	U	N	U	U	U	U	U	U	U	U	U	U	U	U
Score	17	14	18	18	17	16	16	15	10	14	14	16	12	11	16	6	7	15	14	6	9	15	7	8	14

Abbreviations: N = no; Y = yes; N/A, not available / not applicable; non-RCT, non-randomized control trials

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the introduction or methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the distributions of principal confounders in each group of patients to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?
14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?

16. If any of the results of the study were based on “data dredging”, was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention(s) reliable?
20. Were the main outcome measures used accurate (valid and reliable)?
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
23. Were study subjects randomized to intervention groups?
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?

H.1.5 Unpublished data

N/A

H.1.6 Local adaptation

N/A

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

N/A. Previous assessment from NICE TA577 was used to inform post aSCT values.

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

N/A. No other external economic inputs

Appendix K. HES analysis

This appendix presents Kaplan-Meier overall survival estimates for patients with mycosis fungoides (MF) and Sézary disease (SD) derived from the Hospital Episode Statistics (HES) database in England, shown alongside the corresponding curves from the Danish registry standard-of-care cohort (DK SoC) used in the base case of this submission.

The HES estimates are reproduced from a retrospective real-world analysis of HES data. The aim of the study was to describe the demographics, healthcare resource use, and associated outcomes of patients diagnosed with CTCL in the real-world clinical setting in NHS England, with a view to supporting the NICE submission for mogamulizumab.

K.1.1 Data source

HES is a database containing details of all inpatient admissions, A&E attendances, and outpatient appointments at NHS hospitals in England. Each HES record contains clinical information about diagnoses and procedures, patient information such as age group, gender, and ethnicity, administrative information such as dates and methods of admission and discharge, and geographical information. All NHS Clinical Commissioning Groups in England are covered by HES, including private patients treated in NHS hospitals, patients resident outside England, and care delivered by treatment centres (including those in the independent sector) funded by the NHS. Each patient is identified by a unique pseudonymised code, enabling longitudinal pathway analysis across inpatient, outpatient, and A&E settings.

K.1.2 Cohort definition

Patients were eligible for inclusion if they had at least one of the following ICD-10 codes recorded in any diagnostic position (1–20) within HES: C84.0 (mycosis fungoides), C84.1 (Sézary disease), or C84.8 (cutaneous T-cell lymphoma, unspecified). The diagnostic code was required to occur at least once between 1 October 2010 and 31 March 2019 for MF or SD, or between 1 April 2013 and 31 March 2019 for unspecified CTCL (the latter reflecting that the C84.8 code was not introduced until April 2013).

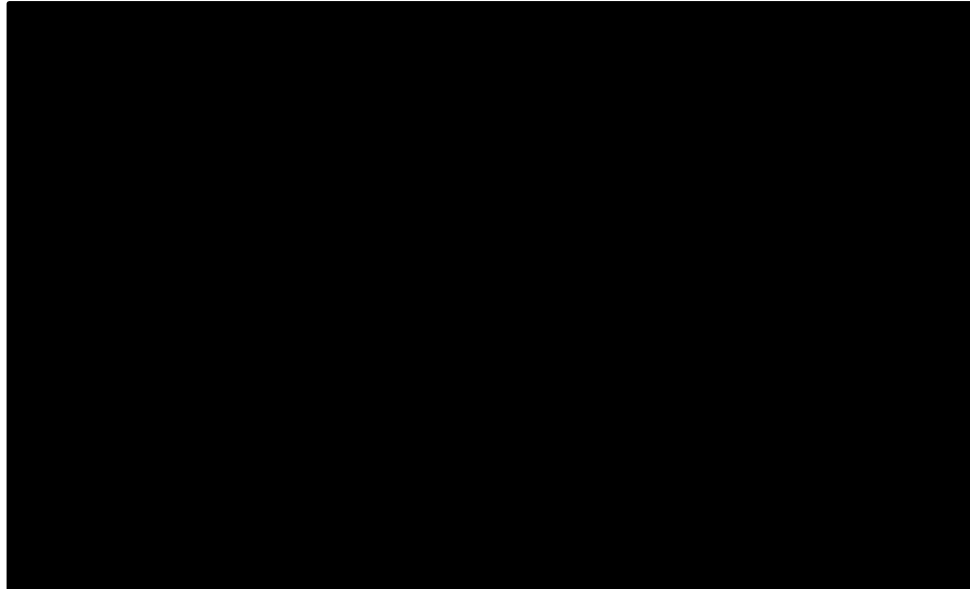
Patients were excluded if they had ICD-10 codes for both MF (C84.0) and SD (C84.1) within their record, or if they had a CTCL-related diagnosis within the 18 months prior to the start of the observation period (i.e. between 1 April 2009 and 30 September 2010 for MF or SD, or between 30 September 2011 and 31 March 2013 for unspecified CTCL). The 18-month lookback was implemented to increase confidence that the first occurrence of the diagnosis code within the study period represented the patient's first ever diagnosis, and was validated through consultation with an experienced physician. All data were collected from the date of the first diagnosis occurrence up to either the date of death or the study end date (31 March 2019).

K.1.3 Survival analysis

Overall survival was defined as time from date of diagnosis until date of death, with patients who did not die censored at the end of the study date. Time-to-event analyses were calculated using the Kaplan-Meier method. Patients diagnosed in 2018 were not

included in Kaplan-Meier risk estimates at the specified annual time-points due to lack of available follow-up. The figure below presents the HES Kaplan-Meier overall survival curves alongside the corresponding Danish registry standard-of-care curves used in the base case.

Figure 66 Overall survival in DK SoC base case and HES



Abbreviations: OS, overall survival; KM, kaplan-meier; DK SoC, Danish standard of care; HES, hospital episode statistics

Danish Medicines Council

Secretariat

Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk