Appendix S1.

SUPPLEMENTARY MATERIAL AND METHODS

Health economic analysis

Cost-effectiveness is calculated in terms of an incremental cost-effectiveness ratio (ICER), i.e. the additional cost per QALY gained (7): Neither costs nor utilities are discounted in the model as the simulation horizon is limited to one year.

Costs

Country-specific unit costs are shown in Table SI. Costs are presented as 2014 Euros, adjusted to 2014 price levels using country-specific consumer price index (CPI) when needed (11–13). The mean exchange rates in 2014 were €1=SEK 9.0968 and €1=NOK 8.3534 (14, 15).

Model

A discrete event microsimulation model that simulates eczema relapses for 10,000 individual patients during a 1-year time-period was developed using Microsoft® Excel.

The model includes 2 health states; eczema-free and eczema. At model entry all patients are in an eczema-free state with maintenance therapy, randomized to either the study cream or the reference cream. In the event of eczema relapse the patient enters the eczema state, during which a 3-week course of corticosteroids treatment is given. After steroid treatment the patient is assumed to be clear of eczema and re-enters the eczema-free state with a new round of maintenance therapy. Maintenance therapy continues until the next recurrence of eczema, and so on. The sequence (of eczema-free episodes with maintenance therapy followed by eczema episodes with steroid treatment) is repeated until the 1-year simulation period (365 days) has passed.

As most patients in the RCT (6) experienced eczema relapse within the first few weeks, a patient in the model could have several eczema recurrences during the simulated year. Yet, there may be within-patient variation in the time-to-relapse, partly due to seasonal variation of AD (18). To control for this the model used a probability (p) that a new time-to-relapse is drawn for each patient that re-enters the eczema-free state, and a probability ($1-p$) that the new time-to-relapse is identical to the time-to-relapse in the patients previous sequence.

Each health state has a corresponding utility, i.e. health-related quality of life (HRQoL) weight. The model calculates a health state–dependent mean yearly utility for each simulated patient and treatment group by multiplying the time spent in each health state with its corresponding utility weight.

The modelled time-to-relapse directly represented observational data from the RCT (6) during the initial 6 months (182 days), or is replaced by a parametrization of the data, while the subsequent 6 months (day 183–365) are parametrized with a parametrization of the user's choice. The simulation curves are user defined and the user can choose between Kaplan–Meier curve (for the initial 6 simulation months only) and parametrizations using either Weibull, exponential, Gompertz, log-normal, log-logistic or generalized gamma. Each simulated patient is assigned a time-to-relapse drawn from these curves. The time-to-relapse is stochastic, while all other model parameters are deterministic. The stochastic sequence operates on a fixed seed that generates a sequence of pseudo-random numbers. The use of a fixed seed ensures that the simulated time-to-relapse is identical for each model simulation given the set of input data, which enabled the model to reproduce its results. This, in turn, helps identify the impact of individual input values.

Table SI. *Unit costs of resources in Finland, Norway and Sweden (2014 price levels in € and local currencies)*

	Finland	Norway		Sweden	
	€	NOK	€	SEK	€
Direct costs					
Maintenance creams, per 500 g					
Study cream	24	383	46	199	22
Reference cream[a]	18	308	37	279	31
Steroids, per 100 g					
Hydrocortisone, betamethasone 1% or desonide 0.1%[a]	13	159	19	115	13
Mometasone or tacrolimus, 0.1%[a]	38	150	18	137	15
Physician visit					
General practitioner	116	335	40	1,424	157
Specialist	70	644	77	2,527	278
Phone consultation	19	88	11	483	53
Indirect costs					
Production loss (2 h)	65	712	85	534	59

[a]Unit costs of the reference cream and steroid creams refer to mean prices of creams available on the market in each country.

Base case input values

In the base case analysis, Kaplan–Meier curves were used to model the initial 182 simulated days in order to directly represent data from the RCT. A Weibull parameterization was used for the subsequent 183 simulation days (Fig. 1) as it was assumed to best represent real-life relapse probabilities. The choice to apply the Weibull parametrization was based on the severity of AD of the included patients and a well-known seasonal variation of AD (18), which makes recurrence during the next winter season likely.

The base case analysis applied a 0.5 probability of drawing a new time-to-relapse when the patient re-enters the maintenance phase after being cleared of eczema.

Patients in the RCT (6) were instructed to apply the study cream twice daily, but were not given an exact quantity. As there was no statistical significant difference in cream consumption between the treatment groups in the RCT (6) the mean consumption of 11.8 g/day (95% CI: 9.81, 13.87) was applied in the base case analysis (Table SII). This amount is in line with the dose indicated by the Swedish Medical Products Agency of 90 g/week, i.e. 12.85 g/day (21).

In the stabilization phase of the RCT (6), corticosteroids were applied once daily and a mometasone furoate cream 0.1% was used on body eczema (non-sensitive areas), while hydrocortisone cream 1% was used for eczema in the face, groins and armpits (sensitive areas). Data from the RCT showed that 62% of recurring eczema was on non-sensitive body areas and 38% was on sensitive body areas. The same proportion was used in the health economic analysis. In the Finnish analysis hydrocortisone was replaced with hydrocortisone or desonide and mometasone was replaced with mometasone or tacrolimus according to clinical practice in Finland. Similarly, hydrocortisone was replaced with hydrocortisone or betamethasone in the Swedish analysis according to Swedish clinical practice. These active treatments of eczemas are all referred to as corticosteroid treatment.

Because there was no information on steroid cream consumption in the data from the RCT, other than a recommendation of a once daily application, we assumed the same cream consumption as with the maintenance cream, but only a once daily application, i.e. 5.9 g/day (Table SII).

In a previous study, 25% of the patients with eczema relapse visited a general practitioner (GP) and 25% visited a specialist/dermatologist, while 50% of patients consulted a physician over the phone or did not visit a doctor at all (5). The same assumptions were made regarding physician visits upon recurrence of eczema in the base case of the present analysis.

Costs of production loss from work absenteeism when visiting a physician was estimated according to the human capital approach using the mean labour cost per working hour in each

Table SII. *Base case model input values in the analyses for Finland, Norway and Sweden*

	Base case values		
Parameter	Finland	Norway	Sweden
Probability of a new relapse time (p)	0.50	0.50	0.50
Time-to-relapse curve during initial 182 days	Kaplan–Meier	Kaplan–Meier	Kaplan–Meier
Time-to-relapse curve during subsequent 183 days	Weibull	Weibull	Weibull
Utilities			
Eczema-free state	0.938	0.938	0.938
Disutility of eczema	–0.108	–0.108	–0.108
Daily amount of maintenance cream used, g	11.8	11.8	11.8
Daily amount of steroid cream used, g	5.9	5.9	5.9
Allocation of steroid cream use, %			
Hydrocortisone, betamethasone 1% or desonide 0.1%	38	38	38
Mometasone 0.1% or tacrolimus, 0.1%	62	62	62
Price of (2014 €)			
Study cream per 500 g	24	46	22
Reference cream per 500 g	18	37	31
Steroid cream per 100 g			
Hydrocortisone, betamethasone 1% or desonide 0.1%	13	19	13
Mometasone 0.1% or tacrolimus, 0.1%	38	18	15
Production loss 2 h (2014 €)			
General practitioner visit	65	85	59
Specialist visit	65	85	59
Allocation of physician visits (%)			
General practitioner visit	25	25	25
Specialist visit	25	25	25
Phone consultation/no visit	50	50	50
Cost of physician visit (2014 €)			
General practitioner visit	116	40	157
Specialist visit	70	77	278
Phone consultation/no visit	9	5	27

country (22–25). Two hours of production loss was assumed per physician visit in the base case analysis.

Utility levels of each health state were based on EuroQol (EQ-5D) data from the RCT (6). Each EQ-5D response was assigned an appropriate weight according to a study by Kind et al. (26), based on a representative sample of the general population in the UK. The mean utility for an eczema-free state was 0.938 and 0.830 for the eczema state. A disutility of eczema of –0.108 was thus applied in the base case analysis. All model inputs used in the base case analysis are presented in Table SII.

Model inputs in the sensitivity analysis

Deterministic sensitivity analyses were performed to explore the robustness of the results and importance of specific model parameters (7). The deterministic sensitivity analyses were conducted 1-way, i.e. everything else equal, and parameters are varied to a minimum and maximum when applicable. The parameter variation is illustrated in Table SIII.

Previous studies have estimated the amount of cream use per full body application of sunscreen. A Danish study recently found that an average person applies 0.4–1 mg/cm^2 body surface area (BSA) (27). With a mean BSA for adults of 1.8 m^2 (28) this corresponds to a cream use of 7.2–18 g/full-body application. Thus, the lower bound of maintenance cream consumption was assumed to correspond to a once daily application, i.e. 7.2 g/day. Similarly, the upper bound was set to the maximum usage at 2 full-body applications, i.e. 36 g/day.

The probability to draw a new time-to-relapse when patients re-enter the maintenance phase after being cleared from eczema was varied in 2 separate deterministic sensitivity analyses. Firstly, the probability was set to zero ($p = 0.0$), indicating that each simulated patient had a constant time-to-relapse throughout the simulated year, i.e. implying that the time-to-relapse is completely driven by patient characteristics. Secondly, a 100% probability ($p = 1.00$) to draw a new time-to-relapse was applied, implying that the time-to-relapse is completely random and independent of individual patient characteristics.

In addition, the curves used to model time-to-relapse were altered in an extensive sensitivity analysis. The Kaplan–Meier curve was replaced with parametric curves (Weibull, exponential, Gompertz, log-normal, log-logistic and generalized gamma) for

Table SIII. *Parameter variation in sensitivity analysis (2014 €).* EQ-VAS: EuroQol Visual Analogue Scale; HRQoL: health-related quality of life

	Values in sensitivity analysis					
	Finland		Norway		Sweden	
Parameter	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum
Deterministic 1-way sensitivity analysis						
Amount of maintenance cream, g	7.2	36	7.2	36	7.2	36
Price of (2014 €)						
Study cream (+10%)		26		50		24
Reference cream	14	26	24	61	14	63
Steroid cream						
Hydrocortisone/betamethasone/desonide	11	16	11	46	12	13
Mometasone/tacrolimus	13	122	18	18	11	19
Production loss (2014 €)						
General practitioner visit	0	129	0	170	0	117
Specialist visit	0	129	0	170	0	117
10% price increase of study cream		26		50		24
Allocation of physician visits at eczema recurrence, %						
General practitioner visit	25	30	25	30	25	30
Specialist visit	10	60	10	60	10	60
Phone consultation/no visit	65	10	65	10	65	10
Probability of a new time-to-relapse (p)	0.00	1.00	0.00	1.00	0.00	1.00
Health states and HRQoL	Eczema-free	Disutility of eczema	Eczema-free	Disutility of eczema	Eczema-free	Disutility of eczema
Burström et al. utility weights (29)	0.954	–0.027	0.954	–0.027	0.954	–0.027
EQ-VAS	0.851	–0.103	0.851	–0.103	0.851	–0.103

Table SIV. *Results of the deterministic sensitivity analysis[a] (2014 €)*

	Cost			Quality Adjusted Life Year			ICER
Parameter variation	Study cream	Reference cream	Difference	Study cream	Reference cream	Difference	
Finland							
Min/Max amount of maintenance cream	627/995	910/1,133	–283/–138	0.911	0.895	0.016	Dominant
10% price increase of study cream	701	946	–245	0.911	0.895	0.016	Dominant
Min/Max price of reference cream	686/686	923/986	–237/–300	0.911	0.895	0.016	Dominant
Min/Max price of steroid creams	596/977	802/1,410	–206/–433	0.911	0.895	0.016	Dominant
No production loss	540	712	–172	0.911	0.895	0.016	Dominant
Production loss of 4 h/physician visit	832	1,179	–347	0.911	0.895	0.016	Dominant
Allocation of physician visits:							
25% GP, 10% specialist, 65% no visit/telephone	601	810	–209	0.911	0.895	0.016	Dominant
30% GP, 60% specialist, 10% no visit/telephone	923	1,325	–402	0.911	0.895	0.016	Dominant
Probability of a new time-to-relapse: 0%	1,051	1,239	–188	0.890	0.879	0.012	Dominant
Probability of a new time-to-relapse: 100%	559	821	–262	0.918	0.901	0.017	Dominant
Burström et al. utility weights (29)	686	946	–260	0.947	0.943	0.004	Dominant
EQ-VAS utility	686	946	–260	0.825	0.809	0.016	Dominant
Norway							
Min/Max amount of maintenance cream	617/1,338	816/1,278	–199/59	0.911	0.895	0.016	Dominant/3,637
10% price increase of study cream	763	891	–128	0.911	0.895	0.016	Dominant
Min/Max price of reference cream	733/733	823/1,016	–90/–283	0.911	0.895	0.016	Dominant
Min/Max price of steroid creams	717/791	865/982	–148/–192	0.911	0.895	0.016	Dominant
No production loss	542	584	–42	0.911	0.895	0.016	Dominant
Production loss of 4 h/physician visit	925	1,197	–273	0.911	0.895	0.016	Dominant
Allocation of physician visits:							
25% GP, 10% specialist, 65% no visit/telephone	626	719	–93	0.911	0.895	0.016	Dominant
30% GP, 60% specialist, 10% no visit/telephone	1,011	1,336	–325	0.911	0.895	0.016	Dominant
Probability of a new time-to-relapse: 0%	992	1,106	–113	0.890	0.879	0.012	Dominant
Probability of a new time-to-relapse: 100%	643	799	–156	0.918	0.902	0.017	Dominant
Burström et al. utility weights (29)	733	891	–157	0.947	0.943	0.004	Dominant
EQ-VAS utility	733	891	–157	0.825	0.809	0.016	Dominant
Sweden							
Min/Max amount of maintenance cream	875/1,406	1,358/2,043	–483/–637	0.911	0.895	0.016	Dominant
10% price increase of study cream	975	1,469	–494	0.911	0.895	0.016	Dominant
Min/Max price of reference cream	961/961	1,423/1,501	–463/–540	0.911	0.895	0.016	Dominant
Min/Max price of steroid creams	947/975	1,446/1,492	–500/–517	0.911	0.895	0.016	Dominant
No production loss	828	1,257	–429	0.911	0.895	0.016	Dominant
Production loss of 4 h/physician visit	1,093	1,681	–587	0.911	0.895	0.016	Dominant
Allocation of physician visits:							
25% GP, 10% specialist, 65% no visit/telephone	691	1, 037	–346	0.911	0.895	0.016	Dominant
30% GP, 60% specialist, 10% no visit/telephone	1,433	2,224	–791	0.911	0.895	0.016	Dominant
Probability of a new time-to-relapse: 0%	1,546	1,917	–371	0.890	0.879	0.012	Dominant
Probability of a new time-to-relapse: 100%	757	1,279	–522	0.918	0.901	0.017	Dominant
Burström et al. utility weights (29)	961	1,469	–508	0.947	0.943	0.004	Dominant
EQ-VAS utility	961	1,469	–508	0.825	0.809	0.016	Dominant

[a]The value of all other variables are kept identical to the value in the base case.

ICER: incremental cost-effectiveness ratio; GP: general practitioner; EQ-VAS: EuroQol Visual Analogue Scale.

the initial 182 simulation days, in combination with a Weibull parameterization for the second simulation period. Similarly, the Weibull curve was replaced with the other parametric curves (exponential, Gompertz, log-normal, log-logistic and generalized gamma) for the subsequent 183 days in combination with the Kaplan–Meier curve during the initial simulation period.

Finally, alternative utilities were estimated using utility weights by Burström et al. based on a Swedish general population survey (29). Furthermore, utility values from visual analogue scale (EQ-VAS) data from the RCT was analysed.

Results of the sensitivity analysis

The results from the deterministic sensitivity analyses are presented in Table SIV and show that the study cream remained the more effective treatment alternative compared with a maintenance cream with no active ingredients in all analysed cases, with a QALY gain of between 0.004 and 0.017. The QALY gains with the study cream reflect the fewer days with eczema compared with the reference cream (40–59 fewer days, data not shown).

The study cream was a cost-saving treatment alternative compared with the reference cream in all deterministic sensitivity analyses except for a Norwegian analysis that assumed the maximal amount of maintenance cream consumption of 36 g/day. This analysis resulted in a cost per gained QALY of €3,637, mainly explained by the higher price of the study cream and the low costs of physician visits in Norway (Table SI).

The choice of parametric curve had no influence on the results and the analyses in all 3 countries indicated cost-effectiveness (data not shown).