For the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.[1]

Adtralza® ▼ (tralokinumab)

Not an actual patient. For illustrative purposes only. Individual results may vary.

The first licensed biologic that inhibits IL-13 alone,[1,2] a key driver of atopic dermatitis signs and symptoms.[3]

Adtralza® maintained disease control for adult patients with atopic dermatitis at 2 years of treatment in the ECZTEND study.[4*]
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Adtralza® was generally well tolerated in ECZTEND at 2 years (n=1,442).[5**] The most common adverse events were viral upper respiratory tract infections (20.5%), atopic dermatitis (17.8%), upper respiratory tract infections (7.0%), headache (5.5%) and conjunctivitis (5.3%).[5**]

IL, interleukin.
*Interim analysis from ongoing open label extension study (data cut off: April 30 2021).[4] The 2-year cohort subgroup (n=86) included patients previously treated with Adtralza® monotherapy for 52 weeks in ECZTRA 1 and 2, followed by a washout period >15 weeks from last treatment in parent trial, then assigned to 104 weeks' treatment in ECZTEND study.[4] Primary endpoint was number of adverse events from baseline to last treatment visit (up to Week 268).[4]
**Data from 2-year interim safety analysis of the ECZTEND study, which included patients from parent trials ECZTRA 1, 2, 3, 4, 5 and 7.[5]

Prescribing information for Adtralza®▼ (tralokinumab) 150 mg solution for injection in pre-filled syringe
Please refer to the full Summary of Product Characteristics (SmPC) (www.medicines.org.uk/emc) before prescribing.
▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. **Indications:** Treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy. **Active ingredients:** Each pre-filled syringe contains 150 mg of tralokinumab in 1 mL solution (150 mg/mL). **Dosage and administration:** *Posology:* The recommended dose of tralokinumab is an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week as subcutaneous injection. Every fourth week dosing may be considered for patients who achieve clear or almost clear skin after 16 weeks of treatment. Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment. Some patients with initial partial response may subsequently improve further with continued treatment every other week beyond 16 weeks. Tralokinumab can be used with or without topical corticosteroids. The use of topical corticosteroids, when appropriate, may provide an additional effect to the overall efficacy of tralokinumab. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas. If a dose is missed, the dose should be administered as soon as possible and then dosing should be resumed at the regular scheduled time. No dose adjustment is recommended for elderly patients, patients with renal impairment or patients with hepatic impairment. For patients with high body weight (>100 kg), who achieve clear or almost clear skin after 16 weeks of treatment, reducing the dosage to every fourth week might not be appropriate. The safety and efficacy of tralokinumab in children below the age of 18 years have not yet been established. *Method of administration:* Subcutaneous use. The pre-filled syringe should be not shaken. After removing the pre-filled syringes from the refrigerator, they should be allowed to reach room temperature by waiting for 30 minutes before injecting. Tralokinumab is administered by subcutaneous injection into the thigh or abdomen, except the 5 cm around the navel. If somebody else administers the injection, the upper arm can also be used. For the initial 600 mg dose, four 150 mg tralokinumab injections should be administered consecutively in different injection sites. It is recommended to rotate the injection site with each dose. Tralokinumab should not be injected into skin that is tender, damaged or has bruises or scars. A patient may self inject tralokinumab or the patient's caregiver may administer tralokinumab if their healthcare professional determines that this is appropriate. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions and warnings:** If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of tralokinumab should be discontinued and appropriate therapy initiated. Patients treated with tralokinumab who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. Patients with pre-existing helminth infections should be treated before initiating treatment with tralokinumab. If patients become infected while receiving tralokinumab and do not respond to antihelminth treatment, treatment with tralokinumab should be discontinued until infection resolves. Live and live attenuated vaccines should not be given concurrently with tralokinumab. **Fertility, pregnancy and lactation:** There is limited data from the use of tralokinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy. It is unknown whether tralokinumab is excreted in human milk or absorbed systemically after ingestion. Animal studies did not show any effects on male and female reproductive organs and on sperm count, motility and morphology. **Side effects:** *Very common (≥1/10):* Upper respiratory tract infections. *Common (≥1/100 to <1/10):* conjunctivitis, conjunctivitis allergic, eosinophilia, injection site reaction. *Uncommon (≥1/1,000 to <1/100):* keratitis. **Precautions for storage:** Store in a refrigerator (2°C-8°C). Do not freeze. Store in the original package in order to protect from light. **Legal category:** POM **Marketing authorisation number and holder:** PLGB 05293/0182, EU/1/21/1554/002. LEO Pharma A/S, Ballerup, Denmark. **Basic NHS price:** 4 pre-filled syringes: £1,070 (each syringe contains 150 mg/mL). **Last revised:** July 2021. **Reference number:** REF-19086(2)

Reporting of Suspected Adverse Reactions
Adverse events should be reported.
Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
Adverse events should also be reported to Drug Safety at LEO Pharma by calling +44 (0)1844 347333 or e-mail: medical-info.uk@leo-pharma.com

References: 1. Adtralza® SPC. **2.** Duggan S. Drugs 2021;81(14):1657–1663. **3.** Bieber T. Allergy 2020;75:54–62. **4.** Data on file, LEO Pharma (002-TRA-APR 2022, REF-21352). **5.** Blauvelt A, *et al.* Poster presented at the American Academy of Dermatology Association Annual Meeting, March 25-29, 2022.

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Cost-effectiveness of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris

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Abstract

Background. Acne vulgaris is a common skin condition that may cause psychosocial distress. There is evidence that topical treatment combinations, chemical peels and photochemical therapy (combined blue/red light) are effective for mild-to-moderate acne, while topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and photodynamic therapy are most effective for moderate-to-severe acne. Effective treatments have varying costs. The National Institute for Health and Care Excellence (NICE) in England considers cost-effectiveness when producing national clinical, public health and social care guidance.

Aim. To assess the cost-effectiveness of treatments for mild-to-moderate and moderate-to-severe acne to inform relevant NICE guidance.

Methods. A decision–analytical model compared costs and quality-adjusted life-years (QALYs) of effective topical pharmacological, oral pharmacological, physical and combined treatments for mild-to-moderate and moderate-to-severe acne, from the perspective of the National Health Service in England. Effectiveness data were derived from a network meta-analysis. Other model input parameters were based on published sources, supplemented by expert opinion.

Results. All of the assessed treatments were more cost-effective than treatment with placebo (general practitioner visits without active treatment). For mild-to-moderate acne, topical treatment combinations and photochemical therapy (combined blue/red light) were most cost-effective. For moderate-to-severe acne, topical treatment combinations, oral antibiotics combined with topical treatments, and oral isotretinoin were the most cost-effective. Results showed uncertainty, as reflected in the wide confidence intervals around mean treatment rankings.

Conclusion. A range of treatments are cost-effective for the management of acne. Well-conducted studies are needed to examine the long-term clinical efficacy and cost-effectiveness of the full range of acne treatments.

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Introduction

Acne vulgaris is the eighth most common disease globally[1] and a common presentation to dermatologists.[2] Acne may have a detrimental physical,

psychological and social impact.[2–4] A network meta-analysis (NMA), assessing topical pharmacological, oral pharmacological, physical and combined treatments, found that topical treatment combinations, chemical peels and photochemical therapy (combined blue/red light) are effective treatments for mild-to-moderate acne, while topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and photodynamic therapy (PDT) are most effective for moderate-to-severe acne.[5] Effective treatments have varying treatment costs, including drug acquisition, time of the healthcare professional [HCP; general practitioner (GP) or specialist dermatologist] and special equipment. Evidence on the cost-effectiveness of acne treatments is currently lacking. Thus, our study objective was to examine the cost-effectiveness of effective treatments for mild-to-moderate and moderate-to-severe acne from the perspective of the National Health Service (NHS) in England, using decision–analytical economic modelling.

This economic analysis informed the development of National Institute for Health and Care Excellence (NICE) guidance for the management of acne in England.[6] NICE considers cost-effectiveness when producing national guidance for health and social care services. The guideline was developed by a committee of clinical academics, HCPs and service users with expertise and experience in acne. The committee contributed to the development of the economic model by providing advice on the natural history of acne and its treatment patterns in England, and on model assumptions where evidence was lacking.

Methods

Population

The study population comprised people with mild-to-moderate and moderate-to-severe acne presenting to primary care services. Separate analyses were conducted for males and females with moderate-to-severe acne because (i) the intervention cost of oral isotretinoin is higher for females due to pregnancy tests and increased monitoring visits, and (ii) sex-specific discontinuation data were available for moderate-to-severe acne.

Interventions

We included treatment classes showing evidence of efficacy vs. placebo [indicated by 95% credible intervals (CrI) around the effects not crossing the 'no effect' line] in the NMA that informed the NICE guideline (the source NMA).[5] We considered only treatment classes with ≥ 50 observations across randomized controlled trials (RCTs) included in the efficacy NMA, as this was deemed the minimum adequate evidence base to enable robust conclusions on clinical and cost-effectiveness.

One intervention from each treatment class was selected as representative for costing purposes. All interventions were assumed to be delivered within the NHS. Selection of interventions assessed in the economic analysis (Table 1) was based on their availability and usage in the UK, practicalities of use (e.g. fixed topical treatment combinations were preferred to non-fixed formulations), the size of their evidence base and their risk of side effects relative to other interventions within the class.

Economic model structure

A decision tree was constructed to estimate total NHS costs and quality-adjusted life years (QALYs) for each treatment over 1 year (Fig. 1). This time horizon, determined by the available follow-up data, was deemed adequate to capture longer-term outcomes and costs of acne treatment without significant extrapolation. Patients were modelled as having excellent, good, moderate or no perceived improvement following treatment (Supplementary Data S1 provides full details of the model).

Clinical model inputs

Relative effects on efficacy [percentage change in total acne lesion count from baseline (%CFB)], discontinuation due to any reason and discontinuation due to side effects were obtained from the source NMA[5] (Supplementary Data S2). For mild-to-moderate acne, the economic analysis considered only treatments with evidence of efficacy in a bias-adjusted NMA, owing to indication of small study bias.[5]

To obtain absolute effects for each treatment and outcome, we combined NMA relative effects with absolute effects of a reference treatment. We selected adapalene (topical retinoid) as the reference treatment based on data availability. Absolute effects for adapalene were estimated from large RCTs included in the source NMA,[5] and discontinuation data from a small non-UK observational study[7] (Supplementary Data S3).

Patients' perception of their acne improvement may differ from the clinical measurement of improvement

Table 1 Types of treatment, classes and interventions assessed in the economic analysis for each level of acne severity.

Class	Intervention
Mild-to-moderate acne	
Topical monotherapies (including topical antibiotic monotherapy)	
Topical retinoids	Adapalene
BPO (own class)	BPO
Topical macrolides	Topical erythromycin
Topical treatment combinations (some include a topical antibiotic)	
BPO + topical retinoids	BPO + adapalene
BPO + topical lincosamides	BPO + topical clindamycin
BPO + topical macrolides	BPO + topical erythromycin
Topical retinoids + topical lincosamides	Topical tretinoin + topical clindamycin
Topical macrolides + topical antifungals	Topical erythromycin + topical bifonazole
Physical treatments	
Chemical peels	Salicylic acid peel[a]
Photochemical therapy (blue light) (own class)	Photochemical therapy (blue light)
Photochemical therapy (combined blue/red light) (own class)	Photochemical therapy (combined blue/red light)
Treatment with placebo[b]	
Treatment with placebo (own class)	Treatment with placebo
Moderate-to-severe acne	
Topical monotherapies (including topical antibiotic monotherapy)	
Topical retinoids	Adapalene
BPO (own class)	BPO
Topical lincosamides	Topical clindamycin
Topical treatment combinations (some include a topical antibiotic)	
BPO + topical retinoids	BPO + adapalene
BPO + topical lincosamides	BPO + topical clindamycin
BPO + topical macrolides	BPO + topical erythromycin
Topical retinoids + topical lincosamides	Topical tretinoin + topical clindamycin
BPO + topical retinoids + topical lincosamides	BPO + topical tretinoin + topical clindamycin
Oral antibiotic monotherapies	
Oral tetracyclines	Oral lymecycline
Oral antibiotics combined with topical treatments	
Oral tetracyclines + topical retinoids	Oral lymecycline + adapalene
Oral tetracyclines + azelaic acid	Oral lymecycline + azelaic acid
Oral tetracyclines + BPO + topical retinoids	Oral lymecycline + BPO + adapalene
Oral isotretinoin	
Oral isotretinoin; total cumulative dose ≥ 120 mg/kg (single course)	Oral isotretinoin daily dose ≥ 0.5 mg/kg
Oral isotretinoin; total cumulative dose < 120 mg/kg (single course)	Oral isotretinoin daily dose ≥ 0.5 mg/kg
Physical treatments	
Photodynamic therapy[c] (own class)	Photodynamic therapy
Photochemical therapy (red light) (own class)	Photochemical therapy (red light)
Treatment with placebo[b]	
Treatment with placebo (own class)	Treatment with placebo

BPO, benzoyl peroxide. [a]Applied and monitored by health professionals; [b]modelled as general practitioner visits without active treatment; [c]form of phototherapy that involves a source of light (e.g. red light, blue light, broad-spectrum light, daylight) and a photosensitizing chemical (e.g. 5-aminolaevulinic acid or methyl aminolaevulinate).

as expressed by %CFB. The relationship between the two (Table 2) was determined using published trial evidence.[8] The same evidence[8] was used to determine the distribution around the mean %CFB at treatment endpoint, in order to estimate the proportion of people with excellent, good, moderate and no improvement for each treatment (Supplementary Data S4). Owing to limited and heterogeneous evidence, the risk of relapse following excellent, good and moderate improvement was based on expert opinion.

Utility data

Utility values express people's preferences regarding health-related quality of life (HRQoL) on a scale from 0 (death) to 1 (perfect health) and are necessary for estimating QALYs. The utility values used in the economic model (Table 2) were determined using utility data from two studies[9,10] identified from a systematic search, a published mapping algorithm,[11] utility values of the UK general young adult population[12] and further assumptions (Supplementary Data S5).

Resource use and cost data

The analysis included intervention costs for people who completed a course of treatment and those who discontinued early and the costs of average acne care (AAC), which comprises a mixture of care currently received by people with acne in the NHS, which may include GP consultations, specialist dermatologist care, drug treatment or no treatment. AAC represented NHS care provided to people with acne following early treatment discontinuation, completion of a course of physical treatment, inadequate improvement or relapse. Costs were estimated by combining resource use with respective unit costs.

Intervention resource use was based on relevant descriptions from RCTs included in the source NMA,[5]

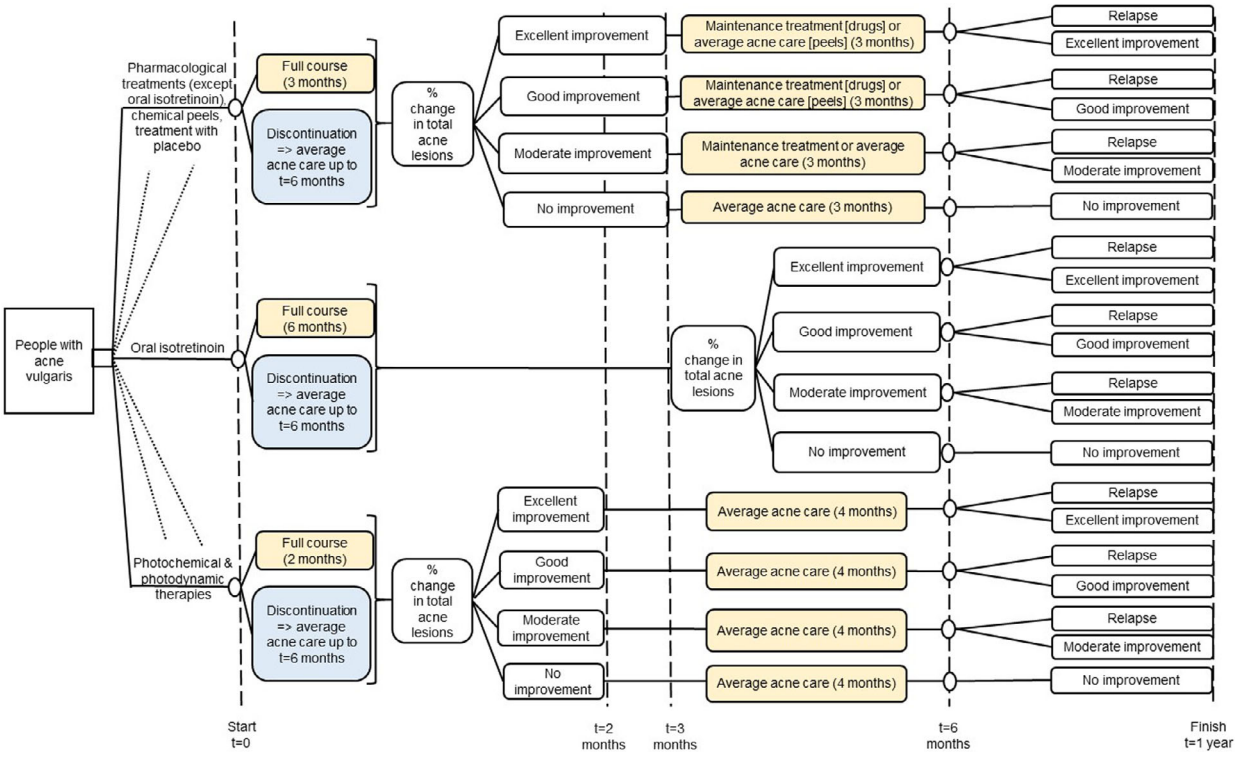

Figure 1 Schematic diagram of the economic model structure for people with mild-to-moderate and people with moderate-to-severe acne vulgaris. Chemical peels were assessed only in people with mild-to-moderate acne. Oral isotretinoin was assessed only in people with moderate-to-severe acne.

Table 2 Relationship between percentage change in total acne lesion count from baseline, perceived acne improvement and utility value.

		Utility value[9–12] and further assumptions[a]	
Acne health state	Perceived improvement[8]	Mild-to-moderate acne	Moderate-to-severe acne
Health states relating to %CFB			
71.26–100% reduction in acne lesions	Excellent	0.94	0.94
53.14–71.26% reduction in acne lesions	Good	0.90	0.87
28.20–53.14% reduction in acne lesions	Moderate	0.86	0.79
< 28.20% reduction or any % increase in acne lesions	None	0.82	0.72
Other health states			
Baseline (start of model)	NA	0.82	0.72
Reduction in utility due to intolerable side effects	NA	−0.04	−0.07

%CFB, percentage change in total lesion count from baseline; NA, not applicable. [a]Supplementary Data S5.

modified to reflect optimal routine practice in the UK. This incorporated (as relevant) the drug dosage and optimal duration, time of the HCP (GP and/or specialist care), laboratory testing for people receiving oral isotretinoin and any equipment used. Resource use related to AAC was obtained from UK primary care consultation and prescription data,[13] supplemented with expert opinion and further assumptions, particularly regarding specialist care received by a proportion of people with acne. Unit costs were obtained from national sources[14–17] and other published literature.[18] Intervention costs are summarized in Table 3, with full details on methods used for their estimation reported in Supplementary Data S6. Details of the estimation of the AAC cost are shown in Supplementary Data S7.

Table 3 Intervention costs of treatments for mild-to-moderate and moderate-to-severe acne following a full course (acute and maintenance treatment) and early discontinuation (2019 prices).

Type of treatment	Treatment class and modelled intervention	Cost[a] (full course)			Cost[a] (early discontinuation)
		Acute	Maint	Total	
Mild-to-moderate acne					
Topical monotherapies[b]	Topical retinoid: adapalene	£110.86	£71.86	£182.72	£55.43
	BPO (topical)	£86.26	£47.26	£133.52	£43.13
	Topical macrolides: erythromycin	£105.75	£66.75	£172.50	£48.25
Topical treatment combinations[c]	BPO + topical retinoid: BPO + adapalene	£117.06	£78.06	£195.12	£58.53
	BPO + topical lincosamide: BPO + clindamycin	£117.42	£78.42	£195.84	£52.14
	BPO + topical macrolide: BPO + erythromycin	£114.01	£75.01	£189.02	£52.38
	Topical retinoid + topical lincosamide: tretinoin + clindamycin	£113.82	£74.82	£188.64	£50.94
	Topical macrolides + topical anti-fungals: erythromycin + bifonazole	£121.90	£79.67	£201.57	£54.71
Physical treatments	Chemical peels: salicylic acid peel	£702.86	NA	£702.86	£216.59
	Photochemical therapy (blue light or combined blue/red light)	£546.14	NA	£546.14	£253.21
Treatment with placebo[d]	Treatment with placebo	£78.00	£39.00	£117.00	£39.00
Moderate-to-severe acne					
Topical monotherapies[b]	Topical retinoid: adapalene	£127.29	£88.29	£215.58	£55.43
	BPO (topical)	£90.39	£51.39	£141.78	£43.13
	Topical lincosamides: clindamycin	£121.30	£73.64	£194.94	£56.32
Topical treatment combinations[c]	BPO + topical retinoid: BPO + adapalene	£136.59	£97.59	£234.18	£58.53
	BPO + topical lincosamide: BPO + clindamycin	£143.70	£91.56	£235.26	£65.28
	BPO + topical macrolide: BPO + erythromycin	£136.64	£88.39	£225.03	£61.63
	Topical retinoid + topical lincosamide: tretinoin + clindamycin	£137.70	£86.76	£224.46	£62.88
	BPO + topical retinoid + topical lincosamide: BPO + tretinoin + clindamycin	£150.09	£99.15	£249.24	£67.01
Oral antibiotic monotherapies	Oral tetracycline: lymecycline	£108.64	£61.98	£170.62	£46.66
Oral antibiotics combined with topical treatments	Oral tetracycline + topical retinoid: lymecycline + adapalene	£157.93	£111.27	£269.20	£63.09
	Oral tetracycline + azelaic acid (topical): lymecycline + azelaic acid	£131.09	£79.94	£211.03	£55.64
	Oral tetracycline + BPO + topical retinoid: lymecycline + BPO + adapalene	£167.23	£120.57	£287.80	£66.19
Oral isotretinoin	Oral isotretinoin: total cumulative dose ≥ 120 mg/kg (single course); daily dose ≥ 0.5 mg/kg	F: £902.20	NA	F: £902.20	F: £309.90
		M: £581.70	NA	M: £581.70	M: £307.90
	Oral isotretinoin: total cumulative dose < 120 mg/kg (single course); daily dose ≥ 0.5 mg/kg	F: £869.32	NA	F: £869.32	F: £298.94
		M: £548.82	NA	M: £548.82	M: £296.94
Physical treatments	Photodynamic therapy	£850.82	NA	£850.82	£354.77
	Photochemical therapy (red light)	£546.14	NA	£546.14	£253.21
Treatment with placebo[d]	Treatment with placebo	£78.00	£39.00	£117.00	£39.00

BPO, benzoyl peroxide; F, costs for females; M, costs for males; Maint, maintenance; NA, not applicable. [a]Costs included drug acquisition, healthcare professional time, laboratory testing for oral isotretinoin, procedure costs for photochemical and photodynamic therapies; no costs of contraception included for oral or topical retinoids. [b]Including topical antibiotic monotherapy; [c]potentially including topical antibiotic component; [d]modelled as general practitioner visits without active treatment.

Costs were expressed in 2019 prices. Discounting of costs and benefits was not needed as the time horizon of the analysis was 1 year.

Statistical analysis

To account for the uncertainty around input parameter point estimates, a probabilistic analysis was

undertaken, with input parameters being assigned probability distributions.[19] Subsequently, 10 000 model iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. The mean costs and QALYs for each treatment were calculated by averaging across the 10 000 iterations. The net monetary benefit (NMB) for each intervention was estimated for each iteration and averaged across the 10 000 iterations, determined by the formula:

$$\mathrm{NMB} = E \times \lambda - C,$$

where E and C are the effects (QALYs) and costs of each intervention respectively, and λ represents the willingness to pay (WTP) per QALY, set at the NICE lower cost-effectiveness threshold of £20 000 per QALY.[20] The intervention with the highest NMB is the most cost-effective.[21] The mean ranking by cost-effectiveness (out of 10 000 iterations) is also reported for each intervention, with a rank of 1 indicating highest cost-effectiveness.

Supplementary Data S8 reports the model input values with probability distributions and additional sensitivity analyses conducted to test the robustness of the results.

Model validation

The economic model was constructed following the guideline committee's expert advice. All inputs and model formulae were systematically checked. The model was tested for logical consistency. The results were discussed with the committee to confirm plausibility.

Results

Table 4 shows the results of the economic analysis for treatments for mild-to-moderate acne (same for both sexes) and for moderate-to-severe acne in females. Results for treatments for moderate-to-severe acne in males (Supplementary Table S1) differed from those for females only in the ranking of oral isotretinoin, which was higher for males and is attributable to its lower intervention cost due to less intensive monitoring compared with females. The results are characterized by uncertainty, reflected in the wide 95% CIs around mean rankings.

The cost-effectiveness plane (Fig. 2) depicts the mean incremental costs and QALYs of all treatments vs. treatment with placebo (placed at the origin) in each analysis, ordered by magnitude of clinical benefits (QALYs). The cost-effectiveness acceptability frontier[21] (Fig. 3) shows the most cost-effective treatments for a range of values of WTP for a QALY (between £0 and £40 000 per QALY) and the probability of each treatment being cost-effective.

The results were overall robust to the scenarios explored through deterministic sensitivity analysis (Supplementary Data S9). The relative cost-effectiveness of physical therapies (chemical peels, photochemical therapies, PDT) and oral isotretinoin was reduced when the efficacy of the reference treatment (topical retinoid) was reduced or when the spread around the mean %CFB was increased. The latter was caused by ceiling effects, as people reached 100% improvement and could not improve further.

Discussion

Our analysis explored the relative cost-effectiveness of a wide range of topical pharmacological, oral pharmacological, physical and combined treatments for acne stratified by severity level. All treatments were more cost-effective than treatment with placebo (modelled as GP visits without active treatment). For mild-to-moderate acne, the most cost-effective treatments included topical treatment combinations and photochemical therapy (combined blue/red light). For moderate-to-severe acne, the most cost-effective treatments included topical treatment combinations, oral antibiotics combined with topical treatments, and oral isotretinoin.

To our knowledge, this is the first analysis exploring the relative cost-effectiveness of a wide range of treatment options for acne from a healthcare perspective, considering, in addition to drug acquisition costs, HCP resource use, including costs associated with inadequate response to treatment or relapse. Previous economic studies (identified through a systematic search conducted to inform the NICE guideline)[6] made limited comparisons of acne treatments, and the majority considered exclusively drug acquisition costs. A number of studies were simple cost analyses and most of them were characterized by important methodological limitations (Supplementary Data S10). Therefore, no robust conclusions can be drawn from the existing economic literature.

In our analysis, we used efficacy and discontinuation data derived from a large systematic review and NMA.[5] This approach combines direct (i.e. head-to-head comparisons) and indirect evidence (e.g. comparisons through a common comparator) and allows

Table 4 Cost-effectiveness results for treatments for mild-to-moderate and moderate-to-severe acne.[a,b]

Type of treatment	Class/Int	n[c]	NMB/ person	Mean per person			Mean rank (95% CI)
				QALY	Int cost	Total cost	
Mild-to-moderate acne (both sexes)							
Physical treatment	Photochemical therapy (blue/red light)	69	£17 163	0.885	£370	£545	4.42 (1–11)
Topical treatment combination	BPO + topical retinoid (adapalene)	1057	£17 123	0.868	£121	£242	3.39 (1–7)
Topical treatment combination	Topical retinoid (tretinoin) + topical lincosamide (clindamycin)	276	£17 105	0.867	£120	£234	3.94 (1–9)
Topical treatment combination	Topical macrolide (erythromycin) + topical anti-fungal (bifonazole)	74	£17 061	0.865	£112	£247	5.37 (1–12)
Physical treatment	Chemical peel (salicylic acid peel)	101	£17 029	0.888	£621	£736	6.63 (1–12)
Topical treatment combination	BPO + topical macrolide (erythromycin)	351	£17 017	0.863	£112	£239	5.83 (1–11)
Topical monotherapy	Topical retinoid: adapalene	1623	£16 957	0.860	£107	£242	6.59 (3–10)
Topical treatment combination	BPO + topical lincosamide (clindamycin)	992	£16 956	0.860	£115	£245	6.75 (3–10)
Topical monotherapy	BPO	1109	£16 937	0.858	£79	£216	7.14 (3–11)
Physical treatment	Photochemical therapy (blue light)	138	£16 928	0.876	£410	£588	7.75 (1–12)
Topical antibiotic monotherapy	Topical macrolide: erythromycin	765	£16 859	0.855	£97	£236	8.96 (5–11)
Treatment with placebo	Treatment with placebo	2005	£16 704	0.846	£67	£217	11.23 (9–12)
Moderate-to-severe acne (females)							
Topical treatment combination	Topical retinoid (tretinoin) + topical lincosamide (clindamycin)	1548	£16 460	0.838	£160	£299	2.92 (1–8)
Oral antibiotic + topical treatment	Oral tetracycline (lymecycline) + BPO + topical retinoid (adapalene)	556	£16 351	0.835	£196	£344	3.43 (1–9)
Oral antibiotic + topical treatment	Oral tetracycline (lymecycline) + topical azelaic acid	50	£16 231	0.827	£132	£306	5.54 (1–15)
Oral isotretinoin	Oral isotretinoin; total cumulative dose ≥ 120 mg/kg	182	£16 122	0.848	£755	£832	5.91 (1–16)
Topical antibiotic monotherapy	Topical lincosamide (clindamycin)	1479	£15 986	0.814	£134	£303	6.44 (2–12)
Topical treatment combination	BPO + topical retinoid (adapalene)	217	£15 975	0.815	£146	£329	6.96 (1–15)
Oral antibiotic + topical treatment	Oral tetracycline (lymecycline) + topical retinoid (adapalene)	379	£15 969	0.816	£162	£349	6.33 (2–11)
Topical monotherapy	BPO	80	£15 798	0.804	£97	£280	8.22 (2–14)
Physical treatment	Photodynamic therapy	298	£15 755	0.835	£705	£945	9.26 (2–16)
Oral isotretinoin	Oral isotretinoin; total cumulative dose < 120 mg/kg	938	£15 715	0.827	£726	£827	9.84 (2–17)
Oral antibiotic monotherapy	Oral tetracycline (lymecycline)	1386	£15 600	0.796	£106	£313	10.69 (7–14)
Physical treatment	Photochemical therapy (red light)	53	£15 547	0.814	£473	£727	11.46 (2–17)
Topical treatment combination	BPO + topical lincosamide (clindamycin)	276	£15 539	0.795	£157	£352	11.43 (4–16)
Topical treatment combination	BPO + topical lincosamide (clindamycin) + topical retinoid (tretinoin)	600	£15 534	0.795	£155	£360	11.29 (4–16)
Topical treatment combination	BPO + topical macrolide (erythromycin)	365	£15 511	0.793	£148	£346	11.70 (6–15)
Topical monotherapy	Topical retinoid: adapalene	3570	£15 219	0.779	£120	£359	14.97 (12–16)
Treatment with placebo	Treatment with placebo	4122	£15 006	0.766	£68	£319	16.62 (15–17)

BPO, benzoyl peroxide; CI, confidence interval; Int, intervention; NMB, net monetary benefit; QALY, quality-adjusted life year. [a]Classes are ordered by NMB (highest NMB indicates highest cost-effectiveness); [b]NMB and ranking estimated using a cost-effectiveness threshold (willingness to pay) of £20 000/QALY; [c]n, number of observations across randomized controlled trials included in the network meta-analysis of efficacy that informed the economic analysis.

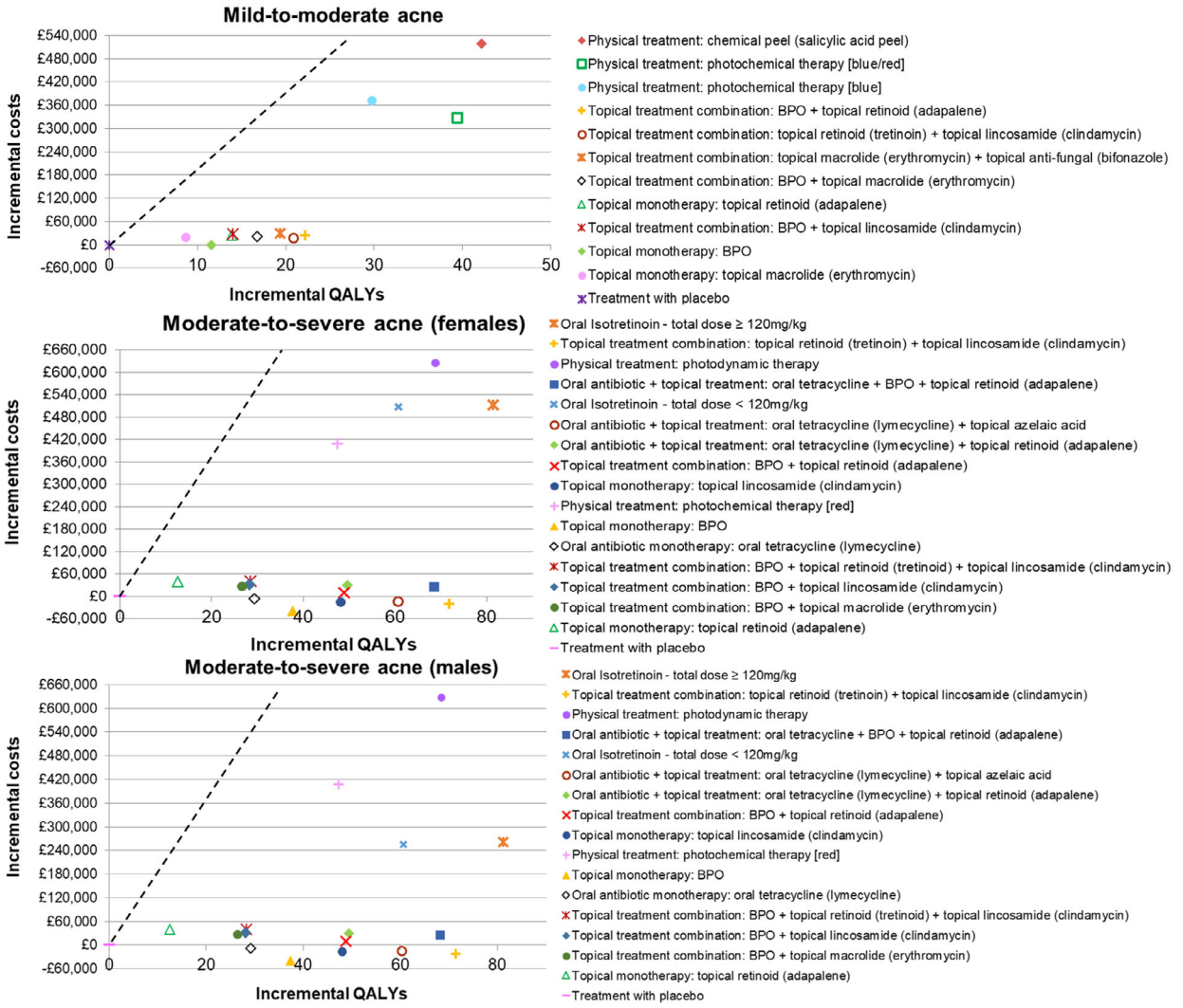

Figure 2 Cost-effectiveness planes. Results for 1000 people with acne vulgaris. In each graph, the points for each treatment show its incremental quality-adjusted life years (QALYs) (horizontal axis) and costs (vertical axis) vs. treatment with placebo, which is placed at the origin. The slope of the dotted line indicates the National Institute for Health and Care Excellence lower cost-effectiveness threshold of £20 000/QALY. Moving towards the right of the horizontal axis, treatments result in more QALYs. For both acne severity levels, all treatments produce more QALYs compared with treatment with placebo. Moving towards the top of the vertical axis, treatments become more costly. For both acne severity levels, all treatments are more costly than treatment with placebo, with the exception of BPO in mild-to-moderate acne, and with the exception of BPO, topical clindamycin, combined topical tretinoin with clindamycin, oral lymecycline, and azelaic acid combined with oral lymecycline in moderate-to-severe acne. In all three graphs, treatments lie on the right side of the dotted line, suggesting that in all three analyses all assessed treatments are cost-effective compared with treatment with placebo.

simultaneous comparisons across all options while preserving randomization.[22,23] There was some inconsistency between the direct and indirect evidence synthesized in the NMA, possibly reflecting heterogeneity in populations, treatments or study design across the included RCTs. However, NMA conclusions were robust to potential bias in the evidence. The RCTs included in the NMAs were of moderate to very low quality. The strengths and limitations of the source NMA and included RCTs should be considered when interpreting the cost-effectiveness results.

The size of the evidence differed considerably across the examined treatments. Topical treatments had the largest evidence base on efficacy (several topical treatments had > 500 observations each), followed by oral treatments alone or combined with topical treatments,

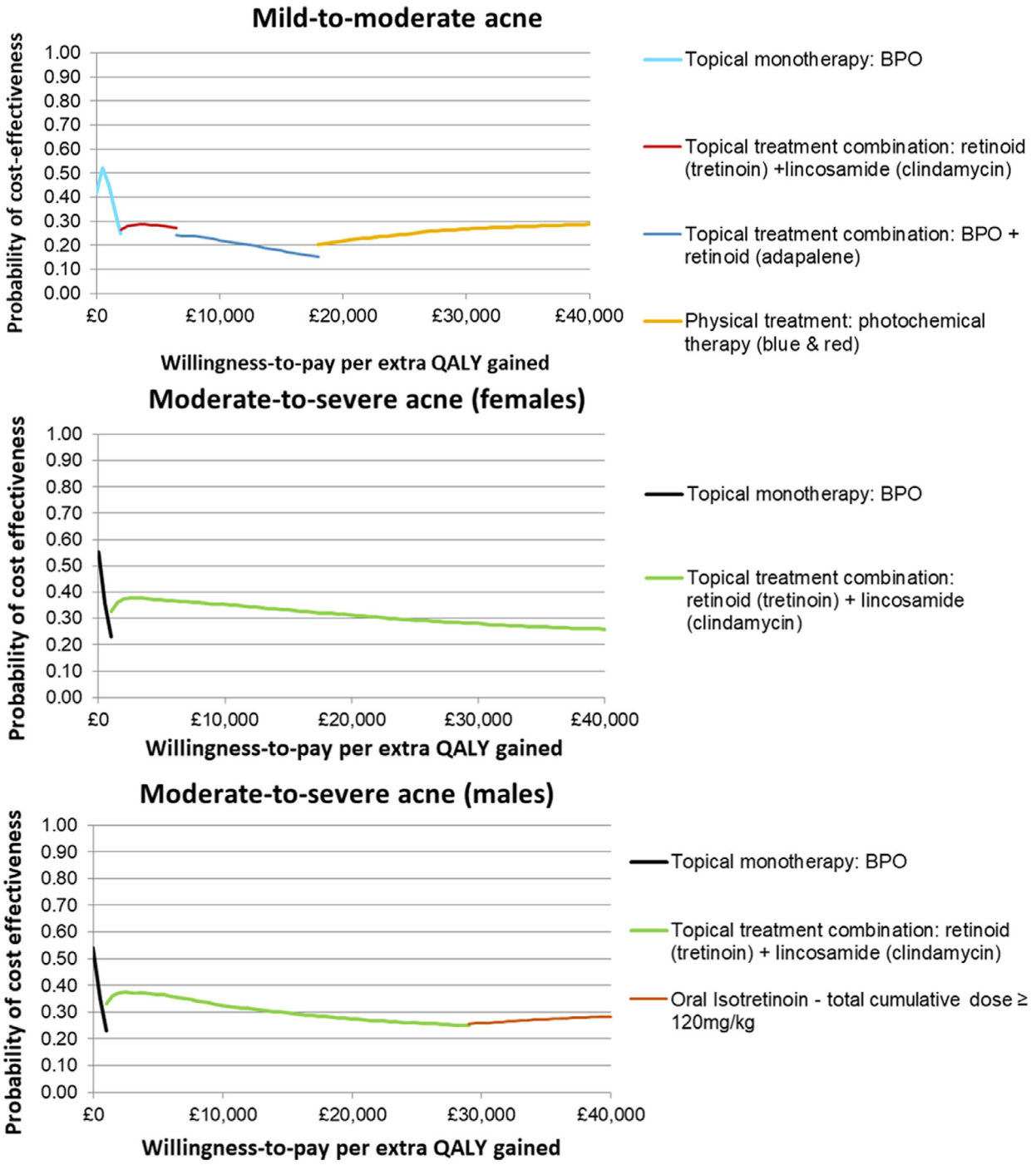

Figure 3 Cost-effectiveness acceptability frontier. Each graph shows the most cost-effective treatment of each analysis, over a range of values of willingness to pay for a quality-adjusted life year (QALY), which was varied between £0 and £40 000 per QALY (horizontal axis) and the probability that this treatment is the most cost-effective of those assessed, reflecting the uncertainty in the results (vertical axis).

whereas the evidence for physical therapies (chemical peels, photochemical therapies, PDT) was based on < 300 observations for each treatment class.

Model input parameters were obtained from sources of varying quality (ranging from RCTs through to large retrospective analyses to expert opinion), depending on

data availability. The time horizon of the analysis (1 year) was considered adequate to capture longer-term outcomes and costs associated with a course of acne treatment, but some long-term effects, such as potential subsequent scarring and associated management costs were not captured because of insufficient evidence. Costs and utility decrements associated with side effects of treatment were not considered; however, we did incorporate the impact of intolerable side effects on HRQoL and costs. Antimicrobial resistance associated with antibiotic use was not considered. These omissions constitute limitations of our analysis.

We carried out probabilistic analyses to handle uncertainty around model parameters and deterministic sensitivity analyses to address gaps in the evidence. The results were characterized by some uncertainty; however, they were overall robust to scenarios tested through deterministic sensitivity analysis.

Our analysis was conducted from the perspective of the NHS in England. The results may be generalizable to other settings with similar funding and structure of healthcare services and comparable care pathways for people with acne. Conclusions on cost-effectiveness ultimately rely on the cost-effectiveness threshold adopted, and this depends on the policymakers' willingness to pay for treatment benefits, which may vary across countries and health systems.

The results of this economic analysis, along with clinical evidence from the NMA[5] and other considerations, informed the NICE national guidance on the management of acne vulgaris.[6] These considerations included concerns about antibiotic resistance, current regulations regarding oral isotretinoin,[24,25] long-term harms of chemical peel use outside specialist settings (e.g. risk for significant skin damage from inappropriate strength or type of peel) and limited availability and use of some treatments in NHS routine practice (e.g. chemical peels, photochemical therapies, PDT, topical antifungals). Doxycycline was considered a suitable alternative to lymecycline, as they have similar efficacy, AE profile and acquisition cost.

Fixed topical treatment combinations [adapalene with benzoyl peroxide (BPO); clindamycin with BPO; tretinoin with clindamycin] were recommended as first-line treatments of mild-to-moderate acne. Fixed topical treatment combinations (adapalene with BPO; tretinoin with clindamycin), or oral tetracyclines (doxycycline or lymecycline) combined with topical treatments (azelaic acid, or a fixed combination of adapalene with BPO) were recommended as first-line treatments of moderate-to-severe acne. Where oral lymecycline or doxycycline are contraindicated or not tolerated, alternative oral antibiotics (trimethoprim or an oral macrolide such as erythromycin) might be considered. BPO might be considered across both severity levels if other recommended first-line treatments are contraindicated (e.g. during pregnancy) or if there is a patient preference against their use. PDT might be considered for adults with moderate-to-severe acne if other treatments are ineffective, not tolerated or contraindicated.

Conclusion

This economic analysis allowed estimation of the relative cost-effectiveness of a range of topical pharmacological, oral pharmacological, physical and combined treatments for acne stratified by severity level. The results informed the NICE national guidance on the management of acne vulgaris. There remains a need for well-conducted studies that examine the long-term clinical efficacy and cost-effectiveness of the full range of acne treatments.

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Conflict of interest

IM, NB, LB and KD received support from the NGA for the submitted work. CHD and NJW received support from the NICE Centre for Guidelines for the submitted work. JW, JCR, DW and EH declared the following interests based on the NICE policy on conflicts of interests: https://www.nice.org.uk/guidance/ng198/documents/register-of-interests. The authors report no other relationships or activities that could appear to have influenced the submitted work.

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Ethics statement

Ethics approval and informed consent not applicable.

Data availability

Data are available in the supplementary files.

What's already known about this topic?

- Acne vulgaris is the eighth most common disease globally.
- In a previous NMA, topical treatment combinations, chemical peels and photochemical therapies were most effective for mild-to-moderate acne; and topical treatment combinations, oral antibiotics combined with topical treatments, oral isotretinoin and PDT were most effective for moderate-to-severe acne.
- Evidence on the cost-effectiveness of acne vulgaris treatments is lacking.
- Identifying acne vulgaris treatments that ensure efficient healthcare resource use is needed.

What does this study add?

- All treatments are more cost-effective than treatment with placebo, modelled as GP visits without active treatment.
- For mild-to-moderate acne, the most cost-effective treatments include topical treatment combinations and photochemical therapy (combined blue/red light).
- For moderate-to-severe acne, the most cost-effective treatments include topical treatment combinations, oral antibiotics combined with topical treatments, and oral isotretinoin.
- These findings, combined with NMA findings and other clinical considerations, informed NICE guidance on the management of acne vulgaris.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Data S1. Description of economic model structure and assumptions.

Supplementary Data S2. Relative effects on efficacy and discontinuation used in the economic analysis.

Supplementary Data S3. Methods of estimation of absolute effects for the reference treatment.

Supplementary Data S4. Distribution around the mean percentage change in total acne lesion count from baseline (%CFB) in the economic model.

Supplementary Data S5. Methods of estimation of utility values used in the economic analysis.

Supplementary Data S6. Intervention costs of treatments for acne vulgaris used in the economic analysis.

Supplementary Data S7. Estimation of the average acne care cost.

Supplementary Data S8. Model input values, probability distributions and scenarios tested in deterministic sensitivity analysis.

Supplementary Data S9. Results of deterministic sensitivity analysis.

Supplementary Data S10. Published economic assessments of acne treatments.

Supplementary Table S1. Cost-effectiveness results for treatments for moderate-to-severe acne in males.