BMJ Open Ophthalmology

Polihexanide (PHMB) 0.08% versus currently used treatments for *Acanthamoeba* keratitis: indirect treatment comparisons

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To cite: Papa V, Galeone C, De Francesco M, *et al*. Polihexanide (PHMB) 0.08% versus currently used treatments for *Acanthamoeba* keratitis: indirect treatment comparisons. *BMJ Open Ophthalmology* 2025;**10**:e002082. doi:10.1136/bmjophth-2024-002082

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjophth-2024-002082).

Received 3 December 2024
Accepted 27 June 2025

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ABSTRACT

Background/aims *Acanthamoeba* keratitis is a rare, severe corneal infection. Until the recent approval of polihexanide (PHMB) 0.08% by the European Medicines Agency, there were no licensed medical therapies and current treatments relied on off-label or compounded products. The purpose of this study is to estimate the relative efficacy of PHMB 0.08% compared with current treatments.

Methods A patient-level indirect treatment comparison (ITC) compared data from a pivotal trial of PHMB 0.08% and a retrospective real-world study of current treatments: (1) any anti-amoebic treatment (AAT), (2) PHMB 0.02% plus a diamidine (propamidine or hexamidine) 0.1% and (3) chlorhexidine (CXL) 0.02% alone or in combination with a diamidine. The primary outcome was the clinical resolution rate (CRR) without surgery within 12 months. ITCs were implemented using propensity scoring analysis with overlap weighting and adjustment for covariates (age, sex, disease stage, treatment delay, prior use of corticosteroid or antiviral).

Results The CRR was 84.8% for PHMB 0.08% (n=66), 43.6% for any AAT (n=227), 55.0% for PHMB 0.02% plus a diamidine (n=111) and 40.0% for CXL 0.02% with or without a diamidine (n=35). In the unweighted analysis, the absolute difference (95% CI) in favour of PHMB 0.08% was 41.2% (28.8%, 51.2%; p<0.001) compared with any AAT, 29.9% (14.5%, 42.1%; p<0.001) compared with PHMB 0.02% plus a diamidine and 44.8% (23.9%, 62.3%; p<0.001) compared with CXL 0.02% with or without a diamidine. Similar results were observed in the weighted analyses.

Conclusions These results suggest that PHMB 0.08% when delivered with the recommended protocol is significantly more effective than currently used treatments in achieving clinical resolution without surgery. The study limitations include differences in recruitment periods, diagnostic criteria and drug delivery methodology, as well as limitations of the ITC adjustment measures which can lead to residual confounding.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Until 2024, there were no licensed therapies for treating *Acanthamoeba* keratitis. This results in a lack of robust relative efficacy estimates covering treatments currently in use.

WHAT THIS STUDY ADDS

⇒ In these analyses, polihexanide (PHMB) 0.08%, a novel and newly licensed treatment, combined with an appropriate treatment delivery protocol, had higher rates of clinical resolution without surgery compared with currently used treatments in *Acanthamoeba* keratitis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results provide evidence supporting the wider use of PHMB 0.08% as a potential effective treatment for patients with *Acanthamoeba* keratitis and could serve to inform future treatment recommendations or guidelines, and pharmacotherapeutic or pharmacoeconomic analyses informing health policy decisions. Further studies are required to confirm these findings.

INTRODUCTION

Acanthamoeba keratitis (AK) is a rare and highly debilitating corneal infection caused by the protozoan *Acanthamoeba*.[1] If not treated promptly, it can lead to visual impairment and even blindness.[2]

Until 2024, no medicinal products were licensed for treating AK; thus, clinical practice has consisted of using various unlicensed anti-amoebic treatments (AATs), such as polihexanide (PHMB), chlorhexidine (CXL), propamidine, hexamidine or miltefosine, often given in combination.[1 3] Some of these treatments are not readily available, so they need to be compounded or imported from other countries. This leads to a delay in treatment initiation, which impacts patient outcomes.

PHMB 0.08% (0.8 mg/mL) is a new preservative-free ophthalmic solution that has been recently approved by the European Medicines Agency as the first licensed product for treating AK. PHMB 0.08% has

been tested in a phase 3, prospective, randomised controlled trial (ClinicalTrials.gov: NCT03274895). This trial (referred to as the 'pivotal trial' throughout this paper) compared PHMB 0.08% (plus placebo) to PHMB 0.02% (0.2 mg/mL) plus propamidine 0.1% (1 mg/mL). The clinical cure rate (CRR), without surgery, within 12 months from randomisation in the PHMB 0.08% group was 84.9% (95% CI 73.9%, 92.5%).[4] Surprisingly, the CRR observed in the control arm was high (88.5%; 95% CI 77.8%, 95.3%) when compared with data from retrospective studies in which approximately only 60% of patients treated with currently available treatments reached a medical cure.[2 5 6] This difference might be considered to reflect a study effect due to the prompt availability of investigational medicine products at clinical sites, the use of a standardised protocol for treatment delivery and the management of adjunctive medications. Therefore, the efficacy observed in the comparator arm of the pivotal trial might be unrepresentative of what is currently achievable in current practice using compounded and off-label treatments, the provision of which may be delayed and for which drug delivery protocols, and the use of adjunctive medication, often differ from one practitioner and one patient to another.

Since no direct evidence exists of PHMB 0.08% versus currently used treatments for AK, outside the setting of the pivotal trial, the aim of this study is to conduct an indirect treatment comparison (ITC).

METHODS

Definitions used

Clinical resolution (cure): clinical evidence of elimination of *Acanthamoeba*; intact epithelium and no clinical signs of ocular inflammation after discontinuing antiamoebic and anti-inflammatory treatments for 1 month.

Clinical cure rate (CRR): Proportion of patients cured without surgery within 1 year of treatment.

ITC: A statistical method[7] to compare the effectiveness of two or more treatments that have not been directly compared in head-to-head trials.

Feasibility assessment

The feasibility of conducting an ITC between PHMB 0.08% and currently used treatments for AK was assessed based on a systematic literature review (SLR) conducted to identify studies that reported clinical outcome data for AK treatments (PROSPERO: CRD42022345288).[8] The SLR included studies with ≥5 patients with AK. The intervention of interest was any agent with an established anti-amoebic activity administered as eye-drops or orally in any concentration or combination. There were no specific eligibility criteria on the comparator treatments. The main outcome of interest was clinical resolution. Data were also extracted on any other relevant reported clinical outcomes. Electronic databases (January 1992–July 2022), conference abstracts (2017–2022), and relevant websites were handsearched, with forward and backward citation searching. Two independent reviewers screened the titles/abstracts followed by the full texts. The SLR identified 37 eligible studies (2043 patients).

The feasibility assessment focused on whether any of the 37 studies identified in the SLR used outcome definitions that were sufficiently aligned with those used in the pivotal trial[4] to allow evidence synthesis, given that heterogeneity between outcome definitions cannot be accounted for within an ITC analysis. As a result, the number of sources potentially informing the ITC, and the scope of the comparisons conducted, were limited by differences in outcome definitions.

The feasibility assessment concluded that, for most outcomes extracted during the SLR, the outcome definitions and assessment timings were too varied to allow meaningful comparison between studies.[8] Therefore, the outcome selected for the ITC was clinical resolution (cure without surgery), which was the primary outcome in the PHMB 0.08% pivotal trial.[4]

In the SLR, 20 studies reported clinical resolution[8]; however, only one retrospective study used a definition of clinical resolution fully aligned (regarding definition, time point and approach towards discontinuation of initial treatment) with the one used in the pivotal trial and was, therefore, selected for the ITC analysis.[2] Since in the pivotal trial (but not in the retrospective study), discontinuations from antiamoebic therapy were considered as treatment 'failures', individual patient data (IPD) from the retrospective study were acquired from the authors, as described in the SLR protocol (PROSPERO: CRD42022345288), to align definitions. Patients or the public were not involved in this research.

Data sources

IPD for PHMB 0.08% were available from its pivotal trial,[4] which was a multicentre randomised, assessor-masked, active-controlled, phase 3 study (2017–2021). The primary endpoint was CRR at 12 months from randomisation, defined as the percentage of patients cured 30 days after discontinuing all study therapies within 12 months. Patients were eligible for inclusion if they were at least 12 years old at baseline and had a diagnosis of AK confirmed by culture±Acanthamoeba nucleic acid by PCR±in vivo confocal microscopy (IVCM). A total of 135 patients were enrolled at 6 sites in three countries and randomised (1:1) to receive the monotherapy PHMB 0.08% plus placebo, or the combination therapy with PHMB 0.02% and propamidine 0.1%. Only the intervention arm (PHMB 0.08% plus placebo) was analysed in this ITC and included the 66 patients in the final analysis set.[4] Online supplemental table 1 shows the diagnostic categories for these 66 patients. The drugs were delivered using a comprehensive protocol. Patients were excluded if diagnosed with concurrent infections other than bacterial keratitis, such as fungal and herpes keratitis.

Comparator data were available from the retrospective study identified in the SLR,[2] which was a multinational, observational study to estimate the efficacy of several

therapies used for people with AK (1991–2012). This retrospective cohort study, conducted at two centres (one in the UK and one in Italy), reported outcomes from 227 patients diagnosed with AK. Patients remained eligible if presenting with concurrent bacterial keratitis or if developing bacterial keratitis as an AK complication. The diagnosis of AK differed for this study and included culture, histopathological confirmation of trophozoites and/or cysts, IVCM and patients without any of the foregoing who had keratitis with perineural corneal infiltrates and/or ring infiltrates and/or a clinical course consistent with AK and a response to AAT. Treatments assessed were topical AAT given at the time of diagnosis (baseline AAT), including biguanides (CXL 0.02% and PHMB 0.02%) and diamidines (propamidine 0.1% and hexamidine 0.1%) either as monotherapy or in combination. In ITC analyses, three populations from the retrospective study were analysed. The first was the whole study population, regardless of which baseline AAT was received, referred to as 'any initial AAT'. The second population included the largest treatment subgroup of patients treated with PHMB 0.02% plus a diamidine (ie, propamidine or hexamidine) 0.1%, and the third population were those patients treated with CXL 0.02% alone or combined with a diamidine. These treatments are commonly used as initial treatment options in clinical practice. Drugs were delivered by individual physicians without the use of an agreed protocol.

Statistical analyses

As IPD were available for both studies being evaluated in the ITC, propensity scoring analysis (PSA) using overlap weighting was used.[9] This analysis approach can provide an estimation of the relative treatment effect, accounting for potential selection bias associated with some treatment-related factors, even if there are substantial differences between patient populations.[9] The overlap weights are used to account for selection assignment differences between treatment and control groups. A propensity score is calculated using a multivariable logistic regression, with the treatment group as the binary outcome and likely prognostic factors or treatment effect modifiers (age; gender; AK disease stage; prior use of corticosteroids; prior use of antivirals; delay in starting treatment from diagnosis)[5 10–12 13] as covariates. The overlap weight was then calculated as 1 minus the propensity score for the corresponding treatment. IPD were reweighted to balance study populations by adjusting for observed cross-trial differences in prognostic factors and treatment effect modifiers considered in the analysis (see below). The overlap weights by treatment arm were transformed so that the sum of the weights represented the actual sample size in each arm.

As overlap weighting was used, the calculated estimate represents the average treatment effect in the overlap population, that is, subjects that are similar in both treatment arms.

CRR was assessed using adjusted logistic regression methods to estimate the absolute difference in cure rate, and corresponding 95% CI between treatments. Six factors were identified as potential prognostic factors and/or treatment effect modifiers for inclusion in the logistic regression models: age; gender; AK disease stage; prior use of corticosteroids; prior use of antivirals; the delay in starting treatment. Patients with missing covariate or outcome data were excluded from the analysis, except for treatment delay and age. Missing treatment delay data were imputed with the median value and missing age data were imputed with the mean value. The results of the analyses were then reweighted to the original sample size to represent the results on the original population sizes.

Analyses were conducted in SAS V.9.4 (SAS Institute).

RESULTS

Key patient characteristics are summarised in table 1. Some differences among populations were observed, the most important being the proportion of advanced (stage 3) disease at baseline (16.7% in the pivotal trial and 27.3% in the retrospective study). Since the stage of disease at baseline, as well as treatment delay and prior use of steroids and antivirals, are risk factors for a poor outcome,[10] these characteristics were weighted. As displayed in table 2, the weighting successfully aligned the populations to be analysed.

The comparison of the CRRs is shown in table 3. The unadjusted CRR was 84.8% for PHMB 0.08% (n=66), 43.6% for 'any initial AAT' (n=227), 55.0% for PHMB 0.02% plus a diamidine 0.1% (n=111) and 40.0% for CXL 0.02% alone or plus a diamidine 0.1% (n=35).

The absolute percentage difference in CRR (95% CI) was 41.2% (28.8%, 51.2%; p<0.001), 29.9% (14.5%, 42.1%; p<0.001) and 44.8% (23.9%, 62.3%; p<0.001) in favour of PHMB 0.08% when compared with 'any initial AAT', PHMB 0.02% plus a diamidine 0.1%, and CXL 0.02% alone or plus a diamidine 0.1%, respectively. Similar results were observed after weighting, with a difference of 36.4% (24.9%, 47.9%; p<0.001), 24.2% (11.3%, 37.1%; p<0.001) and 36.8% (14.2%, 59.5%; p=0.002), respectively.

In these analyses, the effective sample sizes of both the pivotal and retrospective data were only minimally reduced, suggesting that most patients were given a reasonably high weight in the analyses.

DISCUSSION

PHMB 0.08% has recently become the first licensed medicinal product in Europe for the treatment of AK. Prior to this, there were no licensed products in any country. Current clinical practice is based on off-label products that often need to be compounded or imported, and the treatments are delivered in variable ways without the availability of evidence-based treatment delivery protocols.[4]

In the present study, we conducted ITCs to compare the clinical resolution of PHMB 0.08% with that of currently

Table 1 Summary of unweighted characteristics for patients with AK treated with PHMB 0.08%,[4] any initial AAT,[2] PHMB 0.02% plus a diamidine 0.1%[2] or CXL 0.02% alone or plus a diamidine 0.1%[2]

	Dart *et al*[4] 2024‡	Papa *et al*[2] 2020		
	PHMB 0.08%	Any initial AAT	PHMB 0.02% plus diamidine 0.1%	CXL 0.02% alone or plus diamidine 0.1%
Number of patients	66	227	111	35
Age, years				
Mean (SD)	35.2 (13.2)	35.7 (13.8)	34.4 (13.6)	36.2 (13.8)
Median (min, max)	33.5 (15.0, 73.0)	33.0 (13.0, 76.0)	32.0 (13.0, 75.0)	35.0 (17.0, 74.0)
Male, n (%)	27 (40.9)	100 (44.1)	49 (44.1)	19 (54.3)
AK disease stage, n (%)				
1–2	55 (83.3)	149 (72.7)	86 (77.5)	20 (66.7)
3	11 (16.7)	56 (27.3)	25 (22.5)	10 (33.3)
Missing	0	22	0	5
Treatment delay*, days				
Mean (SD)	33.5 (39.2)	44.9 (48.4)	51.3 (52.6)	45.6 (45.7)
Median (min, max)	19.0 (1.0, 177.0)	30.0 (0.0, 330.0)	31.0 (2.0, 330.0)	30.0 (0.0, 233.0)
Prior use of corticosteroids, n (%)	31 (47.0)	101 (44.5)†	46 (41.4)†	14 (40.0)†
Prior use of topical antivirals, n (%)	17 (25.8)	102 (44.9)†	48 (43.2)†	19 (54.3)†

*Time from symptoms onset to treatment initiation.
†Defined as use before baseline therapy.
‡Only the 66 patients randomised to treatment with PHMB 0.08% plus placebo were included in the current analyses.
AAT, anti-amoebic treatment; AK, *Acanthamoeba* keratitis; CXL, chlorhexidine; max, maximum; min, minimum; n, number of patients; PHMB, polihexanide.

used treatments for AK. A population-adjustment approach was used that attempts to overcome the imbalances in study populations described and is an improvement to a naïve approach that does not adjust for imbalances between studies. The ITCs suggest that patients were more likely to achieve clinical resolution when the treatment is initiated with PHMB 0.08% delivered according to the treatment protocol used in the clinical trial. The availability of IPD was a strength because it allowed a more flexible and less biased ITC approach (ie, PSA) to be conducted than if only the published aggregate data were available from the comparator study (ie, the retrospective study). Potential for biases due to differences in the assessment of disease severity and the cure outcome by staff in either study is minimised by

Table 2 Summary of characteristics after weighting for patients with AK treated with PHMB 0.08%,[4] any initial pharmacological treatment,[2] PHMB 0.02% plus a diamidine 0.1%[2] or CXL 0.02% alone or plus a diamidine 0.1%[2]

	PHMB 0.08% vs any initial AAT		PHMB 0.08% vs PHMB 0.02% plus diamidine 0.1%		PHMB 0.08% vs CXL 0.02% alone or plus diamidine 0.1%	
	PHMB 0.08%	Any initial AAT	PHMB 0.08%	PHMB 0.02% plus diamidine 0.1%	PHMB 0.08%	CXL 0.02% alone or plus diamidine 0.1%
Number of patients	66	227	66	111	66	35
Age, years						
Mean (SD)	34.9 (13.0)	34.9 (14.1)	34.1 (12.5)	34.1 (13.5)	34.6 (12.7)	34.6 (15.2)
Median (min, max)	33.0 (15.0, 73.0)	32.0 (13.0, 76.0)	31.0 (15.0, 73.0)	32.0 (13.0, 75.0)	34.0 (15.0, 73.0)	30.0 (17.0, 74.0)
Male, %	40.6	40.6	41.1	41.1	52.7	52.7
AK disease stage 3, %	18.8	18.8	18.0	18.0	26.9	26.9
Treatment delay*, days						
Mean (SD)	35.6 (41.3)	35.6 (36.7)	38.4 (44.1)	38.4 (36.9)	43.5 (47.7)	43.5 (36.5)
Median (min, max)	21.0 (1.0, 177.0)	28.0 (0.0, 257.0)	22.0 (1.0, 177.0)	30.0 (2.0, 330.0)	24.0 (1.0, 177.0)	30.0 (0.0, 233.0)
Prior use of corticosteroids, %	45.2	45.2	44.2	44.2	43.6	43.6
Prior use of topical antivirals, %	30.0	30.0	33.0	33.0	47.5	47.5

*Time from symptom onset to study treatment initiation.
AAT, anti-amoebic treatment; AK, *Acanthamoeba* keratitis; CXL, chlorhexidine; max, maximum; min, minimum; n, number of patients; PHMB, polihexanide.

Table 3 Rates of clinical resolution (with no surgery) within 12 months for patients with *Acanthamoeba* keratitis treated with PHMB 0.08%[4] compared with any initial AAT, PHMB 0.02% plus a diamidine 0.1%,[2] or CXL 0.02% alone or plus a diamidine 0.1%[2] using indirect treatment comparison methods

	Unweighted results			Weighted results*			
Treatment	N cured/ analysed	% CRR (95% CI)	% Difference in CRR (95% CI)	N cured/ analysed	% CRR (95% CI)	% Difference in CRR (95% CI)	ESS
PHMB 0.08% vs any initial AAT							
Any initial AAT[2]	99/227	43.6 (37.1, 50.3)	Referent	109.7/227	48.3 (41.8, 54.8)	Referent	174.4
PHMB 0.08%[4]	56/66	84.8 (73.9, 92.5)	**41.2 (28.8, 51.2)**	55.9/66	84.7 (76.1, 93.4)	**36.4 (24.9, 47.9)**	64.8
P value			**<0.001**			**<0.001**	
PHMB 0.08% vs PHMB 0.02% plus a diamidine 0.1%							
PHMB 0.02% plus a diamidine 0.1%[2]	61/111	55.0 (45.2, 64.4)	Referent	67.6/111	60.9 (51.9, 70.0)	Referent	97.5
PHMB 0.08%[4]	56/66	84.8 (73.9, 92.5)	**29.9 (14.5, 42.1)**	56.2/66	85.1 (76.6, 93.7)	**24.2 (11.3, 37.1)**	62.5
P value			**<0.001**			**<0.001**	
PHMB 0.08% vs CXL 0.02% alone or plus a diamidine 0.1%							
CXL 0.02% alone or plus a diamidine 0.1%[2]	14/35	40.0 (23.9, 57.9)	Referent	16.3/35	46.4 (29.9, 63.0)	Referent	25.7
PHMB 0.08%[4]	56/66	84.8 (73.9, 92.5)	**44.8 (23.9, 62.3)**	55.0/66	83.3 (74.3, 92.3)	**36.8 (14.2, 59.5)**	41.9
P value			**<0.001**			**0.002**	

Statistically significant differences are highlighted in bold.
*Results were adjusted for the following confounders: age, sex, disease stage, prior corticosteroid use, prior antiviral use and treatment delay.
AAT, anti-amoebic treatment; CRR, clinical resolution rate; CXL, chlorhexidine; ESS, effective sample size; PHMB, polihexanide.

having clear cut criteria for both AK disease staging and the definition of a cure in both studies.

The main limitations were:

- Differences in the time periods of the two studies potentially resulting in unmeasurable changes in management, for which we cannot control in the analysis as there are no periods shared by both studies.
- Differences in clinical diagnoses. The retrospective study included some patients with a clinical diagnosis of AK, as well as those with positive diagnostic test criteria, while the prospective clinical trial included only patients with positive diagnostic criteria (IVCM±culture or PCR) as shown in online supplemental table 1. It is difficult to predict what effect this difference might have had on outcomes, although we think it unlikely that many had another disease.
- A further limitation is the difference in treatment delivery in the two studies, for which we cannot control, and which may account for much of the disparity in the outcomes. This difference in treatment delivery was the use of the detailed treatment delivery protocol used in the pivotal trial compared with the use of the broad treatment delivery guidelines that vary by practitioner, based on their assessment of the clinical response; this is in effect a 'make it up as you go along' treatment. This latter approach has been widespread practice for bacterial keratitis[14 15] and fungal keratitis,[16] until the TST protocol was published,[17] as well as in one of the two randomised trials for AK[18] and in recent case series describing AK treatment outcomes.[19 20] This methodology has resulted in treatment regimens that can vary greatly between patients, whereas in the trial, the protocol precisely mandated timings for treatment dosing and the use of adjunctive therapies until a defined endpoint for a cure was achieved.
- Population-adjustment methods can only account for between-trial differences to a certain extent, so there may be residual confounding due to unmeasured/unanalysed confounders, and the reliance on unanchored comparisons (ie, there was not a common comparator arm between the analysed studies). This approach relies on the assumption that all effect modifiers and prognostic factors have been successfully identified and incorporated into the weighting process; a strong assumption that is rarely satisfied. Therefore, the results may be limited due to residual confounding.

Despite these limitations, the results proved consistent, both before and after weighting, suggesting that the limitations may have had little impact on the findings.

In conclusion, based on these ITC results, PHMB 0.08% administered with the protocol used in the pivotal trial appears more effective than the currently used treatments as described in the largest retrospective study published to date, which included 227 patients. The limitations of ITC approaches should be considered when interpreting the results. Such results could support the wider use of PHMB 0.08%, and the associated evidence-based treatment delivery protocol, as an effective treatment for patients with AK and could serve to inform future treatment recommendations or guidelines, and pharmacotherapeutic or pharmacoeconomic analyses informing health policy decisions.

Lastly, it is worthy of note that most issues of currently used AK treatments (no GMP quality, no evidence-based protocol, no guidelines for follow-up, no immediate availability) can be resolved with the availability of a licensed medicinal product, such as PHMB 0.08% when combined with the adoption and adherence to the recommended protocol. This can be expected to lead to better outcomes for most patients with the added benefit of the simplified standardised treatment delivery for both patients and clinicians. Recent support for this statement has come from the evaluation of 12 eyes in 11 patients treated with PHMB 0.08% during a compassionate use programme (thus outside a trial setting) in which half the cases had stage 3 disease and for which the medical cure rate was 11/12 (90%).[21]

Acknowledgements Authors thank Darwin Minassian (Emeritus Reader-biostatistics, the UCL Institute of Ophthalmology) for providing individual patient data from the retrospective study and suggestions given during the preparation of this manuscript.

Contributors Conception and design: VP, MDF and DHB. Conduction: MDF, DHB, RA, ES and CA. Acquisition of data and analysis: DHB, RA and ES. Interpretation of data: VP, CG, MDF, DHB and JKGD. Writing: VP, MDF, DHB and JKGD. Review and editing: VP, CG, MDF, DHB, RA, ES, JKGD and CA. All authors have read and agreed to the published version of the manuscript. Guarantor: VP.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None of the authors have any proprietary or commercial interest in any materials discussed in this article. VP is an employee of SIFI S.p.A. (manufacturer of PHMB 0.08%); CG, MDF and JKGD are consultants of SIFI S.p.A.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study analysed data already published from a phase 3, randomised, double-blind clinical trial and one retrospective clinical study. Both studies were approved by the appropriate ethics committees as follows: City & East Research Ethics Committee Bristol Research Ethics Committee Centre (UK). Date: 12 June 2017. REC reference: 17/LO/0371; IRCCS (Centre of Excellence and Research) Ospedale San Raffaele-Milano (ITALY). Date: 6 April 2017. Register number CE59/2017; Comitato etico per la sperimentazione clinica della provincia di Venezia e IRCCS San Camillo Azienda ULSS 3 SERENISSIMA-Venezia (ITALY). Date: 13 April 2017. Register number 160901, Cat. 05.08; Ethics committee at Medical University of Silesia in Katowice (Poland). Date: 5 December 2017. Register number KNW/0022/KBI/42/V/17; Moorfield's Research Governance Committee-Moorfield's Eye Hospital London (UK). Date: 15 October 2008; Comitato Etico per la sperimentazione clinica Ospedale San Raffaele-Milano (ITALY) Date: 5 September 2008; All studies were performed in accordance with the Declaration of Helsinki; written informed consent was obtained from all patients before they participated in the studies. Researchers had full access to the individual level data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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