HEALTH TECHNOLOGY ASSESSMENT

VOLUME 21 ISSUE 10 MARCH 2017
ISSN 1366-5278

A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial

Joanne R Chalmers, Fenella Wojnarowska, Gudula Kirtschig, James Mason, Margaret Childs, Diane Whitham, Karen Harman, Anna Chapman, Shernaz Walton, Enno Schmidt, Thomas R Godec, Andrew J Nunn and Hywel C Williams

NHS
National Institute for Health Research

DOI 10.3310/hta21100

A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial

Joanne R Chalmers,[1] Fenella Wojnarowska,[2] Gudula Kirtschig,[1] James Mason,[3] Margaret Childs,[4] Diane Whitham,[4] Karen Harman,[5] Anna Chapman,[6] Shernaz Walton,[7] Enno Schmidt,[8] Thomas R Godec,[9] Andrew J Nunn[9] and Hywel C Williams[1]*

[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[2]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
[3]Durham University, School of Medicine, Pharmacy and Health, Stockton-on-Tees, UK
[4]Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Nottingham, UK
[5]University Hospitals Leicester, Dermatology Department, Leicester Royal Infirmary, Leicester, UK
[6]Queen Elizabeth Hospital, Greenwich, London, UK
[7]Princess Royal Hospital, Salthouse Road, Hull, UK
[8]Department of Dermatology, University of Lübeck, Lübeck, Germany
[9]Medical Research Council Clinical Trials Unit, University College London, London, UK

*Corresponding author

Declared competing interests of authors: Hywel C Williams is Programmes Director for the Health Technology Assessment programme.

Published March 2017
DOI: 10.3310/hta21100

This report should be referenced as follows:

Chalmers JR, Wojnarowska F, Kirtschig G, Mason J, Childs M, Whitham D, *et al*. A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial. *Health Technol Assess* 2017;**21**(10).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/403/51. The contractual start date was in October 2008. The draft report began editorial review in June 2015 and was accepted for publication in September 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial

Joanne R Chalmers,[1] Fenella Wojnarowska,[2] Gudula Kirtschig,[1] James Mason,[3] Margaret Childs,[4] Diane Whitham,[4] Karen Harman,[5] Anna Chapman,[6] Shernaz Walton,[7] Enno Schmidt,[8] Thomas R Godec,[9] Andrew J Nunn[9] and Hywel C Williams[1]*

[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK
[2]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK
[3]Durham University, School of Medicine, Pharmacy and Health, Stockton-on-Tees, UK
[4]Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Nottingham, UK
[5]University Hospitals Leicester, Dermatology Department, Leicester Royal Infirmary, Leicester, UK
[6]Queen Elizabeth Hospital, Greenwich, London, UK
[7]Princess Royal Hospital, Salthouse Road, Hull, UK
[8]Department of Dermatology, University of Lübeck, Lübeck, Germany
[9]Medical Research Council Clinical Trials Unit, University College London, London, UK

*Corresponding author hywel.williams@nottingham.ac.uk

Background: Bullous pemphigoid (BP) is an autoimmune blistering skin disorder with increased morbidity and mortality in the elderly.

Objectives: To evaluate the effectiveness, safety and cost-effectiveness of a strategy of initiating BP treatment with oral doxycycline or oral prednisolone. We hypothesised that starting treatment with doxycycline gives acceptable short-term blister control while conferring long-term safety advantages over starting treatment with oral prednisolone.

Design: Pragmatic multicentre two-armed parallel-group randomised controlled trial with an economic evaluation.

Setting: A total of 54 dermatology secondary care centres in the UK and seven in Germany.

Participants: Adults with BP [three or more blisters at two sites and positive direct and/or indirect immunofluorescence (immunoglobulin G and/or complement component 3 immunofluorescence at the dermal-epidermal junction)] and able to give informed consent.

Interventions: Participants were allocated using online randomisation to initial doxycycline treatment (200 mg/day) or prednisolone (0.5 mg/kg/day). Up to 30 g/week of potent topical corticosteroids was permitted for weeks 1–3. After 6 weeks, clinicians could switch treatments or alter the prednisolone dose as per normal practice.

Main outcome measures: Primary outcomes: (1) the proportion of participants with three or fewer blisters at 6 weeks (investigator blinded) and (2) the proportion with severe, life-threatening and fatal treatment-related events at 52 weeks. A regression model was used in the analysis adjusting for baseline disease severity, age and Karnofsky score, with missing data imputed. Secondary outcomes included the effectiveness of blister control after 6 weeks, relapses, related adverse events and quality of life. The economic evaluation involved bivariate regression of costs and quality-adjusted life-years (QALYs) from a NHS perspective.

Results: In total, 132 patients were randomised to doxycycline and 121 to prednisolone. The mean patient age was 77.7 years and baseline severity was as follows: mild 31.6% (three to nine blisters), moderate 39.1% (10–30 blisters) and severe 29.3% (> 30 blisters). For those starting on doxycycline, 83 out of 112 (74.1%) had three or fewer blisters at 6 weeks, whereas for those starting on prednisolone 92 out of 101 (91.1%) had three or fewer blisters at 6 weeks, an adjusted difference of 18.6% in favour of prednisolone [90% confidence interval (CI) 11.1% to 26.1%], using a modified intention-to-treat (mITT) analysis. Per-protocol analysis showed similar results: 74.4% compared with 92.3%, an adjusted difference of 18.7% (90% CI 9.8% to 27.6%). The rate of related severe, life-threatening and fatal events at 52 weeks was 18.2% for those started on doxycycline and 36.6% for those started on prednisolone (mITT analysis), an adjusted difference of 19.0% (95% CI 7.9% to 30.1%; $p = 0.001$) in favour of doxycycline. Secondary outcomes showed consistent findings. There was no significant difference in costs or QALYs per patient at 1 year between doxycycline-initiated therapy and prednisolone-initiated therapy (incremental cost of doxycycline-initiated therapy £959, 95% CI –£24 to £1941; incremental QALYs of doxycycline-initiated therapy –0.024, 95% CI –0.088 to 0.041). Using a willingness-to-pay criterion of < £20,000 per QALY gained, the net monetary benefit associated with doxycycline-initiated therapy was negative but imprecise (–£1432, 95% CI –£3094 to £230).

Conclusions: A strategy of starting BP patients on doxycycline is non-inferior to standard treatment with oral prednisolone for short-term blister control and considerably safer in the long term. The limitations of the trial were the wide non-inferiority margin, the moderate dropout rate and that serious adverse event collection was unblinded. Future work might include inducing remission with topical or oral corticosteroids and then randomising to doxycycline or prednisolone for maintenance.

Trial registration: Current Controlled Trials ISRCTN13704604.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 21, No. 10. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

Glossary

Blinding/masking Procedures designed to ensure that those assessing outcomes in a study are not aware of the treatment allocations.

Bullous pemphigoid An autoimmune blistering skin disease.

Intention to treat The principle of including all those originally randomised in the final analysis.

Non-inferiority comparison An approach to hypothesis testing that sets out to show that a treatment is acceptably inferior to another treatment within a predefined acceptability margin.

Per protocol A form of analysis that evaluates only those participants who adhered strictly to the study protocol.

Skin immunofluorescence A technique for detecting whether or not circulating autoantibodies are present in the skin. In pemphigoid, these are found at the junction between the epidermis and the dermis.

Superiority comparison An approach to hypothesis testing that sets out to show that one treatment is superior to another by a defined margin.

List of abbreviations

AUC	area under the curve
BLISTER	Bullous Pemphigoid Steroids and Tetracyclines
BP	bullous pemphigoid
CI	confidence interval
DLQI	Dermatology Life Quality Index
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions three-level version
EQ VAS	EuroQol visual analogue scale
GP	general practitioner
HES	Hospital Episodes Statistics
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
MAR	missing at random
mITT	modified intention to treat
MRC	Medical Research Council
NCTU	Nottingham Clinical Trials Unit
NIHR	National Institute for Health Research
NMB	net monetary benefit
PCA	Prescription Cost Analysis
PP	per protocol
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year

Plain English summary

Bullous pemphigoid (BP) is an uncommon itchy blistering skin problem that is more common in old age. Steroid tablets are often used to clear up blisters quickly in people with BP, but they can lead to serious side effects such as diabetes, infections and fractures. Antibiotics such as doxycycline are used to treat BP and, although less effective at controlling blisters quickly, they might be safer than steroids over a long period. We set out to compare the benefits and harms of these two treatments. We split 253 people with BP into two similar groups randomly (by chance), starting one group on doxycycline tablets (200 mg daily) and the other group on oral steroids at a daily dose of 0.5 mg/kg of body weight. People could switch from one treatment to another or change the dose after 6 weeks as advised by their doctor. In terms of early control, 74.1% in the doxycycline group had three or fewer blisters at 6 weeks, compared with 91.1% in the steroid group. When we looked at harms, 18.2% of those starting on doxycycline had severe, life-threatening or fatal outcomes within the 1-year follow-up period compared with 36.3% of those on steroids. The results were about the same for people who had mild, moderate or severe BP. We conclude that a policy of starting treatment with doxycycline is reasonably effective in the short term and much safer than starting treatment with oral steroids in the long term.

Scientific summary

Background

Bullous pemphigoid (BP) is an autoimmune disease characterised by antibodies directed at the junction between the dermis and the epidermis. Large, tense blisters form as a result, some of which break down to form open sore areas that can become infected. The blisters and surrounding skin can be very itchy, leading to poor quality of life. BP is more common in older people and seems to be on the increase. It is also associated with neurological conditions, such as dementia and stroke, and with increased mortality in general. Previous studies have shown that potent topical corticosteroids applied to the whole skin surface can be used for treating BP successfully, but this is often not practical in an elderly outpatient population. Oral steroids are still the most commonly used treatment for BP in the UK. Although some dermatologists have used tetracycline antibiotics to treat BP, a Cochrane systematic review concluded that their effects have not been well tested. It is unlikely that tetracyclines would be *more* effective than oral steroids, yet they are likely to be safer given the problems associated with long-term use of oral steroids in the elderly, such as diabetes, fractures and serious infections. We therefore sought to see whether or not a strategy of starting treatment of BP with tetracyclines still produces an acceptable degree of short-term blister control compared with starting on oral corticosteroids (a non-inferiority comparison), while at the same time conferring a long-term advantage over oral corticosteroids in terms of safety (a superiority comparison).

Methods

Trial perspective

This was a pragmatic, two-arm, parallel, multicentre randomised controlled clinical trial of 52 weeks' duration comparing a strategy of starting people with BP on 200 mg of doxycycline daily with a strategy of starting people with BP on 0.5 mg/kg/day of oral prednisolone.

Participants

Adults presenting to secondary dermatological care with a clinical diagnosis of BP with at least three significant blisters or erosions in the last week on at least two body sites and who were able to give informed consent were eligible. In addition, eligible patients had to have positive direct or indirect (serum) immunofluorescence (immunoglobulin G and/or complement component 3 at the epidermal basement membrane zone) to confirm the clinical diagnosis. Patients must have been free of blisters and treatment for previous episodes of BP in the preceding year. Those already on systemic medications for their BP, or those taking either study medication for other reasons in the 12 weeks before the study, were excluded, as were those with mostly or entirely mucosal pemphigoid.

Interventions

This study compared a strategy of initiating treatment with 200 mg daily of doxycycline with a strategy of initiating treatment with 0.5 mg/kg/day of oral prednisolone. Investigators were encouraged to keep the dose fixed for the first 6-week blinded phase to assess short-term blister control, but after this point treatments could be adjusted, switched or changed according to treatment response, as would occur in typical clinical practice. Participants were allowed to use up to 30 g per week of a potent topical corticosteroid (mometasone furoate) on affected areas for the first 3 weeks of treatment only and then again after the 6-week blister count to reflect normal UK practice.

Trial outcomes

Our two primary outcomes were (1) the proportion of patients with three or fewer blisters at 6 weeks (short-term effectiveness – a non-inferiority comparison) and (2) the proportion of patients with

medication-related severe, life-threatening or fatal adverse events at 52 weeks (long-term safety outcome – a superiority comparison). Secondary outcomes included the effectiveness of blister control after 6 weeks, relapse rates, related adverse events of all grades, quality of life and cost-effectiveness.

Randomisation and masking (blinding)

Randomisation was based on a computer-generated pseudorandom code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit. Randomisation was stratified by initial disease severity and concealed from investigators for the initial 6 weeks of treatment. Investigators were blinded to treatment allocation when blister counts were assessed at 6 weeks. Investigators were unblinded after this point to enable medication to be adjusted to reflect normal clinical practice. Participants were not blinded to study medications. Collection of adverse events after 6 weeks was not blinded, but the relatedness of all serious adverse events and deaths was judged by an independent adjudicator.

Sample size

We expected that around 60% of patients starting on oral prednisolone would eventually experience a severe, life-threatening or fatal drug-related adverse event by 52 weeks. To demonstrate at least a 20% reduction in such harms for those initiated on doxycycline, we estimated that 256 patients would be needed (80% power at the 5% significance level and a 1 : 1 allocation), assuming a 20% loss to follow-up at 1 year. Assuming that the 'success rate' of three or fewer blisters at 6 weeks would be around 95% in the group started on oral prednisolone and 70% in the group started on doxycycline, an absolute difference of 25%. The acceptable non-inferiority margin was set at 37% based on the upper bound of the 90% confidence interval (CI) for this difference. Allowing for 5% loss to follow-up at 6 weeks, a total of 234 participants were required at 80% power for such a non-inferiority margin. Analysis for the superiority safety outcomes was on an intention-to-treat (ITT) basis. Analysis of the non-inferiority effectiveness comparison included both an ITT and a per-protocol (PP) analysis. Analysis was conducted using a regression model, adjusting for baseline severity of BP, age and Karnofsky score, and missing data were imputed.

Monitoring and ethics

Trial oversight was by a Trial Steering Committee and an independent Data Monitoring Committee. Ethics permission was granted for all participating sites.

Results

Numbers randomised and baseline characteristics

In total, 278 participants were randomised from 54 UK and seven German dermatology centres, with 25 withdrawn because of ineligibility ($n = 19$ negative immunofluorescence, $n = 1$ too few blisters, $n = 1$ uncertain clinical diagnosis and $n = 4$ other reasons), leaving a total of 253 eligible randomised participants. Overall, 53% of the trial population were men and 47% were women and most (84%) were white. The age distribution of participants was as follows: ≥ 85 years, 25%; 75 to < 85 years, 38%; 65 to < 75 years, 28%; and < 65 years, 10%. Around 29% of participants had severe disease (> 30 blisters), 39% moderate disease (10–30 blisters) and 32% mild disease (three to nine blisters). Baseline characteristics (age, sex, ethnicity, BP severity, Karnofsky score of functional impairment) were well matched between the two groups. The proportion who withdrew or died was 13.0% at 6 weeks and 36.4% at 52 weeks.

Effectiveness outcomes

For the primary effectiveness outcome of three or fewer blisters at 6 weeks, 91.1% of those randomised to prednisolone achieved success compared with 74.1% of those randomised to doxycycline using a modified intention-to-treat (mITT) analysis, a difference of 18.6% (90% CI 11.1% to 26.1%) in favour of prednisolone. A PP analysis showed a similar result, with 92.3% and 74.4% achieving success in the prednisolone and doxycycline groups, respectively, a difference of 18.7% (90% CI 9.8% to 27.6%). There was no evidence to support a difference in effectiveness according to baseline disease severity (*p*-values

for an interaction test on the mITT population for severe and moderate compared with mild disease at baseline of 0.863 and 0.417 respectively). The proportions achieving treatment success at 13 weeks were 75.3% and 58.6% in the prednisolone and doxycycline groups, respectively, a difference of 17.5% (90% CI 6.8% to 28.2%) in favour of prednisolone. Corresponding values for treatment success at 52 weeks were 51.1% and 41.0% for prednisolone and doxycycline, respectively, a difference of 10.0% (90% CI –2.3% to 22.2%) in favour of prednisolone. Relapse rates were similar in the prednisolone and doxycycline groups (35.8% and 32.5%, respectively, a difference of 2.1%, 90% CI –0.83% to 12.5%).

Safety outcomes

Using a mITT analysis, related severe, life-threatening and fatal events by 52 weeks were experienced by 36.3% and 18.2% of those started on prednisolone and doxycycline, respectively, an adjusted difference of 19.0% (95% CI 7.9% to 30.1%; $p = 0.001$). When estimated from an adjusted regression model on a data set where missing data were imputed using multiple imputation there was a difference of 18.4% (95% CI 6.0% to 30.8%; $p = 0.004$) in favour of doxycycline. Total adverse events (including mild and moderate) were similar between the two treatment strategy groups (95.7% and 86.2% in the prednisolone and doxycycline groups respectively). There were 11 treatment-related deaths in the prednisolone treatment strategy group compared with three in the doxycycline treatment strategy group.

Quality of life and cost-effectiveness

Quality of life improved in both groups. The European Quality of Life-5 Dimensions (EQ-5D) showed a difference of 0.045 (95% CI –0.015 to 0.106; $p = 0.143$) between the prednisolone treatment strategy and the doxycycline treatment strategy after adjusting for baseline EQ-5D score, baseline severity, age and Karnofsky score. A similar difference was seen in the Dermatology Life Quality Index scores.

There was no significant difference in costs or quality-adjusted life-years (QALYs) gained comparing the two strategies. Using imputed data for the base-case analysis, after 1 year of treatment the incremental cost of doxycycline-initiated therapy was £959 per patient (95% CI –£24 to £1941), whereas the average quality of life decrement was –0.024 QALYs (95% CI –0.088 to 0.041 QALYs). Using a willingness-to-pay criterion of < £20,000 per QALY gained, the net monetary benefit (NMB) associated with doxycycline-initiated therapy was negative if imprecise (NMB –£1432, 95% CI –£3094 to £230). However, subgroup analysis indicated that for patients presenting with severe blisters doxycycline-initiated therapy was not cost-effective (NMB –£4361, 95% CI –£8283 to –£439), whereas patients presenting with mild or moderate blisters had very similar costs and outcomes at 1 year (NMB –£251, 95% CI –£1987 to £1485). Resources displaced in the NHS by doxycycline-initiated therapy may be greater than the value of benefit gained in the severe blister patient subgroup. Economic model findings were robust under extensive sensitivity analyses.

Conclusions

Main findings

This pragmatic study shows that a strategy of starting people with BP on 200 mg daily of oral doxycycline is safer by a considerable margin than a strategy of starting them on oral prednisolone. These long-term gains in safety were at the expense of short-term compromises in effectiveness, but these fell well within our prespecified non-inferiority margin. There was a suggestion that the relative effectiveness of prednisolone compared with doxycycline varied according to blister severity at baseline, but these differences did not reach statistical significance in our planned subgroup analysis. The overall pattern of treatment differences between the two strategies was consistent throughout the duration of the trial and did not change when tested against a range of sensitivity analyses. It is important to realise that the differences between the two treatment groups reflect the overall *strategy* of initiating treatment with doxycycline or prednisolone, rather than a strict comparison of one drug against the other. Such a strategy permits switching medicines or adjusting doses over the 52-week period as might occur in routine clinical practice.

Strengths and limitations

Study strengths included the large sample size and the fact that participants were representative of those presenting to secondary dermatological care and came from a wide geographical area in two countries; the pragmatic nature of the study, which allowed for dose adjustment and medication switches to match everyday clinical practice; and the rigour in ensuring concealed allocation and blinded assessment of the effectiveness outcome. Study limitations included the exclusion of patients with dementia on ethical grounds and losses to follow-up for longer-term outcomes.

Clinical and research implications

This study has confirmed for the first time that doxycycline does have a useful effect in controlling BP blisters and also that oral prednisolone at a dose of 0.5 mg/kg/day is very effective, albeit at the expense of significant related serious, life-threatening and fatal adverse events. In people with BP in whom extensive application of topical corticosteroids is not practical, a strategy of starting patients on oral doxycycline plus local application of topical corticosteroids to affected areas may be considered in preference to the current standard UK practice of starting BP patients on oral prednisolone. The estimates of the trade-off between reduced short-term effectiveness and increased long-term safety gains for doxycycline-initiated treatment obtained from this study now provide clear data to inform shared decision-making between health-care professionals and patients/carers over BP treatment choices. Because doxycycline may have a slower beneficial effect on blister control than prednisolone, future research might consider a study whereby all patients with BP are brought into rapid remission with a short course of potent topical corticosteroids or low-dose oral steroids and are then randomised to maintenance treatment for a year with either oral doxycycline or continuation with oral corticosteroids.

Trial registration

This trial is registered as ISRCTN13704604.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background

What is pemphigoid?

Bullous pemphigoid (BP) is the most common form of a group of autoimmune pemphigoid diseases characterised by autoantibodies directed at skin adhesion proteins of the epidermal–dermal junction.[1] BP often starts with intense itching followed by an urticated and/or eczematous-looking rash and tense blisters on erythematous or normal-looking skin (*Figure 1*). The blisters may develop several months after the appearance of the initial symptoms and may be quite large and filled with blood. They often break down to form raw skin erosions, which can become infected.

The pain and severe itching associated with BP can greatly impair quality of life. BP typically affects people aged around 80 years and the incidence, which appears to be on the increase, is estimated to be between 6 and 43 cases per million per year.[2,3] The cause of BP is unknown but it is associated with neurological conditions such as cerebrovascular disease, dementia, Parkinson's disease, epilepsy and multiple sclerosis[4,5] and the chronic use of several drugs including spironolactone (Aldactone®, Pharmacia Ltd), neuroleptics, certain diuretics and phenothiazines in some patients.[4,6–9] Neurological disease has been suggested as a predisposing and prognostic factor.[10]

Increased mortality

Mortality rates are increased for people with BP. In one study the risk of death was more than six times that of the general population.[11] Mortality rates for people with BP of between 11% and 41% have been suggested to be related to advanced age and comorbid medical conditions rather than the disease itself.[12,13] It is likely that the increase in mortality rate is owing, at least in part, to side effects of oral prednisolone, which is commonly used to treat BP.[14–17]

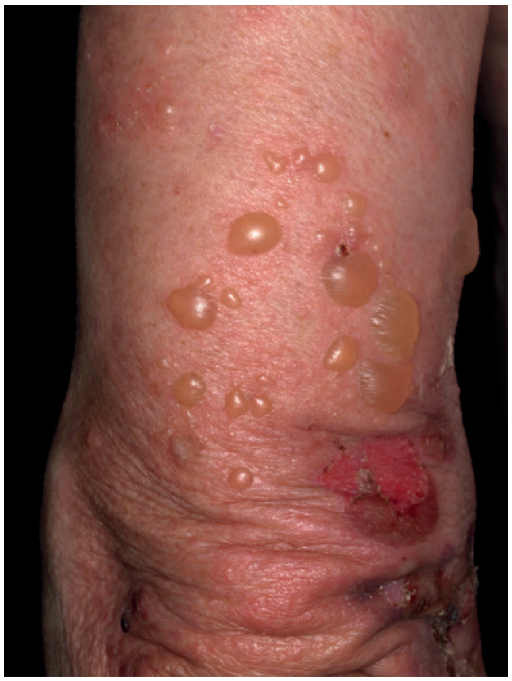

FIGURE 1 Large tense blisters and erosions in a man with BP (by kind permission of Professor Enno Schmidt with written consent from the patient).

Topical treatment

Some widely reported studies have shown that superpotent topical corticosteroids applied to the whole skin surface are effective and safer than oral corticosteroids.[18,19] Practical guidance on how this can be carried out is provided elsewhere.[15] However, the application of topical steroids to the whole body for weeks or possibly months is not a practical option in many elderly outpatients with limited support. Therefore, there still remains a need for a convenient oral treatment that is both effective and safe.

Rationale for testing tetracyclines further

Treatment of BP with antibiotics possessing anti-inflammatory actions, such as those from the tetracycline group, is widely used in clinical practice. In a national survey of 326 UK dermatologists conducted in 2013, around 80% stated that they had used doxycycline (Efracea®, Galderma), minocycline (Aknemin®, Almirall Hermal GmbH) or lymecycline (Tetralysal®, Galderma).[20] However, a Cochrane systematic review[21] found only one small poorly reported clinical trial[22] and concluded that further evidence was needed before the effectiveness of tetracyclines could be established. No further trials of tetracyclines were identified in a subsequent systematic review[23] nor in a search of the Cochrane Central Register of Controlled Trials using 'pemphigoid' as a search term (28 May 2015). The limited data available and practical experience to date suggest that it is very unlikely that tetracyclines would be *more* effective than long-term use of oral corticosteroids, yet they are likely to be safer in this elderly population given the known adverse effects of oral corticosteroids, including diabetes mellitus, serious infections and osteoporosis, leading to fractures and death. Because some patients with BP might not respond to tetracyclines at all, it was clearly important to test how they might be used in clinical practice by permitting additional application of potent topical corticosteroids to affected areas or a switch to oral corticosteroids if symptoms and blister control were inadequate. Similarly, in the UK, those initiated on oral steroids are typically given topical corticosteroids for localised application to blisters to help with initial control and doses of oral corticosteroids are typically adjusted over several months, according to blister control or side effects. We therefore sought to investigate whether or not a strategy of initial treatment of BP with anti-inflammatory tetracyclines (200 mg/day of doxycycline) is effective enough to produce an acceptable degree of blister control compared with initial treatment with oral corticosteroids (0.5 mg/kg/day of prednisolone) in a non-inferiority comparison and whether or not tetracyclines confer a long-term advantage in terms of safety over oral corticosteroids in a superiority comparison.

Chapter 2 Methods

Trial design

The Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial was a two-arm, parallel-group, multicentre, multinational randomised controlled trial of 52 weeks' duration. The design was towards the pragmatic end of the explanatory–pragmatic spectrum.[25] We recruited patients with BP from the UK and Germany who had not started systemic treatment. Participants were randomised to receive either doxycycline or prednisolone as initial treatment and were followed up at weeks 3, 6, 13, 26, 39 and 52, with unscheduled visits as required to reflect normal clinical care.

The two primary outcomes in this trial reflect the need for patients and clinicians to balance the likely differences in effectiveness and safety for oral prednisolone and doxycycline when making a shared decision on treatment. Although topical corticosteroids have been shown to be effective for BP, it is not always practical or cost-effective to admit elderly people into hospital for whole body application[15] and therefore oral treatment alternatives are needed. Although oral prednisolone is thought to be effective at reducing the blisters in BP, it has many side effects as indicated in previous trials comparing topical corticosteroids with oral corticosteroids.[18,19,26] Doxycycline, on the other hand, is perceived to be less effective by clinicians but probably has fewer side effects. Therefore, a non-inferiority comparison was used to assess effectiveness, the results of which could be considered alongside the superiority comparison of safety in clinical decision-making.

The trial protocol was published prior to the analysis.[27]

Choice of intervention

At baseline, patients were randomised to receive either 0.5 mg/kg/day of prednisolone or 200 mg/day of doxycycline, both taken as a single, daily dose (brand not specified). We chose a starting dose of 0.5 mg/kg/day for prednisolone based on safety concerns over higher doses such as 0.75–1 mg/kg/day highlighted in the Cochrane systematic review.[22] The study protocol encouraged investigators to stick to the allocated treatment and dose for the first 6 weeks unless it was medically necessary to change, but after the 6-week effectiveness assessment investigators were free to modify the dose as needed, switch to the other treatment arm or administer an alternative treatment if appropriate, to reflect normal clinical practice. Participants were followed up for the full 52 weeks when possible, regardless of any changes to treatment. Participants recorded study medication use in their diary.

Rescue medication

Up to 30 g/week of topical corticosteroids in the potent class [preferably mometasone furoate (Elocon®, Merck Sharp & Dohme Ltd)] was permitted throughout the study, except between weeks 3 and 6. The cessation of topical corticosteroids from week 3 to week 6 provided a washout period to minimise the potential effect of systemic absorption of topical corticosteroids on the primary effectiveness outcome at 6 weeks. To minimise potential systemic effects, topical corticosteroids were applied only to blisters and erosions. Participants were permitted to apply a moisturiser to blisters and erosions at any time.

Choice of tetracycline

Doxycycline was chosen for this trial because (1) it is associated with a lower incidence of gastrointestinal side effects than other tetracyclines and (2) the alternative option of oxytetracycline would have required participants to swallow approximately eight large tablets a day.

Although the only published randomised controlled trial investigating tetracycline antibiotics for the treatment of BP used a combination therapy of tetracycline plus nicotinamide,[21] a single therapy of doxycycline was chosen for this trial to allow the effects of the tetracycline to be clearly defined.

Trial outcomes

We did not identify any core outcome sets for BP when this study was designed, although some consensus criteria have subsequently been suggested by an international group.[28]

Primary outcomes

The primary outcomes were the absolute difference between the two treatment arms in the:

- *Non-inferiority comparison*. The proportion of participants classed as a treatment success (three or fewer significant blisters present on examination) at 6 weeks. A significant blister was defined as an intact fluid-filled blister at least 5 mm in diameter or a ruptured blister with a flexible (not dry) roof over a moist base. Mucosal blisters were excluded from the count.
- *Superiority comparison*. The proportion of participants with grade 3 (severe), 4 (life-threatening) and 5 (death) adverse events that were possibly, probably or definitely related to the treatment in the 52 weeks following randomisation. A modified version of the Common Terminology Criteria for Adverse Events v3.0 was used [see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (accessed 12 November 2015)] and the relatedness of grade 5 (fatal) adverse events was judged by an independent adjudicator. Although only grade 3 and above related adverse events were captured in the primary outcome, less medically important related adverse events (such as weight gain and skin fragility) can bother patients when taking corticosteroids and so were included in a secondary outcome.

For the primary outcome, treatment success was defined as three or fewer significant blisters, regardless of whether or not treatment had been modified because of a poor response (either by changing the dose or by changing the treatment) during the first 6 weeks. However, for all secondary and tertiary end points, participants were classed as a treatment success at each visit *only* if (1) they had three or fewer significant blisters present on examination *and* (2) their treatment had not been altered because of a poor response prior to that visit.

Secondary outcomes

The secondary outcomes were the absolute difference between the two treatment arms in the following:

- non-inferiority comparisons:
  - proportion of participants classed as a treatment success (three or fewer significant blisters present on examination and no treatment modification) at 6 weeks
  - proportion of participants classed as a treatment success at 13 and 52 weeks
  - proportion of participants who had a further episode of BP during the study
- superiority comparisons:
  - proportion of participants reporting adverse events of *any* grade that were possibly, probably or definitely related to BP medication in the 52 weeks following randomisation
  - quality of life [European Quality of Life-5 Dimension (EQ-5D) and Dermatology Life Quality Index (DLQI) questionnaires at 6, 13, 26, 39 and 52 weeks]
  - cost-effectiveness over 12 months from a NHS perspective
- combined comparison: proportion of participants classed as a treatment success at 6 weeks *and* who were alive at 52 weeks.

Tertiary outcomes

The tertiary outcomes were the absolute difference between the two treatment arms in the following:

- non-inferiority comparisons:
  - proportion of participants completely blister free at 6 weeks
  - proportion of participants classed as a treatment success at 3 weeks (to compare the speed of onset of action)
- superiority comparisons:
  - mortality over the 52-week follow-up period
  - amount of potent and superpotent topical corticosteroids used during the 52 weeks following randomisation.

Participants

Adults (aged ≥ 18 years) who were capable of giving written informed consent and who had a clinical diagnosis of BP were eligible. To ensure that active disease was present, at least three significant blisters (defined as intact, fluid-filled blisters measuring ≥ 5 mm) must have appeared within the week prior to screening and must have been present across at least two body sites. Recent erosions could be included provided that they had a flexible (not dry) roof over a moist base. Positive direct (skin biopsy) *or* indirect (serum) immunofluorescence [immunoglobulin G (IgG) and/or complement component 3 (C3) at the epidermal basement membrane zone) was required to confirm diagnosis. Anonymised samples were tested at the Immunofluorescence Laboratory at the Department of Dermatology, John Radcliffe Hospital, Oxford, and the Institute of Dermatology Immunodermatology Laboratory at St John's Institute of Dermatology, St Thomas's Hospital, London. Samples with appropriately obtained consent were sent to the Clinical Immunological Laboratory, University of Lübeck, Germany, for additional immunology substudies, which will be published separately.

Patients must have been free of blisters and have not received treatment for previous episodes of BP in the preceding year. Patients were excluded if they had predominantly mucosal pemphigoid, had received any systemic medication for the current episode of BP or had received oral prednisolone or doxycycline for any other conditions in the preceding 12 weeks. Women of childbearing potential who were not taking adequate contraception, as well as those who were pregnant or who planned to become pregnant during the study or who were currently lactating, were excluded. Additional exclusions for safety reasons were live virus vaccine administration within the previous 3 months, allergy to any member of the tetracycline family or a pre-existing condition or use of a medication that precluded the use of either study drug or that made the patient unsuitable for this trial, as assessed by the investigator.

Retention of participants

To help retain participants in the study, in addition to being able to speak to the investigator, participants were able to telephone the trial manager if they wished to discuss any aspect of the study. For medical queries, participants were directed to a medical member of staff. In addition, the trial administrator made telephone calls to participants to support them throughout the duration of the study. Participants were sent birthday and Christmas cards while they were participating in the study.

Withdrawal of participants

Patients whose immunofluorescence test results were not available until after randomisation and which were subsequently both negative, indicating that they did not have BP, were withdrawn from the trial, replaced and not included in the analysis. This approach reflects normal practice: if there is a clinical

picture of BP, treatment is commenced and this is changed later if the laboratory tests are subsequently negative.

Participants who withdrew from study treatment were followed up for the remainder of the year unless they had withdrawn their consent.

Informed consent

Patients presenting with suspected BP were assessed by the recruiting investigator as per normal clinical practice. If a diagnosis of BP was suspected, the patient was given details of the study verbally. If the patient was interested in taking part he or she was given time to read the full participant information leaflet and the investigator answered any questions. A consent form was signed before any study procedures were carried out.

If the disease severity was such that immediate oral treatment was required or the patient did not wish to delay the start of treatment, he or she was able to give consent and be randomised to the study during the first visit to the dermatologist. Otherwise, the patient was given a second appointment for consent and randomisation.

Recruitment

To meet the target for this rare disease, recruitment took place at a large number of hospitals, mainly in dermatology clinics (54 in the UK and seven in Germany).

Randomisation

Randomisation was based on a computer-generated pseudorandom code using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (NCTU) in accordance with its standard operating procedure and held on a secure server. Access to the sequence during the trial was confined to the NCTU data manager.

Participants were allocated in a 1 : 1 ratio to the doxycycline and prednisolone treatment arms. Randomisation was stratified by disease severity, which was defined as the number of blisters present at baseline (mild: 1–9; moderate: 10–30; severe: > 30).

The investigator or research nurse randomised participants using the web-based NCTU randomisation system. The treatment allocation was sent directly to the pharmacist who dispensed the appropriate medication directly, which allowed the investigator to remain blinded.

Blinding

Investigators (outcome assessors) were unaware of treatment allocation and remained blinded to treatment allocation for the first 6 weeks of the trial. At the week 6 visit, the investigators carried out the blister count (primary effectiveness outcome) while blinded to treatment allocation. The investigators were unblinded for the remaining assessments: that is, for the primary safety outcome (adverse events over the full 52 weeks) and the long-term effectiveness outcomes. Unblinding before the 6-week point was permitted if required for treatment decisions that affected patient safety. Investigators were asked at week 6 if they were aware of the treatment allocation prior to carrying out the blister count for the primary effectiveness outcome to capture the rate of unblinding. A subgroup analysis to assess any potential bias of unblinding on the blister count at 6 weeks was performed. The patients and pharmacists were not blinded to treatment allocation.

Sample size

In total, 256 participants were needed to detect a clinically important absolute difference of 20% in grade 3, 4 and 5 (mortality) side effects within 1 year of randomisation (primary safety outcome). This was based on an expected 60% incidence with prednisolone compared with 40% with doxycycline[29] with 80% power at the 5% significance level allowing for a 20% loss to follow-up by 1 year using a 1 : 1 allocation ratio. A survey of UK dermatologists showed that a 20% absolute reduction in side effects was considered to be an acceptable and worthwhile clinical difference. More detailed results can be found in *Appendix 1*.

The effectiveness outcome at 6 weeks was expressed as a two-sided 90% confidence interval (CI) for the absolute difference in success rates (based on blister count) between the prednisolone (control) arm and the doxycycline (intervention) arm. It was assumed that the point estimate for this difference would be 25%, based on an expected response rate of 95% in the control (prednisolone) arm and 70% in the intervention (doxycycline) arm. The acceptable non-inferiority margin was set at 37% based on the upper bound of the 90% CI for an expected 25% difference. Because the non-inferiority margin is inversely proportional to the sample size, the number of patients who we could realistically expect to recruit in a rare disease of the elderly was factored in when setting the non-inferiority margin. The closer to the expected difference of 25% we set the non-inferiority margin, the larger the sample size that would be required. With 80% power, a total of 111 evaluable participants per group was required. The attrition rate in the initial 6 weeks was expected to be low (5%) and so a total of 234 participants was required, that is, within the 256 required for the primary safety outcome.

Analysis

All superiority analyses were conducted on a modified intention-to-treat (mITT) basis and all non-inferiority analyses were performed on both the mITT and the per-protocol (PP) population according to recommended practice.[30]

The mITT population consisted of those participants who fulfilled the eligibility criteria, who were randomised to receive either study drug and who had data on the outcome of interest.

For each non-inferiority outcome, the doxycycline arm was considered to be non-inferior to the prednisolone arm if the upper bound of the CI for the difference in proportions was less than the agreed non-inferiority margin of an absolute difference of 37% in *both* the mITT and the PP analyses.

All analyses were adjusted for baseline disease severity to optimise power and reduce possible imbalances in possible response predictors. Age and Karnofsky score[31] were also adjusted for in analyses as continuous variables when possible using a binomial regression with identity links. Methods for dealing with missing data can be found in the statistical analysis plan [see www.nottingham.ac.uk/research/groups/cebd/projects/5rareandother/index.aspx (accessed 19 May 2015)]. Multiple imputation was used to handle missing data because of missed visits for the primary safety analysis.

Patients were excluded from the PP analysis of the primary outcome if, before their 6-week visit, for reasons other than treatment success or failure, they had:

- increased the dose of their allocated treatment
- changed treatment or added a new treatment to their allocated treatment (for a reason other than for treatment failure or success)
- used topical steroids between visit weeks 3 and 6
- missed more than 3 consecutive days of treatment.

For non-inferiority outcomes after week 6, the PP populations consisted of those participants who were included in the PP analysis of the 6-week primary effectiveness outcome and who had:

- not missed more than 3 consecutive weeks of allocated treatment between 6 and 52 weeks (regardless of whether the dose had been increased or decreased) unless they had stopped for good clinical response
- used no more than 30 g of topical steroids per week after week 6
- not added systemic steroids to doxycycline (if allocated) or doxycycline or an immunosuppressant to prednisolone (if allocated) unless for poor clinical response.

For the non-inferiority outcomes, 90% CIs are presented. For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. For the superiority outcomes, 95% CIs are presented. A difference between treatment arms was considered statistically significant at the 5% level, that is, the 95% CIs do not contain zero (no difference between arms).

The primary analysis had a dual outcome, one primary outcome for effectiveness and one for safety. For the study treatment doxycycline to be considered acceptable as an alternative to prednisolone, non-inferiority had to be demonstrated (as defined above) with regard to effectiveness, as well as the superiority of doxycycline over prednisolone for safety.

Subgroup analyses

For some patients the blister count at 6 weeks may have been performed by an investigator who knew what treatment the patient was on. To determine whether or not this introduced bias into the results of the 6-week effectiveness outcome, an interaction test was performed to compare the treatment effects in patients who were and patients who were not assessed by an investigator who knew the treatment allocation. This interaction analysis was performed on both the primary and the secondary definition of treatment success at 6 weeks.

Subgroup analyses of treatment success (using both definitions) at 6 weeks by the three categories of baseline disease severity (mild, moderate and severe) were also performed. A global test for a treatment interaction was used to determine whether or not treatment effects were different in the three categories of disease severity.

Cost-effectiveness

The EuroQoL tool

The EuroQol tool is a two-page questionnaire consisting of the EQ-5D descriptive system and the EuroQol visual analogue scale (EQ VAS).[32] The tool is a standardised measure of current health status developed by the EuroQol group for clinical and economic studies. The EQ-5D three-level version (EQ-5D-3L) was used, consisting of five questions addressing the health dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is assessed at three levels: no problems, some problems and extreme problems. EQ-5D and EQ VAS data were collected using patient-completed questionnaires at baseline and 6, 13, 26, 39 and 52 weeks. Scores were converted to a single health-related index ranging from 0 (death) to 1 (perfect health), with negative scores possible for some health states. Patients who died during the study were subsequently scored 0 at later scheduled follow-up visits.

Resource use

Resource use assessments were carried out at 3, 6, 13, 26, 39 and 52 weeks during mandatory clinical visits and were augmented by telephone calls. Recall was assisted by the use of patient diaries. Patients' use of study and non-study drugs was recorded and costed using weighted average prices determined from Prescription Cost Analysis (PCA) data.[33] Health service contacts were recorded by asking patients to

recall general practitioner (GP) clinic and home visits, practice and district nurse visits, outpatient visits and inpatient stays. Health-care resource use was costed using published national reference costs.[34–36] Patient-level resource costs were estimated as the sum of resources used weighted by their national reference costs.

Economic analysis

The economic analysis followed intention-to-treat (ITT) principles and a prospectively agreed analysis plan (see *Appendix 2*). No discounting was applied to economic data reflecting the follow-up period of 1 year. Costs were estimated in UK pounds sterling using patient resource use and 2013 reference costs.[35] The analysis took an English NHS perspective, reporting generic (EQ-5D, EQ VAS)[32] and disease-specific (DLQI)[37] health outcomes. Repeated scores over time were used to construct area under the curve (AUC) estimates for each patient, using the trapezoidal method. Missing values at individual follow-up points were managed using two scenarios: multiple imputation (the base-case analysis[38]) and analysis of complete cases (in which patients with any missing data were excluded).

Patient estimates of costs and quality-adjusted life-years (QALYs) at 1 year were used to derive an estimate of the cost-effectiveness of doxycycline-initiated therapy compared with prednisolone-initiated therapy for patients with BP. Estimates using imputed missing data provided the base-case analysis and estimates using complete data provided supportive sensitivity analysis. Analysis and modelling were undertaken in Stata 13 (StataCorp, College Station, TX, USA). The base-case analysis included the imputed within-trial incremental cost/QALYs gained, adjusted for trial covariates (age, sex, baseline blister severity and baseline Karnofsky score). QALY estimates were also adjusted for baseline EQ-5D score.

Chapter 3 Results

Study population

Recruitment commenced in March 2009 in the UK and in February 2010 in Germany and was completed in October 2013. In total, 278 patients were randomised from 54 centres in the UK and seven centres in Germany (*Figure 2*).

Of the 1604 patients screened for eligibility, 1326 were excluded, mainly because of an inability to provide informed consent, frailty or their disease being too mild or because they had already been started on prednisolone by their GP (*Figure 3*). Of the 278 patients randomised, 140 were allocated to the doxycycline arm and 138 to the prednisolone arm (*Table 1*). However, 19 patients were excluded because both the direct and the indirect immunofluorescence tests were negative and a further six were excluded for other eligibility reasons. Therefore, 253 patients were included in the analyses, 132 in the doxycycline arm and 121 in the prednisolone arm (see *Figure 3*).

Baseline characteristics

Of the 253 eligible patients randomised, 52.6% were men and 47.4% were women. The average age was 77.7 years, with 25.3% aged > 85 years, 37.9% aged from 75 to < 85 years, 28.1% aged from 65 to < 75 years and 8.7% aged < 65 years. There was a good distribution of baseline severity of disease: 29.3% of patients had severe BP (> 30 blisters), 39.1% had moderate disease (10–30 blisters) and 31.6%

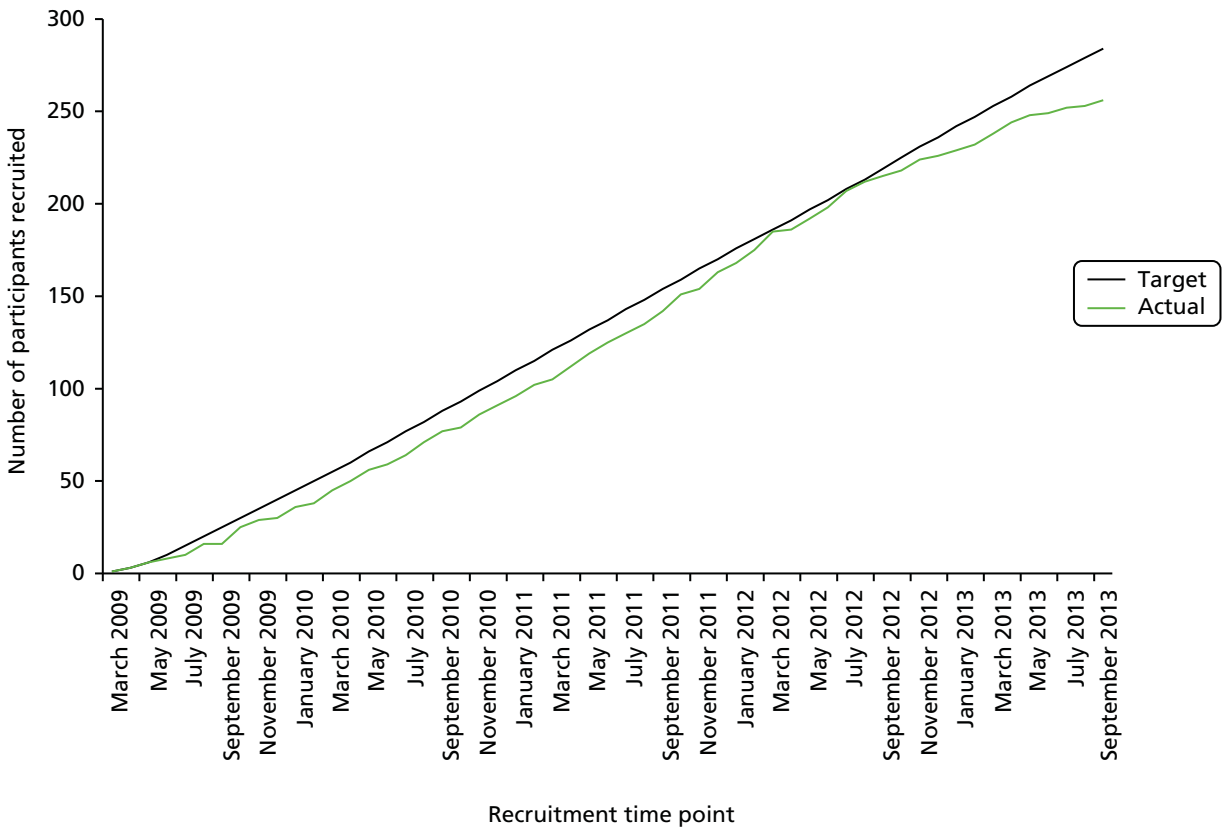

FIGURE 2 Recruitment graph.

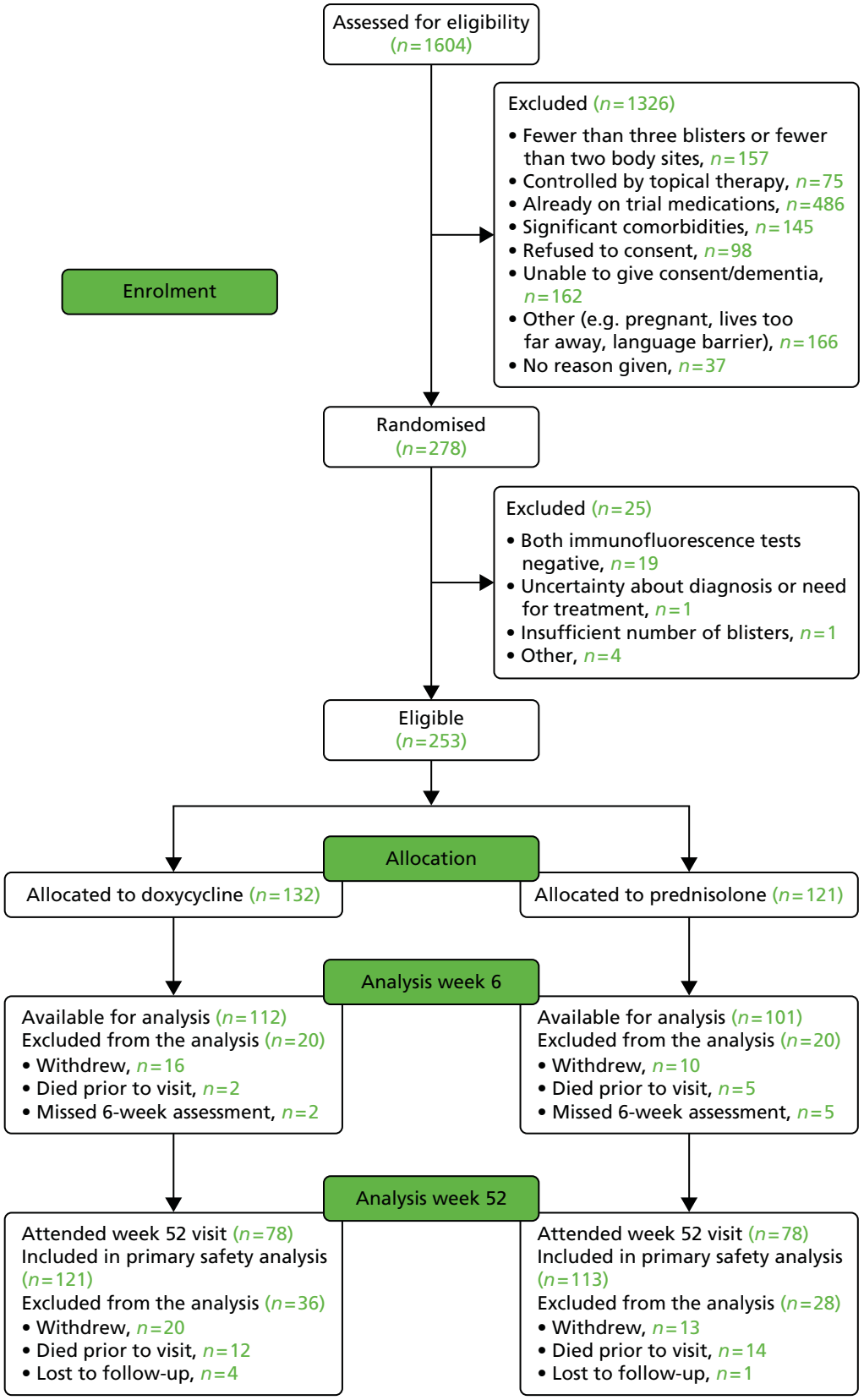

FIGURE 3 Consolidated Standards of Reporting Trials flow chart. Those patients excluded from analysis at week 6 because they missed the week 6 assessment are included in the denominator at week 52 as they have the possibility of attending a visit after week 6 and therefore are not considered lost to follow-up at week 6. Patients who did not attend their week 52 visit are designated as lost to follow-up at week 52. Reproduced from Williams *et al.*[24] under the terms of the Creative Commons Attribution 4.0 licence (CC-BY) (https://creativecommons.org/licenses/by/4.0).

TABLE 1 Numbers of participants randomised to each arm and reasons for ineligibility

Patient status	Doxycycline	Prednisolone	Total
Number randomised	140	138	278
Number withdrawn because of ineligibility	8	17	25
Reasons for ineligibility			
Both direct and indirect immunofluorescence tests were negative	4	15	19
Investigator felt on reflection that patient did not have sufficient blisters to meet the inclusion criteria and therefore should be withdrawn from the trial	0	1	1
Uncertainty initially about diagnosis, negative indirect immunofluorescence, need for treatment	1	0	1
Patient ineligible for other reasons	3	1	4
Number to be analysed	132	121	253

had mild disease (three to nine blisters). The two groups were also balanced for Karnofsky score of functional impairment and ethnicity (*Table 2*).

Withdrawals

A total of 92 patients (36.8%) withdrew from the trial with a similar rate between the two arms (*Tables 3* and *4*). The most common reasons were withdrawal of consent and patient died. The withdrawal rate remained similar throughout the 52-week follow-up period (*Table 5* and *Figure 4*).

Adherence to interventions for primary effectiveness at 6 weeks

Of the participants who had data available for the week 6 primary effectiveness analysis (mITT population), 18.8% in the doxycycline group missed > 3 days of treatment during the first 6 weeks, compared with 5.0% in the prednisolone group (*Table 6*). Nausea was cited as the most frequent reason for reduced adherence to doxycycline in the first 6 weeks (mentioned in 10/21 cases).

Primary outcomes

Primary effectiveness outcome

The primary effectiveness outcome was a non-inferiority comparison of the proportions of patients achieving treatment success at 6 weeks, defined as three or fewer significant blisters. It was anticipated that doxycycline would be less effective than prednisolone but that this would be accompanied by an improvement in the safety profile. As is best practice for non-inferiority comparisons, both mITT and PP analyses were performed.

Modified intention-to-treat analysis

The mITT population included all participants regardless of any changes to treatment, provided that they had survived to week 6 and had received a blister count. This analysis reflects the comparison of the two strategies of starting on doxycycline or starting on prednisolone. In total, 91.1% of patients who were randomised to the prednisolone group were considered to be a treatment success at 6 weeks compared

TABLE 2 Baseline characteristics

Characteristic	Doxycycline, *n* (%)	Prednisolone, *n* (%)	Total, *N* (%)
Female	63 (47.7)	57 (47.1)	120 (47.4)
Male	69 (52.3)	64 (52.9)	133 (52.6)
Age (years)[a]	78.1 (9.5)	77.2 (10.0)	77.7 (9.7)
< 65	8 (6.1)	14 (11.6)	22 (8.7)
65 to < 75	38 (28.8)	33 (27.3)	71 (28.1)
75 to < 85	51 (38.6)	45 (37.2)	96 (37.9)
≥ 85	35 (26.5)	29 (24.0)	64 (25.3)
Karnofsky score[a]	69.0 (18.3)	70.5 (17.6)	69.7 (18.0)
< 40	3 (2.3)	1 (0.8)	4 (1.6)
40 to < 55	32 (24.2)	26 (21.5)	58 (22.9)
55 to < 70	21 (15.9)	24 (19.8)	45 (17.8)
70 to < 85	45 (34.1)	38 (31.4)	83 (32.8)
≥ 85	31 (23.5)	32 (26.4)	63 (24.9)
Unable to care for self	16 (12.1)	11 (9.1)	27 (10.7)
Unable to work	55 (41.7)	51 (42.1)	106 (41.9)
Able[b]	61 (46.2)	59 (48.8)	120 (47.4)
Ethnicity			
White	112 (84.8)	100 (82.6)	212 (83.8)
Black – African	1 (0.8)	1 (0.8)	2 (0.8)
Black – other	0	1 (0.8)	1 (0.4)
Asian – Indian	2 (1.5)	1 (0.8)	3 (1.2)
Asian – Chinese	1 (0.8)	0	1 (0.4)
Asian – other	2 (1.5)	1 (0.8)	3 (1.2)
Other	0	1 (0.8)	1 (0.4)
Not known/given	14 (10.6)	16 (13.2)	30 (11.9)
Severity of BP			
Mild (3–9 blisters)	42 (31.8)	38 (31.4)	80 (31.6)
Moderate (10–30 blisters)	53 (40.2)	46 (38.0)	99 (39.1)
Severe (> 30 blisters)	37 (28.0)	37 (30.6)	74 (29.2)
Total *n*	132	121	253

a Mean (standard deviation).
b Able to carry out normal activity and to work; no special care needed.

with 74.1% of patients who were randomised to the doxycycline group (*Table 7*). Although this is an 18.6% adjusted difference in effectiveness in favour of prednisolone (90% CI 11.1% to 26.1%), the upper CI falls well within the prespecified bounds of non-inferiority (37%) and doxycycline can therefore be considered non-inferior.

There was no evidence of an interaction between disease severity and treatment effect in either the mITT or the PP population.

TABLE 3 Numbers of participants withdrawn from the trial and the primary reasons

Primary reason for withdrawal	Doxycycline ($n = 132$), n	Prednisolone ($n = 121$), n	Total, N
Death	14	19	33[a]
Adverse event	2	1	3
Lost to follow-up	5	4	9
Treatment failure	4	1	5
Withdrew consent	23	16	39
Unable to tolerate trial medications	1	0	1
Other	1	1	2
Total	50	42	92

a In total, 34 deaths occurred in the trial but one participant withdrew consent before they subsequently died and hence the total withdrawn because of death is 33 here.

TABLE 4 Numbers of participants withdrawn from the trial by each visit

Week	Patient status	Doxycycline ($n = 132$), n (%)	Prednisolone ($n = 121$), n (%)	Total ($N = 253$), N (%)
3	Seen	120 (90.9)	110 (90.9)	230 (90.9)
	Died before visit	1 (0.8)	4 (3.3)	5 (2.0)
	Withdrew before visit	9 (6.8)	5 (4.1)	14 (5.5)
	Visit not conducted/status not known	2 (1.5)	2 (1.7)	4 (1.6)
	Total expected	132	121	253
6	Seen	112 (91.8)	101 (90.2)	213 (91.0)
	Died before visit, but after last scheduled visit	1 (0.8)	1 (0.9)	2 (0.9)
	Withdrew before visit, but after last scheduled visit	7 (5.7)	5 (4.5)	12 (5.1)
	Visit not conducted/status not known	2 (1.6)	5 (4.5)	7 (3.0)
	Total expected	122	112	234
13	Seen	99 (86.8)	94 (88.7)	193 (87.7)
	Died before visit, but after last scheduled visit	5 (4.4)	5 (4.7)	10 (4.5)
	Withdrew before visit, but after last scheduled visit	3 (2.6)	6 (5.7)	9 (4.1)
	Visit not conducted/status not known	7 (6.1)	1 (0.9)	8 (3.6)
	Total expected	114	106	220
26	Seen	88 (83.0)	81 (85.3)	169 (84.1)
	Died before visit, but after last scheduled visit	2 (1.9)	6 (6.3)	8 (4.0)
	Withdrew before visit, but after last scheduled visit	9 (8.5)	4 (4.2)	13 (6.5)
	Visit not conducted/status not known	7 (6.6)	4 (4.2)	11 (5.5)
	Total expected	106	95	201

continued

TABLE 4 Numbers of participants withdrawn from the trial by each visit (*continued*)

Week	Patient status	Doxycycline ($n = 132$), *n* (%)	Prednisolone ($n = 121$), *n* (%)	Total ($N = 253$), *N* (%)
39	Seen	81 (85.3)	79 (92.9)	160 (88.9)
	Died before visit, but after last scheduled visit	3 (3.2)	2 (2.4)	5 (2.8)
	Withdrew before visit, but after last scheduled visit	5 (5.3)	3 (3.5)	8 (4.4)
	Visit not conducted/status not known	6 (6.3)	1 (1.2)	7 (4.4)
	Total expected	95	85	180
52	Seen	78 (89.7)	78 (97.5)	156 (93.4)
	Died before visit, but after last scheduled visit	2 (2.3)	1 (1.3)	3 (1.8)
	Withdrew before visit, but after last scheduled visit	3 (3.4)	0	3 (1.8)
	Visit not conducted/status not known	4 (4.6)	1 (1.3)	5 (3.0)
	Total expected	87	80	167

TABLE 5 Cumulative number of participants withdrawn from the trial

Week	Patient status	Doxycycline ($n = 132$), *n* (%)	Prednisolone ($n = 121$), *n* (%)	Total ($N = 253$), *N* (%)
3	Died before visit	1 (0.8)	4 (3.3)	5 (2.0)
	Withdrew before visit	9 (6.8)	5 (4.1)	14 (5.5)
6	Died before visit	2 (1.5)	5 (4.1)	7 (2.8)
	Withdrew before visit	16 (12.1)	10 (8.3)	26 (10.3)
13	Died before visit	7 (5.3)	10 (8.3)	17 (6.7)
	Withdrew before visit	19 (14.4)	16 (13.2)	35 (13.8)
26	Died before visit	9 (6.8)	16 (13.2)	25 (9.9)
	Withdrew before visit	28 (21.2)	20 (16.5)	48 (19.0)
39	Died before visit	12 (9.1)	18 (14.9)	30 (11.9)
	Withdrew before visit	33 (25.0)	23 (19.0)	56 (22.1)
52	Died before visit	14 (10.6)	19 (15.7)	33 (13.0)
	Withdrew before visit	36 (27.3)	23 (19.0)	59 (23.3)

Per-protocol analysis

Patients were excluded from the PP analysis for deviations from the protocol that could significantly affect the outcome. Patients may appear more than once under the various reasons for exclusion if they met more than one of the criteria. The results of the PP analysis were very similar to the results of the ITT analysis, with 92.3% of patients in the prednisolone group achieving success compared with 74.4% in the doxycycline group, an adjusted difference of 18.7% (90% CI 9.8% to 27.6%) (*Table 8*), which falls well within the 37% upper bound for the 90% CI.

Both the mITT and PP analyses are represented graphically in *Figure 5*.

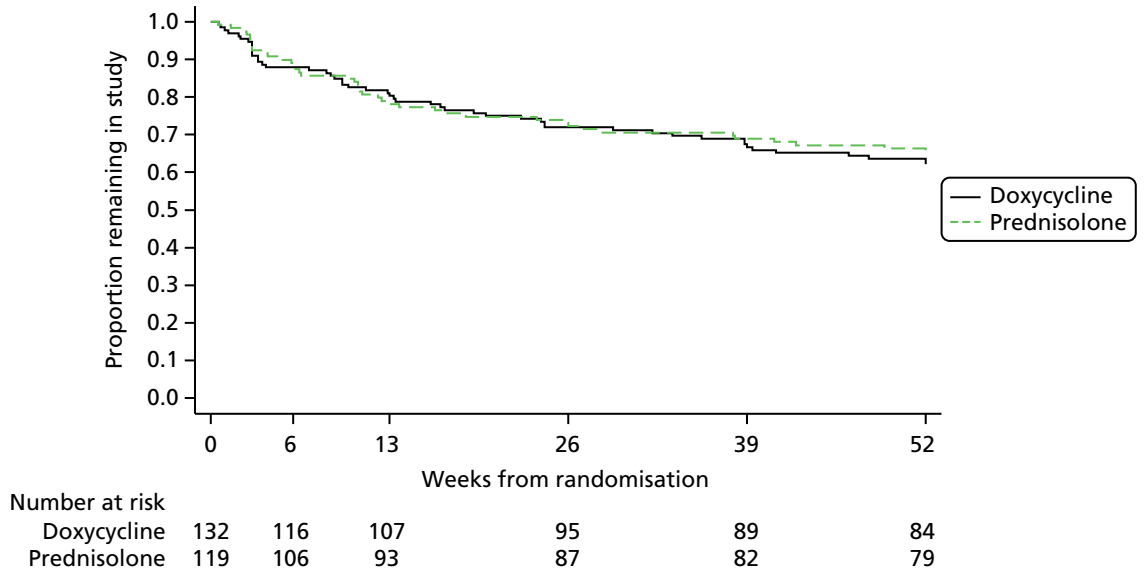

FIGURE 4 Kaplan–Meier survival plot showing time to withdrawal (including death).

TABLE 6 Adherence prior to week 6

Missed > 3 consecutive days of treatment before week 6	Doxycycline, *n* (%)	Prednisolone, *n* (%)	Total, *N* (%)
Yes	21 (18.8)	5 (5.0)	26 (12.2)
No	91 (81.3)	96 (95.0)	187 (87.8)
Total	112	101	213

TABLE 7 Proportions of participants who achieved treatment success at 6 weeks: mITT analysis

	Number (%) of patients	
Outcome	Doxycycline	Prednisolone
Success	83 (74.1)	92 (91.1)
Failure	29 (25.9)	9 (8.9)
Total	112	101
Difference in proportions (prednisolone – doxycycline)	Adjusted:[a] 18.6% (90% CI 11.1% to 26.1%)	
	Unadjusted: 17.0% (90% CI 8.7% to 25.2%)	

a Estimates are from a regression model adjusted for baseline severity of BP and Karnofsky score; however, age was omitted from the model because the model failed to converge when age was added as an adjustment factor.

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. This analysis includes all patients who had a blister count at week 6, and excludes those participants without a blister count at week 6, who were lost to follow-up or who died before week 6. Treatment success = three or fewer significant blisters at week 6; treatment failure = four or more significant blisters at week 6.

TABLE 8 Proportions of participants who achieved treatment success at 6 weeks: PP analysis

Outcome	Number (%) of patients	
	Doxycycline	Prednisolone, *n* (%)
Success	58 (74.4)	84 (92.3)
Failure	20 (25.6)	7 (7.7)
Total	78	91
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 18.7 (9.8 to 27.6)	
	Unadjusted: 17.9 (8.6 to 27.3)	

a Estimates are from a regression model adjusted for baseline severity of BP and Karnofsky score; however, age was omitted from the model because the model failed to converge when age was added as an adjustment factor.

Note

For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. This analysis includes all patients who had a blister count at week 6, and excludes those participants without a blister count at week 6, who were lost to follow-up or who died before week 6. Treatment success = 0–3 significant blisters at week 6; treatment failure = ≥ 4 significant blisters at week 6. (See *Appendix 3*, *Table 58* for reasons for exclusion.)

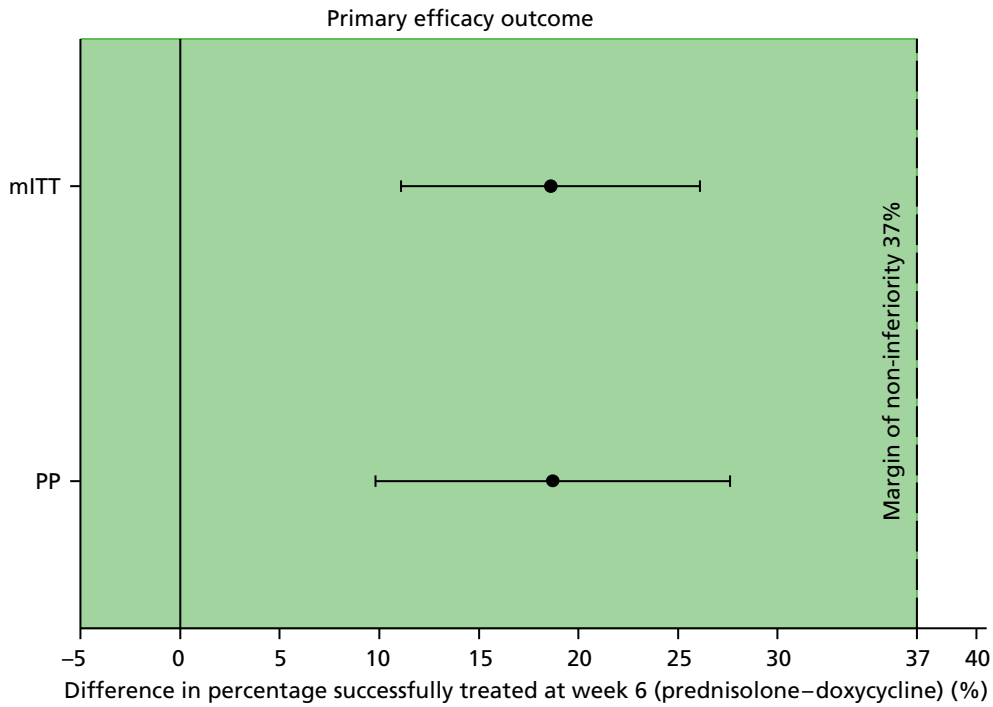

FIGURE 5 Proportions of participants who achieved treatment success at 6 weeks: mITT and PP analyses.

Subgroup analyses

Two subgroup analyses were performed to test for treatment interactions. There were no significant interactions in either the mITT or the PP populations between effectiveness at 6 weeks and baseline disease severity (mild, moderate and severe) (*Tables 9* and *10* respectively) or between effectiveness at 6 weeks and the blinding status of the investigator who carried out the week 6 blister count (*Tables 11* and *12*, respectively).

TABLE 9 Subgroup analysis of baseline disease severity and treatment effect: mITT analysis

Outcome	Subgroup[a]	Number (%) of patients		Proportion a treatment success (90% CI) (%)[b]		Difference in proportions[b] (prednisolone – doxycycline) (90% CI) (%)	Interaction test *p*-value[c]
		Doxycycline (*N* = 112)	Prednisolone (*N* = 101)	Doxycycline	Prednisolone		
Difference in proportions (prednisolone – doxycycline)[b]	Mild baseline severity	37 (33.0)	31 (30.7)	75.7 (64.1 to 87.3)	96.8 (91.6 to 102.0)	21.1 (8.4 to 33.8)	–
	Moderate baseline severity	46 (41.1)	42 (42.6)	78.3 (68.3 to 88.3)	97.6 (93.7 to 101.5)	19.4 (8.6 to 30.1)	0.863
	Severe baseline severity	29 (25.9)	28 (27.7)	65.5 (51.0 to 80.0)	75.0 (61.5 to 88.5)	9.5 (–10.3 to 29.3)	0.417

a Baseline severity: mild: < 10 blisters; moderate: 10–30 blisters; severe: ≥ 30 blisters.
b Estimates are from a regression model adjusted for age and baseline severity; however, not adjusted for Karnofsky score as model would not converge.
c A post-hoc test for interaction comparing severe with mild and moderate disease severity at baseline was also not significant ($p = 0.413$).

TABLE 10 Subgroup analysis of baseline disease severity and treatment effect: PP analysis

Outcome	Subgroup[a]	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline)[b] (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 78)	Prednisolone (*N* = 91)		
Difference in proportions (prednisolone – doxycycline)[b]	Mild baseline severity	22 (28.2)	26 (28.6)	23.4 (6.6 to 40.2)	–
	Moderate baseline severity	34 (43.6)	40 (44.0)	24.8 (9.8 to 43.0)	0.672
	Severe baseline severity	22 (28.2)	25 (27.5)	7.3 (–13.1 to 27.7)	0.477

a Baseline severity: mild < 10 blisters; moderate 10–30 blisters; severe ≥ 30 blisters.
b Estimates are from a regression model adjusted for age and baseline severity; however, not adjusted for Karnofsky score as model would not converge.

TABLE 11 Subgroup analysis of blinding status and treatment effect: mITT analysis

Outcome	Subgroup	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline)[a] (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 112)	Prednisolone (*N* = 101)		
Difference in proportions (prednisolone – doxycycline)[a]	Medication was not known	70 (62.5)	64 (63.4)	20.6 (9.8 to 31.4)	0.333
	Medication was known	42 (37.5)	37 (36.6)	21.9 (10.2 to 33.5)	–

a Estimates are from a regression model not adjusted for age, Karnofsky score or baseline severity as model would not converge.

TABLE 12 Subgroup analysis of blinding status and treatment effect: PP analysis

Outcome	Subgroup	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline)[a] (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 78)	Prednisolone (*N* = 91)		
Difference in proportions (prednisolone – doxycycline)[a]	Medication was not known	53 (68.0)	59 (64.8)	21.5 (10.0 to 33.0)	0.356
	Medication was known	25 (32.1)	32 (35.2)	10.6 (5.0 to 26.3)	–

a Estimates are from a regression model not adjusted for age, Karnofsky score or baseline severity as model would not converge.

Primary safety outcome

The primary safety outcome was the proportion of patients who, during the 52 weeks following randomisation, experienced at least one adverse event that was judged to be either grade 3 (severe), grade 4 (life-threatening) or grade 5 (death) and possibly, probably or definitely related to study treatment. The mITT population for this primary safety outcome included all those with data from at least one scheduled visit, regardless of any changes to treatment. An adjusted regression model in which preceding visits were set to zero was used to impute missing data to determine the sensitivity of the observed results to the missing data.

The risk of experiencing a treatment-related severe, life-threatening or fatal adverse event for patients started on doxycycline was 18.2%; this compared with 36.3% for those starting on prednisolone (*Table 13*). This represents a difference of 19.0% (95% CI 7.9% to 30.1%) after adjusting for baseline severity of BP. Similar results were obtained from a regression model in which missing data had been imputed: 22.5% of patients in the doxycycline group experienced a treatment-related severe, life-threatening or fatal adverse event compared with 40.0% in the prednisolone group, a difference of 18.4% (95% CI 6.0% to 30.8%) after adjusting for baseline severity of BP (*Table 14*).

A higher number of participants in the prednisolone group than in the doxycycline group had a maximum grade of adverse event of grade 3 (severe) and grade 5 (death) (*Table 15*). The pattern was the same for the total number of adverse events of each grade (*Table 16*).

TABLE 13 Proportions of participants experiencing at least one adverse event of grade 3 or higher that was possibly, probably or definitely related to study treatment (raw data set): mITT analysis

	Doxycycline	Prednisolone
Proportion of patients with an adverse event of grade 3 or above (%)[a]	18.2	36.3
Difference in proportions (prednisolone – doxycycline) (95% CI) (%)	Adjusted:[b] 19.0 (7.9 to 30.1); $p = 0.001$	
	Unadjusted: 18.1 (6.9 to 29.3); $p = 0.002$	

a Estimates from unadjusted regression model.
b Estimates are from a regression model adjusted for baseline severity of BP; however, Karnofsky score and age were omitted from the model because the model failed to converge when age and Karnofsky score were added as adjustment factors.

TABLE 14 Proportions of participants experiencing at least one adverse event of grade 3 or higher that was possibly, probably or definitely related to study treatment (with imputed data): mITT analysis

	Doxycycline	Prednisolone
Proportion of patients with an adverse event of grade 3 or above (%)[a]	22.5	40.0
Difference in proportions (prednisolone – doxycycline) (95% CI) (%)	Adjusted:[b] 18.4 (6.0 to 30.8); $p = 0.004$	
	Unadjusted: 17.5 (4.8 to 30.1); $p = 0.007$	

a Estimates from unadjusted regression model on imputed data set.
b Estimates are from a regression model adjusted for baseline severity of BP; however, Karnofsky score and age were omitted from the model because the model failed to converge when age and Karnofsky score were added as adjustment factors.

TABLE 15 The maximum grade of adverse event that each participant experienced during the trial that was considered possibly, probably or definitely related to the study drug: mITT analysis

Adverse event	Number (%) of patients	
	Doxycycline (*N* = 121)	Prednisolone (*N* = 113)
No adverse events or maximum grade of 1 (mild) or 2 (moderate)	99 (81.8)	72 (63.7)
Maximum grade of 3 (severe)	14 (11.6)	25 (22.1)
Maximum grade of 4 (life-threatening)	5 (4.1)	5 (4.4)
Maximum grade of 5 (death)	3 (2.5)	11 (9.7)
Maximum grade of 3, 4 or 5	22 (18.2)	41 (36.3)

Note
Participants counted only once in this table as per their highest grade of adverse event.

TABLE 16 Total number of grade 3, 4 and 5 related adverse events: mITT analysis

Adverse event	Number (%) of adverse events (mean per participant)	
	Doxycycline (*N* = 121)	Prednisolone (*N* = 113)
Grade 3 (severe)	33 (0.3)[a]	59 (0.5)
Grade 4 (life-threatening)	9 (0.1)	9 (0.1)
Grade 5 (death)	3 (< 0.1)	11 (0.1)
Grades 3–5	45 (0.4)	79 (0.7)

a Includes one suspected unexpected serious adverse reaction (hypoglycaemia).
Note
This table includes all patients who have at least one record of an adverse event assessment from the scheduled visit adverse event assessments or a recorded serious adverse event or death.

Secondary outcomes

Secondary effectiveness outcome: weeks 6, 13 and 52

For secondary effectiveness outcomes, the definition of treatment success was different from that used for the primary effectiveness outcome. A participant was required to have three or fewer significant blisters present on examination to be considered a treatment success but, unlike the primary effectiveness analysis, patients who had had their treatment modified because of a poor response (change of medication or dose of randomised medication increased) prior to the visit did *not* qualify as a success in the secondary analyses. This difference is because the primary effectiveness outcome assessed the *strategy* of starting on doxycycline or starting on prednisolone, whereas the secondary outcomes assessed the effectiveness of the treatments used as longer-term monotherapy. All secondary effectiveness outcomes are non-inferiority analyses.

The proportion of patients classed as a treatment success at 6 weeks in the mITT analysis, according to the definition of success described above, was 85.4% in the prednisolone group and 53.6% in the doxycycline group (*Table 17*). This represents a difference of 31.8% (90% CI 22.5% to 41.2%) in favour of prednisolone after adjusting for baseline severity of BP and age. The PP analysis showed similar results, with a difference of 34.4% (90% CI 23.7% to 45.1%) in favour of prednisolone after adjusting for baseline severity of BP and

TABLE 17 Proportions of participants who achieved treatment success at 6 weeks: mITT analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success[a]	60 (53.6)	88 (85.4)
Failure		
High blister count[b]	29 (25.9)	9 (8.7)
Changed treatment	23 (20.5)	4 (3.9)
Died before week 6	0	2 (1.9)
Total	112	103
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[c] 31.8 (22.5 to 41.2)	
	Unadjusted: 31.9 (22.2 to 41.5)	

a Patients who had had their treatment modified because of a poor response prior to the visit did *not* qualify as a success in this secondary analyses.
b More than three blisters.
c Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor.

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister count at week 6 or who had died before week 6 and the cause was considered at least possibly related to treatment were included in this analysis.

age (*Table 18*). The upper CIs for both analyses fall just outside the prespecified upper bound of 37%. Subgroup analyses of the effectiveness outcome data at week 6 using the secondary outcome definition failed to show any evidence of interaction between disease severity and treatment effect (*Tables 19* and *20*) in either the mITT or the PP population. There was no interaction between blinding status and treatment effect at 6 weeks using the secondary outcome definition in the mITT analysis (*Table 21*) but there was some evidence of an interaction effect when a PP analysis was done (*Table 22*).

TABLE 18 Proportions of participants who achieved treatment success at 6 weeks: PP analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success	41 (52.6)	81 (87.1)
Failure		
High blister count	20 (25.6)	7 (7.5)
Changed treatment	17 (21.8)	3 (3.2)
Died before week 6	0	2 (2.2)
Total	78	93
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 34.4 (23.7 to 45.1)	
	Unadjusted: 34.5 (23.6 to 45.4)	

a Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor. (See *Appendix 3*, *Table 59* for reasons for exclusion.)

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister count at week 6 or who had died before week 6 and the cause was considered at least possibly related to treatment were included in this analysis.

TABLE 19 Subgroup analysis of baseline disease severity and the proportion of participants who achieved treatment success at 6 weeks: mITT analysis

Outcome	Subgroup	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline) (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 112)	Prednisolone (*N* = 103)		
Difference in proportions (prednisolone – doxycycline)[a]	Mild baseline blister severity (< 10)	37 (33.0)	32 (31.1)	28.5 (12.9 to 44.2)	–
	Moderate baseline blister severity (10–30)	46 (41.1)	42 (40.8)	31.7 (17.5 to 45.8)	0.806
	Severe baseline blister severity (> 30)	29 (25.9)	29 (28.2)	37.9 (18.0 to 58.8)	0.543

a Estimates are from a regression model adjusted for age and baseline severity; however, not adjusted for Karnofsky score as model would not converge. Patients who died before they had a week 6 blister count were counted as 'not a success'.

TABLE 20 Subgroup analysis of baseline disease severity and the proportion of participants who achieved treatment success at 6 weeks: PP analysis

Outcome	Subgroup	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline) (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 78)	Prednisolone (*N* = 93)		
Difference in proportions (prednisolone – doxycycline)[a]	Mild baseline blister severity (< 10)	22 (28.2)	27 (29.0)	33.4 (14.3 to 52.5)	–
	Moderate baseline blister severity (10–30)	34 (43.6)	40 (43.0)	34.2 (18.2 to 50.2)	0.956
	Severe baseline blister severity (> 30)	22 (28.2)	26 (28.0)	36.1 (14.1 to 58.1)	0.878

a Estimates are from a regression model adjusted for age and baseline severity; however, not adjusted for Karnofsky score as model would not converge.

At 13 weeks, in the mITT analysis, 75.3% of patients in the prednisolone group were considered a treatment success compared with 58.6% in the doxycycline group, a difference of 17.5% (90% CI 6.8% to 28.2%) in favour of prednisolone after adjusting for baseline severity of BP and age (*Table 23*). Again, similar results were noted for the PP analysis (a difference of 17.3% in favour of prednisolone, 90% CI 4.9% to 29.7%) (*Table 24*).

TABLE 21 Subgroup analysis of baseline blinding status and the proportion of participants who achieved treatment success at 6 weeks: mITT analysis

Outcome	Subgroup	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline) (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 112)	Prednisolone (*N* = 101)		
Difference in proportions (prednisolone – doxycycline)[a]	Medication was not known	70 (62.5)	64 (63.4)	25.1 (13.7 to 36.5)	–
	Medication was known	42 (37.5)	37 (36.6)	46.2 (31.6 to 60.9)	0.059

a Estimates are from a regression model adjusted for age and baseline severity; however, not adjusted for Karnofsky score as model would not converge.

TABLE 22 Subgroup analysis of baseline blinding status and the proportion of participants who achieved treatment success at 6 weeks: PP analysis

Outcome	Subgroup	Number (%) of patients		Difference in proportions achieving treatment success (prednisolone – doxycycline) (90% CI) (%)	Interaction test *p*-value
		Doxycycline (*N* = 78)	Prednisolone (*N* = 91)		
Difference in proportions (prednisolone – doxycycline)[a]	Medication was not known	53 (67.9)	59 (64.8)	25.0 (12.2 to 37.8)	–
	Medication was known	25 (32.1)	32 (35.2)	57.7 (40.3 to 75.1)	0.013

a Estimates are from a regression model adjusted for age and baseline severity; however, not adjusted for Karnofsky score as model would not converge.

TABLE 23 Proportions of participants who achieved treatment success at 13 weeks: mITT analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success	58 (58.6)	76 (75.2)
Failure		
High blister count	12 (12.1)	6 (5.9)
Changed treatment	29 (29.3)	12 (11.9)
Died before week 13	0	7 (6.9)
Total	99	101
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 17.5 (6.8 to 28.2)	
	Unadjusted: 16.7 (5.9 to 27.4)	

a Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor.

Note

For the study treatment doxycycline to be considered non-inferior to the control treatment the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister count at week 13 or who died before week 13 and the cause was considered at least possibly related to treatment were included in this analysis.

TABLE 24 Proportions of participants who achieved treatment success at 13 weeks: PP analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success	38 (60.3)	71 (78.0)
Failure		
High blister count	5 (7.9)	5 (5.5)
Changed treatment	20 (31.8)	9 (9.9)
Died before week 13	0	6 (6.6)
Total	63	91
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 17.3 (4.9 to 29.7)	
	Unadjusted: 17.7 (5.3 to 30.1)	

a Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor. (See *Appendix 3*, *Table 60* for reasons for exclusion.)

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister counts at week 13, or have died before week 13 and the cause was considered at least possibly related to treatment were included in this analysis.

The longer-term assessment of effectiveness (the proportion classed as a success at 52 weeks) shows that, in the adjusted mITT analysis, 41.0% of patients started on doxycycline compared with 51.1% of those started on prednisolone achieved treatment success, a difference of 10.0% (90% CI –2.3% to 22.2%) in favour of prednisolone (*Table 25*). Similar results were seen for the PP analysis, with a difference of 7.1% (90% CI –7.1% to 21.3%) in favour of prednisolone (*Table 26*).

TABLE 25 Proportions of participants who achieved treatment success at 52 weeks: mITT analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success	34 (41.0)	45 (51.1)
Failure		
High blister count	3 (3.6)	3 (3.4)
Changed treatment	43 (51.8)	29 (33.0)
Died before week 52	3 (3.6)	11 (12.5)
Total	83	88
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 10.0 (–2.3 to 22.2)	
	Unadjusted: 10.2 (–2.3 to 22.6)	

a Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor.

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister count at week 52 or who died before week 52 and the cause was considered at least possibly related to treatment were included in this analysis.

TABLE 26 Proportions of participants who achieved treatment success at 52 weeks: PP analysis

	Number (%) of patients	
Treatment outcome	Doxycycline	Prednisolone
Success	24 (45.3)	41 (53.3)
Failure		
High blister count	2 (3.8)	3 (3.9)
Changed treatment	25 (47.2)	23 (29.9)
Died before week 52	2 (3.8)	10 (13.0)
Total	53	77
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 7.1 (–7.1 to 21.3)	
	Unadjusted: 8.0 (–6.7 to 22.6)	

a Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor. (See *Appendix 3*, *Table 61* for reasons for exclusion.)

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister count at week 52 or who died before week 52 and the cause was considered at least possibly related to treatment were included in this analysis.

Secondary outcome: relapse rates

Another measure of the long-term effectiveness of the two treatments was the proportion of participants who had a further episode of BP during their participation in the study after previously being classed as a treatment success. A participant was classed as having a relapse if he or she had a further episode of BP, defined as more than three significant blisters, or a change or escalation of treatment because of worsening of disease during participation in the study after previously being classed as a treatment success (either three or fewer significant blisters present on prior examination or previously classed as a treatment success on the treatment log). After adjusting for baseline severity, age and Karnofsky score, a similar number of relapses occurred in the doxycycline group and the prednisolone group in the mITT population (2.1% more in the prednisolone group, 90% CI –8.3% to 12.5%) (*Table 27*). A larger difference was noted in the PP analysis (11.0% more relapses in the prednisolone group, 90% CI –1.2% to 23.2%) (*Table 28*).

TABLE 27 Proportions of participants who had a further episode of BP after previously being classified as a treatment success: mITT analysis

	Number (%) of patients	
Outcome	Doxycycline	Prednisolone
Relapse	37 (32.5)	39 (35.8)
No relapse	77 (67.5)	70 (64.2)
Total	114	109
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 2.1 (–8.3 to 12.5)	
	Unadjusted: 3.3 (–7.1 to 13.8)	

a Estimates are from a regression model adjusted for baseline severity of BP, age and Karnofsky score.

Note
All patients who had at least one physical examination in the study and who had been classed as a treatment success at some point in the trial were included in this analysis.

TABLE 28 Proportions of participants who had a further episode of BP after previously being classified as a treatment success: PP analysis

Outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Relapse	20 (27.0)	34 (38.6)
No relapse	54 (73.0)	54 (61.4)
Total	74	88
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 11.0 (–1.2 to 23.2)	
	Unadjusted: 11.6 (–0.4 to 23.7)	

a Estimates are from a regression model adjusted for baseline severity of BP, age and Karnofsky score. (See *Appendix 3*, *Table 62* for reasons for exclusion.)

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment the upper bound of the 90% CI should fall below 37%. All patients who had at least one physical examination in the study and who had been classed as a treatment success at some point in the trial were included in this analysis.

Secondary outcome: combined outcome of effectiveness at 6 weeks and safety over 52 weeks

To provide an overall measure of success, a combined analysis of effectiveness and safety is presented in a superiority analysis. In the prednisolone group, 74.8% of patients were classed as a treatment success at 6 weeks *and* were alive at 52 weeks whereas in the doxycycline group 50.0% of patients were classed as a treatment success at 6 weeks *and* were alive at 52 weeks (*Table 29*). This represents a difference of 25.0% (95% CI 13.1% to 37.0%) in favour of prednisolone after adjusting for baseline severity and age.

Secondary safety outcome: all adverse events

This secondary outcome includes *all* adverse events that are possibly, probably or definitely related to the trial medication, regardless of severity. All analyses were carried out on a superiority basis. The maximum

TABLE 29 Proportions of patients who were classed as a treatment success at 6 weeks *and* were alive at 52 weeks

Treatment success	Number (%) of patients	
	Doxycycline	Prednisolone
Success	56 (50.0)	77 (74.8)
Failure		
Success at week 6 but not alive at week 52	4 (3.6)	11 (10.7)
Not successful at week 6 because of high blister count	29 (25.9)	9 (8.7)
Not successful at week 6 because of treatment change before week 6	23 (20.5)	4 (3.9)
Not successful at week 6 because of death before week 6	0	2 (1.9)
Total	112	103
Difference in proportions (prednisolone – doxycycline) (95% CI) (%)	Adjusted:[a] 25.0 (13.1 to 37.0); $p < 0.001$	
	Unadjusted: 24.8 (14.3 to 35.2); $p < 0.001$	

a Estimates are from a regression model adjusted for baseline severity of BP and age; however, Karnofsky score was omitted from the model because the model failed to converge when Karnofsky score was added as an adjustment factor.

Note
This analysis includes all patients with a blister count at week 6 or who died before week 6 and the death was considered at least possibly related to the treatment.

grade of related adverse events experienced by participants during the trial is shown in *Table 30*. Patients in the prednisolone group were significantly more likely to experience an adverse event that was related to the study medication than those in the doxycycline group (95.7% vs. 86.2%, 95% CI 1.8% to 17.2%; $p = 0.016$, unadjusted because of non-convergence in the model) (*Table 31*). The total numbers of related adverse events by grade (raw data) are shown in *Table 32*.

Secondary outcome: quality of life

Quality of life was assessed using the generic EQ-5D and the skin-specific DLQI. For a specific visit, the EQ-5D tabulations and analyses were conducted on all patients in the ITT population who had all five scores for the five questions for that visit (mobility, self-care, usual activity, pain/discomfort and anxiety/depression). Only patients who had at least one visit (not including baseline) for which data were available were included in the analysis. The EQ-5D score (social preference score) was obtained, with a value assigned to each combination of scores from the individual five questions (see *Chapter 4*, *Data sources*). For the DLQI, the tabulations and analyses were conducted for a specific visit on all patients in the ITT population who had all 10 scores for the 10 questions for that visit. Only patients who had at least one visit (not including baseline) for which data were available were included in the analysis. The DLQI score was calculated as the sum of each of the scores for the 10 questions asked at each visit.

TABLE 30 The maximum grade of adverse event that each participant experienced during the trial that was considered possibly, probably or definitely related to the study drug (any grade): raw data

	Number (%) of patients	
Adverse event	Doxycycline ($N = 121$)	Prednisolone ($N = 113$)
No adverse events	23 (19.0)	13 (11.5)
Maximum grade of adverse event grade 1 (mild)	20 (16.5)	16 (14.2)
Maximum grade of adverse event grade 2 (moderate)	56 (46.3)	43 (38.1)
Maximum grade of adverse event grade 3 (severe)	14 (11.6)	25 (22.1)
Maximum grade of adverse event grade 4 (life-threatening)	5 (4.1)	5 (4.4)
Maximum grade of adverse event grade 5 (death)	3 (2.5)	11 (9.7)
Adverse event of *any* grade	98 (81.0)	100 (88.5)

Note
This table includes all patients with at least one record of an adverse event assessment from the scheduled visit adverse event assessments or a recorded serious adverse event or death.

TABLE 31 Proportions of patients with any related adverse event during the trial: mITT analysis

	Doxycycline	Prednisolone
Proportion of patients with an adverse event (%)[a]	86.2	95.7
Difference in proportion of patients with an adverse event (prednisolone – doxycycline) (95% CI) (%)	Unadjusted:[b] 9.5 (1.8 to 17.2); $p = 0.016$	

a Estimates are from an unadjusted regression model on the imputed data set.
b Estimates are from a regression model not adjusted for baseline severity of BP, Karnofsky score and age because the model failed to converge when they were added as adjustment factors.

TABLE 32 Total number of related adverse events by grade: raw data

Adverse event	Number of adverse events (mean per participant)	
	Doxycycline ($n = 121$)	Prednisolone ($n = 113$)
Grade 1 (mild)	210 (1.7)	234 (2.1)
Grade 2 (moderate)	158 (1.3)	129 (1.1)
Grade 3 (severe)	33 (0.3)	59 (0.5)
Grade 4 (life-threatening)	9 (0.1)	9 (0.1)
Grade 5 (death)	3 (< 0.1)	11 (0.1)
Grades 1–5	413 (3.4)	442 (3.9)

Note
This table includes all patients who have at least one record of an adverse event assessment from the scheduled visit adverse event assessments or a recorded serious adverse event or death.

There was a median change in EQ-5D score from baseline to week 52 of +0.090 in the doxycycline group and +0.071 in the prednisolone group (*Table 33*). When this was adjusted for baseline EQ-5D score, baseline severity, age and Karnofsky score, the difference was not significant (0.045, 95% CI –0.015 to 0.106; $p = 0.143$) (*Table 34*). Patients in the two groups had a similar improvement in DLQI score, with a median improvement from baseline to week 52 of 9 points in the doxycycline group and 10 points in the prednisolone group (*Table 35*). When adjusted for baseline DLQI score, baseline severity, age and Karnofsky score, there was a significant difference of –1.8 (95% CI –2.58 to –1.01) in favour of doxycycline (*Table 36*).

Tertiary outcomes

The mITT analysis showed that there was a higher proportion of participants who were completely blister free at 6 weeks (rather than three or fewer significant blisters) in the prednisolone group (73.3% vs.

TABLE 33 Difference in EQ-5D scores (raw data): mITT analysis

Time point	Doxycycline ($n = 110$)			Prednisolone ($n = 101$)		
	Median (IQR)	Median change from baseline	Total patients with data	Median (IQR)	Median change from baseline	Total patients with data
Baseline	0.656 (0.273–0.796)	0	110	0.656 (0.273–0.760)	0	101
Week 6	0.620 (0.353–0.805)	–0.036	108	0.746 (0.587–1.000)	+0.090	96
Week 13	0.710 (0.450–1.000)	+0.054	96	0.779 (0.639–0.925)	+0.123	92
Week 26	0.746 (0.587–1.000)	+0.090	85	0.796 (0.638–0.850)	+0.140	80
Week 39	0.727 (0.587–1.000)	+0.071	79	0.710 (0.587–1.000)	+0.054	77
Week 52	0.746 (0.587–1.000)	+0.090	78	0.727 (0.587–1.000)	+0.071	74

IQR, interquartile range.

TABLE 34 Difference in EQ-5D scores: mITT analysis

Difference in EQ-5D scores (prednisolone – doxycycline) (95% CI)	Adjusted:[a] 0.045 (–0.015 to 0.106); $p = 0.143$
	Unadjusted:[b] 0.062 (–0.006 to 0.130); $p = 0.076$

a Visit was entered into the model as a random intercept nested within the patient. Estimates from a mixed-effects regression model adjusted for baseline EQ-5D score, baseline severity of BP, age and Karnofsky score.
b Visit was entered into the model as a random intercept nested within the patient. Estimates from a mixed-effects regression model unadjusted for baseline severity of BP, age and Karnofsky score but adjusted for baseline EQ-5D score.

TABLE 35 Difference in DLQI scores (raw data): mITT analysis

	Doxycycline ($n = 108$)			Prednisolone ($n = 101$)		
Time point	Median (IQR)	Median change from baseline	Total patients with data	Median (IQR)	Median change from baseline	Total patients with data
Baseline	10 (6–15)	0	108	11 (6–14)	0	101
Week 6	5 (2–9)	–5	106	1 (0–3)	–10	96
Week 13	2 (1–6)	–8	98	1 (0–4)	–10	90
Week 26	2 (0–4)	–8	86	1 (0–3)	–10	80
Week 39	1 (0–4)	–9	80	1 (1–3)	–10	77
Week 52	1 (0–3)	–9	79	1 (0–3)	–10	75

IQR, interquartile range.

TABLE 36 Difference in DLQI scores: mITT analysis

Difference in DLQI scores (prednisolone – doxycycline) (95% CI) (%)	Adjusted:[a,b] –1.80 (–2.58 to –1.01); $p < 0.001$

a Visit was entered into the model as a random intercept nested within the patient. Estimates from a mixed-effects regression model adjusted for baseline DLQI score, baseline severity of BP, age and Karnofsky score.
b The model did not converge in the unadjusted analysis and so this has been omitted.

45.9%) (*Table 37*). This is a difference of 28.6% in favour of prednisolone after adjusting for baseline severity, age and Karnofsky score (90% CI 18.1 to 39.1%). *Table 38* lists the number of patients in the mITT population excluded from the PP analysis. The PP analysis showed very similar results (*Table 39*).

Tertiary effectiveness outcome: proportion of participants who achieved treatment success at 3 weeks (non-inferiority)

As a measure of the speed of onset of action, the proportions of participants classed as a treatment success (three or fewer significant blisters) were assessed after only 3 weeks of treatment. In the mITT population, a higher proportion of those started on prednisolone were classed as a treatment success at 3 weeks than those started on doxycycline, with a difference of 23.4% (90% CI 14.4% to 32.5%) after adjusting for baseline severity, age and Karnofsky score (*Table 40*), although this remains within the prespecified bounds of non-inferiority. A similar difference was seen in the PP analysis (*Table 41*).

TABLE 37 Proportions of participants who were completely blister free at week 6: mITT analysis

Outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Blister free	51 (45.9)	74 (73.3)
Not blister free	60 (54.1)	27 (26.7)
Total	111	101
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 28.6 (18.1 to 39.1)	
	Unadjusted: 27.3 (16.7 to 38.0)	

a Estimates are from a regression model adjusted for baseline severity of BP, age and Karnofsky score.

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. All patients who had data on whether or not they were blister free at week 6 were included in this analysis. One patient who was included in the primary efficacy analysis but who did not have data available on whether or not they were blister free at week 6 was excluded from the analysis.

TABLE 38 Number of patients in the mITT population excluded from the PP analysis

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 6	1	0
Changed treatment or added a new treatment to the allocated treatment before week 6	17	3
Used topical steroids between weeks 3 and 6	7	3
Missed more than 3 consecutive days of treatment before week 6	21	5
Total number of non-PP patients	34	10

Note
Some patients may appear in more than one row.

TABLE 39 Proportions of participants who were completely blister free at week 6: PP analysis

Outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Blister free	35 (45.5)	68 (74.7)
Not blister free	42 (54.5)	23 (25.3)
Total	77	91
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 30.2 (18.4 to 42.0)	
	Unadjusted: 29.3 (17.3 to 41.2)	

a Estimates are from a regression model adjusted for baseline severity of BP, age and Karnofsky score.

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. All patients who had data on whether or not they were blister free at week 6 were included in this analysis. One patient who was included in the primary efficacy analysis but who did not have data available on whether or not they were blister free at week 6 was excluded from the analysis.

TABLE 40 Proportions of participants who achieved treatment success at 3 weeks: mITT analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success	67 (56.3)	90 (81.1)
Failure		
High blister count	42 (35.3)	17 (15.3)
Changed treatment	10 (8.4)	3 (2.7)
Died before week 3	0	1 (0.9)
Total	119	111
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 23.4 (14.4 to 32.5)	
	Unadjusted: 24.8 (15.1 to 34.4)	

a Estimates are from a regression model adjusted for baseline severity of BP and Karnofsky score; however, age was omitted from the model because the model failed to converge when age was added as an adjustment factor.

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. Only patients with available data on blister count at week 3 or who died before week 3 and the cause was considered at least possibly related to treatment were included in this analysis.

TABLE 41 Proportions of participants who achieved treatment success at 3 weeks: PP analysis

Treatment outcome	Number (%) of patients	
	Doxycycline	Prednisolone
Success	56 (57.1)	85 (81.7)
Failure		
Severe baseline disease	33 (33.7)	16 (15.4)
Changed treatment	9 (9.2)	3 (2.9)
Died before week 3	0	0
Total	98	104
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 23.7 (13.3 to 34.0)	
	Unadjusted: 24.6 (14.3 to 34.9)	

a Estimates are from a regression model adjusted for Karnofsky score; however, baseline severity of BP and age were omitted from the model because the model failed to converge when they were added as adjustment factors. (See *Appendix 3*, *Table 63* for reasons for exclusion.)

Note
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%.

Tertiary safety outcome: mortality over the 52-week follow-up period (superiority)

An assessment of all deaths, regardless of any relatedness to the study medication, was performed. Those who started on prednisolone were more likely to die during the year of follow-up than those started on doxycycline (83.5% alive at 1 year compared with 89.4%, respectively) (*Table 42*). The hazard ratio for reduction in death in favour of doxycycline, adjusted for baseline severity, age and Karnofsky score, was 0.61 (95% CI 0.30 to 1.24; $p = 0.173$) (*Table 43*). Time to death is shown in the Kaplan–Meier plot in *Figure 6*.

TABLE 42 Mortality over the 52-week follow-up period: mITT analysis

Mortality outcome	Number (%) of patients	
	Doxycycline (*N* = 132)	Prednisolone (*N* = 121)
Died during trial follow-up	14 (10.6)	20[a] (16.5)
Related[a]	3 (2.3)	11 (9.1)
Unrelated[b]	11 (8.3)	9 (7.4)
Alive at the end of follow-up (1 year)	118 (89.4)	101 (83.5)

a Includes a participant who withdrew consent and who subsequently died.
b Related refers to the death being considered at least possibly related to the trial treatment.

TABLE 43 All-cause mortality: mITT analysis

All-cause mortality (hazard ratio) (95% CI)	Adjusted:[a] 0.61 (0.30 to 1.24); $p = 0.173$
	Unadjusted: 0.59 (0.29 to 1.19); $p = 0.139$

a Estimate is from a Cox regression model adjusted for baseline severity of BP, age and Karnofsky score.

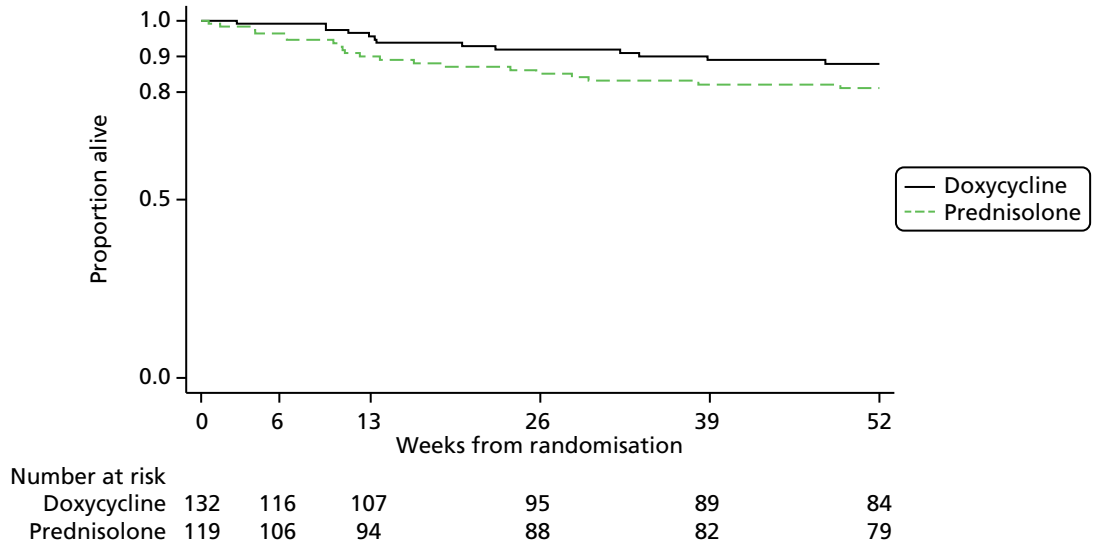

FIGURE 6 Kaplan–Meier survival plot showing time to death.

Tertiary effectiveness outcome: use of potent and superpotent topical corticosteroids during the 52-week follow-up period (superiority)

Use of topical steroids (potent or superpotent) was permitted during the first 3 weeks of treatment for symptomatic relief (no more than 30 g per week to localised lesions only) and also after 6 weeks, as might occur in normal practice in the UK. Although use of topical steroids was discouraged from the end of week 3 to the week 6 effectiveness assessment, some participants did use topical corticosteroids for local relief of the affected area. Data on quantities of topical corticosteroids used were not collected accurately over the 1-year study period and so *Table 44* presents topical corticosteroid use during different study periods. As anticipated, topical corticosteroid use for symptomatic relief was greater at all time points for those initiated on doxycycline treatment.

TABLE 44 Potent and superpotent topical corticosteroid use according to study period and treatment allocation

	Doxycycline (*N* = 112), *n* (%)			Prednisolone (*N* = 101), *n* (%)		
Time period	Potent	Superpotent	Patients using topical corticosteroids	Potent	Superpotent	Patients using topical corticosteroids
After randomisation up to 3 weeks	6 (5.4)	1 (0.9)	7 (6.3)	3 (3.0)	1 (1.0)	4 (4.0)
After 3 weeks up to 6 weeks	12 (10.7)	11 (9.8)	23 (20.5)	6 (5.9)	0	6 (5.9)
After 6 weeks	5 (4.5)	7 (6.3)	12 (10.7)	2 (2.0)	0	2 (2.0)
At any time during the trial	13 (11.6)	11 (9.8)	24 (21.4)	6 (5.9)	1 (1.0)	7 (6.9)

Additional post-hoc analysis

Post-hoc analysis: primary effectiveness outcome repeated at week 52

The primary effectiveness outcome at 6 weeks assessed the *strategy* of starting on doxycycline or prednisolone by including all participants regardless of any treatment modification. It was decided at the Trial Steering Committee meeting to conduct an additional post-hoc effectiveness analysis using the same definition of the population included to assess the *strategy* of starting on doxycycline or prednisolone over the whole 52-week period. There was no significant difference between the two groups when assessed over the full 52 weeks in either the mITT analysis (*Table 45*) or the PP analysis (*Table 46*).

Post-hoc analysis: action (treatment changes) taken in response to relapse

In total, 76 patients were identified as having relapsed after previously being classified as a treatment success, either because they had three or fewer significant blisters present or because they had ceased trial medication because of treatment success (*Table 47*). For those started on prednisolone, if they experienced a relapse, patients usually either received an increased dose of prednisolone (30/39, 76.9%) or recommenced prednisolone if treatment had ceased completely (8/39, 20.5%). For those who started on

TABLE 45 Proportions of participants who achieved treatment success at 52 weeks: mITT analysis

	Number (%) of patients	
Outcome[a]	Doxycycline	Prednisolone
Success	77 (96.3)	74 (96.1)
Failure	3 (3.8)	3 (3.9)
Total	80	77
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)[b]	–0.1 (–5.2 to 4.9)	

a Three or fewer significant blisters at week 6 = treatment success; four or more significant blisters at week 6 or died before week 6 = treatment failure.
b Estimates are from a regression model unadjusted for baseline severity of BP, age and Karnofsky score as adding any of these covariates into the model led to non-convergence of the model.

Notes
This analysis includes all patients with a blister count at week 52 and excludes those who did not have a blister count at week 6 and who were lost to follow-up or who died before week 52.
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%.

TABLE 46 Proportions of participants who achieved treatment success at 52 weeks: PP analysis

Outcome[a]	Number (%) of patients	
	Doxycycline	Prednisolone
Success	49 (96.1)	64 (95.5)
Failure	2 (3.9)	3 (4.5)
Total	51	67
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)[b]	–0.6 (–6.7 to 5.5)	

a Three or fewer significant blisters at week 6 = treatment success; four or more significant blisters at week 6 or died before week 6 = treatment failure.
b Estimates are from a regression model unadjusted for baseline severity of BP, age and Karnofsky score as adding any of these covariates into the model led to non-convergence of the model. (See *Appendix 3*, *Table 64* for reasons for exclusion.)

Note
This analysis includes all patients with a blister count at week 52 and excludes those who did not have a blister count at week 6 and who were lost to follow-up or who died before week 52.
For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%.

TABLE 47 Action taken in response to disease relapse

Action taken in response to disease relapse	Number (%) of patients	
	Doxycycline ($n = 37$)	Prednisolone ($n = 39$)
Treatment changed to prednisolone	13 (35.1)	0
Treatment changed to doxycycline	0	0
Dose of prednisolone increased	16 (43.2)	30 (76.9)
Dose of doxycycline increased	3 (8.1)	0
Prednisolone restarted	3 (8.1)	8 (20.5)
Doxycycline restarted	2 (5.4)	0
Other treatment change	0	1 (2.6)

Note
This table refers to changes made at the point of relapse. In some instances, when a patient was allocated to a particular treatment, the action may be to increase the dose, restart the allocated drug or start or restart the unallocated drug. This is because the patient may have already changed treatment to an unallocated treatment prior to relapse, e.g. because of treatment failure.

doxycycline, the most common course of action on relapse after having previously achieved disease control was to change to prednisolone (13/37, 35.1%) or increase the dose of prednisolone (16/37, 43.2%).

Post-hoc analysis: time to switching treatment

For those patients who switched treatments, the time between starting the study and switching treatment was assessed in a post-hoc analysis. This included all of the patients in the mITT population who contributed to the secondary efficacy analysis at week 6. The rate of switching from doxycycline was greatest during the first 6 weeks; after 13 weeks there was very little switching (*Figure 7*). There was a lower rate of switching for those starting on prednisolone and the rate was more constant over the whole 52 weeks.

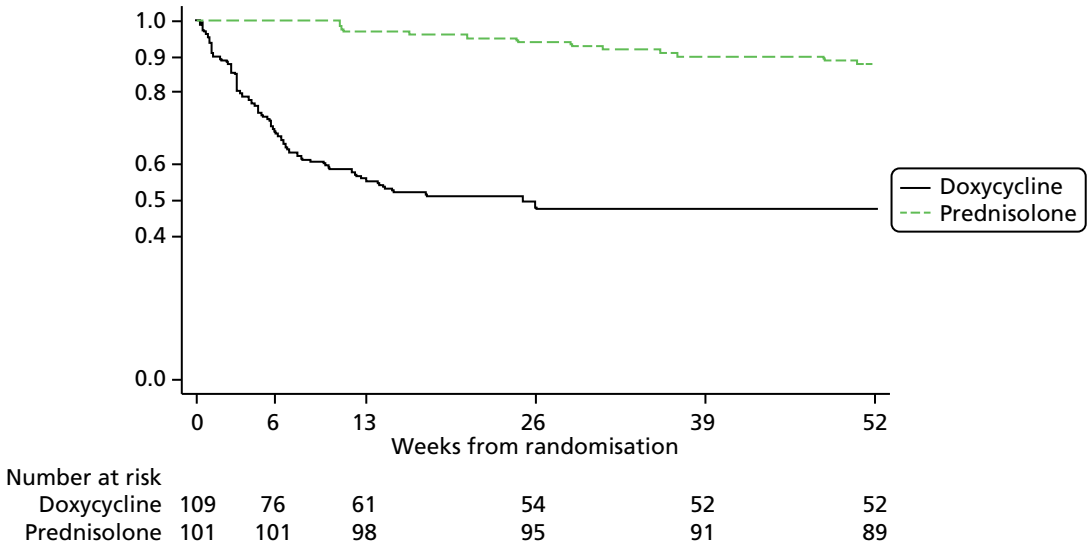

FIGURE 7 Kaplan–Meier survival plot showing time to change of treatment. Note: A change in treatment refers to a change from the allocated treatment (either doxycycline or prednisolone) to the other treatment. This graph includes the 213 patients who formed the mITT population for the primary efficacy outcome.

Post-hoc analysis: sensitivity of the primary effectiveness outcome at 6 weeks to topical corticosteroid use

A slightly different definition of a PP violator was used from that defined in the statistical analysis plan so that any use of a prohibited potent or superpotent topical corticosteroid between weeks 3 and 6 resulted in exclusion from the PP analysis of blister control at 6 weeks. The results of this post-hoc analysis are shown in *Table 48*. This shows that the non-inferiority status of doxycycline was robust to excluding those who used additional topical corticosteroids in the 3 weeks prior to the 6-week blister count assessment, at which the presence of three or fewer significant blisters was considered a treatment success.

TABLE 48 Proportions of participants who achieved treatment success at 6 weeks: PP analysis using any topical corticosteroid use in weeks 3–6 as a reason for exclusion from the PP analysis population

	Number (%) of patients	
Outcome	Doxycycline	Prednisolone
Success	49 (74.2)	82 (93.2)
Failure	17 (25.8)	6 (6.8)
Total	66	88
Difference in proportions (prednisolone – doxycycline) (90% CI) (%)	Adjusted:[a] 19.3 (9.6 to 29.0)	
	Unadjusted: 18.9 (9.0 to 28.8)	

a Estimates are from a regression model adjusted for baseline severity of BP and Karnofsky score; however, age was omitted from the model because the model failed to converge when age was added as an adjustment factor.

Note

For the study treatment doxycycline to be considered non-inferior to the control treatment, the upper bound of the 90% CI should fall below 37%. This analysis includes all patients with a blister count at week 6 and excludes those who were lost to follow-up or who died before week 6.

Post-hoc analysis: safety data at 52 weeks according to baseline disease severity

To assist with interpreting the health economic analysis, an additional post-hoc analysis was performed for the primary safety data according to baseline disease severity (*Table 49*).

Similar post-hoc subgroup analyses for imputed data showed similar results: the differences in the percentages experiencing a related adverse event (prednisolone – doxycycline) were 25.2% (95% CI 4.0% to 46.3%) for mild baseline severity, 28.6% (95% CI 9.9% to 47.3%) for moderate baseline severity and –6.1% (95% CI –32.0% to 19.7%) for severe baseline severity.

TABLE 49 Participants reporting an adverse event of at least grade 3 that is possibly, probably or definitely related to BP medication in the 52 weeks following randomisation (raw data)

	Number (%) of patients		Number (%) experiencing a related adverse event (from raw data)		Difference in percentage (prednisolone – doxycycline) (95% CI)[b]
Subgroup[a]	Doxycycline	Prednisolone	Doxycycline	Prednisolone	
Mild baseline severity	40 (33.1)	35 (31.0)	6 (15.0)	14 (40.0)	25.0 (5.4 to 44.6)
Moderate baseline severity	47 (38.8)	43 (38.1)	5 (10.6)	17 (39.5)	28.9 (11.8 to 46.0)
Severe baseline severity	34 (28.1)	35 (31.0)	11 (32.4)	10 (28.6)	–3.8 (–25.5% to 17.9)
Total	121	113	22 (18.2)	41 (36.3)	18.1%

a Baseline severity: mild < 10 blisters; moderate 10–30 blisters; severe ≥ 31 blisters.
b Estimates are from an unadjusted regression model.

Chapter 4 Cost-effectiveness

Objective

The objective of the economic analysis was to estimate the cost-effectiveness of doxycycline-initiated therapy compared with that of prednisolone-initiated therapy for patients with BP from the perspective of the English NHS.

Overview

Economic analysis is intended to inform decision-makers about the value for money of treatment alternatives, in a context in which health-care resources are limited and prioritisation is informed, at least in part, by the efficient use of resources.[39] The economic analysis within the BLISTER trial followed a prospectively agreed analysis plan and provides robust and unbiased evidence of cost-effectiveness, augmenting the trial estimates of clinical effectiveness. The BLISTER trial featured a pragmatic multicentre design reflecting real-world clinical practice and thus cost and outcome profiles are likely to reflect routine care in NHS settings. Individual patient data collected within the BLISTER trial included NHS treatment costs and health status, estimated as QALYs. Cost-effectiveness analysis captures the effect of treatment as changes in costs and QALYs. Given that follow-up was limited to 1 year, no discounting of future costs and benefits was applied.

The analysis followed ITT principles, with patients included in the analysis according to the treatment allocated by randomisation, irrespective of subsequent care.

Because of some missing data during trial follow-up, a base-case analysis was constructed in which missing data were imputed using multiple imputation. Supportive sensitivity analyses included only patients with complete data, thus exploring the impact of imputation.

Methods

Data sources

Resource use and quality-of-life measurements were collected from patients by health-care professionals at mandatory clinics at baseline and 6, 13, 26, 39 and 52 weeks. Generic health-related quality of life was assessed using the EuroQol questionnaire (containing the EQ-5D-3L and EQ VAS). The DLQI was included as a disease-specific quality-of-life measure.

The EQ-5D scores were converted to health status scores using the value set (time trade-off recommended by the EuroQol group).[40,41] Using the trapezoidal rule, the AUC of health status scores was calculated, providing patient-level QALY estimates for the cost-effectiveness analysis.[42] Similarly, EQ VAS and DLQI scores were integrated discretely over time. As AUC estimates were predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates were adjusted for baseline scores.[43] Sensitivity analyses explored adjusted and unadjusted estimation including a range of patient covariates: age, sex, baseline blister severity and baseline Karnofsky score as well as baseline outcome measure score.

Resource capture included use of study and non-study drugs as well as health service contacts: GP clinic and home visits, practice and district nurse visits and outpatient visits and inpatient stays. Patients were asked to recall use of resources since their last clinic visit and were given a diary at the beginning of the study to aid recall. Drugs recorded related to the management of BP or its sequelae. For health service

contacts patients were asked to identify all patient contacts as well as those related directly to the management of BP or its sequelae. Consequently, 'attributable costs' are used in the base-case analysis and a sensitivity analysis included 'all costs'.

Unit costs of resources were estimated or drawn from national reference sources for 2013 and are shown in *Table 50*. Study and non-study drugs were prescribed at varying doses. Using national PCA data,[33] average costs per unit weight of therapeutic were determined and applied to patient drug use records. The list of drugs used included a number of occasionally prescribed drugs; pragmatically, drugs that were prescribed on more than five occasions during the course of the trial were costed. Costs for inpatient stays (in days) and outpatient visits were estimated using Hospital Episodes Statistics (HES)[36] and NHS reference costs.[35] National HES data were explored for inpatient episodes with a primary diagnosis of *International Classification of Diseases* L12.0 Bullous Pemphigoid. The 10 most common Healthcare Resource Group (HRG) HRG4+ codes associated with that diagnosis were included, accounting for 96.2% of admissions. Per diem costs for each HRG4+ code were estimated from NHS reference costs and a volume-weighted average cost per admission for BP was estimated allowing for mean stay and cost per day. GP clinic and home visits, and practice and district nurse visits were costed using unit costs provided by the Personal Social Services Research Unit (PSSRU).[34] Patient costs were estimated as the sum of resources used weighted by their reference costs. The base-case analysis included only BP-related resource use.

Multiple imputation

In any form of analysis, missing data can cause serious problems. The problem is greater than a simple loss of statistical power as missing data may be not a random event but related to treatment and outcome. Examples include getting better (and no longer needing care) or dying, although QALY estimates allow for and include patients who die during follow-up. Quality-of-life measures typically feature repeated assessments over time, which are used to construct AUC estimates. This approach is both a strength and a weakness. With a complete-case analysis the weakness is evident: more observations may mean more incomplete assessments and loss of one follow-up assessment means the non-inclusion of that patient.

TABLE 50 Unit costs applied to patient resource use (2013 cost base)

Resource	Cost (£)	Unit	Source
Drug			
Doxycycline	0.0015	Per mg	PCA[33]
Prednisolone	0.0221	Per mg	PCA[33]
Azathioprine (Imuran®, Aspen)	0.0034	Per mg	PCA[33]
Betamethasone valerate (Betnovate®, GlaxoSmithKline UK)	0.0582	Per g	PCA[33]
Clobetasol propionate (Dermovate®, GlaxoSmithKline UK)	0.0828	Per g	PCA[33]
Mometasone furoate	0.1368	Per g	PCA[33]
Clobetasone butyrate (Eumovate®, GlaxoSmithKline UK)	0.0588	Per g	PCA[33]
Contact			
Inpatient	334.22	Per day	HES,[36] NHS reference costs[35]
Outpatient	98.00	Per visit	HES,[36] NHS reference costs[35]
GP clinic	46.00	Per visit	PSSRU[34]
GP home	92.00	Per visit	PSSRU[34]
Practice nurse	13.34	Per visit	PSSRU[34]
District nurse	39.00	Per visit	PSSRU[34]

PSSRU, Personal Social Services Research Unit.

However, repeated observations may provide (partial) assessments on more patients, allowing their experience to be reliably imputed. The base-case analysis used multiple imputation, conducted according to good practice guidance.[44,45] A range of alternative model specifications provided sensitivity analyses.

Multiple imputation provides a method of replacing each missing value with a predicted value, potentially permitting analysis of the entire trial sample. The process begins with reporting levels of missingness and the missing at random (MAR) assumption is then explored in the data. The MAR assumption requires that the probability of data being unobserved is dependent on the observed values but independent of unobserved values. Multiple imputation provides unbiased estimates of treatment effect if data are MAR. Additionally, complete-case analysis provides unbiased estimates only if data are missing completely at random, that is, the probability of data being unobserved is independent of both observed and unobserved values. The imputation model included all variables used within analysis models to preserve correlation structures.

A regression model was used to generate multiple imputed data sets (or 'draws'), in which missing values were predicted drawing on predictive covariates. These included age, sex, baseline blister severity and baseline Karnofsky score as predictors only and outcome measures (at each time point) and costs as predictors and imputed variables. Each draw provided a complete data set that reflected the distributions and correlations between variables. Predictive mean matching was used to enhance the plausibility and robustness of imputed values, as normality could not be assumed. The model used fully conditional Markov chain Monte Carlo methods (multiple imputation by chained equations), which are appropriate when missing and correlated data occur in more than one variable. Each draw was analysed independently and the estimates obtained were pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule, a method that captures within and between variances for imputed samples.[46] To minimise the information loss of finite imputation sampling, 50 draws were taken.[46] This resulted in a loss of efficiency relative to infinite sampling of $< 0.5\%$ in all imputed values. The distribution of imputed and observed values was compared to establish that imputation did not introduce bias into subsequent estimation.

Incremental analysis

The goal of economic analysis is to inform decision-makers about the incremental costs and benefits of change; when expressed together in the cost/QALY metric this facilitates comparison with other technology choices. The analysis reports costs, QALYs and cost per QALY comparing doxycycline-initiated therapy with prednisolone-initiated therapy for patients with BP.

Bivariate regression using seemingly unrelated regression equations was used to model incremental changes in costs and QALYs. This method respects the correlation of costs and outcomes within the data and allows adjustment for a set of covariates that can be explored.[47] Baseline quality-of-life scores were included within all QALY estimation models to allow for potential baseline imbalances.[38] The incremental cost-effectiveness ratio (ICER) was estimated as the difference in mean total costs between treatments divided by the difference in mean total QALYs. Value for money is determined by comparing the ICER with a threshold value, typically the National Institute for Health and Care Excellence threshold of £20,000–30,000 per QALY for UK studies. This represents the willingness to pay for an additional QALY and lower values than the threshold could be considered cost-effective for use in the NHS. The net monetary benefit (NMB) of changing treatment was also reported as a recalculation of the ICER at a range of thresholds of willingness to pay for an additional QALY. The NMB succinctly describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at the same threshold.[48]

Uncertainty

A range of decisions are made in the construction of cost-effectiveness models, for example which costs to include, whether or not to adjust for covariates and whether or not to impute missing values. These options are presented and the most plausible assumptions form the base-case analysis; assumptions are explored using a range of supportive sensitivity analyses. The analyses carried out in this study are described in *Table 51*.

TABLE 51 Base-case and sensitivity analyses

Analysis	Costs	Outcome	Covariate adjustment[a]
Base case	Attributed costs, imputed	EQ-5D, imputed, baseline adjusted	Yes
Sensitivity analyses			
1	Attributed costs, imputed	EQ-5D, imputed, baseline adjusted	No
2	Attributed costs, complete case	EQ-5D, complete case, baseline adjusted	Yes
3	Attributed costs, complete case	EQ-5D, complete case, baseline adjusted	No
4	All costs, imputed	EQ-5D, imputed, baseline adjusted	Yes
5	All costs, imputed	EQ-5D, imputed, baseline adjusted	No

a All models were adjusted for baseline EQ-5D score; other covariates adjusted for included age, sex, baseline blister severity and baseline Karnofsky score.

The imputation data set provides the most plausible base-case analyses, but a complete-case analysis and unadjusted analysis provide useful sensitivity analyses. No method of analysis can provide protection from bias if the assumption that data are MAR does not hold (adequately). Joint distributions of costs and outcomes were generated using the (non-parametric) bootstrap method, with replicates used to populate the cost-effectiveness plane and generate cost-effectiveness acceptability curves. The cost-effectiveness acceptability curve compares the likelihood that treatments are cost-effective as the willingness-to-pay threshold varies.[49] Bootstrapping jointly resamples costs and outcomes from the original data with replacement (maintaining the sample correlation structure) to create a new bootstrap sample from which a change in costs and QALYs is estimated. Using bias-corrected non-parametric bootstrapping, 5000 bootstraps were taken per model evaluated. Means estimates are reported with 95% CIs.

Results

Completeness of data

Of the 253 patients included in the primary analysis of effectiveness, 220 patients (87%) had at least one EQ-5D record during follow-up and were included in the economic analysis (*Table 52*). Subsequent discussion of the completeness of the data focuses on the 220 included patients as most relevant when considering the extent of imputation. In total, 164 patients (75%) had complete EQ-5D assessments for all time periods. Patients who died were subsequently scored zero on visits that followed for both cost and EQ-5D score and are included as observed data. There was a pattern of decreasing completeness as follow-up proceeded. Cost data were complete for 191 patients (87%). It was not possible to explore completeness of health-care costs by follow-up visit as patients could use diaries to complete missing data at a later follow-up visit and the study drug report covered the entire follow-up period. When considering both utilities and resource use, complete information was available for 143 patients (65%). Completeness of data was similar when comparing treatment arms (see *Table 52*).

Thirty-four patients died during the trial period, 14 (10.6%) in the doxycycline arm and 20 (16.5%) in the prednisolone arm. Missing values were imputed to provide a base-case analysis including all 220 patients.

Complete-case estimates

To describe the observed data, findings in this section are reported unadjusted for patient-level covariates. Models in this section (*Tables 53–55*) are adjusted as shown in *Table 51*.

Mean EQ-5D scores by treatment group are reported in *Table 53*. There was a small non-significant difference in health status at baseline (lower in doxycycline-initiated patients). Over the 1-year follow-up period there were no significant differences in QALYs when comparing treatments.

TABLE 52 Completeness of data by follow-up visit

	Prednisolone ($n = 108$), *n* (%)	Doxycycline ($n = 112$), *n* (%)	Total: analysis ($n = 220$), *n* (%)	Total: trial ($n = 253$), %
Health status				
EQ-5D baseline	107 (99.1)	112 (100.0)	219 (99.5)	86.6
EQ-5D 6 weeks	102 (94.4)	108 (96.4)	210 (95.5)	83.0
EQ-5D 13 weeks	101 (93.5)	101 (90.2)	202 (91.8)	79.8
EQ-5D 26 weeks	96 (88.9)	93 (83.0)	189 (85.9)	74.7
EQ-5D 39 weeks	94 (87.0)	90 (80.4)	184 (83.6)	72.7
EQ-5D 52 weeks	92 (85.2)	90 (80.4)	182 (82.7)	71.9
EQ-5D all visits	83 (76.9)	81 (72.3)	164 (74.5)	64.8
Resource use				
Drug use	95 (88.0)	102 (91.1)	197 (89.5)	77.9
Health service contacts	103 (95.4)	107 (95.5)	210 (95.5)	83.0
Costs	92 (85.2)	99 (88.4)	191 (86.8)	75.5
Health status and resource use				
Costs and EQ-5D	72 (66.7)	71 (63.4)	143 (65.0)	(56.5)

TABLE 53 Health status scores: complete cases

	Prednisolone		Doxycycline		Doxycycline – prednisolone[a]	
	Mean	SD	Mean	SD	Mean	95% CI
EQ-5D baseline	0.42	0.31	0.39	0.31	–0.034	–0.117 to 0.046
EQ-5D 6 weeks	0.52	0.33	0.43	0.34	–0.094	–0.188 to –0.001
EQ-5D 13 weeks	0.51	0.33	0.42	0.37	–0.084	–0.179 to 0.013
EQ-5D 26 weeks	0.46	0.34	0.45	0.35	–0.010	–0.107 to 0.087
EQ-5D 39 weeks	0.41	0.34	0.40	0.34	–0.009	–0.106 to 0.092
EQ-5D 52 weeks	0.38	0.33	0.39	0.32	0.007	–0.091 to 0.106
EQ-5D AUC	0.46	0.30	0.42	0.30	–0.034	–0.126 to 0.057

SD, standard deviation.
a Ordinary least squares regression bootstrap-estimated means and 95% CIs.

Resource use (in natural units) by treatment group is reported in *Table 54*. Predictably, study drug use for prednisolone and doxycycline was significantly higher in patients allocated to each treatment. However, there was significantly subsequent crossover to the alternative study drug in patients with poor outcomes. Of patients starting on prednisolone, 12.6% subsequently received at least one prescription of doxycycline; of patients starting on doxycycline, 57.8% subsequently received at least one prescription of prednisolone. Patients commonly used four topical corticosteroids; the overall use of any topical steroid during the trial was very similar for prednisolone (76.8%) and doxycycline (72.5%) patients. However, the level of use (and steroid potency) was notably lower in the prednisolone group (average prescribed amount of all topical steroids among users: prednisolone 121 g vs. doxycycline 277 g). Similar proportions of patients received the immunosuppressant azathioprine (prednisolone 4.2% vs. doxycycline 8.8%) although again

TABLE 54 Resource use: complete cases

	Prednisolone		Doxycycline		Doxycycline – prednisolone[a]	
Resource use	Mean	SD	Mean	SD	Mean	95% CI
Drug use (g)[b]						
Prednisolone[c]	4.18	2.47	2.07	2.48	–2.11	–2.74 to –1.43
Doxycycline[c]	1.30	5.92	16.50	18.52	15.20	11.50 to 18.97
Azathioprine	0.11	0.64	1.00	4.92	0.89	0.09 to 1.86
Betamethasone valerate	18.83	81.15	11.99	61.15	–6.84	–27.48 to 12.97
Clobetasol propionate	16.26	74.33	73.18	210.20	56.92	19.27 to 103.59
Mometasone furoate	46.63	58.21	83.37	150.4	36.74	7.72 to 66.49
Clobetasone butyrate	0.65	6.77	14.2	128.7	13.5	–1.0 to 44.7
NHS contacts (all)[b]						
Inpatient days	7.77	22.44	8.09	22.27	0.32	–5.59 to 6.1
Outpatient visits	2.58	3.43	2.57	4.07	–0.01	–1.02 to 1.04
GP clinic visits	2.70	3.32	1.96	3.20	–0.74	–1.63 to 0.12
GP home visits	1.11	2.47	0.81	1.51	0.30	–0.89 to 0.24
Practice nurse visits	2.38	7.61	8.52	65.39	6.14	–1.48 to 19.7
District nurse visits	6.59	13.14	15.21	43.24	8.62	1.62 to 16.87
NHS contacts (attributed to BP)[b]						
Inpatient days	3.30	8.75	5.14	12.53	1.84	–0.9 to 4.7
Outpatient visits	0.87	1.61	1.64	3.12	0.77	0.14 to 1.44
GP clinic visits	0.81	1.61	0.64	1.79	–0.17	–0.61 to 0.29
GP home visits	0.38	1.24	0.30	0.95	–0.08	–0.39 to 0.22
Practice nurse visits	1.05	6.27	1.77	7.61	0.72	–1.19 to 2.75
District nurse visits	4.60	10.26	10.57	39.73	5.97	–0.02 to 13.75

SD, standard deviation.
a Ordinary least squares regression bootstrap-estimated means and 95% CIs.
b For numbers contributing to each category see *Table 52*.
c Study drugs; other drugs listed are frequently used non-study drugs.

TABLE 55 Costs: complete cases (£, 2013)

	Prednisolone (£)		Doxycycline (£)		Doxycycline – prednisolone (£)[a]	
Cost item	Mean	SD	Mean	SD	Mean	95% CI
Study drugs	106	49	77	53	–29	–42 to –15
Non-study drugs	10	12	25	41	15	7 to 23
Study and non-study drugs	116	53	102	73	–14	–31 to 3
NHS contacts, all	3364	7574	3827	7863	463	–1591 to 2501
NHS contacts, attributed	1454	3044	2371	4822	917	–109 to 1990
Total, all[b]	3657	7953	3987	8120	330	–1904 to 2546
Total, attributed[b]	1687	3197	2455	4945	768	–318 to 1911

SD, standard deviation.
a Ordinary least squares regression bootstrap-estimated means and 95% CIs.
b Costs of drugs and care had different missing values; overall cost is not a simple sum of these items.

the quantity of prescribed use was far lower in the prednisolone group (average prescribed amount among users: prednisolone 2.9 g vs. doxycycline 12.4 g).

Although resource-use comparisons (attributed to BP) were generally not statistically significant, there was a pattern of greater care received by doxycycline patients, consistent with a lower level of clinical effectiveness reflected (by design) in the primary outcome.

Patterns of resource use were costed using national reference values (see *Table 50*) and are reported in *Table 55*. Although costs for patients starting on doxycycline treatment appeared greater over 1 year, the increase was not statistically significant.

Cost-effectiveness analysis

The joint distribution of incremental cost and outcome for the base-case analysis is shown graphically in *Figure 8*. Patients allocated initially to doxycycline experienced a slightly lower average quality of life (–0.024 QALYs, 95% CI –0.088 to 0.041) while tending to incur higher average health costs (£959, 95% CI –£24 to £1941), although neither finding was statistically significant (*Table 56*). These findings are consistent with the results of the clinical trial, which by design demonstrated a compromise between reduced effectiveness and increased safety for doxycycline. However, there remains the suggestion that doxycycline-initiated care may result in greater medium-term care costs, as shown by the 95% CI in *Figure 8*.

The likelihood of being cost-effective at different thresholds is shown in *Figure 9*.

Using a willingness-to-pay criterion of < £20,000 per QALY gained, there is a 4.6% probability that doxycycline-initiated treatment is cost-effective; conversely, there is a 95.4% chance that prednisolone-initiated therapy is cost-effective. [Note that these (one-sided) model probabilities should not be compared with inferential findings from (two-sided) statistical tests reported in *Chapter 3*.]

The NMB associated with doxycycline-initiated treatment was found to be negative and diminished with willingness to pay (*Figure 10*). Using a willingness-to-pay criterion of < £20,000 per QALY gained, the NMB associated with doxycycline-initiated therapy was negative but failed to reach statistical significance (–£1432, 95% CI –£3094 to £230). Although statistically imprecise, analysis of the NMB suggests that resources displaced in the NHS by doxycycline-initiated therapy would be greater than the value of benefit gained.

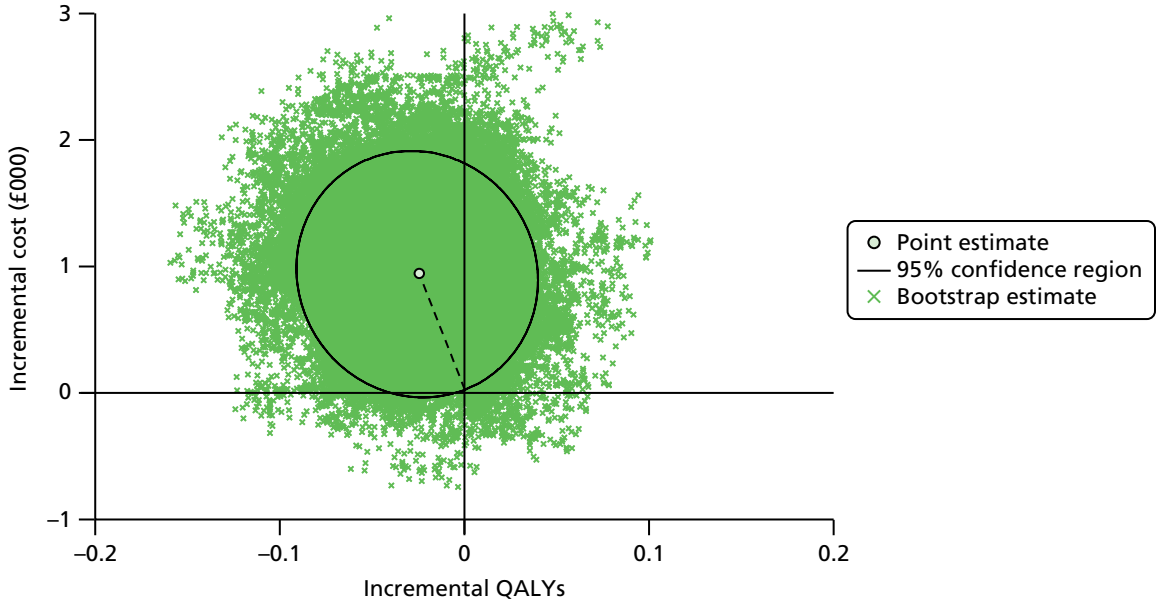

FIGURE 8 Cost-effectiveness plane: base-case analysis [cost per QALY (£), 2013].

TABLE 56 Cost-effectiveness analysis (£, 2013)

Doxycycline-initiated vs. prednisolone-initiated therapy	Incremental cost (95% CI) (£)	Incremental QALYs (95% CI)	ICER (95% CI) (£)	*p*-value[a]	*p*-value[b]	NMB (95% CI) (£)[a]	NMB (95% CI) (£)[b]
Base case							
Imputed attributable costs and QALYs, covariate adjusted	959 (–24 to 1941)	–0.024 (–0.088 to 0.041)	Dominated[c]	0.046	0.070	–1432 (–3094 to 230)	–1669 (–3886 to 549)
Sensitivity analyses							
1. Imputed attributable costs and QALYs, baseline EQ-5D score adjusted	925 (–126 to 1977)	–0.026 (–0.094 to 0.042)	Dominated	0.060	0.083	–1443 (–3263 to 377)	–1702 (–4112 to 708)
2. Complete-case attributable costs and QALYs, covariate adjusted	1214 (33 to 2495)	–0.021 (–0.107 to 0.063)	Dominated	0.063	0.101	–1628 (–3738 to 437)	–1834 (–4726 to 961)
3. Complete-case attributable costs and QALYs, baseline EQ-5D score adjusted	1343 (50 to 2754)	–0.019 (–0.108 to 0.065)	Dominated	0.083	0.110	–1720 (–4132 to 538)	–1909 (–5060 to 1077)
4. Imputed total costs and QALYs, covariate adjusted	435 (–1481 to 2351)	–0.024 (–0.088 to 0.041)	Dominated	0.228	0.213	–909 (–3295 to 1477)	–1146 (–3967 to 1676)
5. Imputed total costs and QALYs, baseline EQ-5D score adjusted	461 (–1564 to 2487)	–0.026 (–0.094 to 0.042)	Dominated	0.230	0.215	–981 (–3580 to 1617)	–1241 (–4319 to 1836)
Base case: subgroup analysis							
Blister: mild or moderate	269 (–662 to 1199)	0.001 (–0.074 to 0.076)	298,586 (undefined)	0.388	0.422	–251 (–1987 to 1485)	–243 (–2647 to 2161)
Blister: severe	2558 (–82 to 5198)	–0.090 (–0.222 to 0.042)	Dominated	0.015	0.019	–4361 (–8283 to –439)	–5263 (–10237 to –288)

a Probability cost-effective or NMB if willing to pay £20,000 per QALY.
b Probability cost-effective or NMB if willing to pay £30,000 per QALY.
c Dominance indicates average costs were less and average benefits greater for prednisolone-initiated therapy.

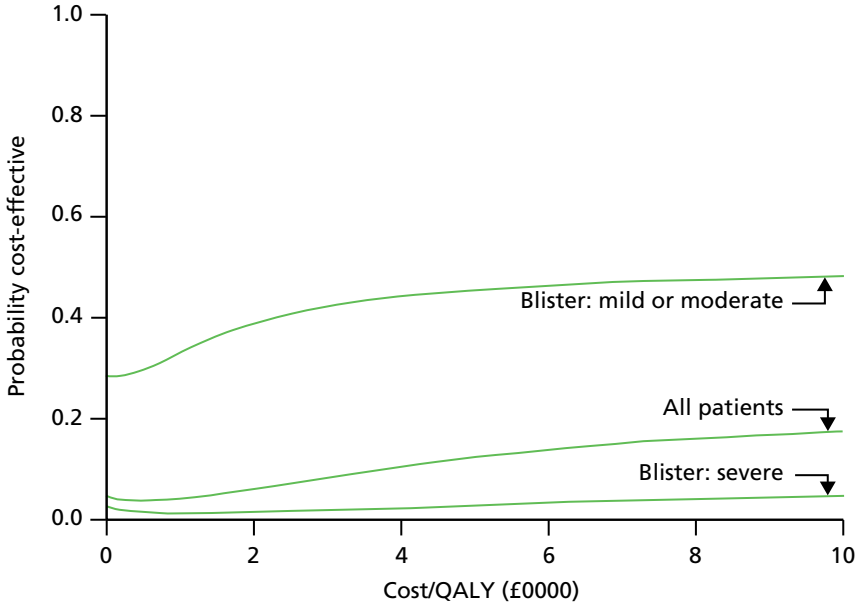

FIGURE 9 Cost-effectiveness acceptability curve: base-case analysis – doxycycline-initiated therapy.

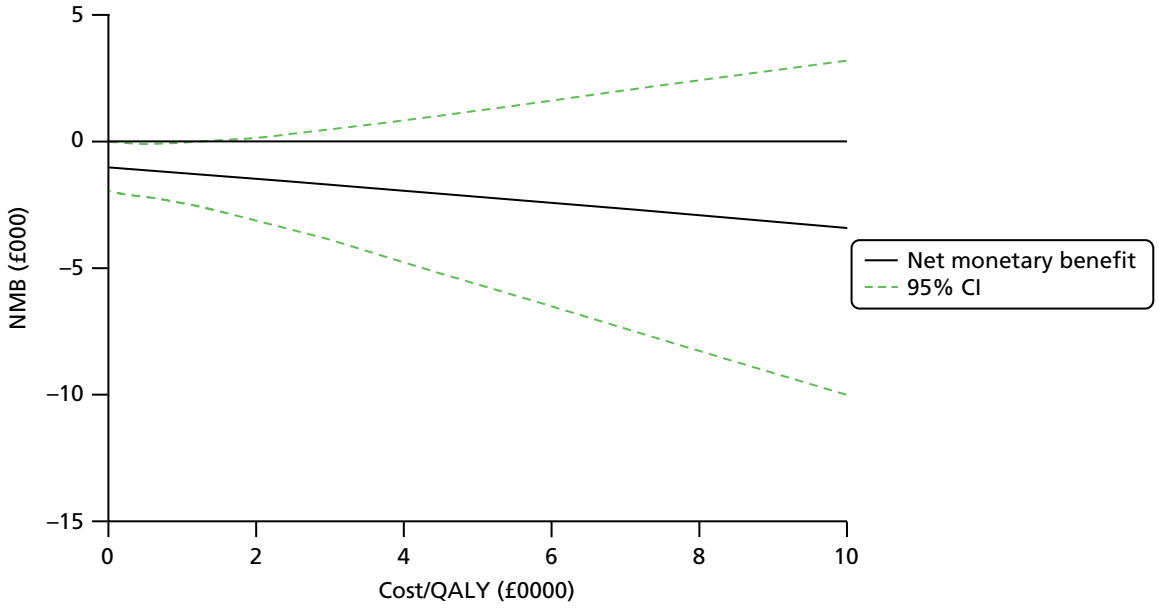

FIGURE 10 Relationship between net monetary benefit and willingness to pay for doxycycline-initiated treatment.

Sensitivity and subgroup analyses

Comparing mean costs and QALY estimates using different modelling assumptions supports the base-case finding (see *Table 56*). The qualitative similarity of NMB estimates comparing imputed and complete-case analysis, covariate adjustment and range of costs included supports the validity of the imputation process and assumptions.

There was no interaction between treatment effect and trial stratifying variables, except in the case of blister severity. Patients recruited with severe blisters demonstrated a different cost and outcome pattern from patients with mild or moderate blisters, as shown in *Table 56* and *Figures 9* and *11*. For patients presenting with mild or moderate blisters, differences in costs and QALYs are very small and thus the costs and outcomes can be thought to be similar. For patients presenting with severe blisters, doxycycline-initiated treatment

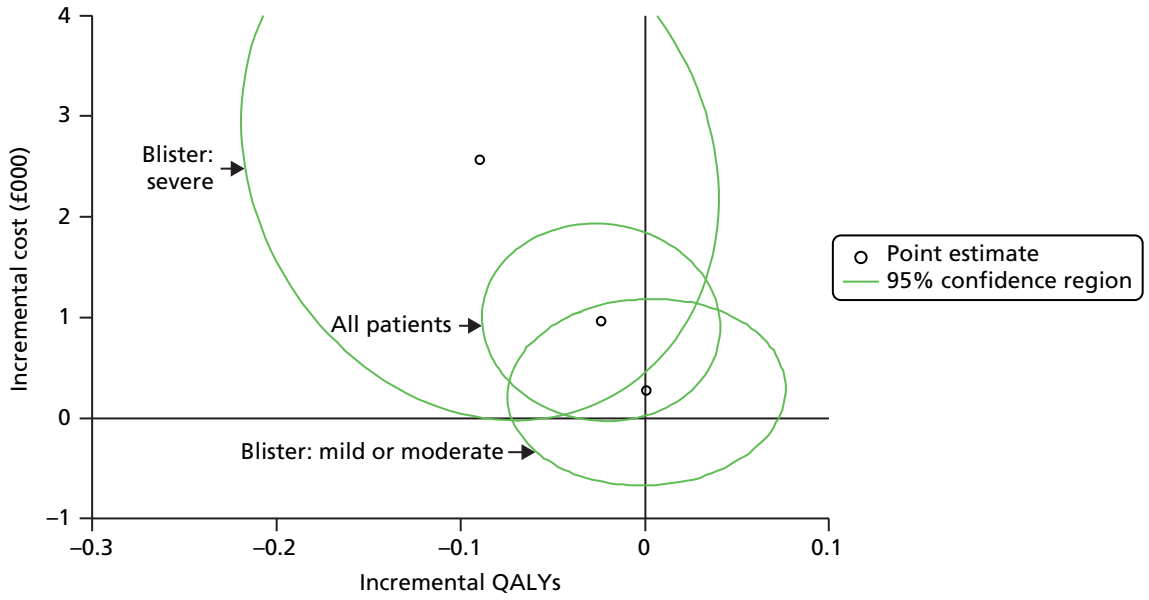

FIGURE 11 Cost-effectiveness plane: subgroup analysis [cost per QALY (£), 2013].

presents greater costs (£2558, 95% CI –£82 to £5198) and poorer quality of life (–0.090 QALYs, 95% CI –0.222 to 0.042), which together make this strategy appear a poor investment (NMB –£4361, 95% CI –£8283 to –£439) using a willingness-to-pay criterion of < £20,000 per QALY gained.

Other quality-of-life measures

Additionally, EQ VAS and DLQI scores were used to derive AUC scores over the course of the 1-year follow-up period (*Table 57*).

The EQ VAS is scored from 1 to 100; equivalent QALY scores are obtained by dividing by 100, although the EQ VAS is not recommended for QALY estimation within trials as values are self-rated rather than societal. As with the EQ-5D estimates, there was no significant difference between treatments. DLQI estimates were significantly higher (denoting a poor outcome for doxycycline-initiated therapy). Being a disease-specific quality-of-life measure, the DLQI is potentially more sensitive to change than a generic measure; nonetheless, the changes correspond to an average of 1 point on a 30-point scale and are of uncertain clinical importance.

Conclusion

Patient-level data from the BLISTER trial provide the most robust evidence to date on whether or not doxycycline-initiated therapy is cost-effective as a treatment for patients with BP. The trial is concerned with the comparative short-term healing and long-term safety of doxycycline and prednisolone. Summatively, the profile of EQ-5D scores draws together the short-term and long-term patterns (see *Table 52*). A small quality-of-life benefit for prednisolone may occur in the first few months but would

TABLE 57 EuroQol visual analogue scale and DLQI AUC estimates

Analysis	Incremental cost (95% CI) (£)	Incremental outcome (95% CI)
EQ VAS, imputed, covariate adjusted	804 (–177 to 1785)	0.005 (–5.138 to 5.147)
EQ VAS, imputed, baseline adjusted	808 (–248 to 1864)	–0.555 (–5.874 to 4.764)
DLQI, imputed, covariate adjusted	841 (–144 to 1826)	1.162 (0.376 to 1.948)
DLQI, imputed, baseline adjusted	832 (–228 to 1892)	1.162 (0.376 to 1.948)

disappear by 6 months. Hence, although an extrapolation exercise was originally planned as part of the economic analysis, with modelling beyond 12 months, there was no rationale to pursue this.

In the base-case analysis (using multiple imputation) similar costs and outcomes were found regardless of whether patients received doxycycline-initiated therapy or prednisolone-initiated therapy. The joint distribution of costs and QALYs nonetheless suggests that doxycycline-initiated therapy may not be cost-effective. However, this finding seems to have been driven by the performance of the subgroup of patients with severe blisters. For patients presenting with mild or moderate blisters the economic and clinical findings align; given similar costs and outcomes, treatment decisions should be patient led and informed by the different profile of the two drugs. The clinical and economic findings for patients with severe blisters are different from the findings for those with moderate and mild disease. The economic analysis provides a clear preference for prednisolone-initiated therapy for patients presenting with severe blisters. This finding is returned to in the discussion (see *Chapter 5*).

The findings were robust to a range of sensitivity analyses using the complete-case data set; all rather than attributed costs; and different levels of model adjustment.

Chapter 5 Discussion

Main findings

This pragmatic study suggests that a strategy of starting people with BP on 200 mg/day of oral doxycycline is significantly safer over the course of a year than a strategy of starting with oral prednisolone (0.5 mg/kg/day). These long-term gains in safety for doxycycline are at the expense of short-term compromises in effectiveness in terms of blister control at 6 weeks, as we had anticipated. Both of our primary end points in this study supported our a priori hypothesis of non-inferiority of short-term blister control and superiority of safety for doxycycline compared with prednisolone, and these findings were robust to ITT and PP analysis and a range of sensitivity analyses.

Although the time point for assessing our primary outcome of short-term control of blisters was at 6 weeks, the non-inferiority of doxycycline compared with prednisolone was maintained within our prespecified margin when assessed at 13 and 52 weeks.

Treatment success was defined as having three or fewer significant blisters remaining, rather than complete clearance. There was a greater difference between the groups when the proportions of patients who were completely blister free were compared, but, in clinical practice, treatment is usually considered successful when only a few blisters remain because achieving complete clearance risks potentially 'overtreating' the patient.

Given that untreated BP tends to get worse, the study has also produced compelling new evidence that doxycycline does produce a genuine clinical effect in controlling blisters in BP. How tetracyclines, such as doxycycline, work in BP is still unclear, but it is suggested that they may exert an anti-inflammatory effect by inhibiting chemotaxis of neutrophils and eosinophils and blocking certain metalloproteinases.[26]

The study also shows that oral prednisolone at a dose of 0.5 mg/kg/day (rather than a higher dose of 1 mg/kg/day) is very effective in controlling blisters for mild and moderately severe BP, with response rates of 97% and 98%, respectively, and provides a clinically useful response rate of 75% for those with severe disease, an evidence gap that has been highlighted in previous guidelines.[15] Corresponding response rates for doxycycline for mild, moderate and severe disease were 76%, 78% and 66%, respectively – still clinically useful given the potential long-terms reduction in adverse effects compared with prednisolone. It should be noted, however, that, although there was a suggestion of less difference between the two treatment strategies in those with severe baseline blisters, we did not find any statistical evidence that the *differences in response rates* between prednisolone and doxycycline varied according to baseline disease severity according to our planned interaction tests (see *Tables 9*, *19* and *20*).

All safety outcomes pointed in the same direction, showing that is a safer to embark on a strategy of starting patients with BP on doxycycline rather than prednisolone. There were fewer severe, life-threatening or fatal treatment-related adverse events in those started on doxycycline and analysis of all-cause mortality showed that there were fewer deaths, both total and treatment related, in the doxycycline group. The overall differences between the groups are likely to be larger if higher doses of oral prednisolone are used, such as 0.75 mg/kg/day, as recommended in recent guidelines.[15] The safety advantage of doxycycline-initiated treatment appeared to be lost in those with severe disease at baseline in a post-hoc analysis (see *Table 49*). Overall adverse events (including mild and moderate) were similar in both groups, however, and quite high overall (> 80%) and mainly in keeping with the known adverse event profile for each drug. Nuisance adverse events such as nausea were higher in the first 6 weeks of treatment with doxycycline, which might have accounted for a greater lack of adherence to this treatment policy (see *Table 6*) compared with prednisolone.

Patients were able to switch treatments in this pragmatic study, which meant that some of the short-term effectiveness at 6 weeks of a strategy of starting with doxycycline could be attributed to oral prednisolone and, conversely, some of the severe, life-threatening and fatal events at 1 year in the doxycycline group could be attributed to those patients who switched to oral prednisolone. It is important therefore to be aware of the pragmatic perspective of this study, that is, to test the *strategy* of starting a patient with BP on doxycycline rather than a policy of starting with oral prednisolone. Although there was a considerable degree of switching, differences between the groups were clear throughout the study. At 6 weeks there was no switching in the prednisolone group but approximately one-quarter of those started on doxycycline had switched treatment. By 52 weeks approximately half of those who started on doxycycline had switched treatment compared with only approximately 10% of those who started on prednisolone. If all patients started on doxycycline switched to oral prednisolone it is likely that there would be no difference in effectiveness and safety.

The quality of life of patients in both groups improved over time and there were only small differences between the groups by 52 weeks. Although both groups showed a similar improvement in quality of life, as measured by the skin-specific DLQI, the prednisolone group improved more rapidly than the doxycycline group, probably reflecting the more rapid onset of blister control for those taking oral prednisolone.

Cost-effectiveness

Patient-level data from the BLISTER trial provide the most robust evidence to date on whether or not doxycycline-initiated therapy is cost-effective as a treatment for patients with BP. The base-case analysis (using multiple imputation) found similar costs and outcomes regardless of whether patients received doxycycline-initiated therapy or prednisolone-initiated therapy. The joint distribution of costs and QALYs nonetheless suggests that doxycycline-initiated therapy may not be cost-effective, with only a 4.6% probability of doxycycline being more cost-effective than prednisolone if societal willingness to pay is capped at £20,000 per QALY. However, post-hoc subgroup analysis of patients with and without severe blisters produced discrepant findings. For patients presenting with mild or moderate blisters the economic and clinical findings align. Prednisolone- and doxycycline-initiated treatments result in similar costs and outcomes and thus treatment decisions should be patient led and informed by the different profiles of the two drugs. It should be noted that both drugs are inexpensive and widely available worldwide. From a health policy point of view, the clinical and economic analyses both show some variation in findings for patients with severe blisters at baseline; on the grounds of cost-effectiveness there is a clear preference for prednisolone-initiated therapy for those with severe disease.

How our evidence fits with existing evidence

The 2010 Cochrane review on interventions for BP[21] found that combination treatment with tetracycline and nicotinamide may be effective, but this was based on only one small and inadequately reported trial. Because tetracyclines are widely used in practice, it was concluded that this treatment option needs further investigation. No further trials of tetracyclines were identified in a subsequent systematic review[23] nor in a search of the Cochrane Central Register of Controlled Trials database using 'pemphigoid' as a search term (28 May 2015).

Guidelines for the management of BP produced by the British Association of Dermatologists in 2012[14] discuss the use of potent topical corticosteroids over the entire body (except the face), as these have been shown to be effective and much safer than oral steroids.[18] Potent topical steroids are associated with some adverse effects, such as thinning of the skin and easy bruising. The risk of experiencing adverse effects from use of topical steroids depends on the strength of the steroid, how long it is used for, which area of the body it is applied to and the kind of skin problem; if a high-strength, potent steroid is used, enough may be absorbed through the skin to cause systemic adverse effects such as adrenal insufficiency or

Cushing syndrome. For those patients for whom applying topical corticosteroids is not practical, oral steroids are the main recommended systemic medications. Oral steroids are effective in the treatment of BP; however, common adverse effects of oral steroids include weight gain, diabetes, infections, fractures and high blood pressure. The British guidelines recommend oral prednisolone at doses varying from 0.3 mg/kg/day to 1 mg/kg/day, depending on disease severity.[14] Spanish guidelines from 2014 recommended oral prednisolone at doses of 0.5–0.75 mg/kg/day[26] and the same doses were recommended in guidelines produced by the European Dermatology Forum in 2015.[15] All three guidelines mention tetracyclines as a possible treatment for BP and point to the need for further high-quality evidence for tetracyclines.

The BLISTER study has now addressed the recommendation in the Cochrane 2010 review and a range of guidelines to further investigate the effects of tetracyclines in patients with BP, confirming its modest effectiveness and superior safety compared with oral prednisolone at a dose of 0.5 mg/kg/day.

Strengths and limitations

Strengths

This was a large, multicentre, multinational trial of 253 evaluable participants that had the power to detect clinically important differences. The trial had good external validity as patients were recruited from a large number of hospitals all over the UK and Germany, covering those with all types of disease severity, and from a range of hospital settings and socioeconomic areas. Additionally, patients were not excluded on the grounds of comorbidities and any patient with active BP was eligible. With the exception of incapacity to consent, patients were excluded only on safety grounds. Typically, BP patients are elderly and present with several comorbidities and so inclusion of such a population as in this study was an important issue.

This trial was designed to reflect clinical practice as far as possible, making the results useful in the real-life setting of a dermatology clinic. We assessed the degree to which the study was pragmatic using the pragmatic–explanatory continuum indicator summary tool[25] and concluded that the trial was more pragmatic than explanatory.

There is no evidence of selection bias as the two groups were well matched for all baseline characteristics. Allocation of treatment was concealed by blinding the investigator until the 6-week blister count had been carried out (primary effectiveness outcome). Treatment allocation was revealed only once the blister count was entered into the trial database, thereby minimising the potential for performance and information bias. The investigator was unblinded for the remaining assessments for that participant, for example the primary safety outcome (adverse events over the full 52 weeks), as the investigator was often also the treating physician for this trial and it was not feasible to have a second (blinded) outcome assessor to collect adverse event data at every recruiting site. A relatively objective measure (adverse events graded according to the Common Terminology Criteria for Adverse Events) was chosen to minimise bias for the primary safety outcome measure.

As the investigator was blinded for the first 6 weeks of treatment (until the primary effectiveness outcome had been assessed), it was difficult for local investigators to comment on the relatedness of adverse events. Therefore, an independent adjudicator judged the relatedness of any adverse events to trial medication so that the blinding of the investigator for the primary effectiveness outcome could be maintained. In addition, *all* severe, life-threatening and fatal adverse events were independently assessed for relatedness to the trial medication to ensure that relatedness was being properly attributed.

The primary effectiveness results were similar in both the ITT population and the PP population. This is particularly important in this trial because of the non-inferiority comparisons, in which dependence on the ITT population alone risks falsely concluding a lack of difference between groups when there are significant amounts of missing data.[50] Similarly, findings from the cost-effectiveness analysis were robust to a range of sensitivity analyses, providing confidence in the modelling assumptions.

To minimise selective reporting bias, the trial was registered before recruitment started, the protocol published and the statistical analysis plan made freely available on the trial website [see https://ctsu.nottingham.ac.uk/ts0614/summary.asp (accessed 12 November 2015)]. All planned outcomes and analyses are reported here and any post-hoc analyses have been clearly indicated as such.

Limitations

This trial was a comparison between *initiating* treatment with doxycycline and *initiating* treatment with prednisolone rather than an explanatory trial evaluating the pharmacological effects of these treatments. It is very likely therefore that some of the treatment response in patients who switched from initial doxycycline treatment to prednisolone can be attributed to prednisolone. Despite treatment switches, there were still fewer medically serious side effects in those starting on doxycycline than in those starting on prednisolone over the course of 1 year. The *strategy* of initiating treatment with doxycycline and thus reducing the overall dose of corticosteroids is a safer treatment approach than starting on prednisolone over the course of 1 year.

To reflect clinical practice in which topical corticosteroids are often used early on in addition to systemic treatments,[14] the use of potent topical corticosteroids applied *only to blisters* was permitted for the first 3 weeks. A washout period from week 3 to week 6 allowed a clearer assessment of the effectiveness of doxycycline at 6 weeks. It is unlikely therefore that topical corticosteroid use only in the first 3 weeks of treatment was responsible for the blister control observed at 6 weeks, given such a substantial 3-week washout period that followed.[51] More participants in the doxycycline group had to use potent topical corticosteroids during the washout period, although the non-inferiority findings for the primary effectiveness outcomes were robust to excluding such participants in a sensitivity analysis. Localised use of topical corticosteroids was permitted after week 6 when needed to reflect clinical practice and so assessments at all other time points could be affected to some degree by such usage.

The prespecified non-inferiority margin for effectiveness was relatively wide (with an upper CI of 37%), resulting in an effectiveness estimate for doxycycline that was both non-inferior and inferior compared with the prednisolone strategy, a paradox that was anticipated beforehand.[52] When surveyed prior to the trial starting (see *Appendix 1*), there was clearly a willingness among UK dermatologists to accept a considerable reduction in short-term effectiveness of doxycycline for a treatment that did not result in such severe long-term side effects.

There was a relatively high dropout rate in this trial, reflecting the multiple morbidities and frailty of a mainly elderly study population, with the potential for differential reporting bias. A low dropout rate of no more than 5% was predicted for the week 6 visit given the morbidity of the disease, but the dropout rate was higher than anticipated (although it should be noted that 2.8% dropped out as a result of death). There was a gradual loss over time resulting in a higher dropout rate than the 20% at 52 weeks allowed for in the sample size calculation.

It is unlikely that the success of both treatments at 6 weeks is a result of regression to the mean, reflecting the natural progression of the disease, because BP is a progressive disease.[53,54] Additionally, there is evidence that very low doses of prednisolone (0.3 mg/kg/day) are not effective,[55] suggesting that there is little evidence to support a placebo effect. Even if one postulates a placebo/natural resolution response of around 20% at 6 weeks, the study response rates for effectiveness at 6 weeks (74.4% and 92.3% for doxycycline and prednisolone, respectively) are much higher and are likely to represent a true therapeutic response. Including a third placebo arm would have been unethical and would have probably failed to recruit.

As we collected data only on adverse events that were deemed to be possibly, probably or definitely related to the study treatment, the side effects of which are well known, it is possible that some degree of attribution bias could have occurred, for example sepsis occurring in a patient taking oral prednisolone might have been more likely to have been attributed to the drug rather than being recorded as a natural

event. We think that this is unlikely because it was expected that the rate of severe adverse effects would be higher in the prednisolone group, based on knowledge from other trials,[18] and because the number of deaths (regardless of attribution) was higher in the prednisolone group. Mild and moderate treatment-related adverse events for both drugs were fairly similar between groups, with grade 3 and above adverse events more common in the prednisolone group (see *Table 32*), arguing against a differential bias towards attributing more events to prednisolone. Determining the true attribution of adverse events to drugs is difficult in clinical practice and all unclear grade 3, 4 and 5 events in this trial were reviewed by a senior independent dermatologist who had access to the medical backgrounds of study participants and the chronology of events. In the absence of data on all adverse events, which was deemed unnecessary by the regulatory authorities for two such study drugs with well-established adverse effect profiles, some degree of attribution bias could have occurred in this study, but in a way that reflects how such attribution would be judged in everyday clinical practice, as per the pragmatic design of the study.

The generalisability of these results may be reduced by not including patients with dementia. Such patients were not included, as ethics committees insist that people with dementia, the majority of whom are unable to give informed consent, should not be recruited into trials *if a trial can be delivered without involving such patients*. However, in a disease that affects mainly the elderly, a large part of the patient population will be affected by dementia. It is unclear, though, whether or not having dementia would be likely to affect the treatment comparisons described in this study, as issues such as adherence are likely to have been similar in both groups. It is also worth noting that large numbers of potentially eligible new cases of BP for our study ended up not being eligible because their GP had already started them on oral prednisolone.

Although relapse rates were assessed, the results should be interpreted with some caution. To make it practical for clinicians in busy clinics to be able to include patients in this trial, they had to decide only whether or not the patient had < 4 significant blisters at each blister count (other than baseline), rather than undertake the time-consuming process of carrying out a full blister count. This means that it is possible that a patient who was considered a treatment success because of the presence of only two significant blisters could then 'relapse' by having just four at the next visit. Other patients may go from being almost blister free to having ≥ 30 blisters, which might be considered a more 'true' relapse. However, our relapse definition does give some indication of relapse rates and the direction is reflective of the other effectiveness outcomes in the trial.

All economic analyses in modelling the bivariate distribution of costs and QALYs involve assumptions. For example, judgements are made about the base-case model, the estimation method, adjustment for covariates, attribution of resource use and unit costs applied, as well as the quality-of-life measure used and societal weighting applied. As levels of missing data increase, complete-case analyses become progressively less satisfactory, whereas multiple imputation inevitably requires strong assumptions about data being MAR, which are only partially testable. Careful consideration of modelling issues and use of sensitivity analyses, exploring assumptions, provide some indication of the robustness of findings.

Patient and public involvement was not as strong as it could have been in this study. We failed to identify patients with BP or their carers who were willing to join our study team, despite repeated requests across study sites. Most patients were elderly and infirm and not able to travel to team meetings and no patient support group exists for BP that we could tap into. Perhaps we did not try hard enough. We did manage to find a patient and a carer who kindly joined the independent Trial Steering Group, one of whom (Penny Standen) was able to advise the team on the interpretation of the study. She also helped to write the plain English summary once the study was completed. Further qualitative work with patients to explore their views on the trade-off between short-term blister control and long-term safety gains would be worthwhile.

Implications for practice

This was a pragmatic trial, designed to be relevant to the sorts of people with BP typically seen in secondary care. All suitable patients who gave consent were included and the use of localised topical corticosteroids was allowed in the initial few weeks of the trial, along with the ability to change the treatment and the dose as required during the trial.

Some clinicians expressed the view at the study outset that doxycycline, if effective at all, would be useful only in those with mild disease, an assertion not borne out by this study. We found no evidence that the difference in short-term effectiveness between the two treatment strategies was dependent on the baseline disease severity. Higher absolute response rates for mild to moderate disease were seen for both treatment policies, but even those with severe disease had a clinically useful response at 6 weeks (75% and 66% treatment success at 6 weeks for prednisolone and doxycycline respectively). In terms of short-term effectiveness, the policy of starting treatment with doxycycline appears to be a potentially useful approach for patients with all severities of BP. With regard to serious related adverse effects, most of the advantage of doxycycline-initiated therapy resided in the mild and moderate severity groups, and cost-effectiveness analysis suggests that doxycycline-initiated therapy is not cost-effective in those with severe disease at baseline. BP is a disease associated with significant morbidity and mortality and the possible harms of treatment need to be given more attention.

The work by Joly *et al.*[18] shows that whole-body application of topical corticosteroids is a good treatment strategy for BP. However, such an approach is not always practical: very elderly or immobile patients would need considerable additional support to be able to apply a cream all over their body every day, and in many clinical settings this is not available. This study has suggested that initiating treatment with oral doxycycline is an effective and safe treatment and so, when application of topical corticosteroids is not a practical option, doxycycline may be offered as a safer alternative to oral corticosteroids whenever possible. It is important that patients understand the trade-off between doxycycline and prednisolone. Starting on doxycycline may mean that symptoms last longer than if starting on oral prednisolone and they may experience more mild side effects such as gastrointestinal problems, but they are less likely to experience severe and life-threatening side effects, even if they have to eventually switch to oral prednisolone.

In circumstances in which treatment with oral prednisolone is still indicated, these results have demonstrated that, although not as safe as doxycycline, a dose of 0.5 mg/kg/day probably produces a clinically worthwhile treatment response that is comparable to that seen with higher doses such as 1.0 mg/kg/day mentioned in guidelines,[15] even for those with severe disease.

Implications for research

Qualitative work exploring patients' views on the trade-off between short-term blister control and long-term safety might also be worthwhile, perhaps accompanied by a patient decision aid. Follow-up surveys of the clinicians from the UK Dermatology Clinical Trials Network who took part in determining the initial non-inferiority margin might also be useful to see whether or not the results have changed their practice.

It is clear from the results presented here that reducing the total amount of prednisolone, even if it is not avoided altogether, was beneficial to patients. Therefore, it would be useful to evaluate in a clinical trial whether a strategy of initiating treatment with prednisolone to achieve early disease control followed by a switch to maintenance therapy with doxycycline is safer than maintenance therapy with a reducing dose of prednisolone.

In the absence of a placebo-controlled study of doxycycline in BP, some might argue that such a study should be carried out, perhaps for mild disease and for a short duration of 6 weeks. We think that such a

study would be unethical, given that the high response rates for doxycycline seen in this study (74% at 6 weeks) are likely to be much higher than any placebo or natural regression effects for what is thought to be a persistent and progressive disease in most people.

It might also be useful to investigate whether or not other antibiotics such as lymecycline, which are reported to have fewer side effects than doxycycline, are also beneficial in BP. Although doxycycline was far safer than prednisolone with respect to severe and life-threatening side effects, there was a high number of mild and moderately severe side effects with doxycycline, which are a nuisance to people taking long-term medicines. Inclusion of patients with dementia may also be considered in future studies, as they may respond to treatments differently.

A range of other systemic treatments such as azathioprine, methotrexate, dapsone, mycophenolate, high-dose intravenous immunoglobulin, plasmapheresis or rituximab have been used for BP that is more severe or unresponsive to first-line treatments such as topical or oral corticosteroids, but, apart from some combination therapies,[56] most have been poorly evaluated. As this study has indicated how conclusions may differ for those with severe disease, future trials should present results according to baseline severity and consider planned subgroup analyses for those with severe disease. Consideration should be given to adopting clearer definitions of remission and early, intermediate and late observation points as recommended in 2012 by an international group.[57] There is also scope for establishing a core outcome set for future clinical trials of pemphigoid which includes outcomes that are important to patients so that the results of new trials can be compared in meta-analysis.

Chapter 6 Conclusions

This study has shown that a strategy of starting people with BP on doxycycline at a dose of 200 mg/day is safer than standard oral treatment with prednisolone at a dose of 0.5 mg/kg/day over the course of a year. Blister control with doxycycline in the first 6 weeks of treatment is inferior to that of oral prednisolone but it is still reasonably effective and was well within our prespecified non-inferiority margin. Overall, there is no significant difference in cost-effectiveness between the two treatment strategies although doxycycline-initiated therapy may not be cost-effective for those with severe baseline disease. The combined analysis of short-term effectiveness and long-term safety in this study provides critical information for clinicians to share with patients in a shared decision-making model, as well as providing reliable data to inform national and international guidelines, especially for those patients in whom extensive daily application of topical corticosteroids is not feasible. Further research may consider the evaluation of oral doxycycline to maintain remission in those who have initially been brought under rapid control with topical or oral corticosteroids.

Acknowledgements

We would like to thank Ms Sunita Rehal and Dr Daniel Bratton for their input into the trial and Dr Natasha Rogers for help with writing, editing and formatting the report. We would also like to thank all of the patients who gave up their time to participate in the trial. We thank the members of our trial oversight committees (see *Appendix 4*), all those from the Nottingham and Medical Research Council (MRC) Clinical Trials Units (see *Appendix 5*) who contributed to trial management at various stages of the project and all those who contributed to recruitment and follow-up from the recruiting centres (see *Appendix 6*).

This trial would not have been possible without the support of the UK Dermatology Clinical Trials Network [see www.ukdctn.org (accessed 6 October 2015)], which helped with various surveys prior to the main study and who were key in identifying recruitment centres. We would also like to acknowledge the support of the UK Clinical Research Network, particularly in providing research nurse support at the many centres around the UK.

This report presents independent research commissioned by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, NIHR, MRC, Central Commissioning Facility (CCF), NIHR Evaluation, Trials and Studies Co-ordinating Centre, Health Technology Assessment programme or Department of Health.

Contributions of authors

Dr Joanne R Chalmers was a lead applicant on the funding application, contributed to the design of the study and was part of the writing team.

Professor Fenella Wojnarowska conceived the study, was a coapplicant on the funding application, contributed to the design of the study and was part of the writing team.

Dr Gudula Kirtschig conceived the study, was a coapplicant on the funding application, contributed to the design of the study, liaised with the study sites in Germany and was part of the writing team.

Professor James Mason was a coapplicant on the funding application, contributed to the design of the study and conducted the cost-effectiveness analysis and was part of the writing team.

Ms Margaret Childs managed the trial and was part of the writing team.

Ms Diane Whitham provided senior clinical trials unit support and contributed to and reviewed the report.

Dr Karen Harman was a principal investigator who contributed to and reviewed the report.

Dr Anna Chapman was a principal investigator who contributed to and reviewed the report.

Dr Shernaz Walton was a principal investigator who contributed to and reviewed the report.

Professor Enno Schmidt was the lead investigator for Germany and was part of the writing team.

Mr Thomas R Godec was the trial statistician and conducted the effectiveness and safety analyses and was part of the writing team.

Professor Andrew J Nunn was senior statistician, a coapplicant on the funding application, contributed to the design of the study and conducted the cost-effectiveness analysis and was part of the writing team.

Professor Hywel C Williams was chief investigator, a coapplicant on the funding application and contributed to the design of the study and was part of the writing team.

Publications

Bratton DJ, Nunn AJ, Wojnarowska F, Kirtschig G, Sandell A, Williams HC. The value of the pragmatic–explanatory continuum indicator summary wheel in an ongoing study: the Bullous Pemphigoid Steroids and Tetracyclines study. *Trials* 2012;**13**:50.

Bratton DJ, Williams HC, Kahan BC, Phillips PP, Nunn AJ. When inferiority meets non-inferiority: implications for interim analyses. *Clin Trials* 2012;**9**:605–9.

Chalmers JR, Wojnarowska F, Kirtschig G, Nunn AJ, Brattan DJ, Mason J, *et al.* A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: a protocol for the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial. *Br J Dermatol* 2015;**173**:227–34.

Williams HC, Wojnarowska F, Kirtschig G, Mason J, Godec TR, Schmidt E, *et al.* Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial [published online ahead of print 6 March 2017]. *Lancet* 2017.

Data sharing statement

Data included in this manuscript are not able to be included in a public repository because of ethical restrictions. Requests for access to the data should be made to Professor Hywel Williams (hywel.williams@nottingham.ac.uk).

References

1. Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013;**381**:320–32. http://dx.doi.org/10.1016/S0140-6736(12)61140-4
2. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris – incidence and mortality in the UK: population based cohort study. *BMJ* 2008;**337**:a180. http://dx.doi.org/10.1136/bmj.a180
3. Joly P. Incidence of bullous pemphigoid and pemphigus vulgaris. *BMJ* 2008;**337**:a209. http://dx.doi.org/10.1136/bmj.a209
4. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V, Wojnarowska F. The association of bullous pemphigoid with cerebrovascular disease and dementia: a case–control study. *Arch Dermatol* 2010;**146**:1251–4. http://dx.doi.org/10.1001/archdermatol.2010.322
5. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: a population-based case–control study. *J Invest Dermatol* 2011;**131**:631–6. http://dx.doi.org/10.1038/jid.2010.357
6. Cordel N, Chosidow O, Hellot MF, Delaporte E, Lok C, Vaillant L, *et al.* Neurological disorders in patients with bullous pemphigoid. *Dermatology* 2007;**215**:187–91. http://dx.doi.org/10.1159/000106574
7. Bastuji-Garin S, Joly P, Lemordant P, Sparsa A, Bedane C, Delaporte E, *et al.* Risk factors for bullous pemphigoid in the elderly: a prospective case–control study. *J Invest Dermatol* 2011;**131**:637–43. http://dx.doi.org/10.1038/jid.2010.301
8. Lloyd-Lavery A, Chi CC, Wojnarowska F, Taghipour K. The associations between bullous pemphigoid and drug use: a UK case–control study. *JAMA Dermatol* 2013;**149**:58–62. http://dx.doi.org/10.1001/2013.jamadermatol.376
9. Yang YW, Chen YH, Xirasagar S, Lin HC. Increased risk of stroke in patients with bullous pemphigoid: a population-based follow-up study. *Stroke* 2011;**42**:319–23. http://dx.doi.org/10.1161/STROKEAHA.110.596361
10. Fichel F, Barbe C, Joly P, Bedane C, Vabres P, Truchetet F, *et al.* Clinical and immunologic factors associated with bullous pemphigoid relapse during the first year of treatment: a multicenter, prospective study. *JAMA Dermatol* 2014;**150**:25–33. http://dx.doi.org/10.1001/jamadermatol.2013.5757
11. Joly P, Baricault S, Sparsa A, Bernard P, Bedane C, Duvert-Lehembre S, *et al.* Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol* 2012;**132**:1998–2004. http://dx.doi.org/10.1038/jid.2012.35
12. Parker SR, Dyson S, Brisman S, Pennie M, Swerlick RA, Khan R, *et al.* Mortality of bullous pemphigoid: an evaluation of 223 patients and comparison with the mortality in the general population in the United States. *J Am Acad Dermatol* 2008;**59**:582–8. http://dx.doi.org/10.1016/j.jaad.2008.07.022
13. Hogan DJ. Mortality of bullous pemphigoid. *J Am Acad Dermatol* 2009;**60**:704. http://dx.doi.org/10.1016/j.jaad.2008.10.003
14. Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. *Br J Dermatol* 2012;**167**:1200–14. http://dx.doi.org/10.1111/bjd.12072

15. Feliciani C, Joly P, Jonkman MF, Zambruno G, Zillikens D, Ioannides D, *et al.* Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. *Br J Dermatol* 2015;**172**:867–77. http://dx.doi.org/10.1111/bjd.13717

16. Rzany B, Partscht K, Jung M, Kippes W, Mecking D, Baima B, *et al.* Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol* 2002;**138**:903–8. http://dx.doi.org/10.1001/archderm.138.7.903

17. Schmidt E, Goebeler M, Hertl M, Sárdy M, Sitaru C, Eming R, *et al.* S2k guidelines for the diagnosis of pemphigus vulgaris/foliaceus and bullous pemphigoid. *J Dtsch Dermatol Ges* 2015;**13**:713–27. http://dx.doi.org/10.1111/ddg.12612

18. Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, *et al.* A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002;**346**:321–7. http://dx.doi.org/10.1056/NEJMoa011592

19. Joly P, Roujeau JC, Benichou J, Delaporte E, D'Incan M, Dreno B, *et al.* A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. *J Invest Dermatol* 2009;**129**:1681–7. http://dx.doi.org/10.1038/jid.2008.412

20. Taghipour K, Mohd Mustapa MF, Highet AS, Venning VA, Kirtschig G. The approach of dermatologists in the UK to the treatment of bullous pemphigoid: results of a national survey. *Clin Exp Dermatol* 2013;**38**:311–13. http://dx.doi.org/10.1111/ced.12042

21. Kirtschig G, Middleton P, Bennett C, Murrell DF, Wojnarowska F, Khumalo NP. Interventions for bullous pemphigoid. *Cochrane Database Syst Rev* 2010;**10**:CD002292. http://dx.doi.org/10.1002/14651858.cd002292.pub3

22. Fivenson DP, Breneman DL, Rosen GB, Hersh CS, Cardone S, Mutasim D. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 1994;**130**:753–8. http://dx.doi.org/10.1001/archderm.1994.01690060083010

23. Singh S. Evidence-based treatments for pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid: a systematic review. *Indian J Dermatol Venereol Leprol* 2011;**77**:456–69. http://dx.doi.org/10.4103/0378-6323.82400

24. Williams HC, Wojnarowska F, Kirtschig G, Mason J, Godec TR, Schmidt E, *et al.* Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial [published online ahead of print 6 March 2017]. *Lancet* 2017.

25. Bratton DJ, Nunn AJ, Wojnarowska F, Kirtschig G, Sandell A, Williams HC. The value of the pragmatic–explanatory continuum indicator summary wheel in an ongoing study: the bullous pemphigoid steroids and tetracyclines study. *Trials* 2012;**13**:50. http://dx.doi.org/10.1186/1745-6215-13-50

26. Fuertes de Vega I, Iranzo-Fernandez P, Mascaro-Galy JM. Bullous pemphigoid: clinical practice guidelines. *Actas Dermosifiliogr* 2014;**105**:328–46. http://dx.doi.org/10.1016/j.ad.2012.10.022

27. Chalmers JR, Wojnarowska F, Kirtschig G, Nunn AJ, Brattan DJ, Mason J, *et al.* A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: a protocol for the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial. *Br J Dermatol* 2015;**173**:227–34. http://dx.doi.org/10.1111/bjd.13729

28. Murrell DF, Marinovic B, Caux F, Prost C, Ahmed R, Wozniak K, *et al.* Definitions and outcome measures for mucous membrane pemphigoid: recommendations of an international panel of experts. *J Am Acad Dermatol* 2015;**72**:168–74. http://dx.doi.org/10.1016/j.jaad.2014.08.024

29. Goon AT, Tan SH, Khoo LS, Tan T. Tetracycline and nicotinamide for the treatment of bullous pemphigoid: our experience in Singapore. *Singapore Med J* 2000;**41**:327–30.

30. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. *Stat Med* 2003;**22**:169–86. http://dx.doi.org/10.1002/sim.1425

31. Joly P, Benichou J, Lok C, Hellot MF, Saiag P, Tancrede-Bohin E, *et al.* Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 2005;**141**:691–8. http://dx.doi.org/10.1001/archderm.141.6.691

32. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998;**316**:736–41. http://dx.doi.org/10.1136/bmj.316.7133.736

33. NHS Precription Services. *Prescription Cost Analysis (PCA) Data, England 2013*. 2013. URL: www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx (accessed 19 March 2015).

34. Curtis L. *Unit Costs of Health and Social Care 2014*. Canterbury: PSSRU, University of Kent; 2014.

35. Department of Health. *NHS Reference Costs 2013 to 2014*. URL: www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 (accessed 19 March 2015).

36. Health and Social Care Information Centre (HSCIC). *Hospital Episode Statistics, Admitted Patient Care, England – 2013–14*. URL: www.hscic.gov.uk/searchcatalogue?productid = 17192 (accessed 19 March 2015).

37. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;**19**:210–16. http://dx.doi.org/10.1111/j.1365-2230.1994.tb01167.x

38. Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy* 2005;**4**:65–75. http://dx.doi.org/10.2165/00148365-200504020-00001

39. Drummond MF, Sculpher MJ, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press; 2005.

40. Szende A, Oppe M, Devlin N. *EQ-5D Value Sets: Inventory, Comparative Review and User Guide.* EuroQol Group Monographs. Dordrecht: Springer Netherlands; 2007. http://dx.doi.org/10.1007/1-4020-5511-0

41. Dolan P, Gudex C, Kind P, Williams A. *A Social Tariff for EuroQol: Results from a UK General Population Survey*. Discussion Paper 138. York: Centre for Health Economics, University of York; 1995.

42. Billingham LJ, Abrams KR, Jones DR. Methods for the analysis of quality-of-life and survival data in health technology assessment. *Health Technol Assess* 1999;**3**(10).

43. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;**14**:487–96. http://dx.doi.org/10.1002/hec.944

44. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;**338**:b2393. http://dx.doi.org/10.1136/bmj.b2393

45. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *BMJ* 2011;**342**:d40. http://dx.doi.org/10.1136/bmj.d40

46. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. http://dx.doi.org/10.1002/sim.4067

47. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004;**13**:461–75. http://dx.doi.org/10.1002/hec.843

48. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal*. London: NICE; 2013.

49. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–15. http://dx.doi.org/10.1002/hec.903

50. Schiller P, Burchardi N, Niestroj M, Kieser M. Quality of reporting of clinical non-inferiority and equivalence randomised trials – update and extension. *Trials* 2012;**13**:214. http://dx.doi.org/10.1186/1745-6215-13-214

51. Castela E, Archier E, Devaux S, Gallini A, Aractingi S, Cribier B, *et al.* Topical corticosteroids in plaque psoriasis: a systematic review of risk of adrenal axis suppression and skin atrophy. *J Eur Acad Dermatol Venereol* 2012;**26**(Suppl. 3):47–51. http://dx.doi.org/10.1111/j.1468-3083.2012.04523.x

52. Bratton DJ, Williams HC, Kahan BC, Phillips PP, Nunn AJ. When inferiority meets non-inferiority: implications for interim analyses. *Clin Trials* 2012;**9**:605–9. http://dx.doi.org/10.1177/1740774512453220

53. Lever WF. Pemphigus. *Medicine (Baltimore)* 1953;**32**:1–123. http://dx.doi.org/10.1097/00005792-195302000-00001

54. Savin JA. The events leading to the death of patients with pemphigus and pemphigoid. *Br J Dermatol* 1979;**101**:521–34. http://dx.doi.org/10.1111/j.1365-2133.1979.tb11881.x

55. Roujeau JC, Guillaume JC, Morel P, Crickx B, Dalle E, Doutre MS, *et al.* Plasma exchange in bullous pemphigoid. *Lancet* 1984;**2**:486–8. http://dx.doi.org/10.1016/S0140-6736(84)92565-0

56. Beissert S, Werfel T, Frieling U, Bohm M, Sticherling M, Stadler R, *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007;**143**:1536–42. http://dx.doi.org/10.1001/archderm.143.12.1536

57. Murrell DF, Daniel BS, Joly P, Borradori L, Amagai M, Hashimoto T, *et al.* Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol* 2012;**66**:479–85. http://dx.doi.org/10.1016/j.jaad.2011.06.032

Appendix 1 Survey results

Q1: What reduction in effectiveness would be acceptable?

(a) Assuming the *mortality rate* with oxytetracycline is *1% less* than with prednisolone and prednisolone is 95% effective:

- a minimum median effectiveness rate of *50%* would be required for oxytetracycline to have *any place* in the management of BP
- a minimum median effectiveness rate of *80%* would be required oxytetracycline to have *potential* as primary treatment for BP.

(b) Assuming the *mortality rate* with oxytetracycline is *10% less* than with prednisolone and prednisolone is 95% effective:

- a minimum median effectiveness rate of **40%** would be required for oxytetracycline to have **any place** in the management of BP
- a minimum median effectiveness rate of **70%** would be required oxytetracycline to have **potential** as primary treatment for BP.

Q2: What reduction in mortality would be useful?

(a) Assuming oxytetracycline is *5% less effective* than prednisolone and the mortality rate of prednisolone is 40%:

- a maximum median mortality rate of *35%* would be acceptable for oxytetracycline to have *any place* in the management of BP
- a maximum median mortality rate of *23%* would be acceptable for oxytetracycline to have *potential* as primary treatment for BP.

(b) Assuming oxytetracycline is *10% less effective* than prednisolone and the mortality rate of prednisolone is 40%:

- a maximum median mortality rate of *30%* would be acceptable for oxytetracycline to have *any place* in the management of BP
- a maximum median mortality rate of *20%* would be acceptable for oxytetracycline to have *potential* as primary treatment for BP.

(c) Assuming oxytetracycline is *20% less effective* than prednisolone and the mortality rate of prednisolone is 40%:

- a maximum median mortality rate of *30%* would be acceptable for oxytetracycline to have *any place* in the management of BP
- a maximum median mortality rate of *15%* would be acceptable for oxytetracycline to have *potential* as primary treatment for BP.

Recruitment feasibility

Question	Averages
Approximately how many new cases of BP do you *personally* see per year?	5
Approximately how many new cases of BP are seen in your *whole department* per year?	14
Are you interested in helping recruit patients for this study? *(approximately two patients per year, followed up for 1 year each)*	Most yes
Do you think that it would be feasible for your colleagues to refer patients to you for this study?	Most yes
If yes, what proportion of the total number of BP patients presenting to your department would you be able to get referred to you for the study?	Approximately half

Appendix 2 Health economics analysis plan

The Bullous Pemphigoid Steroids And Tetracyclines (BLISTER) Study

Health Economics Analysis Plan

V1.1
3rd March 2014

Study No:	UKCRN ID2611
EUDRACT:	2007-006658-24
ISRCTN:	ISRCTN13704604
Funded by:	NIHR Health Technology Assessment Programme (06/403/51)
Sponsor:	Nottingham University Hospitals NHS Trust

Prepared by: **Prof. James Mason**
XXXX

Approved by:

CONTENTS

1 Introduction

1.1 Study Background

Bullous pemphigoid is the most common autoimmune blistering disease in Western Europe, occurring mainly in the elderly, with significant morbidity and mortality. In particular, widespread blistering, skin erosions and severe itching cause distress and pain. Bullous pemphigoid is frequently treated with oral corticosteroids which, it is thought, contribute to the high mortality and morbidity rate of treated patients. A Cochrane review has suggested that treatment with tetracyclines may be effective but that there is a lack of high quality, randomised controlled trials to confirm this. The BLISTER trial was designed to determine the effectiveness and safety of doxycycline compared with prednisolone for the treatment of bullous pemphigoid.

BLISTER is a multi-centre, randomised, controlled trial of 52 weeks duration with two parallel arms: 200mg/day of doxycycline for 6 weeks or 0.5mg/kg/day of prednisolone for 6 weeks; from weeks 6 - 52, investigators can amend the medication in line with patient need. A total of 256 patients with bullous pemphigoid from the United Kingdom and Germany are being recruited into the study.

The primary outcomes are i) effectiveness, measured by an assessor-blinded blister count at week 6 and ii) safety, measured by the proportion of patients experiencing adverse events during the year of follow up that are related to the trial medication and graded as 3 or above (using the Common Terminology Criteria for Adverse Events version 3.0). Secondary outcomes include relapse rates, the number of patients experiencing any grade of adverse event related to treatment, death, quality of life and cost effectiveness. The primary analysis for effectiveness will be to assess whether doxycycline can be considered non-inferior to prednisolone at 6 weeks; analyses will be conducted both by per protocol and intention to treat. The primary analysis for safety is a superiority analysis and will be by intention to treat. Planned recruitment was completed by September 2013 and results will be available from March 2015.

1.2 Health Economics Objective

The BLISTER trial objectives, inclusion criteria, sample size, endpoints and analysis plan are described within the study protocol.

This document describes the planned cost-effectiveness analysis, where the objective is to establish the relative cost-effectiveness of oral doxycycline-led and oral prednisolone-led therapy using incremental cost and cost-effectiveness analyses using disease specific and generic quality of life measures - Dermatology Life Quality Index (DLQI) and Euroqol (EQ-5D-3L and EQ-VAS).

1.1 Health economics Analysis Plan

The objective of this analysis plan is to describe the cost-effectiveness analyses to be carried out for the BLISTER randomised controlled trial for the final analyses. It does not address the trial analysis set out in Statistical Analysis Plan (SAP). Analyses will be conducted by model building in Excel, producing macro-generated bootstrapped estimates of cost-effectiveness to generate (within-trial) incremental cost-effectiveness ratio (ICER) planes and cost-effectiveness acceptability curves (CEAC) using standard methods.

2 Analysis

2.1 Study Perspective

All analyses will be at the patient level, by intention to treat and will take a NHS perspective.

2.2 Contributory Outcomes

2.2.1 Resources

Resource use is recorded by asking patients to recall: GP clinic and home visits, practice and district nurse visits, outpatient visits and inpatient stays. Resource assessments occur at 3, 6, 13, 26, 39 and 52 weeks. Collection of data occurs at mandatory clinical visits, augmented by telephone calls. Healthcare resource use will be costed using published national reference costs [1,2]. Costs of study medications will also be included using British National Formulary Tariffs [3]. Patient level costs will be estimated as the sum of resources used weighted by their National reference costs. Effect of treatment on resource use and cost will be estimated using Student's t-test for unpaired data and bootstrapping.

2.2.2 Quality of Life

The trial includes the use of the Dermatology Life Quality Index (DLQI) [4] and Euroqol (EQ-5D-3L and EQ-VAS) [5] questionnaires, which will be completed at baseline, 6, 13, 26, 39 and 52 weeks. Repeated scores over time will be used to construct area-under-curve (AUC) estimates for each patient, using the trapezoidal method. The within trial difference in quality-adjusted survival expressed as quality-adjusted life years (QALYs) gained will be estimated using the EQ-5D-3L measure with the EQ-VAS providing a supportive estimate. No discounting will be applied to quality-adjusted survival data reflecting the follow-up period (< 1 year). Effect of treatment on quality of life measures will be estimated using Student's t-test for unpaired data and bootst.

1.2.1 Cost-Effectiveness Analysis

Patient-level cost and quality of life data will be bootstrapped (sampled with replacement, N=10,000) to populate incremental cost effectiveness (ICER) planes, to estimate average (median) cost-effectiveness and pseudo 95% confidence interval (2.5 and 97.5 centile values) [6,7]. Findings will be visualised by generating cost-effectiveness acceptability curves (CEAC).

2 References

[1] Curtis L. Unit Costs of Health and Social Care.
Personal Social Services Research Unit University of Kent University of Kent, 2012.
[last accessed 21-1-14]; Available from:
http://www.pssru.ac.uk/archive/pdf/uc/uc2012/full-with-covers.pdf

[2] Department of Health.
NHS reference costs: financial year 2011 to 2012
[last accessed 21-1-14]; Available from:
https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012

[3] British National Formulary, BNF 67.
[last acc. 11-2-14]; Available from:
http://bnf.org/bnf/index.htm

[4] Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210-6.

[5] Kind P, Dolan P, Gudex C, Williams A. (1998) Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 316: 736-41.

[6] Barber J, Thompson S. Analysis of cost data in randomised controlled trials: an application of the non-parametric bootstrap. Statistics in Medicine 2000;19:2319-2336.

[7] Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ. 1998 Dec;7(8):723-40.

Appendix 3 Reasons for exclusion from the per-protocol analyses

TABLE 58 Reasons for exclusion from the primary efficacy analysis at week 6

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment during weeks 0–6	1	0
Changed treatment or added a new treatment to the allocated treatment	17	3
Used topical steroids between weeks 3 and 6	7	3
Missed more than 3 consecutive days of treatment	21	5
Total number of non-PP patients	34	10

Some participants may appear in more than one row.

TABLE 59 Reasons for exclusion from the secondary efficacy analysis at week 6

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 6	1	0
Changed treatment or added a new treatment to the allocated treatment before week 6	17	3
Used topical steroids between weeks 3 and 6	7	3
Missed more than 3 consecutive days of treatment before week 6	21	5
Total number of non-PP patients	34	10

Some participants may appear in more than one row.

TABLE 60 Reasons for exclusion from the secondary efficacy analysis at week 13

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 6	1	0
Changed treatment or added a new treatment to the allocated treatment before week 6	16	2
Used topical steroids between weeks 3 and 6	6	3
Missed more than 3 consecutive days of treatment before week 6	19	4
Missed more than 3 consecutive weeks of treatment between week 6 and week 13	2	0
Received > 30 g of topical steroids per week between week 6 and week 13	5	0
Added systemic steroids to doxycycline (if allocated) or doxycycline or another immunosuppressant to prednisolone (if allocated) between week 6 and week 13	5	1
Total number of non-PP patients	36	10

Some participants may appear in more than one row.

TABLE 61 Reasons for exclusion from the secondary efficacy analysis at week 52

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 6	1	0
Changed treatment or added a new treatment to the allocated treatment before week 6	13	2
Used topical steroids between weeks 3 and 6	5	1
Missed more than 3 consecutive days of treatment before week 6	15	1
Missed more than 3 consecutive weeks of treatment between week 6 and week 52	2	0
Received > 30 g of topical steroids per week between week 6 and week 52	3	2
Added systemic steroids to doxycycline (if allocated) or doxycycline or another immunosuppressant to prednisolone (if allocated) between week 6 and week 52	7	8
Total number of non-PP patients	30	11

Some participants may appear in more than one row.

TABLE 62 Reasons for exclusion from the secondary analysis of the proportion of participants who have a further episode of BP during their participation in the study after previously being classified as a treatment success

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 6	1	0
Changed treatment or added a new treatment to the allocated treatment before week 6	16	3
Used topical steroids between weeks 3 and 6	7	3
Missed more than 3 consecutive days of treatment before week 6	21	8
Missed more than 3 consecutive weeks of treatment between week 6 and week 52	3	0
Received > 30 g of topical steroids per week between week 6 and week 52	5	2
Added systemic steroids to doxycycline (if allocated) or doxycycline or another immunosuppressant to prednisolone (if allocated) between week 6 and week 52	7	9
Total number of non-PP patients	40	21

Some participants may appear in more than one row.

TABLE 63 Reasons for exclusion from the tertiary analysis of the proportion of participants classed as a treatment success at week 3

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 3	1	0
Changed treatment or added a new treatment to the allocated treatment before week 3	14	2
Missed more than 3 consecutive days of treatment before week 3	10	6
Total number of non-PP patients	21	7

Some patients may appear in more than one row.

TABLE 64 Reasons for exclusion from the tertiary analysis of the proportion of participants who achieved treatment success at 52 weeks

Reason for exclusion	Doxycycline, *n*	Prednisolone, *n*
Increased the dose of the allocated treatment before week 6	1	0
Changed treatment or added a new treatment to the allocated treatment before week 6	12	1
Used topical steroids between weeks 3 and 6	5	1
Missed more than 3 consecutive days of treatment before week 6	14	1
Missed more than 3 consecutive weeks of treatment between week 6 and week 52	2	0
Received > 30 g of topical steroids per week between week 6 and week 52	3	2
Added systemic steroids to doxycycline (if allocated) or doxycycline or another immunosuppressant to prednisolone (if allocated) between week 6 and week 52	7	8
Total number of non-PP patients	29	10

Some patients may appear in more than one row.

Appendix 4 Trial oversight committees

Trial Steering Committee

Independent members

- Professor Jonathan Barker (chairperson), St John's Institute of Dermatology, Guy's Hospital, London, UK.
- Professor Pascal Joly (clinical expert), Hôpital Charles Nicolle, Rouen, France.
- Dr Jonathan Leonard (clinical expert), St Mary's Hospital, London, UK.
- Ms Helena Haywood (dermatology nurse), Amersham Hospital, Amersham, UK.

Patient representatives

- Penny Standen.
- Brian Lockwood.

Non-independent members

- Professor Hywel Williams (chief investigator), Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK.
- Professor Fenella Wojnarowska (lead clinician), Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK.
- Dr Gudula Kirtschig (clinical expert and co-ordinator for German sites), Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK.
- Professor Andrew Nunn (senior trial statistician), MRC Clinical Trials Unit at University College London, London, UK.
- Daniel Bratton, Sunita Rehal, Tom Godec (trial statisticians), MRC Clinical Trials Unit at University College London, London, UK.
- Dr Karen Harman (principal investigator representative), University Hospitals Leicester, Dermatology Department, Leicester Royal Infirmary, Leicester, UK.
- Dr Phillip Hampton (principal investigator representative), Royal Victoria Infirmary, Newcastle, UK.
- Dr Joanne Chalmers (research fellow), Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK.

The current trial manager was also a non-independent member of the Trial Steering Committee.

Trial Management Group

- Professor Hywel Williams (chief investigator), Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK.
- Professor Fenella Wojnarowska (lead clinician), Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK.
- Dr Gudula Kirtschig (clinical expert and co-ordinator for European sites), Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK.
- Professor Andrew Nunn (senior trial statistician), MRC Clinical Trials Unit at University College London, London, UK.
- Daniel Bratton, Sunita Rehal, Thomas R Godec (trial statisticians), MRC Clinical Trials Unit at University College London, London, UK.

- Professor James Mason (health economist), Durham University, School of Medicine, Pharmacy and Health, Stockton-on-Tees, UK.

The current trial manager was also a member of the Trial Management Group.

Data Monitoring Committee

- Professor S Lamb (chairperson), Warwick Clinical Trials Unit, University of Warwick, Coventry, UK
- Dr R Graham-Brown (independent member), Department of Dermatology, Leicester Royal Infirmary, Leicester, UK
- Dr Tracey Young (independent member), Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK.

Appendix 5 Trial management team

All trial management was conducted by the NCTU, Nottingham Health Science Partners, Queen's Medical Centre, Nottingham, UK.

Senior trial managers

- Margaret Childs.
- Diane Whitham.

Trial managers

- Caroline Onions.
- Dr Katharine Foster.
- Dr Anna Sandell.

Data managers, trial co-ordinators and administrators

- Daniel Simpkins.
- Aisha Shafayat.
- Robert Allen.
- Aimee Tooley.
- Sally Kucyj.

Appendix 6 Recruiting centres

Recruiting group (UK) in centre number order

1. Walton Hospital, Liverpool (principal investigator: Dr A Alkali; coinvestigator: Dr G Wong; research nurses: Ms M Harrison and Ms P Taylor).
2. Blackpool Victoria Hospital, Blackpool (principal investigator: Dr W Bottomley).
3. St Luke's Hospital, Bradford (principal investigator: Dr A Wright; coinvestigator: Dr M Whittmann; research nurses: Ms J Ott and Mr A Liu).
4. Brighton General Hospital, Brighton (principal investigator: Dr C DeGiovanni; coinvestigators: Dr S Gossain, Dr S George and Dr F Imran; research nurses: Ms H Santander and Ms M Flowerdew).
5. Addenbrooke's Hospital, Cambridge (principal investigator: Dr J Sterling; coinvestigators: Dr J Batchelor, Dr M Chattopadhyay, Dr M Wallace, Dr G Ben-Zvi, Dr S Haque-Hussain and Dr A Ranasinghe).
6. Sunderland Royal Infirmary, Sunderland (principal investigator: Dr S Wahie; coinvestigators: Dr K Freeman, Dr S Nataranjan, Dr N Rajan and Dr R Ellis; research nurse: Ms A Thomson).
7. University Hospital of North Durham, Durham (principal investigator: Dr S Wahie; coinvestigators: Dr T Sripathy, Dr V Bajaj, Dr M Vatve and Dr K Freeman; research nurse: Ms A Thomson).
8. London Road Community Hospital, Derby (principal investigator: Dr A Ferguson; research nurse: Ms K Riches).
9. Corbett Hospital, Stourbridge, West Midlands (principal investigators: Dr I Verpetinske, Dr S Cheung; dermatology clinical nurse specialist: Miss M Taylor).
10. Kent and Canterbury Hospital, Canterbury (principal investigator: Dr E Duarte-Williamson; coinvestigators: Dr C Cowley, Dr E Kulakov and Dr J Mann; research nurse: Ms A Potter).
11. Frimley Park Hospital, Frimley, Surrey (principal investigator: Dr F Antony; coinvestigator: Dr J Williams; research nurse: Ms L Moore; dermatology nurse specialist: Mrs J Herzke; clinical researcher: Ms S Atkinson).
12. Guy's and St Thomas' Hospital, London (principal investigator: Dr R Groves; coinvestigator: Dr E Benton; research nurses: Ms H Sreeneebus and Ms S Jones).
13. Harrogate District Hospital, Harrogate (principal investigator: Dr A Layton; coinvestigators: Dr A Whitton, Dr B Walker, Dr R Strauss, Dr S Das, Dr E Marshall, Dr N Goddard, Dr L Savage, Dr J Kwok and Dr M Walker; research nurses: Ms M Broome, Ms G Law and Mrs A Wray; clinical trials assistant: Mrs J Hussey; research and development administrator: Mrs J Pearson).
14. Hull Royal Infirmary, Hull (principal investigator: Dr S Walton; coinvestigators: Dr R Zaman, Dr A Kapdia and Dr V Smith; research nurses: Mr P Jones and Ms K Ashton).
15. Ipswich Hospital, Ipswich (principal investigators: Dr O Aziz, Dr S Gibbs, Dr D Rallan; research nurse: Ms S Hood).
16. James Paget Hospital, Great Yarmouth (principal investigators: Dr I Salvary, Dr R Graham; coinvestigator: Dr V Gajawada; research nurses: Ms S Simmons and Ms J Woods).
17. Cannock Chase Hospital, Cannock, Staffordshire (principal investigators: Dr A Azam, Dr R Rotarescu; coinvestigator: Dr S Cheung; research nurses: Miss K Amor, Ms M Harry, Ms N Smith, Ms S Hendy, Miss D Sirdefield and Mrs S Johnson).
18. Norfolk and Norwich University Hospital, Norwich (principal investigator: Dr N Levell; coinvestigators: Dr N Cassie-Chetty, Dr R Coelho, Dr G Millington, Dr M McDermott, Dr A Yong and Dr M Chriba; research nurses: Ms K Banks-Dunnell and Ms D Butcher).
19. Cumberland Infirmary, Carlisle (principal investigators: Dr N Cox and Dr M Nik; research nurse: Ms K Gilbanks).
20. North Devon District Hospital, Barnstaple, Devon (principal investigator: Dr K Davies; research nurses: Mr N Lawton and Ms L Wells).

21. Queen's Medical Centre, Nottingham (principal investigator: Dr J English; coinvestigators: Dr M Malik, Dr C Wooton, Dr R Murphy, Dr J Batchlor, Dr R Simpson, Dr E Burden-Teh, Dr A Yaakub and Dr M Lam; research nurses: Ms S Davies-Jones and Ms J Llewellyn).
22. Churchill Hospital, Oxford (principal investigator: Dr V Venning; coinvestigators: Dr T McPherson and Dr S Cooper; research nurses: Ms L Matter, Ms M Westmoreland and T McPherson).
23. Queen Elizabeth Hospital, Greenwich (principal investigator: Dr A Chapman; coinvestigators: Dr Y Estfan and Dr N Miller; research nurse: Ms G Reeves).
24. Royal Berkshire Hospital, Reading (principal investigators: Dr G Kaushal, Dr D Seukeran, Dr I Nasr and Dr H Malhomme; coinvestigators: Dr J Dua, Dr C Higgins, Dr A Lloyd Lavery, Dr S Ong, Dr C Allen and Dr R Clayton; research nurses: Ms K Wilmott, Ms J Foxton, Ms J King and Ms G Grimwood).
25. Royal Devon and Exeter Hospital, Exeter (principal investigator: Dr C Bower; coinvestigators: Dr C Charman and Dr J Varghese; research nurses: Mr R James and Ms T Hill; clinical trials administrator: Miss M Hayward).
26. Broadgreen Hospital, Liverpool (principal investigators: Dr H Bell and Dr R Azurdia; coinvestigators: Dr M Walsh, Dr K Ngan, Dr P Jayasekera and Dr C Angit; research nurses: Ms A Turner, Ms P Taylor, Ms D Marsh, Ms A Young and Ms T O'Rourke).
27. Royal United Hospital, Bath (principal investigator: Dr C Lovell).
28. Sandwell General Hospital, Birmingham (principal investigator: Dr S Velangi; coinvestigators: Dr W Szczecinska, Dr N Talsamia, Dr G Jutley, Dr M Ogboli and Dr J Halpern; research nurse: Ms T Shumba).
29. Royal Hallamshire Hospital, Sheffield (principal investigator: Professor D Gawkrodger; coinvestigators: Dr P Cousen, Dr N Aldoori, Dr C Morgan and Dr A Diaz).
30. King's Mill Hospital, Sutton-in-Ashfield, Nottinghamshire (principal investigator: Dr J Ravenscroft; coinvestigators: Dr M Panchal, Dr E Bayliss, Dr J English, Dr A Yaakub and Dr H Trinh; research nurses: Ms C Heeley and Mr A Novak).
31. Torbay Hospital, Torquay (principal investigators: Dr J Adams and Dr T Frost; research nurses: Ms S Burns, Dr A Clepa and Dr D Benham).
32. James Cook University Hospital, Middlesbrough (principal investigator: Dr A Carmichael; coinvestigators: Dr R Ellis, Dr A Kapadia, Dr H Reddy, Dr S Fatah and Dr J Dalrimple).
33. Warwick Hospital, Warwick (principal investigator: Dr R Charles-Holmes; coinvestigators: Dr J Carter and Dr A Bedlow; research nurses: Ms C Jones, Ms W Seaton and Ms K Hotchkiss).
34. St George's Hospital, London (principal investigator: Dr V Akhras; coinvestigator: Dr J Wee).
35. St Helens Hospital, St Helens (principal investigator: Dr S Winhoven; research nurse: Ms K Rutter).
36. Great Western Hospital, Swindon (principal investigators: Dr D Buckley, Dr S Gibbs; coinvestigators: Dr L Whittam, Dr H Hempel and Dr J Gingell; research nurses: Ms S Toft and Ms J Arnold).
37. Musgrove Park Hospital, Taunton (principal investigator: Dr V Lewis; coinvestigators: Dr J Adams and Dr R Wachsmuth).
38. Royal Victoria Infirmary, Newcastle (principal investigator: Dr P Hampton).
39. Whittington Hospital, London (principal investigator: Dr K Taghipour; coinvestigators: Dr N Kapur, Dr R Wakeel, Dr A Friedman; research nurse: Ms L Reeves and Ms B Akworth).
40. Lincoln County Hospital, Lincoln (principal investigator: Dr K Hussain; research nurses: Ms K Horton and Ms K Warner).
41. University Hospital, Coventry (principal investigator: Dr A Ilchyshyn; coinvestigator: Dr B Dharma; research nurse: Ms K Hotchkiss).
42. Bristol Royal Infirmary, Bristol (principal investigator: Dr G Dunnill; coinvestigator: Dr A Bray).
43. Leicester Royal Infirmary, Leicester (principal investigators: Dr K Harmen, Dr A Alexandrov; coinvestigators: Dr K Narayana, Dr G Johnston and Dr I Helbling; research nurses: Ms C Shelley and Ms A Hill).
44. Weston General Hospital, Weston-super-Mare (principal investigators: Dr M Kirkup, Dr D Simmons and Dr H Lloyd-Jones; research nurse: Mr G Saunders).
45. Whipps Cross University Hospital, London (principal investigator: Dr K Gibbon; coinvestigator: Dr A Bewley).
46. Yeovil District Hospital, Yeovil (principal investigator: R Wachsmuth; coinvestigators: Ms F Edwards and Dr J Boyle; research nurse: Ms M Davey).

47. York Hospital, York (principal investigator: Dr C Lyon; research nurse: Ms J Green).
48. Aberdeen Royal Infirmary, Aberdeen (principal investigator: Dr A Ormerod; coinvestigators: Dr F Craig and Dr F Hussain; research nurse: Ms L Lawson).
49. Royal Gwent Hospital, Newport (principal investigator: Professor A Anstey; coinvestigator: Dr J Ingram; research nurses: Ms S Mitchell and Ms C Watkins).
50. Raigmore Hospital, Inverness (principal investigator: Dr J Vestey; coinvestigator: Ms S Halliday; research nurses: Ms P Martin and Ms S Ross).
51. Glangwili General Hospital, Carmarthen (principal investigators: Dr D Shipley and Dr E Veysey; research nurse: Ms A Johnson).
52. Singleton Hospital, Swansea (principal investigators: Dr E Veysey and Dr S Blackford; coinvestigator: Dr S Sidhu; research nurse: Ms C Thomas).
53. University Hospital of Wales, Cardiff (principal investigators: Dr G Patel and Dr J Ingram; coinvestigators: Dr R Motley, Dr A Morris, Dr C Long, Dr R Abbott, Dr M Chowdhury and Dr S Scourfield; research nurse: Ms A Thomas).
54. Ninewells Hospital, Dundee (principal investigator: Professor J Ferguson; coinvestigators: Dr A Waters, Dr R Dawe and Dr P Rakvit; research nurse: Ms S Yule).

Recruiting group (Germany) in centre number order

1. Universitätsklinikum Carl Gustav Carus, Dresden (principal investigators: Dr C Günther and Professor Wozel; research nurse: Fr Blümlein).
2. Universitätsklinikum Erlangen (principal investigator: Professor M Sticherling; coinvestigator: Dr R Renner; research nurses: Fr P Alt and Fr S Friedel).
3. Universitätsklinikum Schleswig-Holstein, Lübeck [principal investigator: Professor E Schmidt (and chief investigator for Germany); coinvestigators: Dr D Meyersburg and Dr N Van Beek; research nurse: Fr D Knuth-Rehr].
4. Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz (principal investigator: Dr K Steinbrink; research nurse: Fr G Hagedorn).
5. Universitätsklinikum Münster, Münster (principal investigator: Professor Luger; coinvestigators: Dr A Tsianakas and Dr AM Perusquia Ortiz).
6. Klinik und Poliklinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum Würzburg, Würzburg (principal investigators: Professor E Broecker and Dr Benoit; coinvestigators: Dr C Hosp, Dr J Stoevesandt, Dr D Anders and Dr H Poppe; research nurse: Fr S König).
7. Universitätsklinikum Schleswig-Holstein, Kiel (principal investigator: Professor R Gläser; coinvestigators: Dr Rainer Hügel and Dr F Lipowsky; research nurse: Fr L Wedler).

Appendix 7 Data collection tools

Please log any changes that have been made to the patient's ORAL Bullous Pemphigoid medication

A	DRUG NAME (USE BLOCK CAPITALS)	ACTION	NEW TOTAL DAILY DOSE (mg)	DATE OF ACTION (DD/MON/YYYY)	REASON FOR ACTION AND EXTRA INFORMATION	
1	BLINDED ALLOCATED TREATMENT	START			0	TRIAL START
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
B	Please tick if Treatment Log is continued onto an additional page ☐					

ACTION CODES		REASON FOR ACTION CODES	
START new medication	**SWITCH** to other systemic medication	**0** = Trial Start	**4** = Adverse Event
STOP medication	Increase dose (**INC**)	**1** = Treatment failure	**5** = Completed trial week 52
RESTART medication (if previously stopped)	Reduce dose (**RED**)	**2** = Treatment success	**6** = Never started medication
	Tapering of dose (**TAP**)	**3** = Worsening of disease (relapse)	**7** = Withdrawn from study
			8 = Other (please specify)

Please log any changes that have been made to the patient's TOPICAL Bullous Pemphigoid medication

NAME OF CREAM OR OINTMENT (USE BLOCK CAPITALS)	START DATE (DD/MON/YYYY)	STOP DATE (DD/MON/YYYY)	APPROX. TOTAL USED BETWEEN DATES (g)	REASON FOR USING TOPICAL STEROIDS (please use action codes below)	
Part 1 – trial start to week 3 visit (up to 30g of potent steroid permitted each week)					
MOMETASONE				10	
Part 2 – weeks 4, 5 and 6 (topical steroid use **not** permitted by trial protocol)					
Part 3 – weeks 7 to 52 (up to 30g per week of a potent topical steroid allowed whilst reducing systemic treatment)					

REASON FOR ACTION CODES	
10 = Permitted by trial protocol for extra itching relief	**14** = Adverse Event
11 = Treatment failure	**15** = Completed trial week 52
12 = Worsening of disease (relapse)	**16** = Never started medication
13 = Part of weaning off oral treatment	**17** = Withdrawn from study
	18 = Other (please specify)

Please log any changes that have been made to the patient's ORAL Bullous Pemphigoid medication

A	DRUG NAME (USE BLOCK CAPITALS)	ACTION	NEW TOTAL DAILY DOSE (mg)	DATE OF ACTION (DD/MON/YYYY)	REASON FOR ACTION AND EXTRA INFORMATION	
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						
31						
32						
33						
34						
35						
36						
37						
38						
39						
40						
41						
42						
43						

ACTION CODES		REASON FOR ACTION CODES	
START new medication	**SWITCH** to other systemic medication	**0** = Trial Start	**4** = Adverse Event
STOP medication	Increase dose (**INC**)	**1** = Treatment failure	**5** = Completed trial week 52
RESTART medication (if previously stopped)	Reduce dose (**RED**)	**2** = Treatment success	**6** = Never started medication
	Tapering of dose (**TAP**)	**3** = Worsening of disease (relapse)	**7** = Withdrawn from study
			8 = Other (please specify)

Please log any changes that have been made to the patient's ORAL Bullous Pemphigoid medication

Medical Condition	Not present	Mild	Moderate	Severe	Life threatening	Death
Adrenal insufficiency						
Cushingoid						
Diabetes						
Hypertension						
Glaucoma						
Cataracts						
Infection						
(please specify type of infection):						
Pneumonitis						
Bruising						
Photosensitivity						
Skin atrophy						
Striae						
Telangiectasia						
Osteoporosis						
Muscle weakness						
Oedema: limb						
Diarrhoea						
Gastritis						
Nausea						
Ulcer, GI						
Weight gain						
Thrombosis/ embolism						
Mood alteration (e.g. depression, euphoria)						
Other:						
Other:						
Other:						
Other:						
Other:						

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library