

**STUDY OF TREATMENTS FOR PYODERMA GANGRENOSUM  
PATIENTS – AN RCT OF ORAL PREDNISOLONE VERSUS  
CICLOSPORIN  
(STOP GAP)**

**STATISTICAL ANALYSIS PLAN**

**(FINAL ANALYSIS)**

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# **1. INTRODUCTION**

## **1.1. STUDY BACKGROUND**

Pyoderma gangrenosum (PG) is a mutilating, painful skin disease that often affects people with an underlying internal disease (such as inflammatory bowel disease, monoclonal gammopathy and rheumatoid arthritis). Treatment of PG usually involves immunosuppression or immunomodulation. Many of these treatments are associated with unpleasant and damaging side-effects, making their formal evaluation a matter of urgency. These treatments are currently being used for patients with PG without rigorous testing or understanding of their relative efficacy, cost and side-effect profile.

An audit conducted by the UK Dermatology Clinical Trials Network (UK DCTN) of all cases of PG occurring in 11 centres over 3 years was carried out in 2007 which included 188 episodes of PG occurring in 155 patients. Patients required an average of 2 treatments per episode. 22% of episodes were treated solely with topical treatment; the remaining 78% required systemic treatments, either alone or in combination with topical treatment. The most commonly used systemic treatments were prednisolone (in 56%), ciclosporin (29%), tetracyclines (20%), biologics (9%) and azathioprine (8%). Only 56% of episodes were documented as having healed, in a median time of 5 months.

This study seeks to address the lack of evidence for the treatment of patients with PG. It will compare head-to-head the two most commonly used systemic treatments. Oral prednisolone (historically most commonly used for patients requiring systemic therapy), will be compared with ciclosporin. As this is a relatively rare condition, patients who initially require topical therapy will be asked to enter a parallel observational study and outcome data will be collected over the study period. Should the ulcer(s) fail to respond to topical therapy, then participants will be asked to take part in the randomised trial of systemic therapy.

## **1.2. STUDY OBJECTIVES**

To determine whether systemic ciclosporin (4 mg/kg/day) is more clinically effective than systemic prednisolone (0.75 mg/kg/day) for oral therapy of PG, and to evaluate the relative safety and cost-effectiveness of these drugs.

### **1.2.1. PRIMARY OBJECTIVES**

It is hypothesised that ciclosporin gains control of the disease more rapidly, and reduces the time to healing for patients with PG compared to treatment with oral prednisolone, so the primary objective is to assess the speed of the response to treatment. The primary outcome is the velocity of healing.

### **1.2.2. SECONDARY OBJECTIVES**

Our secondary objectives are:

1. To assess time to complete healing
2. To assess improvement using the global assessment of improvement, as assessed by the clinician and the patient
3. To assess inflammation using the inflammation assessment scale assessed by the clinician and the patient

4. To assess pain using the self-reported pain in the patients' diaries
5. To assess the health-related quality of life using:
  - a. Dermatology Life Quality Index (DLQI)
  - b. EQ-5D
  - c. EQ-VAS
6. To assess time to recurrence
7. To assess the number of treatment failures. Treatment failures for this outcome are determined as all of the lesions which remain unhealed after 6 months.
8. To assess the safety and tolerability of the two treatments
9. To assess the cost-effectiveness of the two treatments

### **1.3. STUDY DESIGN**

This is a multi-centre, parallel group, randomised controlled trial. The study is single blind for the assessment of the primary outcome of speed of response at 6 weeks (digital images taken in clinic will be assessed centrally using specialist software). Because of logistic and methodological difficulties in blinding treatment allocation, both patients and treating physicians will be aware of treatment allocation.

Patients will be randomised to receive either oral prednisolone (0.75 mg/kg/day) or oral ciclosporin (4 mg/kg/day), using a computer generated pseudo-random list using permuted blocks of randomly varying size between 2 & 6, created using the ralloc Stata add-on. Randomisation is stratified by lesion size (lesions  $\geq 20\text{cm}^2$  versus lesions  $< 20\text{cm}^2$ ) and presence or absence of underlying systemic disease (eg. inflammatory bowel disease). Treatment will be continued until remission is achieved.

Patients for whom first line topical therapy is indicated will be invited to enter the observational study – only if this treatment fails will participants be invited to take part in the randomised trial.

Patients will continue to be monitored until the lesion has healed, or for a maximum of 6 months (whichever is sooner). Consent will also be obtained for the research team to contact the patients after this time (or to access medical records), in order to capture details of future episodes of PG.

Patients will be recruited from approximately fifty acute hospitals in the UK and Ireland over a three-four year recruitment period. Patients will be a mixture of inpatients and outpatients depending on local practice.

In the UK, recruitment is through UK DCTN. Patients will be referred through colleagues to the investigator and information will be displayed in the relevant clinical areas to encourage recruitment. Previous patients will also be contacted and provided with information about the trial.

All recruited patients who give consent will have baseline data on their general health (demographic information, medical history, physical information), the target lesion (digital image, assessment by both patient and clinician, measurements of lesion) and questionnaires recorded at the initial baseline visit.

The second visit at week 2, allows collection of the same data as at baseline (excluding the medical history, demographic information, Quality of Life Questionnaire (QoL) and digital image) and will also include information on any adverse events. The response to treatment will be assessed and any required adjustments to the trial medication dose will be made as necessary.

The third visit at week 6 allows assessment of the primary outcome, by means of digital images, and side-effects. It collects all information collected at the second visit, along with side effects, and additionally updated digital images and the QoL questionnaire.

Further visits up to six months after the baseline visit will be made at the discretion of the treating physician. Limited details relating to treatment response, safety and health service resource use will be captured on the CRF's and/or medical notes.

## **1.4. SAMPLE SIZE AND POWER**

One hundred and forty patients, randomised 1:1 to systemic prednisolone or systemic ciclosporin, will give the study at least 80% power at a 5% significance level using a two-sided two sample t-test to detect a difference in means of 0.5 standard deviations of the primary outcome of velocity of healing at 6 weeks. The velocity of healing at six weeks is defined as the percentage change in surface area (measured by planimetry using digital photographs) over baseline of the target lesion. This sample size allows for an approximate 10% loss to follow-up at 6 weeks.

## **1.5. STUDY POPULATION**

Patients in the UK and Ireland with a clinical diagnosis of PG.

### **1.5.1. INCLUSION CRITERIA**

1. PG as diagnosed by the recruiting dermatologist (see current version of the study protocol for further details).
2. Must have a measurable ulceration (eg. not pustular pyoderma gangrenosum)
3. Age over 18 years
4. Able to provide written, informed consent.

### **1.5.2. EXCLUSION CRITERIA**

1. Granulomatous PG – this condition is very rare and may respond differently to treatment
2. Ciclosporin or prednisolone or IVIG therapy in the previous month
3. Already participating in another clinical trial
4. Pregnant, lactating or at risk of pregnancy
5. Hypersensitivity to prednisolone or ciclosporin
6. Biopsy consistent with a different diagnosis (see the study protocol for further details).
7. Clinically significant renal impairment that would result in the investigator not normally treating with either study drug
8. Any pre-treatment investigations, the results of which would prompt the investigator not to use either study drug
9. A diagnosis of malignancy or pre-malignant disease where treatments might interfere with ongoing therapy or might cause harm (eg. history of lymphoma, multipla lymphoma, leukaemia, cervical epithelial neoplasia – CIN, systemic cytotoxic therapy)
10. The patient has a concurrent medical condition that means the investigator would not normally treat the patient with either of the study drugs (see the study protocol for further details).
11. Administration of a live vaccine (BCG, Measles, Mumps, Rubella, Yellow Fever, Oral Polio, Oral Typhoid) within the last two weeks.

12. The patient is currently taking Rosuvastatin (Crestor®) for the treatment of hypercholesterolaemia, since this is contra-indicated when taking Neoral® (cyclosporin)

## **1.6. STATISTICAL ANALYSIS PLAN (SAP)**

### **1.6.1. SAP OBJECTIVES**

The objective of this SAP is to describe the statistical analyses to be carried out for the final analyses of the STOP GAP randomised controlled trial. This SAP does not cover the statistical analyses of the parallel observational cohort, nor does it cover any statistical issues arising from the Health Economics Analyses. These will be addressed in separate documents.

### **1.6.2. GENERAL PRINCIPLES**

Categorical variables will be summarised with the number and proportion of participants falling in each category. Continuous variables will be summarised using the number available, number missing, mean, standard deviation (SD), median, 25<sup>th</sup> and 75<sup>th</sup> quartiles (Q1 and Q3 respectively), minimum and maximum values.

Appropriate regression models (eg. linear, Cox, logistic), adjusting for baseline covariates, will be used to compare the treatment groups for the primary outcome, any other continuous secondary outcomes, the time to healing of the target lesion, the time to recurrence, the proportion healed at 6 weeks, and then also at the final visit..

Proportional odds models, adjusting for baseline covariates, will be used to analyse the categorical secondary outcomes, including global assessment of improvement and the inflammation assessment scale. The self reported pain and the EQ-5D score will be summarised by the area under the curve (AUC), using Generalized linear models with the appropriate distribution. Patients are required to have the data recorded at the initial time point, and at the 6 week time point (for the 6 week analyses) or the final visit (for the final visit analyses), so only patients with at least the first observation and the last observation for the self reported pain data, or those with both time points for the EQ-5D data, will be analysed in the first instance. Sensitivity analyses will be carried out for the self reported pain outcome using the 'last value carried forward' method for patients who have data recorded at least at the initial time point and the last time point and any missing interim data will use the last recorded value prior to the missing visit. Where appropriate, the secondary outcomes will be adjusted for baseline values.

The stratification variables to be included in all models are:

- the size of the lesion at randomisation as a continuous measurement using the same method of measurement at baseline as is used for the outcome and is detailed in the assumptions document.
- An indicator of the presence of underlying systemic disease at baseline.

As an additional sensitivity analysis, the following variables will also be adjusted for in an extended multivariable model for the primary outcome and the first secondary outcome (time to healing), regardless of statistical significance:

- The size of the centre, computed using a 3-level grouping of the number of patients randomised at each centre (1-2 patients, 3-4 patients and 5 or more patients)
- The age of the patient at baseline

- The sex of the patient
- The weight of the patient at baseline
- The geographical region as a substitute for environmental factors.

### **1.6.3. CURRENT PROTOCOL**

The current study protocol at the time of writing is version 4, dated 30<sup>th</sup> August 2011. Any updates to the protocol, after the approval of this version of the SAP, will be reviewed for their impact on this SAP, which will only be updated if the changes to the protocol require it. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre Change Impact Assessment processes.

### **1.6.4. SOFTWARE**

Data will be analysed using SAS for Windows v9.2 or later, or R version 2.10.1 or later.

## **2. ANALYSIS**

### **2.1. STUDY POPULATIONS**

#### **Full Analysis Set**

All randomised patients excluding those whose later diagnosis was determined to be something other than PG.

### **2.2. BASELINE CHARACTERISTICS**

Baseline characteristics will be summarised for each randomised treatment group separately and overall and compared informally, for the full analysis set. All baseline data will be obtained from the CRF's used during the baseline visit.

The following baseline characteristics will be reported:

#### Randomisation Strata

- Lesion size ( $> 20\text{cm}^2$  or  $\leq 20\text{cm}^2$ )
- Presence of Underlying systemic disease

#### Demographic and lifestyle characteristics

- Age (years), Sex
- Ethnicity
- Geographical region

#### Baseline measurements

- Weight
- Systolic Blood Pressure, Diastolic Blood Pressure

#### Current medications, medical history and other relevant conditions

- Methotrexate, Azathioprine, Leflunomide, Anti-TNF, Mercaptopurine (6-MP, Puri-Nethol®), Tetracyclines, Mycophenolate
- Other treatment that could influence pyoderma gangrenosum



- Ever been diagnosed with: Crohn's Disease; ulcerative colitis; Myeloma; Haematological malignancy; an other malignancy; Rheumatoid arthritis; other inflammatory arthritis; Monoclonal gammopathy
- Current diagnosis of: diabetes; mild renal impairment; epilepsy

#### Diagnosis of PG

- Presentation of PG
- Previous episode of PG
- Specialty referred from
- Out-patient or in-patient

#### Target lesion information

- Location of target lesion
- Number of ulcers on entire body
- Measurement of target lesion (includes maximum longitudinal length and maximum perpendicular width)
- Erythema, Border elevation, Exudate
- Digital imaging information (includes height, width, lsize and hue)
- Baseline measurement to be used for analysis of primary outcome (see separate assumptions document for details)
- Baseline measurement to be used for summarising change in area at week 6 (see separate assumptions document for details)
- Baseline measurement to be used for summarising change in area at final visit (see separate assumptions document for details)
- Baseline measurement to be used for analysis of other efficacy and safety outcomes (see separate assumptions document for details)

#### Questionnaires

- Patient questionnaire (includes: Colour, thickness of the edge of the ulcer, pus or discharge, pain)
- EQ-5D
- EQ-VAS
- Dermatology Life Quality Index (DLQI)

## 2.3. EFFICACY OUTCOMES

All efficacy outcomes will be analysed for the full analysis set. Any missing data on the primary outcome at the follow-up visits will be imputed using multiple imputation where possible, using the assumption that the data is missing at random.

### 2.3.1. PRIMARY OUTCOME

The primary outcome of the study is the velocity of healing at 6 weeks. This is captured for a single target lesion per patient and measured using digital photography and computerised planimetry<sup>1</sup>. If multiple lesions are present, the target lesion should be the lesion that is most able to be photographed on a single plane (i.e. not around the curvature of a limb) for study will be the largest of those present. Digital images will be taken at baseline, 6 weeks and when the ulcer has healed (max 6 months). In addition, maximum longitudinal length and maximum perpendicular width will be measured by the clinician in order to provide some measure of improvement in case of difficulties with the digital images. This will be converted to approximate area by the formula:

length x width x 0.785, which approximates to the area of an ellipse. This will be summarised overall and by treatment group at 6 weeks. Linear models for the velocity of healing at the 6 week follow-up visit will be fitted adjusting for the stratification variables and the treatment group. Results will be presented as a mean difference between the treatment groups and corresponding 95% confidence interval and p-value. Depending on numbers, the primary outcome will be further analysed where possible using a sensitivity analyses which includes additional baseline covariates, also detailed in the general principles section.

### **2.3.2. SECONDARY OUTCOMES**

The secondary outcomes are obtained from the list of objectives in section 1.2.2 above.

Secondary outcomes 1 (time to healing) and 6 (time to recurrence) will be analysed using Cox regression models, adjusting for the stratification variables, and the treatment group.

Secondary outcomes 2 (global assessment of improvement) and 3 (inflammation assessment scale) will be analysed using proportional odds models, adjusting for the value at baseline, stratification variables, and the treatment group.

Secondary outcome 4 (self reported pain from the patient diaries) will be analysed as the area under the curve for the average pain at each of weeks 1, through 6, using Generalized Linear Models with the appropriate distribution, adjusting for the stratification variables and the treatment group.

The change in secondary outcome 5a (dermatology life quality index score) from baseline at 6 weeks and final visit (or when the lesion healed) will be analysed using linear regression, adjusting for the baseline dermatology life quality index score, the stratification variables and treatment group.

Secondary outcome 5b (EQ-5D) will be analysed as the area under the curve from baseline to 6 weeks, from 6 weeks to the final visit, and from baseline to the final visit, using Generalized Linear Models with the appropriate distribution, adjusting for the stratification variables and treatment group.

The change in secondary outcome 5c (EQ-VAS) from baseline, at each of 6 weeks and the final visit, will be analysed using an analysis of covariance adjusting for the stratification variables, baseline EQ-VAS and treatment group.

Secondary outcome 7 (treatment failures) will be analysed using logistic regression models with the appropriate distribution, adjusting for the stratification variables and the treatment group.

The first secondary outcome (time to healing) will also be further analysed using a sensitivity analyses which includes additional baseline covariates, also detailed in the general principles section.

## **2.4. SAFETY OUTCOMES**

All safety data will be analysed for the full analysis set.

### **2.4.1. TREATMENT COMPLIANCE**

The number and percentages of patients taking their study medication as reported in the patient diary (every day, most days, some days or never) will be summarised by treatment group and overall.

#### **2.4.2. HEALTH CARE CONTACTS**

Patient contact with health care facilities will be summed, both for each individual contact (eg. GP at the surgery, GP at home) and for all potential health care facilities, using the total number of contacts with the particular facility over the 6 weeks, and also over the full study follow-up (to a maximum of 6 months). This will be summarised by treatment group and overall, and will be analysed using either a Poisson model or a Negative Binomial model, depending on the distribution of the data, and adjusted for the stratification variables and the treatment group.

#### **2.4.3. PREMATURE WITHDRAWAL**

Withdrawals from the randomised treatment will be summarised for each treatment group as an overall number of withdrawals, and also for the following reasons:

- Treatment failure (defined as treatment intolerance or worsening of the PG)
- Adverse events
- Other reason

Withdrawals will be tabulated by treatment group.

#### **2.4.4. ADVERSE EVENTS**

Adverse reactions (ARs) classed as possibly, probably or definitely relating to the study medication, Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be tabulated, both overall and by treatment group for all adverse reactions, and for the patients with at least one serious adverse reaction, and also listed, using a hierarchy coding system as noted in the appendix of the current protocol.

#### **2.4.5. DEATHS**

A listing of all deaths will be provided.

#### **2.4.6. CONCOMITANT MEDICATIONS**

Specific medications listed in the medications CRF (as note dbelow) will be summarised by treatment group and overall:

- Methotrexate
- Azathioprine
- Leflunomide
- Anti-TNF
- Mercaptopurine
- Tetracyclines
- Myxophenolate

The other medications recorded that could influence pyoderma gangrenosum will be listed along with treatment group received.

### **3. Data Conventions**

An assumptions document will be produced detailing the calculation of any derived variables.

### **4. DOCUMENT HISTORY**

This is version 1.0 of the statistical analysis plan, dated 11th June 2013.

### **5. TABLES**

#### **5.1. STUDY ANALYSIS SETS**

**Table 1.1** Number of patients randomised, withdrawn, lost to follow-up, died and completed study.

**Table 1.2** Number of patients withdrawn and reason for withdrawal.

#### **5.2. PROTOCOL VIOLATORS**

**Table 1.3** Protocol violators, as defined in the statistical assumptions document, summarised by treatment group and overall.

#### **5.3. BASELINE CHARACTERISTICS**

**Table 2.1** Randomisation strata, summarised by treatment group and overall.

**Table 2.2** Demographic and lifestyle characteristics, summarised by treatment group and overall

**Table 2.3** Baseline measurements, summarised by treatment group and overall

**Table 2.4.1** Current medications, medical history and other relevant conditions, summarised by treatment group and overall

**Table 2.4.2** Medical history and other relevant conditions, summarised by treatment group and overall

**Table 2.5** Diagnosis of PG, summarised by treatment group and overall

**Table 2.6.1** Target lesion information (number and location of ulcers), summarised by treatment group and overall

**Table 2.6.2** Target lesion information (lesion measurements), summarised by treatment group and overall

**Table 2.6.3** Target lesion information (erythema, border elevation and exudate), summarised by treatment group and overall

**Table 2.7** Ulcer Information Questionnaire, summarised by treatment group and overall

**Table 2.8** EQ-5D, EQ-VAS and Dermatology Life Quality Index Questionnaire, summarised by treatment group and overall

## 5.4. EFFICACY OUTCOMES

**Table 3.1.1** Primary outcome: velocity of healing at 6 weeks, overall and summarised by treatment group.

**Table 3.1.2** Primary outcome: velocity of healing at 6 weeks (using just the date the lesion stopped requiring dressings); analysis of covariance p-value, adjusted mean difference [ciclosporin – prednisolone] and corresponding 95% confidence interval

**Table 3.1.3** Primary outcome: velocity of healing at 6 weeks (using the date of visit if the date the lesion stopped requiring dressings is not available); analysis of covariance p-value, adjusted mean difference [ciclosporin – prednisolone] and corresponding 95% confidence interval

**Table 3.2** Secondary outcome: change in area of target lesion from baseline at 6 weeks, summarised overall and by treatment group

**Table 3.3** Secondary outcome: change in area of target lesion from baseline at final visit, summarised overall and by treatment group

**Table 3.4.1** Secondary outcome: time to healing, overall and summarised by treatment group; Cox proportional hazards model hazard ratio, 95% confidence interval and p-value, adjusted by stratification factors and baseline covariates.

**Table 3.4.2** Secondary outcome: time to healing event rates, overall and summarised by treatment group.

**Table 3.5.1** Secondary outcome: Global assessment of improvement at week 2, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted by stratification factors.

**Table 3.5.2** Secondary outcome: Patient Reported Global assessment of improvement at week 2, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.6.1** Secondary outcome: Global assessment of improvement at week 6, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.6.2** Secondary outcome: Patient Reported Global assessment of improvement at week 6, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.6.3** Secondary outcome: Digital Imaging Global assessment of improvement at week 6, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.7.1** Secondary outcome: Global assessment of improvement at final visit, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.7.2** Secondary outcome: Patient Reported Global assessment of improvement at final visit, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.7.3** Secondary outcome: Digital Imaging Global assessment of improvement at final visit, overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.8.1** Secondary outcome: Inflammation Assessment Scale (erythema) at baseline, week 2 (as recorded) and the change at week 2 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale erythema.

**Table 3.8.2** Secondary outcome: Inflammation Assessment Scale (border elevation) at baseline, week 2 (as recorded) and the change at week 2 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale border elevation.

**Table 3.8.3** Secondary outcome: Inflammation Assessment Scale (exudate) at baseline, week 2 (as recorded) and the change at week 2 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale exudate.

**Table 3.8.4** Secondary outcome: Inflammation Assessment Scale at week 2: resolution of inflammation (if both the erythema and border elevation are reduced to a score of “None”), overall and summarised by treatment group; odds ratio for the treatment effect obtained using logistic regression model, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.8.5** Secondary outcome: Inflammation Assessment Scale (colour in the patient questionnaire) at baseline, week 2 (as recorded) and the change at week 2 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale erythema.

**Table 3.8.6** Secondary outcome: Inflammation Assessment Scale (thickness in the patient questionnaire) at baseline, week 2 (as recorded) and the change at week 2 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale border elevation.

**Table 3.8.7** Secondary outcome: Inflammation Assessment Scale (pus of discharge in the patient questionnaire) at baseline, week 2 (as recorded) and the change at week 2 from baseline (recorded

as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale exudate.

**Table 3.8.8** Secondary outcome: Inflammation Assessment Scale at week 2: resolution of inflammation (if both the colour and thickness in the patient questionnaire are reduced to a score of “None”), overall and summarised by treatment group; odds ratio for the treatment effect obtained using logistic regression model, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.9.1** Secondary outcome: Inflammation Assessment Scale (erythema) at baseline, week 6 (as recorded) and the change at week 6 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale erythema.

**Table 3.9.2** Secondary outcome: Inflammation Assessment Scale (border elevation) at baseline, week 6 (as recorded) and the change at week 6 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale border elevation.

**Table 3.9.3** Secondary outcome: Inflammation Assessment Scale (exudate) at baseline, week 6 (as recorded) and the change at week 6 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale exudate.

**Table 3.9.4** Secondary outcome: Inflammation Assessment Scale at week 6: resolution of inflammation (if both the erythema and border elevation are reduced to a score of “None”), overall and summarised by treatment group; odds ratio for the treatment effect obtained using logistic regression model, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.9.5** Secondary outcome: Inflammation Assessment Scale (colour in the patient questionnaire) at baseline, week 6 (as recorded) and the change at week 6 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale erythema.

**Table 3.9.6** Secondary outcome: Inflammation Assessment Scale (thickness in the patient questionnaire) at baseline, week 6 (as recorded) and the change at week 6 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale border elevation.

**Table 3.9.7** Secondary outcome: Inflammation Assessment Scale (pus of discharge in the patient questionnaire) at baseline, week 6 (as recorded) and the change at week 6 from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale exudate.

**Table 3.9.8** Secondary outcome: Inflammation Assessment Scale at week 6: resolution of inflammation (if both the colour and thickness in the patient questionnaire are reduced to a score of “None”), overall and summarised by treatment group; odds ratio for the treatment effect obtained using logistic regression model, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.10.1** Secondary outcome: Inflammation Assessment Scale (erythema) at baseline, final visit (as recorded) and the change at final visit from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale erythema

**Table 3.10.2** Secondary outcome: Inflammation Assessment Scale (border elevation) at baseline, final visit (as recorded) and the change at final visit from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale border elevation.

**Table 3.10.3** Secondary outcome: Inflammation Assessment Scale (exudate) at baseline, final visit (as recorded) and the change at final visit from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale exudate.

**Table 3.10.4** Secondary outcome: Inflammation Assessment Scale at final visit: resolution of inflammation (if both the erythema and border elevation are reduced to a score of “None”), overall and summarised by treatment group; odds ratio for the treatment effect obtained using logistic regression model, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.10.5** Secondary outcome: Inflammation Assessment Scale (colour in the patient questionnaire) at baseline, final visit (as recorded) and the change at final visit from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale erythema

**Table 3.10.6** Secondary outcome: Inflammation Assessment Scale (thickness in the patient questionnaire) at baseline, final visit (as recorded) and the change at final visit from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale border elevation



**Table 3.10.7** Secondary outcome: Inflammation Assessment Scale (pus of discharge in the patient questionnaire) at baseline, final visit (as recorded) and the change at final visit from baseline (recorded as worse than baseline, the same as baseline or improvement on baseline), overall and summarised by treatment group; odds ratio for the treatment effect obtained using proportional odds models, corresponding 95% confidence interval and p-value, adjusted for stratification factors and baseline inflammation assessment scale exudate.

**Table 3.10.8** Secondary outcome: Inflammation Assessment Scale at final visit: resolution of inflammation (if both the colour and thickness in the patient questionnaire are reduced to a score of “None”), overall and summarised by treatment group; odds ratio for the treatment effect obtained using logistic regression model, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.11.1** Secondary outcome: Average of self reported pain at each of weeks 1 through 6, overall and summarised by treatment group.

**Table 3.11.2** Secondary outcome: Self reported pain area under the curve, overall and summarised by treatment group; initial analysis of covariance p-value, adjusted mean difference [ciclosporin – prednisolone] and corresponding 95% confidence interval.

**Table 3.12.1** Secondary outcome: Average of self reported pain at each of weeks 1 through 6 for the sensitivity analysis, overall and summarised by treatment group.

**Table 3.12.2** Secondary outcome: Self reported pain area under the curve for the sensitivity analysis, overall and summarised by treatment group; initial analysis of covariance p-value, adjusted mean difference [ciclosporin – prednisolone] and corresponding 95% confidence interval.

**Table 3.13.1** Secondary outcome: Number of days painkillers have been used in the first 6 weeks, overall and summarised by treatment group; non-parametric p-value to test the difference in the medians between groups.

**Table 3.13.2** Secondary outcome: Number of days painkillers have been used in the entire study, overall and summarised by treatment group; non-parametric p-value to test the difference in the medians between groups.

**Table 3.14.1** Secondary outcome: Baseline, 6 weeks and change in Dermatology Life Quality Index at 6 weeks, overall and summarised by treatment group; analysis of covariance estimate for the change, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.14.2** Secondary outcome: Baseline, final visit and change in Dermatology Life Quality Index at final visit, overall and summarised by treatment group; analysis of covariance estimate for the change, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.15.** Secondary outcome: EQ-5D Quality of Life score at baseline, 6 weeks and final visit and EQ-5D AUC, overall and summarised by treatment group; analysis of covariance estimate, corresponding 95% confidence interval and p-value, adjusting for stratification factors.

**Table 3.16.1** Secondary outcome: Baseline, 6 weeks and change in EQ-5D VAS at 6 weeks, overall and summarised by treatment group; analysis of covariance estimate for the change, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.16.2** Secondary outcome: Baseline, final visit and change in EQ-5D VAS at final visit, overall and summarised by treatment group; analysis of covariance estimate for the change, corresponding 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.17.1** Secondary outcome: time to recurrence, overall and summarised by treatment group; Cox proportional hazards model hazard ratio, 95% confidence interval and p-value, adjusted for stratification factors.

**Table 3.17.2** Secondary outcome: time to recurrence event rates, overall and summarised by treatment group.

**Table 3.18** Secondary outcome: Patients who are a treatment failure, overall and summarised by treatment group; Logistic regression odds ratio and 95% confidence interval and p-value, adjusted for stratification factors.

## **5.5. SAFETY**

**Table 4.1** All deaths, summarised by treatment group and overall

**Table 4.2** Treatment compliance, summarised by treatment group and overall

**Table 4.3.1** Number of Health Care contacts over the first 6 weeks, summarised by treatment group and overall; appropriate generalised linear models effect estimate for the treatment effect, 95% confidence interval and p-value, adjusted for the stratification factors.

**Table 4.3.2** Number of Health Care contacts over the full trial, summarised by treatment group and overall; appropriate generalised linear models effect estimate for the treatment effect, 95% confidence interval and p-value, adjusted for the stratification factors.

**Table 4.4** All Adverse Reactions, summarised by treatment group and overall

**Table 4.5** All patients with at least one Adverse Reaction, summarised by treatment group and overall.

**Table 4.6** All Serious Adverse Reactions, summarised by treatment group and overall.

**Table 4.7** All patients with at least one Serious Adverse Reaction, summarised by treatment group and overall.

**Table 4.8** Concomitant Medications, summarised by treatment group and overall.

## **6. FIGURES**

**Figure 5.1.1** Secondary outcome, time to healing, Kaplan-Meier curves for all patients

**Figure 5.1.2** Secondary outcome, time to healing, Kaplan-Meier curves for ciclosporin and oral prednisolone

**Figure 5.2.1** Secondary outcome, time to recurrence, Kaplan-Meier curves for all patients

**Figure 5.2.2** Secondary outcome, time to recurrence, Kaplan-Meier curves for ciclosporin and oral prednisolone

**Figure 5.3** Secondary outcome, mean self reported pain and 95% confidence intervals at each of the first 6 weeks for ciclosporin and oral prednisolone

## **7. LISTINGS**

**Listing 6.1** Listing of all protocol violation details categorised by treatment group.

**Listing 6.2** Listing of any premature withdrawals, categorised by treatment group.

**Listing 6.3** Listing of any adverse reactions, categorised by treatment group.

**Listing 6.4** Listing of any serious adverse reactions, categorised by treatment group.

**Listing 6.5** Listing of any suspected unexpected serious adverse reactions, categorised by treatment group.

**Listing 6.6** Listing of any deaths, categorised by treatment group.

## **8. REFERENCES**

Wunderlich RP, Peters EJG, Armstrong DG, Lavery LA: Reliability of digital videometry and acetate tracing in measuring the surface area of cutaneous wounds. *Diabetes Research and Clinical Practice* (2000); 29:87-92.