2 STUDY OBJECTIVES

The objectives of the study, as stated in the protocol, were to compare the efficacy, safety and tolerability of 3 dose regimens of Topical NO with placebo in patients with anogenital warts and to establish the optimal dose of Topical NO in this population of patients.

3 SUBJECTS AND METHODS

3.1 STUDY DESIGN

3.1.1 OVERALL STUDY DESIGN AND PLAN

This was a prospective, double-blind, placebo-controlled, randomised, parallel-group, multicentre study. Patients with between 2 and 50 warts in the anogenital region were randomised to treatment with Topical NO:

- Placebo – twice daily
- Dose A - 3% sodium nitrite + 4.5% citric acid twice daily (once in the morning and once in the evening)
- Dose B - 6% sodium nitrite + 9% citric acid once daily (in the evening) with placebo once daily (in the morning)
- Dose C - 6% sodium nitrite + 9% citric acid twice daily (once in the morning and once in the evening)

Randomisation was by centre and was stratified according to sex such that the ratio of male patients to female patients was similar in each of the 4 treatment groups. In order to obtain a total of 62 patients per treatment group with post-baseline assessments, the planned sample size was a total of around 300 randomised patients. Patients had all of their identified warts treated. Patients used study treatment for 12 weeks or until clearance, if sooner. Whenever possible, patients were assessed 4, 8 and 12 weeks after stopping therapy.

3.1.2 STUDY TIMING

Patients attended a Screening visit (Visit 1) up to 2 weeks before study randomisation at the Baseline Visit (Week 0, Visit 2) (see In-text Table 3). The patients were given information on the study, provided with a Patient Information Sheet and asked to sign a consent form for participation in the study. Demographic details were recorded and medical history, including wart history, taken. The Investigator conducted both a physical and anogenital examination and the patient was asked to assess the wart symptoms. Inclusion and exclusion criteria were checked and if the patient potentially met all the inclusion and none of the exclusion criteria, a urine sample was collected and a blood sample was taken for haematology and biochemistry tests. The patient was tested for concomitant STDs and, if applicable, a urine pregnancy test was performed. Vital signs were recorded. Concomitant medications were noted. The patient was asked to return within 2 weeks for the Baseline Visit.

At the Baseline Visit (Week 0, Visit 2), the Investigator reviewed the haematology and biochemistry blood results and checked the remaining inclusion and exclusion criteria. Patients that met all the inclusion and none of the exclusion criteria were allocated randomisation numbers and were randomised to one of the 4 treatment groups. Each patient was given a pre-packed treatment pack containing a morning and an evening treatment pack. Each morning and each evening treatment pack contained 2 tubes of cream, one sodium nitrite or placebo and one citric acid or placebo. The Investigator issued
a dosing instruction leaflet and explained it fully. Baseline assessments also included recording of vital signs, tolerability, concomitant medications and adverse events.

At the Baseline Visit (Week 0, Visit 2), the Investigator photographed the anogenital region of the patient. The photograph showed the position, size and appearance of the warts. The total number of warts was recorded. Up to 10 target warts representative of the patient’s disease were selected. At Baseline and subsequent visits, the diameter of each target wart was measured, the type was recorded as keratinised or haemorrhagic and the height recorded as either flat or raised. Photographs were also taken at every visit. Only baseline warts were assessed throughout the study, but the total number of warts (new and baseline) was also recorded at the final visit (Week 12, Visit 9) in the treatment phase.

The patients returned 1, 2, 4, 6, 8, 10 and 12 weeks later for assessment and medication was dispensed at 1, 2, 4, 6, 8 and 10 weeks. Global response was assessed at Week 12 (Visit 9) only. Visits 5 and 7 (Weeks 4 and 8) could be replaced by telephone assessments as long as the Investigator felt this was acceptable from a safety perspective.

Vital signs and patient and Investigator assessment of tolerability were made at each visit during the treatment phase and adverse events and concomitant treatments were recorded throughout this phase.

Pregnancy tests, where applicable, were repeated at Weeks 2, 6, 10 and 12 (Visits 4, 6, 8 and 9). Haematology and biochemistry tests and urine dipstick tests were repeated on samples taken at Week 12 (Visit 9); there was also a physical examination at this visit.

Wherever possible, all patients were followed up for a 12-week period after stopping treatment. There were 3 follow-up visits: at 4, 8 and 12 weeks after end of treatment. Those who received other therapy for their anogenital warts were withdrawn from the study and did not enter follow-up. The aim of the follow-up period was to assess improvement or recurrence after ceasing treatment (if clearance was achieved during treatment). Total number of warts, a photographic clinical assessment of the number of warts, a measurement of the warts and their diameter and a concomitant medication check was carried out at all visits. Adverse events that were not resolved at the end of treatment were also followed up.

In-text Table 3 shows the timing of the study assessments for both the treatment and follow-up phases of the study.
### In-text Table 1: Timing of Study Assessments

<table>
<thead>
<tr>
<th>Visit</th>
<th>1/Scr</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5†</th>
<th>6</th>
<th>7†</th>
<th>8</th>
<th>9</th>
<th>4, 8 and 12 of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks (+/- 3 days)</td>
<td>-2 (max)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12*</td>
<td>4, 8 and 12 of follow-up</td>
</tr>
<tr>
<td>Patient information/informed consent</td>
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<td></td>
<td></td>
<td></td>
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<td>Inclusion/exclusion criteria</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Demography</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Medical history</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Anogenital examination</td>
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<td></td>
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<td></td>
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<tr>
<td>Wart history</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient assessment of wart symptoms</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematology/biochemistry</td>
<td>X</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Examination/samples for concomitant STD</td>
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<td></td>
<td></td>
<td></td>
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</tr>
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<td>Urine dipstick</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wart number/area/type/size</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Local examination by Investigator</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator assessment of total number of warts (new and baseline)</td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient and Investigator assessment of global response</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient assessment of tolerability</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense study medication</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* or at time of premature withdrawal if the patient withdrew
† visit could be changed to telephone assessment as long as acceptable from a safety perspective

#### 3.1.3 STUDY LOCATION

The study was conducted at centres in Germany, The Netherlands, Poland, the United Kingdom and Sweden. Patients were screened at 40 centres in total: 19 in Germany, 9 in The Netherlands, 5 in Poland, 4 in the United Kingdom and 3 in Sweden. A further 12 centres (9 in Germany, 2 in the United Kingdom and one in The Netherlands) were initiated but did not screen any patients (see Section 17.1.4).

#### 3.1.4 PROTOCOL AMENDMENTS

The final protocol dated 26 June 2001 was amended twice.

Protocol Amendment 1, dated 25 October 2001, added one additional non-barrier method of contraception for women (depot injection), described the Medication Reference Number, noted that Regulatory Affairs Manager (not the independent Medical Advisor) would hold decode envelopes and deleted the sentence describing the breaking of the code by the Medical Advisor, stated that the medical history of the patient was to cover chronic diseases and significant illnesses and added total protein, albumin, calculated globulin and GGT to the biochemistry screen. The selection of up to 10 representative warts by the Investigator,
which had to be measured and described as flat or raised with wart type was added. One of
the withdrawal criteria was modified to read ‘lost to follow-up or missed two or more visits
during the study period’. There were also several clarifications and corrections to the text.
Details are provided in Section 9.8.1 of this report.

Protocol Amendment 2, dated 7 May 2002, revised several exclusion criteria such that
patients who had used medication known to adversely affect their haematology profile,
patients who were known to have a concomitant STD that inhibited accurate assessment of
the warts, or who required treatment other than surgery or laser for internal warts were
excluded. The exclusion criterion that excluded males with intra-urethral warts was deleted.
Patients with recalcitrant warts were allowed to enter the study provided that they also had
non-recalcitrant warts, that the recalcitrant warts were not counted as target warts and that
they did not count towards the 2-50 warts inclusion criterion. The Investigator assessment of
the total number of warts (new and baseline) was added as a secondary endpoint in all
relevant sections. It was added that biochemistry and haematology tests could be
performed at a central laboratory (in addition to the local laboratory). ‘Calculated globulin’
was removed from the list of specified tests. There were also several clarifications and
corrections to the text. Details are provided in Section 9.8.1.

The methods described in this report reflect the changes incorporated by the amendments.

3.2 DISCUSSION OF STUDY DESIGN

Anogenital warts can resolve spontaneously without treatment, although in most cases
active treatment is required to clear the infection and to prevent the infection spreading. A
double-blind, placebo-controlled design was chosen so that effects of Topical NO could be
differentiated from those improvements – and deteriorations – that can occur naturally.
Recurrence rates are high (4) and so a treatment-free follow-up period was incorporated into
the study design to assess the effects of prior treatment on recurrence. The study was
stratified according to sex as it was known that women with anogenital warts respond
significantly better to topical treatment with imiquimod than men (4, 18). A better response
rate in women than men has also occasionally been found with topical podophyllotoxin (19).

3.3 STUDY POPULATION

3.3.1 NUMBER OF PATIENTS

The planned number of randomised patients was 300 in total, such that 62 patients per
treatment group would provide post-baseline data. The number of patients to be
randomised was based upon a sample size calculation (see Section 3.7.2). A sample size of
62 patients per treatment group had 80% power to demonstrate a statistically significant
difference at an alpha of 0.05 between clearance rates of 40% and 15% in patients treated
with active and placebo creams, respectively.

3.3.2 SELECTION CRITERIA

Patients satisfying the following selection criteria were eligible for the study. (Note that the
identification letters and order of the selection criteria are those shown in the protocol and
amendments; the protocol and CRF differed in this respect. (A full explanation of the
differences appear in Section 9.8.2.1). Furthermore, the selection criteria in the protocol
were modified by protocol amendments.)

3.3.2.1 Inclusion Criteria

(a) Males and females ≥ 18 years of age.
(b) Presence of between 2 and 50 warts in the anogenital region.
(c) Female patients of child-bearing potential willing to use a non-barrier method of contraception (combined oral contraceptive pill, IUD, surgical sterilisation, depot injection) at study entry and for the duration of the study. ['Depot injection' was added by Protocol Amendment 1, 25 October 2001.]

(d) Male and female patients willing to use barrier protection for the duration of the study to prevent internal exposure to Topical NO.

(e) Patients able to comply with the requirements of the protocol and likely to return for follow-up visits.

(f) Patients contactable for the duration of the study (address or telephone number that they could be contacted on), if required.

(g) Patients who had given written (and where required witnessed) informed consent having read and understood the Patient Information Sheet.

3.3.2.2 Exclusion Criteria

(a) Patients with clinically relevant abnormal haematology or biochemistry results (determined from the sample taken at Visit 1).

(b) Patients who had used an active therapy for anogenital warts within 2 weeks of randomisation to study drug, i.e. Visit 2.

(c) Patients who had used any local supportive medication, including topical corticosteroids or beta-interferon, within 2 weeks of study entry.

(d) Patients who had used medication known to adversely affect their haematology profile, including local anaesthetics (benzocaine, lidocaine, etc), nitrofurantoin, sulphonylureas and sulphonamides within 2 weeks of study entry. [Word ‘adversely’ added by Protocol Amendment 2, 7 May 2002.]

(e) Patients with abnormal anogenital skin, such as eczema, or skin that had not healed following surgery (cryosurgery, laser ablation or similar).

(f) Patients who were known to have a concomitant STD that inhibited accurate assessment of their warts. [Changed from ‘Patients with concomitant STD, unless the STD was treated successfully prior to randomisation (Week 0)’ by Protocol Amendment 2, 7 May 2002.]

(g) Patients who required treatment other than surgery or laser for internal warts. [Changed from ‘Female patients who required treatment for intra-vaginal warts’ by Protocol Amendment 2, 7 May 2002.]

(h) Male patients with intra-urethral warts [deleted by Protocol Amendment 2, 7 May 2002].

(i) Patients with diabetes (Type I or Type II diabetes).

(j) Patients who were known to be HIV-positive.

(k) Patients who were known to be immunosuppressed and/or using immunosuppressive therapies.

(l) Patients known to abuse alcohol and/or drugs or with a history of chronic alcohol or drug abuse.

(m) Patients with recalcitrant warts (warts still present despite 6 months therapy with a licensed medication, laser or surgical treatment). Patients who had both recalcitrant and non-recalcitrant warts could be entered provided the recalcitrant wart(s) were not counted as target warts and did not count towards the 2-50 inclusion criterion. [Changed from ‘Patients who had had anogenital warts present for more than 6 months, unless they had not had any active treatment for their anogenital warts’ by Protocol Amendment 2, 7 May 2002.]
Patients with an individual anogenital wart more than 15 mm in diameter. [Changed from ‘1.5 cm’ by Protocol Amendment 2, 7 May 2002.]

Female patients who were pregnant (confirmed by a urine pregnancy test) or lactating.

Patients who had received another investigational drug within 2 months of randomisation to study drug.

Any other reason that the Investigator felt would preclude safe inclusion of the patient.

### 3.3.3 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were withdrawn from the study for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up, or missed 2 or more visits during the study period [changed from ‘lost to follow-up for 2 or more consecutive visits during the study period’ by Protocol Amendment 1, 25 October 2001]
- Significant protocol violation
- Non-compliance with the study protocol
- Non-compliance to treatment, defined as a patient missing 6 or more consecutive dose applications
- Becoming pregnant during the study
- Significant worsening of the anogenital warts such that alternative therapy was required
- Treatment for anogenital warts in addition to the study medication
- A severe or serious adverse event that in the opinion of the Investigator required discontinuation of treatment and withdrawal.

The reason for withdrawal could also be given as ‘other’ and an explanation provided.

Patients were informed that they were free to withdraw from the study at any time and for any reason. In addition, the Investigator could remove a patient from the study if, in the Investigators’ opinion, it was not in the best medical interest of the patient to continue the study.

The date the patient was withdrawn from the study and the reason for withdrawal were recorded on the CRF. Patients who withdrew from the study were not to be replaced.

### 3.4 STUDY TREATMENTS

#### 3.4.1 TREATMENTS ADMINISTERED

Each patient received one of 4 treatments:

<table>
<thead>
<tr>
<th>Dose</th>
<th>a.m. (morning)</th>
<th>p.m. (evening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo sodium nitrite + Placebo citric acid</td>
<td>Placebo sodium nitrite + Placebo citric acid</td>
</tr>
<tr>
<td>Dose A</td>
<td>3% sodium nitrite + 4.5% citric acid</td>
<td>3% sodium nitrite + 4.5% citric acid</td>
</tr>
<tr>
<td>Dose B</td>
<td>Placebo sodium nitrite + Placebo citric acid</td>
<td>6% sodium nitrite + 9% citric acid</td>
</tr>
<tr>
<td>Dose C</td>
<td>6% sodium nitrite + 9% citric acid</td>
<td>6% sodium nitrite + 9% citric acid</td>
</tr>
</tbody>
</table>
Treatments were applied topically twice daily for up to 12 weeks, as described in Section 9.4.6.

3.4.2 DESCRIPTION OF INVESTIGATIONAL PRODUCTS

All concentrations of sodium nitrite creams, citric acid creams and matching placebo creams for this study were manufactured under Good Manufacturing Practice by the contract manufacturer Hermal Kurt Herrmann GmbH & Co, Scholtzstrasse 3, D-21465 Reinbek, Germany, on behalf of the Sponsor. Sodium nitrite cream, citric acid cream and matching placebo creams were packed in HDPE tubes containing 10 g of cream.

In order to maintain the double-blind, the tubes containing sodium nitrite or matching placebo creams were labelled ‘Cream A’ and the tubes containing citric acid or matching placebo creams were labelled ‘Cream B’. Outer boxes were provided labelled ‘am’ and ‘pm’. The tubes were also labelled with ‘am’ or ‘pm’. The label on each tube included the following information (translated into the local language, as appropriate):

- Name of the Sponsor
- Medication reference number
- Visit number (Visit 2, 3, 4, 5, 6, 7 and 8)
- Directions for use
- The wording ‘for the treatment of anogenital warts’
- The wording ‘for clinical trial use only’
- The wording ‘for external use only’
- The expiry date
- The storage conditions
- The wording ‘keep out of reach of children’
- The wording ‘avoid contact with the eyes, nose or mouth’.

(See Section 16.1.7 for an example label.)

Two Cream A tubes (one ‘am’ and one ‘pm’) and 2 Cream B tubes (one ‘am’ and one ‘pm’) were placed in individual boxes labelled ‘am’ and ‘pm’. These boxes were placed in another box (‘Treatment Pack’). Each tube contained 10 g of cream. The box had a 2-part (tear-off) label on the outside containing the same information as the tube label. On dispensing the Treatment Pack to the patient, one of the labels was removed and attached to a ‘Dispensing Record Form’ in the Pharmacy File (i.e. a file containing dispensing documents). The other label remained on the pack. The pharmacist (or delegate) was responsible for maintaining a full record of the number of packs dispensed and the date they were dispensed.

Batch numbers and brief descriptions of the supplies are shown in In-text Table 4. (Copies of supporting Certificates of Analysis, provided by Hermal Kurt Herrmann GmbH & Co., are given in Section 17.1.6.)

<table>
<thead>
<tr>
<th>Cream Description</th>
<th>Batch number</th>
<th>Manufacturing date</th>
<th>Expiry date</th>
<th>Description</th>
<th>Odour</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% sodium nitrite</td>
<td>144191</td>
<td>1 Nov 2001</td>
<td>30 Nov 2003</td>
<td>Smooth soft yellow cream</td>
<td>Odourless to faint characteristic</td>
</tr>
<tr>
<td>6% sodium nitrite</td>
<td>144192</td>
<td>1 Nov 2001</td>
<td>30 Nov 2003</td>
<td>Smooth soft yellow cream</td>
<td>Odourless to faint characteristic</td>
</tr>
<tr>
<td>Placebo sodium nitrite</td>
<td>144211</td>
<td>29 Oct 2001</td>
<td>30 Nov 2003</td>
<td>Smooth soft yellow cream</td>
<td>Odourless to faint characteristic</td>
</tr>
<tr>
<td>4.5% citric acid</td>
<td>144193</td>
<td>31 Oct 2001</td>
<td>30 Nov 2003</td>
<td>Smooth soft white cream</td>
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<td>9% citric acid</td>
<td>144194</td>
<td>1 Nov 2001</td>
<td>30 Nov 2003</td>
<td>Smooth soft</td>
<td>Odourless to faint characteristic</td>
</tr>
</tbody>
</table>
3.4.3 BLINDING

The active and placebo citric acid creams were the same in appearance and odour, as were the active and placebo sodium nitrite creams. The double-blind was maintained by identical packaging and labelling of active and placebo creams.

Sealed randomisation codes for each patient were provided to the Investigator at each centre and to the Origin Regulatory Affairs Manager (2 copies). The code could be broken by the Investigator or the Regulatory Affairs Manager for reasons of safety or emergency. If the code was broken, the date and time of opening the code had to be recorded on the CRF.

The Origin Regulatory Affairs Manager was appointed to unblind unexpected serious adverse events and was provided with a full set of randomisation envelopes. If a serious adverse event occurred and the Medical Advisor determined that the event was unexpected and should therefore be reported, the envelope was opened for that specific patient and the date and time recorded. If the patient was on active medication, the serious adverse event was reported to the appropriate regulatory authority and to each ethics committee.

Responsibility for reporting serious adverse events was transferred to the Sponsor half-way through the study.

3.4.4 SELECTION OF DOSES IN THE STUDY

Studies have shown that Topical NO is effective in patients with recalcitrant warts (14), children with molluscum contagiosum (15) and patients with tinea pedia (13). However, these studies used Topical NO formulations containing different concentrations of nitrite and different acids from those used in this study. For example, salicylic acid was combined with sodium nitrite, which may be more irritant than the citric acid formulation used in this study.

In 2 previous Phase I dermal tolerance studies, Topical NO was applied twice daily to large areas of normal anogenital skin of healthy subjects (16). In the first study, no effects were seen with the 3% sodium nitrite + 4.5% citric acid or the 6% sodium nitrite + 9% citric acid. Treatment at a dose of 9% sodium nitrite + 13.5% citric acid was found to cause irritation at some dosing sites within 3 days. A second study investigated 6% sodium nitrite + 9% citric acid applied twice daily for up to 23 days. Minor irritation was observed in some subjects, but not to a degree that would prevent use of this dose concentration in patients with anogenital warts.

As the combinations of 3% sodium nitrite + 4.5% citric acid and 6% sodium nitrite + 9% citric acid creams were well tolerated by normal anogenital skin of men and women, it was justifiable to use these creams for treatment of patients with anogenital warts in this study. The use of 3 different dose regimens allowed the efficacy and tolerability of different strengths and frequency of application, to be ascertained.

3.4.5 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

Patients who met all the inclusion and none of the exclusion criteria were randomised to treatment. Randomisation to treatment was stratified by sex. Numbered medication supplies were distributed to participating centres in block sizes of 4 for each sex. (Each of the 4 treatments appeared once per block of 4 in a random order.) Patients were randomised to one of the 4 treatment groups by receiving the next numbered medication supply as appropriate from the randomisation list for men or women. Each patient therefore had a unique medication reference number but was identified throughout the study by CRF number.
Medication reference numbers were in the ranges M501 to M802 for male patients and F701 to F981 for female patients.

### 3.4.6 SELECTION AND TIMING OF DOSE FOR INDIVIDUAL SUBJECTS

Patients were dispensed a Treatment Pack at the Baseline Visit and each subsequent visit until Visit 9 (Week 12). Patients were instructed to return all used and unused tubes at the next scheduled visit.

Patients were instructed to apply the creams twice daily, every 12 hours, to individual warts. Dosing guidelines provided to the patient detailed the amount of cream to be applied. Investigators gave a demonstration (using the placebo demonstration creams) of the amount of cream from each tube to be applied, which was equal to the spot shown below:

![Spot Illustration](image)

The tip of the patient's finger was covered with a finger cot. Patients were instructed to squeeze out a small amount of cream from the tube containing Cream A. This procedure was repeated with Cream B, using a fresh finger cot. The patient mixed the 2 creams together at the site of infection (to initiate the reaction between the nitrite and the acid). Finger cots were to be disposed of after each application. Treatment of unaffected areas was avoided. Where possible, treatment was applied to cleaned and dried skin.

At the Baseline Visit, patients were given a dosing leaflet in their native language. The leaflet was explained fully by the Investigator. Patients were asked not to apply the cream within a 3-hour period before a clinic visit.

Patients did not stop treating an infected area until the Investigator had confirmed it was 'clear' at a clinic visit. If the patient thought clearance had occurred between visits, a clinic appointment had to be made in order for the Investigator to confirm this.

If the Investigator felt it was appropriate, the patient could miss a treatment dose and still continue in the study; however, if a patient missed 3 consecutive days of treatment i.e. 6 consecutive doses the patient had to be withdrawn.

### 3.4.7 PRIOR AND CONCOMITANT THERAPY

Patients who had used active therapy for their anogenital warts within 2 weeks of randomisation to study drug could not enter the study. Those patients who had used medication known to adversely affect their haematology profile, including local anaesthetics, nitrofurantoin, sulphonylureas and sulphonamides, within 2 weeks of randomisation were also excluded. Patients also could not have received any other investigational drug within 2 months of randomisation.

Patients were told not to apply any other topical treatments to their warts or receive any other treatment (including cryotherapy or any other form of surgical removal/therapy) for their anogenital warts during the treatment phase of the study. Patients who did receive other therapy for their anogenital warts had to be withdrawn from the study, both during treatment and follow-up phase.

The dosing leaflet instructed patients to avoid sexual contact while the cream was on the skin. They were also instructed to avoid shaving, waxing or using depilatory products around the affected area during the study. In the dosing guidelines for men, the male patients were also provided with instructions in daily foreskin hygiene for the duration of the study.

Patients were required to use barrier protection for the duration of the study to prevent their sexual partners being exposed to Topical NO.
3.4.8 COMPLIANCE

Investigators were asked to determine whether patients had been fully compliant since the previous visit. The assessment was subjective, not objective, as the patients did not keep diary cards recording such information. The Investigator answered ‘Yes’ or ‘No’ to the question ‘In your opinion, has the patient been compliant since the previous visit?’ posed in the CRF. If the answer was no, a comment was made on the CRF. Patients who had missed 6 or more consecutive dose applications had to be withdrawn.

3.4.9 TOTAL EXPOSURE

Maximal exposure to treatment was estimated by collecting and weighing all used and unused tubes from each patient at the end of the study.

It should be noted that the individual tubes for each patient were not weighed before use and the estimates of amount of cream used were based upon the mean weight of 8 representative sealed tubes of 14.3 g.

3.5 STUDY ASSESSMENTS

3.5.1 PHARMACODYNAMIC/EFFICACY ASSESSMENTS

3.5.1.1 Wart Examinations

At Screening, the Investigator performed an anogenital examination. The patient could not be included in the study if the anogenital skin was abnormal, such as presence of eczema, or skin that had not healed following surgery (such as cryotherapy or laser ablation). A medical history of anogenital warts was taken. This history included the number of previous infections, the duration of the current infection, treatments taken and dates when treatments for the current infection were stopped.

At the Baseline Visit, the Investigator photographed the anogenital region of the patient. The photograph(s) showed the position, size and appearance of warts. At subsequent visits, new photographs were taken to track the clearance of baseline warts. New warts could appear during the course of the study but only baseline warts were assessed.

At Baseline, the number of warts was recorded and at subsequent visits, the number of remaining baseline warts was noted. At the final visit in the treatment phase, the total number of warts (new and baseline) was also recorded.

At Baseline, the Investigator selected up to 10 representative target warts. It was the intention that all warts would be measured if the patient presented with 10 warts or fewer and that 10 warts would be identified as target warts in those patients who presented with more than 10 warts. In practice, however, it was agreed that the number of target warts selected would be at the discretion of the investigator as atypical warts were not to be included as target warts. At this and subsequent visits, the diameter of each target wart was measured and the height was recorded as either ‘flat’ or ‘raised’. Target warts were also described as keratinised (yes/no) or haemorrhagic (yes/no), as appropriate.

Only target warts were included in the statistical analysis of the proportion of patients with wart clearance.

3.5.1.2 Global Response as Assessed by the Patient

At Week 12 (Visit 9) (or at the time of premature withdrawal), the patient was asked to assess the response to treatment on the following scale:

1 = Complete clearance
2 = Significant improvement
3 = Partial improvement
4 = No change
5 = Worsening

3.5.1.3 Global Response as Assessed by the Investigator

At Week 12 (Visit 9) (or at the time of premature withdrawal), the Investigator assessed the response to treatment on the same scale as the patient:
1 = Complete clearance
2 = Significant improvement
3 = Partial improvement
4 = No change
5 = Worsening

3.5.1.4 Primary Efficacy Variable

The primary efficacy variable was the proportion of patients with complete clearance of their target warts during treatment in the Intent-to-Treat (ITT) population. This primary efficacy variable was defined in the Data Analysis Plan; the protocol defined the primary efficacy variable as the proportion of patients with complete clearance of their baseline warts in the ITT population.

3.5.1.5 Appropriateness of Efficacy Parameters

A count of the number of baseline warts is an appropriate objective measure of efficacy. As warts can appear over a period of time, it was appropriate to distinguish between baseline and new warts developing during treatment. The primary endpoint, complete clearance (of target warts), was the aim of treatment.

3.5.2 SAFETY ASSESSMENTS

3.5.2.1 Local Tolerability as Assessed by the Patient

At Visit 1 (Screening), the patient was asked to assess the level of itching, pain and burning at the site of the warts on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) as these could be symptoms of the disease. At Visit 3 (Week 1) and at each subsequent visit up to Visit 9 (Week 12), the patient was asked to assess any increases in the level of itching, pain and burning at the site of application. The protocol stated that any scores could be recorded as adverse events. The CRF stated that any increase in the level of itching and/or pain and/or burning since the last visit had to be recorded as an adverse event.

3.5.2.2 Local Tolerability as Assessed by the Investigator

In order to assess any evidence of irritation, the Investigator assessed the site of application and surrounding skin for erythema, eschar and oedema, using modified Draize scales (described below) at each visit from Week 0 (Visit 2) onwards (20). The presence of staining at the site of application (yes/no) was also noted from Week 1 (Visit 3) onwards. The protocol stated that any scores for erythema/eschar and oedema could also be recorded as adverse events. However, the CRF stated that any increases in scores for either erythema/eschar or oedema since the last visit or staining at the application site had to be recorded as adverse events.

**Modified Draize Scales (20)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Erythema/eschar</th>
<th>Oedema</th>
</tr>
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<tbody>
<tr>
<td></td>
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</table>
0  No erythema                          No oedema
1  Very slight erythema (barely perceptible)  Very slight oedema (barely perceptible)
2  Well defined erythema            Slight oedema (edges of area well defined by definite raising)
3  Moderate to severe erythema      Moderate oedema (raised approximately 1 mm)
4  Severe erythema (beet redness) to slight eschar formation (injuries in depth) Severe oedema (raised more than 1 mm and extending beyond area of exposure)

3.5.2.3 Adverse Events

All adverse events that occurred (whether treatment-related or not) had to be recorded at each visit, for the duration of the study. The site of adverse events was also recorded and was classed as local (i.e. local to the site of application), systemic or ‘other’.

As far as possible, each adverse event had to be described by its duration (start and end dates or ongoing), its frequency (single episode, intermittent, continuous), its severity (mild, moderate, severe), an assessment of its cause (the underlying study indication, coexisting disease, concomitant medication, the study medication, or other cause), its relationship to study medication (unrelated, unlikely, possible, probable, definite), whether this influenced the course of study medication and whether it required specific action or therapy.

It should be noted that complete concordance between the tolerability assessments and adverse event reports was not anticipated and does not occur. The tolerability assessment can be regarded as a ‘snapshot’ of the patient at the time of the assessment, whereas adverse events could be recorded as beginning and ending at any time during the study. Although increases in tolerability assessment scores from the previous visits were also recorded as adverse events, adverse event reports relating to symptoms were not necessarily noted in the tolerability assessment.

It should also be noted that erythema/eschar and oedema were rated by the Investigator on modified Draize scales (from 0 to 4) and itching, pain and burning by the patient on a scale of 0 to 3 (none to severe). When one of these tolerability parameters was also recorded as an adverse event, the severity given was that of the adverse event and not the severity of the symptom.

The protocol noted that due to the vasodilatory properties of the cream a certain degree of erythema was expected shortly after application. This was taken into account when adverse events were assessed.

The protocol gave the following definitions of severity:

Mild Symptom barely noticeable to patient; did not influence performance or functioning. Prescription drug not normally needed for relief of symptom but could be given because of personality of patient.

Moderate Symptom of sufficient severity to make the patient uncomfortable; performance of daily activities influenced; subject was able to continue in the study; treatment for the symptom could be needed.

Severe Symptom caused severe discomfort. Could be of such severity that the patient could not continue; severity could cause cessation of treatment with the test drug; treatment of the symptom could be given and/or the patient hospitalised.

All adverse events had to be rated with respect to their causal relationship to the study medication according to the following categories:
Not related  This category applied to those adverse events which, after careful consideration, were clearly and incontrovertibly due to extraneous causes (disease, environment etc.).

Unlikely  In general, this category could be considered applicable to those adverse events which, after careful medical consideration at the time they were evaluated, were judged to be unrelated to the test drug. An adverse experience could be considered unlikely related if 2 or more of the following applied:

- It did not follow a reasonable temporal sequence from administration of the study medication.
- It could readily have been produced by the patient’s clinical state, environment or toxic factors, or other modes of therapy administered to the patient.
- It did not follow a known pattern of response to the study medication.
- It did not reappear or worsen when the study drug was re-administered.

Possibly  This category applied to those adverse events which, after careful medical consideration at the time they were evaluated, a connection with the study medication appeared unlikely but could not be ruled out with certainty. An adverse event could be considered possibly related if 2 or more of the following applied:

- It followed a reasonable temporal sequence from administration of the study medication.
- It could not readily have been produced by the patient’s clinical state, environment or toxic factors, or other modes of therapy administered to the subject.
- It followed a known pattern of response to the study medication.

Probably  This category applied to those adverse events which, after careful medical consideration at the time they were evaluated, were felt with a high degree of certainty to be related to the study medication. An adverse event could be considered probably related if 3 or more of the following applied:

- It followed a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It disappeared or decreased on cessation or reduction of dose. There were important exceptions when an adverse event did not disappear upon discontinuation of the drug, yet drug-relatedness clearly existed. (For example, bone marrow depression, fixed drug eruptions, tardive dyskinesia.)
- It followed a known pattern of response to the study medication.

Definitely  This category applied to those adverse events which the Investigator felt were incontrovertibly related to the study medication. An adverse event could be assigned as definitely related if all the following applied:
It followed a reasonable temporal sequence from administration of the study medication.
It could not be reasonably explained by the known characteristics of the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
It disappeared or decreased on cessation or reduction in dose and recurred with re-exposure to drug. (Note: this was not to be construed as requiring re-exposure of the patient, however, a category of definitely related could only be used when recurrence was observed.)
It followed a known pattern of response to the test drug.

A serious adverse event (SAE) was defined in the protocol as one of the following:

- An event causing the death of the patient
- A life-threatening* event
- An event causing hospitalisation** or prolongation of existing hospitalisation
- An event causing significant disability or incapacity
- An event causing congenital abnormality, birth defect in the offspring of a woman treated before or during pregnancy.

* The term “life-threatening” in the definition of “serious” referred to an event in which the patient was at risk of death at the time of the event; it did not refer to an event which hypothetically might have caused death if it were more severe.

** Elective surgery was not classed as a serious adverse event.

The following events also had to be considered as serious:

- Pregnancy
- Important medical events (they were not immediately life-threatening or did not result in death or hospitalisation but required urgent and intensive intervention to prevent one of the other outcomes listed in the definition above; for example, intensive treatment at home or in an emergency room for bronchospasm, convulsion).

All serious adverse events, occurring during the study or within 15 days following the completion of the study by the patient, had to be reported to the Project Manager. The serious adverse event had to be reported within 24 hours even if it did not appear to be drug-related. The regulatory authorities were informed as appropriate.

3.5.2.4 Laboratory Tests

Laboratory tests could be performed locally or at a central laboratory. A number of centres in Germany used the central laboratory but all others used local facilities. The laboratories used are identified in Appendix 17.1.9.

The tests specified in the protocol are shown below.

Biochemistry
At Screening and at Week 12 (Visit 9) (or at the time of premature withdrawal), 2 ml of blood was taken for measurement of creatinine, ALT, AST, total bilirubin, total protein, albumin, GGT, alkaline phosphatase, total cholesterol, HDL, LDL and triglycerides.

Haematology
At Screening and at Week 12 (Visit 9) (or at the time of premature withdrawal), 2 ml of blood was taken for measurement of haemoglobin, haematocrit, white blood cells and full differential, platelet count, red cell count, mean cell volume and mean cell haemoglobin units.

**Urinalysis**

At Screening and at Week 12 (Visit 9) (or at or at the time of premature withdrawal from the study), a urine sample was taken for measurement of glucose, ketones, blood, protein, nitrate and leukocytes. The centres in Poland used the local laboratory for urinalysis but all other centres used dipsticks. If there was a trace or positive result on the dipstick, a sample was sent to the laboratory for quantitative testing.

**Pregnancy Test**

At Screening and at 4-week intervals thereafter, all women of child-bearing potential had a pregnancy test.

3.5.2.5 **Vital Signs**

After the patient had been seated for 5 minutes, heart rate (measured as pulse rate in beats per minute) and diastolic and systolic blood pressure (mmHg) were measured using a sphygmomanometer at every visit, including Week 12 (Visit 9) (or at the time of premature withdrawal from the study).

3.5.2.6 **Physical Examination**

A full physical examination was carried out at Screening and at Week 12 (Visit 9) (or at the time of premature withdrawal from the study). It included observation of the patient’s general appearance and an examination of the skin, neck, eyes, ears, nose, throat, lungs, breasts, heart, abdomen, back, lymph nodes and neurological condition. Any newly occurring or worsening condition or disability or a worsening of a condition observed at visits was recorded as an adverse event.

3.6 **DATA QUALITY ASSURANCE**

3.6.1 **INVESTIGATOR AND MONITOR TRAINING**

Before the study began, 2 training sessions were held: one for the Study Monitors and one for the Investigators. The purpose of these sessions was to familiarise both Monitors and Investigators with the study assessments and procedures so as to increase consistency both between and within centres.

The session for Study Monitors was held on 23 August 2001 at The Renaissance Hotel, Amsterdam, The Netherlands. The topics that were covered were the protocol and SAE reporting, the primary efficacy parameter, monitoring, the CRF, SOPs, responsibilities and timelines and randomisation and supplies.

The meeting for Investigators was held on 24 August 2001 at The Renaissance Hotel, Amsterdam, The Netherlands. The topics covered were the product and the Topical NO study programme, the protocol and SAE reporting, the primary efficacy parameter, ICH GCP, the CRF and randomisation and supplies. In addition, there was a group exercise and a practical session covering use of the camera and demonstration of the creams, dosing and application technique. Additional training of the Investigators took place on 21 June 2002 at the Courtyard Marriott, Frankfurt, Germany.

Additional training of the monitors took place on 17 April 2001 at Taplow House Hotel, near Maidenhead, UK, on 21 June 2002 at the Courtyard Marriott, Frankfurt, Germany and for 2 new CRAs on 25 June 2002 in Poland.
3.6.2 SITE AUDITS

Strakan-appointed auditors, Qualogy Ltd, conducted a Facilities audit of Hartington Statistics and Data Management Ltd on 28 February 2002 and a Facilities audit of Origin Pharmaceutical Services Ltd (UK) on 5 July 2001. Two Trial Master File and Project Management audits were conducted by Qualogy Ltd during the study: Origin Pharmaceutical Services Ltd (UK) was audited on 12-13 March 2002 and PharmaScope (The Netherlands) was audited on 5 April 2002.

Three site audits were performed during the study. Qualogy audited Centre 4 (Dr Bönninghoff, Bockum, Germany) on 11 April 2002 and File-Away Ltd audited Centre 62 (Prof Majewski, Warsaw, Poland) on 18 November 2002 and Centre 64 (Prof Opala, Poznań, Poland) on 19 November 2002. The audits were independent of and separate from routine monitoring or quality control audits.

The audits assessed the conduct of the trial, the site facilities, adverse event reporting, archiving, clinical supplies, data handling, Ethics Committee approval, Informed Consent, compliance with the study protocol and GCP, randomisation and blinding and trial file maintenance. In addition, discussions were held with the staff involved in the conduct of the trial: the involvement of and knowledge of the trial of the Investigator, Co-investigator and CRA were ascertained. Audit certificates are provided in Section 17.1.7.

3.6.3 DATABASE AUDITS

QC audits of the database were performed by the following personnel at Hartington and were completed on 20 December 2002.

Merlyn Woon Soong (Clinical Data Monitor)
Rohit Nogan (Industrial Placement Student)
Kajal Pancholi (Industrial Placement Student)

Overall responsibility for the QC check of the data resided with Cynthia Haliburn (Managing Director of Hartington Statistics and Data Management).

All 299 patients randomised into the study received a 100% QC check of key safety and efficacy data; this was performed by comparing the CRF against a printout of key data held on the database and the database audit trail.

The key data checked were as follows:

a) Inclusion / Exclusion Criteria
b) Patient Details
c) General History of Anogenital Warts
d) Anogenital Examination
e) Wart Details
f) Patient Assessment of Warts and Local Examination
g) Global Response/Compliance/Dispensed Study Medication
h) End of Study
i) Adverse Events (including Adverse Events between Screening and Baseline)

All errors found were corrected on the database.

Following this, 39 patients were randomly selected from the study. These patients received 100% QC check of all data by comparison of the CRF with the database and DCRs. All errors found were corrected. The database error rate was <0.2% (4/3900 = 0.1%) for numeric data and <0.5% (8/7000 = 0.1%) for text data (which are the acceptable limits of error rates detailed in Hartington’s SOP 7.5 Database Quality Control) and therefore the database was accepted.
3.7 DATA MANAGEMENT AND EVALUATION

3.7.1 DATA MANAGEMENT

Data were entered, stored and maintained on a DELL PENTIUM POWEREDGE SP 5133-2 computer in SAS system (version 6.12) in accordance with Hartington Statistics and Data Management SOP 7.1 to 7.6.

All analyses and reporting were performed using the SAS system (version 6.12).

Adverse events were coded using MedDRA version 3.3 and concomitant medications were coded using WHO DRL 2000.

QC procedures are described in section 9.6.3.

For all patients who withdrew or completed the study prior to Week 12 (Visit 9), the end of study visit was reallocated to the nearest week and is tabulated at this week as well as at ‘Final visit’. This was not done for patients lost to follow-up as they did not return for an end of study visit, i.e. patients who were not assessed at end of treatment do not have a ‘final visit’.

The study blind was broken to the study statistician on 3 December 2002. (Note that the Per-Protocol population was defined after the study blind had been broken (see Section 9.7.4.1.).)

3.7.2 DETERMINATION OF SAMPLE SIZE

Previous controlled studies with imiquimod, the treatment most recently approved for anogenital warts, had shown a clearance rate ranging from 37% to 52% and from 0% to 11% in patients treated with active and vehicle, respectively (17). In order to determine the sample size requirements for this study, it was assumed that the clearance rates would be 40% and 15% in patients treated with active and vehicle, respectively.

A sample size of 62 patients per treatment group had 80% power to demonstrate a statistically significant difference at an alpha of 0.05 between clearance rates of 40% and 15% in patients treated with active and vehicle, respectively.

This calculation was based on the following formula (21) and was not adjusted for continuity.

\[
n = \frac{p_1 \times (100 - p_2) + p_2 \times (100 - p_1)}{(p_2 - p_1)^2} \times f(\alpha, \beta)
\]

where

- \( n \) = number of patients required per treatment group
- \( p_1 = 15\% \) (the clearance rate for the placebo group)
- \( p_2 = 40\% \) (the clearance rate for the active group)
- \( \alpha = 0.0167 \) (the significance level for detecting a treatment difference)
- \( \beta = 0.20 \) (since \( 1 - \beta \) is the power = 0.80)

\[f(\alpha, \beta) = 10.5 = [\Phi^{-1}(\alpha/2) + \Phi^{-1}(\beta/2)]^2 \]

where \( \Phi \) is the cumulative distribution function of a standardised normal deviate.

In this study, interest lay in demonstrating efficacy in a population of patients, randomised to the study, who returned for a post-baseline assessment. Thus, in order to obtain a total of 62 patients per treatment group in a population of patients randomised who returned for a post-baseline assessment, it was anticipated that 300 patients would be required to be randomised.
It should be noted that these patient numbers did not allow for an active versus active comparison if the response rates were similar.

3.7.3 PLANNED STATISTICAL ANALYSIS

The study protocol contained an outline of the proposed methods of analysis. It was supplemented by a full Data Analysis Plan Revised II (DAP) dated 28 November 2002, which gave full details of all statistical methods. The DAP was based upon the version of the protocol dated 25 October 2001 (i.e. the version incorporating Protocol Amendment 1 but not Protocol Amendment 2).

3.7.4 ANALYSES PERFORMED

There were 3 comparisons of interest (each active versus placebo) and so the 5% significance level was adjusted to allow for this: an adjusted significance level of 1.67% was employed.

3.7.4.1 Changes from Planned Analyses

The decision to exclude a subject from the PP population was to have been made prior to unblinding the study, but after all data had been entered onto the database. However, delays in resolution of data queries meant that the PP population was defined on 9 January 2003 after the blind had been broken on 3 December 2002. (The blind was broken on this date to allow the ITT analysis to proceed on schedule.) In order to avoid bias as a result of prior knowledge of treatment assignment, unblinded personnel were kept to a minimum (only Cynthia Haliburn and Susan Inglis from Hartington were unblinded) and these persons provided no input or opinion regarding any inclusions and exclusions from the PP and Week 4 Completers Populations, other than to provide relevant data to enable others to make an informed decision. All decisions to include or exclude patients from the populations were made by the sponsor, Strakan Pharmaceutical Limited. (See file note provided in Appendix 17.1.8.)

There was a deviation from the DAP with regard to the summary statistics for the percentage reduction in area of target warts: summary statistics were to include quartiles but these are not presented as the distribution of data was adequately described using the summary statistics of mean (SD), median, minimum and maximum and n.

The DAP stated that laboratory data would be summarised by absolute values and also by the change from Screening. In practice, the change from Screening was not computed as it was considered that the laboratory data were adequately summarised in tables showing as absolute values and shifts.

The Week 4 Completers population was defined to include patients who had completed at least 4 weeks of treatment (>24 days), regardless of whether they had completed the Week 4 visit assessments (see Section 9.7.4.2).

The major protocol violations defined in the DAP differed from those actually applied as the DAP did not consider the changes to the selection criteria incorporated by Protocol Amendment 2. Furthermore, one of the specified major protocol violations was defined in the DAP as: ‘Patients who attend their Week 12 visit more than 7 days later than scheduled (> 91 days)’. At the meeting to define the patient populations on 9 January 2003, it was decided that only patients achieving complete clearance of target warts whose Week 12 visit was more than 7 days later than scheduled (>91 days) would be considered major protocol violators and not patients who simply received treatment for longer than planned as the analysis includes in the numerator only those patients who had achieved complete clearance of their target warts.
An analysis of clearance was performed in which patients with a clearance status of ‘Not recorded’ were classed as ‘Not cleared’. This analysis was not described in the DAP; the decision to perform the analysis was made, after breaking the blind and inspection of the primary efficacy analysis for ITT, PP and Week 4 Completers populations, on the advice of Strakan’s independent statistician following review of the 12 week draft report. The results were reported in an addendum to the Statistical report for the treatment phase of the study.

3.7.4.2 Analysis Populations

Five populations were considered for analysis:

**Total Population**
The total population consisted of all patients who were screened (defined as patients for whom CRFs were completed). All recorded data were reported in listings for this population.

**Safety Population**
This population consisted of all patients screened and randomised with the exception of those who had documented evidence indicating that they did not receive any study treatment. All patients who withdrew after randomisation were included in this population. This was the population for the analysis of all safety data.

**Intent-to-Treat Population**
This population consisted of all patients screened and randomised who had had at least one post-baseline assessment, with the exception of those who had documented evidence indicating that they did not receive any study treatment. All patients who withdrew post randomisation were included in this population, providing they had at least one post-baseline assessment of efficacy. This was the primary population for the analysis of all efficacy data.

**Per-Protocol Population**
The Per-Protocol (PP) population consisted of all patients in the ITT population who did not have any protocol violations that could affect their efficacy assessment. This population constituted a secondary population for the primary efficacy analysis if the PP population was less than 90% of the ITT population.

Protocol violations resulting in a patient being excluded from the PP population were detailed explicitly in the DAP. It was intended that the decision to exclude a subject from the PP population would be made prior to unblinding the study, but after all data had been entered onto the database. However, delays in resolution of data queries (that had an impact on inclusion/exclusion of patients in the PP population) meant that the PP population was defined after the blind had been broken.

**Week 4 Completers Population**
This population was defined as all patients in the ITT population who had at least 4 weeks (>24 days) of treatment and completed the Week 4 visit assessments and all patients who achieved complete clearance of target warts before the Week 4 assessment having had up to 4 weeks (24 days) of treatment. All patients who withdrew were to be included in this population, provided they had at least 4 weeks (>24 days) of treatment and completed the Week 4 visit assessments. At the meeting on 9 January 2003 (to identify the PP and Week 4 Completer patients), the definition of the Week 4 Completer population was revised such that patients who had completed at least 4 weeks of treatment (>24 days) were included, regardless of whether they had completed the Week 4 assessments.

The Week 4 Completers population was a secondary population for the analysis of efficacy data.

**Follow-up**
Efficacy data from the follow-up assessments are summarised for:
Follow-up ITT population: comprises all patients in the ITT treatment population who returned for one or more follow-up visits.

Follow-up Efficacy population: comprises the follow-up ITT population minus patients who used a treatment for anogenital warts during the follow-up visits.

Week 4 Completers Follow-up ITT population: comprises all patients who returned for one or more follow-up visits and were in the original Week 4 Completers population.

Week 4 Completers Follow-up Efficacy population: comprises the Week 4 Completers Follow-up ITT population minus patients who used a treatment for anogenital warts during the follow-up visits.

Safety data are summarised for the Safety population; this population comprises all patients in the original safety population (i.e. 299 patients) and all patients assessed at follow-up (i.e. 101 patients).

3.7.4.3 General Considerations for Data Analyses

All summary tables, data listings and statistical analyses were programmed using SAS® Version 6.12.

Centres

As the statistical methodology was dependent upon a suitable number of patients within each centre, it was necessary to combine some centres prior to analysis. Centres were pooled according to country and number of patients at each centre, in order to create pooled centres with at least 12 patients, equally balanced by country and overall.

Covariates

Sex, the total number of warts at Baseline and target wart area recorded at Baseline were included as covariates in the analyses of complete clearance of target warts, time to complete clearance of target warts and percentage reduction in target wart area.

Examination of Subgroups

No subgroup analyses were planned for this study.

Premature Discontinuation and Missing Data

A completer was defined as a patient who had complete clearance of target warts at or prior to Week 12, or who remained in study until Week 12.

Patients withdrawn without providing complete data were included in the analyses where possible and missing data was included in ‘Not recorded’ categories in the summary tables except for percentage reduction, see below.

For the analysis of complete clearance of target warts and time to complete clearance of target warts, missing data were not imputed. A sensitivity analysis was carried out on complete clearance. All the placebo patients with no data were considered ‘cleared’ while all the other patients with no data in the active groups were considered ‘not cleared’.

There was also an additional analysis of clearance in which patients with no clearance data were classed as ‘not cleared’. (This analysis is reported in an addendum to the Statistical Report for the treatment phase of the study.)

In the analysis of percentage reduction in target wart area, all missing post-baseline efficacy data were imputed using the Last Observation Carried Forward (LOCF) technique on the most recent, post-baseline measurement. Baseline data were not carried forward. Summaries are provided of the actual data at each week (i.e. with missing data not imputed) and as well as summaries at each week with missing data imputed. For the purpose of analysis, missing data were imputed.
Derived and Transformed Data

Complete clearance

Complete clearance was defined as clearance of target warts during 12 weeks of study treatment or sooner.

Target Warts

At the Baseline Visit, the Investigator identified up to 10 of the total warts present as ‘target’ warts. Details of target warts were recorded at each visit.

Target Wart Area

Target wart area (mm\(^2\)) was defined as the total of the individual areas of each target wart.

At each visit, the diameter of each target wart, d, was recorded on the CRF.

The area of each target wart was calculated as \(\pi(d/2)^2\).

Reduction in Target Wart Area

Reduction in target wart area was calculated as a percentage, relative to the target wart area at Baseline.

Duration of Study Medication

Duration of study medication (days) was calculated as the time from the date of first application of cream to the date of last application of cream. (If the date of the last application was missing, the date of withdrawal was used to calculate exposure.) This calculation did not account for any missed dose applications.

Elapsed Time of Current Infection

Elapsed time of current infection was calculated as the time from the date of start of the current infection to the date of the Baseline Visit (Week 0), defined in months and rounded to the nearest integer.

For dates with missing days, elapsed time of current infection was calculated using the number of months and years, (i.e. number of months + (number of years x 12)).

For dates with missing days and months, elapsed time of current infection was calculated using the number of years, (i.e. number of years x 12).

Elapsed Time since First Infection

Elapsed time since first infection was calculated as the time from the date of start of the first infection to the date of the Baseline Visit (Week 0), defined in months and rounded to the nearest integer.

For dates with missing days, elapsed time of current infection was calculated using the number of months and years, (i.e. number of months + (number of years x 12)).

For dates with missing days and months, elapsed time of current infection was calculated using the number of years, (i.e. number of years x 12).

Weight of Study Medication Used

The weight of each dispensed tube of medication (tube and cream) was assumed to be 14.3 grams.

Weight of study medication used during the study was calculated as the difference between the weight of the dispensed medication tubes and the weight of the returned medication tubes, summed over all visits.

Percentages
Percentages were calculated relative to the number of patients in the relevant population or subgroup for whom values were recorded for that parameter (i.e. those with values 'Not Recorded' were not included in the percentage calculation for the particular visit).

**Summary Statistics**

Summary statistics were calculated as appropriate to each summary table in the report. Mean, median, standard deviation, minimum, maximum and number of observations are presented for continuous data; number of observations and percentages are presented for discrete, categorical data. Means, standard deviations and medians are given to one more decimal place than the raw data.

3.7.4.4 Study Population

Summaries of the total number of patients in each of the patient populations are presented. The reasons for withdrawal were summarised and presented.

Demographic data and baseline characteristics are summarised for the ITT population, the PP population and the Week 4 Completers population. No statistical testing was performed on these characteristics.

3.7.4.5 Efficacy Analyses

The efficacy data are listed for the Total population and summarised/analysed on the populations detailed below. All confidence intervals calculated were of size 95%. All tests performed were two-sided.

Treatment differences were assessed using a two-sided significance test.

i Primary Efficacy Endpoint

The primary efficacy analysis was a comparison of the proportion of patients with complete clearance of their target warts in the Intent-to-Treat (ITT) population.

The proportion of patients with complete clearance, with a 95% confidence interval, is presented for each treatment group, for overall, males and females.

The proportion of patients with complete clearance was analysed using logistic regression, fitting a model consisting of treatment, total number of warts at Baseline, target wart area recorded at Baseline, centre and sex.

The analysis investigated the presence of interactions. If the effect of including treatment by centre, treatment by baseline (total number of warts and target wart area) or treatment by sex interaction terms in the model was found to be statistically significant ($p < 0.05$), further investigation into the source of the interaction was to be performed and appropriate measures taken.

The fit of the model was checked using the Hosmer-Lemeshow goodness-of-fit test.

Pairwise comparisons were performed as follows:

- Dose A versus placebo
- Dose B versus placebo
- Dose C versus placebo

The results from the analysis are presented as the odds ratio for each of the treatment comparisons, the 95% confidence interval for the odds ratio and the associated $p$-value.

It was possible that a high proportion of the placebo group could have been lost to follow-up. Therefore, their wart status at Week 12 could not be known and the true clearance rates not be estimated. In this event, a sensitivity analysis was to be conducted to assess the effects of dropouts on clearance rates among the treatment groups.
In order to assess how dropouts affected the study results, the above analysis was to be repeated using several worst case scenarios: it was assumed that none of the dropouts had complete clearance of target warts in the 3 active treatment groups and 5, 10, 15, 20, etc., (up to the total number of dropouts in the placebo group, in multiples of 5) of the total number of dropouts in the placebo group had complete clearance of target warts.

There was also an additional analysis in which all patients with a clearance status of 'Not recorded' were assumed to have not cleared. This analysis was not described in the DAP and was reported as an addendum to the Statistical Report for the treatment phase. In this post hoc analysis, the data were analysed in the same way as in the primary efficacy analysis. The analysis was performed for the ITT, PP and Week 4 Completers populations.

ii Secondary Efficacy Endpoints

Proportion of Patients with Complete Clearance of Target Warts in the PP Population

The analysis of the proportion of patients with complete clearance of target warts was also performed for the PP population.

The proportion of patients with complete clearance, with a 95% confidence interval, is presented for each treatment group, for overall, males and females.

The proportion of patients with complete clearance was analysed using logistic regression, fitting a model consisting of treatment, total number of warts at Baseline, target wart area recorded at Baseline, centre and sex, as described for the primary efficacy analysis.

The results from the analysis are presented as the odds ratio for each of the treatment comparisons, the 95% confidence interval for the odds ratio and the associated p-value.

Proportion of Patients with Complete Clearance of Target Warts in the Week 4 Completers Population

The analysis of the proportion of patients achieving complete clearance of their target warts was also performed for the Week 4 Completers population.

The proportion of patients with complete clearance was analysed using logistic regression, fitting a model consisting of treatment, total number of warts at Baseline, target wart area recorded at Baseline, centre and sex, as described for the primary efficacy analysis.

The results from the analysis are presented as the odds ratio for each of the treatment comparisons, the 95% confidence interval for the odds ratio and the associated p-value.

Time to Complete Clearance of Target Warts

The analysis of the time to complete clearance of baseline warts was performed for both the ITT population and the Week 4 Completers population.

The median time to complete clearance can be defined as the median time-point where 50% of the patients are completely cleared. Therefore, if less than 50% of the patients are cleared, the median cannot be calculated.

The median time to complete clearance was estimated in weeks using life table methods for overall, males and females. This method examines the number of patients who are completely cleared, relative to the number of patients 'at risk'.

If any patients withdrew (including those who were lost to follow-up) during a week, their data were censored at the time at which they withdrew from the study and Kaplan-Meier estimates of the distribution of time to complete clearance were used.

For each timepoint, the following frequencies are presented in the life tables: the number of patients who are completely cleared during each week, the number of patients who complete the week without complete clearance and the number of patients who withdrew before the end of the week and not completely cleared at this point.
The Cox proportional hazards regression model was used to test for differences in the time to clearance between the treatment groups; treatment, total number of warts at Baseline, target wart area recorded at Baseline, centre and sex were fitted in the model.

The presence of treatment by centre, treatment by baseline (total number of warts and target wart area) and treatment by sex interactions in the analysis was investigated at the 5% level of significance. The validity of the proportional hazards assumption was also assessed by the inclusion of a time-dependent explanatory variable in the model and by inspection of Cox-Snell and Martingdale residual plots.

The results from the analysis are presented as the estimate of the hazard ratio for each of the pairwise treatment comparisons, the 95% confidence interval for the hazard ratio and the associated p-value.

**Percentage Reduction in Target Wart Area**

The analysis of the percentage reduction in total wart area during treatment was performed for both the ITT population and for the Week 4 Completers population.

Summary statistics (mean, median, sd, minimum, maximum, n) for the target wart area and the percentage reduction in target wart area are presented for each treatment group, at each visit, for males and females and overall.

Where no data were available for a patient, all missing post-baseline efficacy data were imputed using the Last Observation Carried Forward (LOCF) technique on the most recent, post-baseline measurement. Baseline data were not carried forward. Summaries are provided of the actual data at each week (i.e. with missing data not imputed) and as well as summaries at each week with missing data imputed. For the purpose of analysis, missing data were imputed.

In addition, percentage reduction in target wart area was also categorised as complete clearance or partial clearance (>50% reduction in target wart area), no change (0-50% reduction in target wart area) or worsening (increase in target wart area) of target wart area during treatment. Frequency tabulations of the number and percentage of patients in each category are presented for each treatment group, at each visit, for overall, males and females.

Percentage reduction in wart area, at the final visit, was analysed using analysis of covariance techniques. A model consisting of treatment, total number of warts at Baseline, target wart area recorded at Baseline, centre and sex was fitted to the data. The total number of warts at Baseline and target wart area recorded at Baseline were included in the analysis as covariates. Treatment, centre and sex were considered as fixed effects.

The presence of treatment by centre, treatment by baseline (total number of warts and target wart area) and treatment by sex interactions in the analysis was investigated at the 5% level of significance.

The assumptions of normality and homogeneity of variance were assessed by inspection of normal probability plots and residual plots. Plots of standardised residuals versus predicted values were also produced to aid the diagnostics.

If the assumptions of normality and homogeneity of variance were not satisfied then a non-parametric analysis was to be performed, using the Wilcoxon Rank Sum Test.

The results from the analysis are presented as the estimate of the treatment difference for each of the pairwise treatment comparisons, the 95% confidence interval for the treatment difference and the associated p-value.
Investigator Assessment of Total Number of Warts

Summary statistics of the total number of warts at the end of the study are presented for each treatment group, at each visit, for overall, males and females, for the ITT, PP and Week 4 Completers populations.

Patient Assessment of Efficacy

The analysis of the patient assessment of global response at the end of the study (or at the time of premature withdrawal from the study) was performed for both the ITT population and for the Week 4 Completers population.

Frequency tabulations of the number and percentage of patients in each category are presented for each treatment group, for overall, males and females. The proportions of patients with a recording of complete clearance, with a 95% confidence interval, are also presented for each treatment group, for overall, males and females.

The patient assessment of efficacy was analysed using logistic regression, which accounts for the ordinal nature of the data, fitting a model consisting of treatment, centre and sex.

The presence of treatment by centre and treatment by sex interactions in the analysis was investigated at the 5% level of significance. The validity of the proportional odds assumption was investigated using the score test.

The fit of the model was tested using the Hosmer-Lemeshow goodness-of-fit test.

The results from the analysis are presented as the odds ratio for each of the treatment comparisons, the 95% confidence interval for the odds ratio and the associated p-value.

Investigator Assessment of Efficacy

The analysis of the Investigator assessment of global response at the end of the study (or at the time of premature withdrawal from the study) was performed for both the ITT population and for the Week 4 Completers population.

Frequency tabulations of the number and percentage of patients in each category are presented for each treatment group, for overall, males and females. The proportion of patients with a recording of complete clearance, with a 95% confidence interval, are also presented for each treatment group, for overall, males and females.

The Investigator assessment of efficacy was analysed using logistic regression, which accounts for the ordinal nature of the data, fitting a model consisting of treatment, centre and sex.

The presence of treatment by centre and treatment by sex interactions in the analysis was investigated at the 5% level of significance. The validity of the proportional odds assumption was investigated using the score test.

The fit of the model was tested using the Hosmer-Lemeshow goodness-of-fit test.

The results from the analysis are presented as the odds ratio for each of the treatment comparisons, the 95% confidence interval for the odds ratio and the associated p-value.

3.7.4.6 Safety and Tolerability

All safety data are listed for the Total population and summarised for the Safety population.

Patient Assessment of Tolerability

Frequency tabulations of the number and percentage of patients in each category (none, mild, moderate, severe) and with any positive results, are presented for each treatment group, at each visit, for each assessment (itching, pain, burning) for overall, males and females.
A 95% confidence interval for the proportion of patients recording no symptoms for each assessment is also presented for each treatment group, for overall, males and females.

**Investigator Assessment of Tolerability**

Frequency tabulations of the number and percentage of patients in each category (0, 1, 2, 3, 4) for each assessment (erythema/eschar, oedema) are presented for each treatment group, at each visit, for overall, males and females.

A 95% confidence interval for the proportion of patients scoring zero for each assessment is also presented for each treatment group, for overall, males and females.

The presence/absence of staining is summarised by frequency tabulations of the number and percentage of patients at each visit by treatment group for overall, males and females.

**Adverse Events**

Adverse events were coded using the MedDRA dictionary and grouped by body system.

A treatment-emergent adverse event refers to any symptom, physical sign, syndrome or disease, irrespective of causality, which either occurred during the study, having been absent at Baseline, or, if present at Baseline, appeared to worsen.

Separate listings of treatment-emergent and non-treatment-emergent adverse events are presented for each treatment group.

Only treatment-emergent adverse events were included in the analysis. All treatment-emergent adverse event summaries are presented, within each treatment group, for overall, males and females. Within each treatment group, the number of patients and percentage of patients experiencing the adverse event, together with the total number of occurrences of the adverse event, are presented, by body system and preferred term. Separate summaries of adverse events are given overall, by site, by severity, by relationship to study medication, for serious adverse events and for adverse events leading to withdrawal.

In addition, adverse events with >5% incidence in any treatment group are also summarised and presented by order of descending frequency for overall, males and females within each treatment group.

Treatment groups were compared statistically with respect to the overall incidence of adverse events and also the incidence of serious adverse events.

The proportion of patients with adverse events was analysed using logistic regression, fitting a model consisting of treatment, centre and sex.

The fit of the model was tested using the Hosmer-Lemeshow goodness-of-fit test.

The results from the analysis are presented as the odds ratio for each of the treatment comparisons, the 95% confidence interval for the odds ratio and the associated p-value. The proportion of patients with adverse events, with a 95% confidence interval, is also presented.

**Laboratory Data**

Haematology, biochemistry and urinalysis data are summarised by visit and treatment group. In addition, the change from Screening (Week –2) to Week 12 (Visit 9) (or at the time of premature withdrawal from the study) is summarised by visit and treatment group.

Shift tables are presented showing shifts (to abnormally low, to normal/no change or to abnormally high) from Screening (Week –2) to Week 12 (or at the time of premature withdrawal from the study) (i.e. to final visit) by treatment group.

Abnormal laboratory data are flagged in the listings (H = above normal range, L = below normal range).

**Vital Signs**
Vital signs are summarised by visit and treatment group. The change from Baseline (Week 0) at each visit is also summarised by visit and treatment group. (Note that the protocol described the change from Screening but the DAP used the more appropriate change from Baseline.)

Physical Examination

Physical examination data are summarised by visit and treatment group. In addition, the change from Screening (Week –2) to Week 12 (Visit 9) (or at the time of premature withdrawal from the study) is also summarised by visit and treatment group.

Concomitant Medication

Concomitant medications were coded using the WHO DRL dictionary and grouped by drug class.

Concomitant medications were categorised into medication starting and stopping prior to study treatment and medication starting prior to/during study treatment and stopping during study/ongoing throughout study. Separate listings of concomitant medications in each category are presented for each treatment group.

Within each treatment group, for each category, the number of patients and percentage of patients using the concomitant medication, together with the total number of uses of the concomitant medication are presented by drug class and preferred term.

3.7.4.7 Follow-up Period

Wherever possible, patients were assessed 4, 8 and 12 weeks after stopping treatment. Wart details, adverse events unresolved at the end of treatment, concomitant medications and local examination (by Investigator) data were summarised at the follow-up visits by treatment group.

3.7.5 INTERIM ANALYSES

There was no interim analysis of the study results.

3.8 CHANGES IN THE CONDUCT OF THE STUDY

3.8.1 PROTOCOL AMENDMENTS

There were two amendments to the final protocol dated 26 June 2001.

The first amendment, dated 25 October 2001, made the following changes to the procedures:

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>Under item c), depot injection was added as an acceptable form of non-barrier method of contraception for women of child-bearing potential.</td>
</tr>
<tr>
<td>Patient randomisation number</td>
<td>Numbering of patients revised such that each patient had a unique medication reference number as well as a CRF number.</td>
</tr>
<tr>
<td>Decode envelopes</td>
<td>Decode envelopes were to be held by the Investigator and Origin Project Manager and Regulatory Affairs Manager and the code could be broken for reasons of safety or emergency by the Investigator or Project Manager but not the independent medical advisor. (Final protocol had Investigator, Project Manager and independent Medical Advisor)</td>
</tr>
<tr>
<td>Demographics</td>
<td>The final protocol stated that the medical history of the patient had to</td>
</tr>
</tbody>
</table>

...
<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical History and Concomitant Medication</td>
<td>be recorded with illnesses in the past 12 months noted. The amendment stated that the medical history had to be recorded, detailing chronic diseases and significant illnesses (i.e. not just those in the past 12 months).</td>
</tr>
<tr>
<td>Wart Examination and Wart History</td>
<td>Up to 10 representative warts had to be selected at Baseline. At Baseline and subsequent visits, the diameter of each target wart was to be measured and the height recorded as either ‘flat’ or raised. The wart type of the target warts also had to be recorded. (The final protocol specified that the diameter of all warts had to be recorded.)</td>
</tr>
<tr>
<td>Blood biochemistry</td>
<td>Bilirubin changed to total bilirubin. Total protein, albumin, calculated globulin and GGT were added.</td>
</tr>
<tr>
<td>Discontinuation and withdrawal</td>
<td>Text changed from ‘lost to follow-up for two or more consecutive visits’ to ‘lost to follow-up, or missed two or more visits’</td>
</tr>
</tbody>
</table>

The second amendment, dated 7 May 2002, made the following changes to the study procedures:

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Advisor/Contact list</td>
<td>Names changed</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>The word ‘adversely’ was added to the exclusion criterion covering medications affecting haematology tests: the revised criterion read ‘Patients who have used medication known to adversely affect their haematology profile.’</td>
</tr>
<tr>
<td></td>
<td>The final protocol excluded patient with concomitant STD unless the STD was treated successfully prior to Week 0. The amended text read ‘Patients who are known to have a concomitant STD which inhibits accurate assessment of the warts’. (The study flowchart was amended to incorporate this change.)</td>
</tr>
<tr>
<td></td>
<td>The final protocol excluded women who required treatment for intra-vaginal warts and male patients with intra-urethral warts. These 2 exclusion criteria were deleted and replaced with a criterion that excluded patients who required treatment other than surgery or laser for internal warts.</td>
</tr>
<tr>
<td></td>
<td>The final protocol excluded patients who had anogenital warts present for more than 6 months unless they had not had any active treatment for these warts. This criterion was revised to read: ‘Patients with recalcitrant warts (warts still present despite 6 months therapy with a licensed medication, laser or surgical treatment). Patients who have both recalcitrant and non-recalcitrant warts can be entered provided the recalcitrant wart(s) are not counted as target warts and does not count towards the 2-50 inclusion criterion.’</td>
</tr>
<tr>
<td></td>
<td>The final protocol excluded patients with an individual anogenital wart more than 1.5 cm in diameter. This criterion was amended to read ‘more than 15 mm in diameter’.</td>
</tr>
<tr>
<td>Secondary Endpoint and Wart Numbers, Diameter and Type</td>
<td>A new secondary endpoint (Investigator assessment of total number of warts (new and baseline) was added. The flowchart was amended to show this assessment at Visit 9 (Week 12) and at Weeks 4, 8 and 12 of follow-up.</td>
</tr>
<tr>
<td>Section</td>
<td>Change</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study plan</td>
<td>The study plan was amended to state that Visits 5 and 7 (Weeks 4 and 8) could be changed to telephone assessments as long as this was acceptable from a safety perspective.</td>
</tr>
<tr>
<td>Labelling, Storage and Dispensing</td>
<td>The information on the label was to include the medication reference number and Visit number (Visit 2, 3, 4, 5, 6, 7 and 8) rather than the patient randomisation number and Visit number (Visit 1, 2, 3, 4, 5, 6, 7, 8 and 9) as stated in the final protocol.</td>
</tr>
<tr>
<td>Blood biochemistry and haematology and urinalysis</td>
<td>It was stated that the blood samples could be analysed either in a central laboratory or locally. (The final protocol stated locally only.) The urine sample was to be sent to a laboratory (which meant it could be sent to either a central or local laboratory for testing).</td>
</tr>
<tr>
<td>Blood biochemistry</td>
<td>‘Calculated globulin’ was removed from the list of specified tests.</td>
</tr>
<tr>
<td>Labelling</td>
<td>‘Patient randomisation number’ changed to ‘medication reference number’.</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>The Origin Regulatory Affairs Manager (not the Medical Advisor) was appointed to unblind treatment in the event of an unexpected SAE.</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>The total number of warts present at the end of the study and the number of new warts present at the end of the study were to be summarised for each treatment group, for males and females and overall.</td>
</tr>
<tr>
<td>Monitoring</td>
<td>The sentence ‘Where local rules do not allow direct access to the source data, the monitor will verify entries in the CRF by asking direct questions of a person or person with authorised access to source data’ was deleted.</td>
</tr>
</tbody>
</table>