A randomized, double-blind, four-arm parallel-group, placebo-controlled Phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon® E in the treatment of external genital warts

G Gross,* K-G Meyer,† H Pres,‡ C Thielert,§ H Tawfik,§ A Mescheder§

† Private Dermatology Practice, Berlin, Germany
‡ Private Dermatology Practice, Berlin, Germany
§ MediGene AG, Planegg/Martinsried, Germany

Original Article

Keywords
antioxidant, antitumour, catechins, genital warts, green tea, human comparative study, topical

Abstract

Objective Clinical efficacy and safety of Polyphenon® E, a defined green tea extract, in external genital warts.

Design Randomized, double-blind, placebo-controlled study for up to 12 weeks with a 12-week treatment-free follow-up.

Setting Twenty-eight hospitals and practices in Germany and Russia.

Patients Two hundred forty-two outpatients (125 men, 117 women) with 2 to 30 warts (total wart area, 12–600 mm²).

Intervention(s) Topical application of Polyphenon® E 10% Cream, Polyphenon® E 15% Ointment or placebo to all external genital warts three times a day.

Main outcome measure(s) Measurement of total wart area and local reactions/adverse events.

Results For 15% ointment, statistically significant differences to placebo were achieved regarding complete clearance of all baseline external genital warts (61.0% vs. 40.5% in males, 56.8% vs. 34.1% in females; combined gender: \( P = 0.0066 \)) and 75% to 100% clearance (80.8% vs. 51.8%; \( P = 0.0001 \)) in both the intent-to-treat and per-protocol populations. For 10% cream, 53.8% males and 39.5% females achieved complete clearance. Recurrence rates 12 weeks after end of treatment were 10.6%, 11.8% and 10.3% for 15% ointment, 10% cream and placebo, respectively.

Adverse events were observed in only 7.9% of patients, with no serious adverse events or deaths reported. Local skin reactions were generally mild to moderate and resolved with continued treatment without sequelae.

Conclusions Polyphenon® E 15% ointment, composed of a defined green tea extract, proved to be efficacious and safe for both gender in the treatment of external genital warts.

Introduction

External genital warts are non-malignant squamous cell tumours caused by infections of human papillomaviruses (HPV). The low-risk HPV genotypes 6 and 11 are found in > 90% of cases.¹ ² Genital wart infections have one of the fastest growing incidence rates of all sexually transmitted diseases. Overall, 0.5% to 1% of the general population is infected with HPV.² Few treatments with varying degrees of efficacy are available. Nevertheless, for topical agents...
such as imiquimod (Aldara®) and podofilox (Condylox®, Condyline® and Wartec®), common application-site reactions, including erythema, oedema, scaling, erosions, ulcerations, pain, burning, and itching, have been reported. For the provider-administered therapies, such as cryotherapy, curettage and electrodesiccation, laser surgery, podophyllin resin, and trichloroacetic acid, the treatments are often painful and may cause scarring.2–7 Additionally, because these therapies do not eliminate the source of disease, recurrence of warts is often observed.8

Polyphenon® E is a defined extract of catechins of green tea leaves of Camellia sinensis, a species of the Theaceae family. It contains more than 80% of tea polyphenols/catechins accountable for the major biological properties, an immunomodulatory activity (unpublished data) and protein binding, particularly to enzymes, as well as strong antioxidant activity.9,10 Antitumour activity has been observed potentially as a result of blocking the mitotic signal transduction pathway, which in turn has an effect on proliferation, on cell cycle progression and even apoptosis.10 These potential properties are supportive of its use in wart treatment together with the observed anti-inflammatory activities.10 Initial studies in China have shown that tea polyphenols were effective in the treatment of external genital warts, with minimal pain and inflammation (personal communication from Dr. Shu-Jun Cheng, Cancer Institute of the Chinese Academy of Medical Sciences, Beijing, China). MediGene has developed two new formulations, a 10% cream and a 15% ointment, with enhanced penetration properties to further improve the efficacy of patient-applied Polyphenon® E in the treatment of external genital warts.

Materials and methods

Objective

The objective of this study was to investigate the clinical efficacy and safety of Polyphenon® E 10% cream and Polyphenon® E 15% ointment in comparison with placebo in the treatment of external genital warts in male and female patients.

Study design

The study was a multicentre, Phase II/III, randomized, double-blind, placebo-controlled, four-arm parallel-group trial. The maximum duration of treatment was 12 weeks or until complete clearance of all baseline warts, whichever came first, followed by a 12-week treatment-free follow-up phase for complete responders. The first patient was enrolled on 27 December 2000, and the last patient completed the study on 18 November 2001.

Study population

Male and female patients, 18 years of age or older, with 2 to 30 clinically diagnosed external genital warts with a total wart area of 12 to 600 mm² were enrolled. Data were collected at 20 German and 8 Russian centres, including University hospitals, hospitals and clinical practices. Locations of warts were glans penis, penile shaft, scrotum, and foreskin for men; vulva for women; and the inguinal, perineal, and perianal skin areas for both gender. Female patients and partners of male patients with childbearing potential had negative pregnancy tests and used effective contraception during the treatment period. Patients were not enrolled if they had a current episode of Herpes genitalis or any other current and/or recurrent genital or uncontrolled infection. Patients who had participated in an investigational trial, had treatment of anogenital warts or had systemic intake of acyclovir or immunosuppressive medication within 30 days prior to enrolment were excluded. Patients with organ allograft, with skin conditions that may interfere with the study drug, with internal (vaginal or rectal) warts that required treatment or who were lactating were also excluded. Written informed consent was obtained after providing detailed information about the study and allocating sufficient time to consider whether to participate. Patients with less than 50% clearance of total baseline wart area after 8 weeks of treatment could discontinue treatment and were then regarded as treatment failures.

Ethics

The responsible local and/or national independent ethics committee approved the study protocol and any other relevant study documentation prior to enrolment. The study was done according to the Declaration of Helsinki (Somerset West, 1996)11 and the ICH GCP guidelines as well as the demands of national drug and data protection laws and other applicable regulatory requirements. It was fully monitored and audited.

Randomization, study medication and treatment

Patients were randomly assigned to one of the four treatment groups in a 2:1 active: placebo allocation ratio, stratified by gender. The active treatments were Polyphenon® E 10% cream and Polyphenon® E 15% ointment. In the corresponding placebos, Polyphenon® E was replaced by higher amounts of all base ingredients in the cream and of white petrolatum and white wax in the ointment base and inert colours added to ensure blinding. Centers were provided with medication kits that had a pre-assigned 4-digit number, with each patient allocated to the lowest available number. Randomization sequence was generated...
by Almedica HPS AG, Switzerland. Patients were instructed to apply the medication topically to all external genital warts three times a day, whether they were baseline or new warts. Dosing was anticipated to be < 250 mg of study medication per application. Each tube contained 15 g of ointment, cream or placebo defined for a 2-week application period.

**Study assessments**

During the 12-week treatment period, patient visits were scheduled at baseline, at every other week until week 8, with a final visit at week 12. Disease and medical history, demographic data and concomitant medications were recorded during screening. At the baseline visit, the inclusion and exclusion criteria were reviewed, and the treatment was initiated.

Wart measurements, as the product of wart length and the rectangular width, were taken at baseline and weeks 2, 4, 6, 8, and 12 and documented in a dermagram. Drug compliance was checked at weeks 2, 4, 6, 8 and 12.

At baseline visit and at week 12, patients underwent physical examination, vital signs were measured and photographs including a ruler were taken (optional, for documentation not for evaluation purposes). Blood and urine samples were collected for a standard range of haematology, blood chemistry and urinalysis laboratory evaluations, including pregnancy tests, if applicable. Local reactions at the application site are of special interest for topical treatments. Thus, they were evaluated and described separately from the other adverse events (AE). At baseline and at all subsequent visits, the blinded investigator assessed local signs, including erythema, oedema, induration, vesicles, erosion/ulceration, and global reaction and questioned the patient about local skin symptoms, including burning, itching, pain, other and overall reaction. Intensity of all skin reactions at the site of application were graded as either none, mild, moderate or severe.

AEs, concomitant medications and changes to concomitant medications were also recorded at all visits.

**Follow-up visits**

Patients with complete clearance of all baseline warts stopped treatment and went into follow-up with assessments after 4 and 12 weeks (if wart-free) to assess recurrence rates. At these visits, local tolerability was evaluated and previously reported AEs and concomitant medications were updated.

**Number of patients required and statistical analyses**

Complete clearance rates of baseline warts of 5% (male) and 15% (female) for the placebo group and 35% (male) and 50% (female) for the active treatment groups (10% cream, 15% ointment) were assumed. Using a two-sided Fisher’s exact test with a significance level (type I error) of \( \alpha = 0.025 \), 80% power required at least 38 patients in each subgroup to compare active treatments with pooled placebo by gender. Thus, allowing a dropout rate of 10%, it was planned to recruit 130 male and 130 female patients. Subsequently, the data were pooled to perform analysis between the active treatment groups and placebo stratified by gender (Mantel & Haenszel test, two-sided, \( \alpha = 0.05 \)). Descriptive statistics were used to analyse secondary efficacy involving complete/partial clearance, time to complete/partial clearance and recurrence rates as well as safety parameters involving local signs/symptoms, AEs, physical examination, vital signs, or laboratory parameters. Complete clearance of all (baseline and new warts occurring during treatment) warts was additionally analysed as requested for the subsequent pivotal Phase 3 trials by the US Federal Drug Administration. Baseline comparisons were done using Wilcoxon’s two-sample test (two-sided, \( \alpha = 0.05 \)). In addition, an influence analysis (logistic regression model) was done on wart location and area, age and numbers of warts, age of patients, usage of cream and ointment, and previous treatments to investigate contributing prognostic factors.

**Results**

**Study patients**

Intent-to-treat (ITT) population included 238 patients (122 men and 116 women). Per-protocol (PP) population consisted of 225 patients (115 men and 110 women), and the safety population included 242 patients (125 male and 117 female). A total of 221 patients completed the study (fig. 1), whereas 21 patients discontinued the study prematurely: 6 patients were lost to follow-up, 3 patients reported AEs (allergic reaction, hypersensitivity/allergic vulvitis, severe itching and burning), 9 dropouts were evenly distributed over lack of efficacy, non-compliance and other reasons, 2 patients withdrew their consent, and 1 patient was withdrawn by the investigator. The first and second follow-up visits were completed by 97.3% and 85.0%, respectively, of all patients with complete clearance.

The three treatment groups were comparable with respect to baseline characteristics. Total mean age was 33.2 years (range, 18–69 years). In the age groups < 20 years, 3 (3.8%), 8 (10.1%) and 8 patients (9.6%), < 25 years, 22 (27.5%), 17 (21.5%) and 13 patients (15.7%), < 30 years, 12 (15.0%), 10 (12.7%) and 13 patients (15.7%), and ≥ 30 years, 43 (53.8%), 44 (55.7%) and 49 patients (59.0%) were from the 15% ointment, 10% cream and
placebo groups, respectively. Mean weight was 72.4 kg (range, 48–113 kg), and mean height was 173.3 cm (range, 155–198 cm). Majority of males were uncircumcised (96 patients, 78.7%). Most patients had never smoked (161 patients, 67.6%), and 105 patients (44.1%) had never consumed alcohol.

Most patients (151 patients, 63.4%) had not had any previous episodes of external genital warts, 52 patients (21.8%) previously had one episode, 24 patients (10.1%) two episodes, and 11 patients (4.6%) three or more episodes. Ninety-two patients (38.7%) had warts previously treated (64 males and 28 females). Most males (33 patients, 27.0%) and only 6 females (5.2%) had their warts previously treated with curettage and electrodesication. Use of 0.5% podofilox was more common in male patients (24, 19.7%) than in female patients (3, 2.6%). The majority of females who had received previous treatments had chosen laser surgery (11 patients, 9.5%). The number of female patients with previous episodes was much lower than that of male patients.

Baseline warts in male patients were mainly located at the penile shaft (70 patients, 57.4%) followed by the glans penis (30 patients, 24.6%), the perianal area (29 patients, 23.8%) and the foreskin (23 patients, 18.9%). Female patients had their baseline warts mainly located at the vulva (75 patients, 64.7%) followed by the perianal area (37 patients, 31.9%) and the perineal area (22 patients, 19.0%). In most instances, the treatment groups were comparable for both male and female patients regarding the locations of baseline warts.

### Compliance

At the end of the study, all used and unused study medication was collected and weighed. As recorded by the investigators, overall assessment of compliance revealed that 94.5% of patients in the ITT population showed an at least adequate compliance (≥75%) at each study visit. Compliance was found to be poor (<75%) in at least one visit for 13 patients (5.5%), 1 patient in the 10% cream

---

**fig. 1** Study patients: flow diagram of patient progress through the phases of this randomized, placebo-controlled study. Patients were randomly assigned to one of the treatment groups in a 2 : 1 active: placebo allocation ratio, stratified by gender.
group, 4 patients in the 15% ointment group and 8 patients in the placebo group. Compliance was comparable for both genders.

**Efficacy analysis: primary endpoint**

With respect to complete clearance rates of baseline warts (primary efficacy endpoint), differences between the 10% cream placebo group and the 15% ointment placebo group for male and female patients in the ITT as well as in the PP population were negligible (10% cream: 37.2%; 15% ointment: 37.5%; Fisher’s exact test, P = 1.0000). Thus, pooling of placebo groups was justified. All analyses were also done by individual placebo groups, and the results mimic the results from the pooled placebo group.

Differences between the 10% cream and the pooled placebo groups in male and female patients were not statistically significant (Fisher’s exact test, P = 0.2693 for males and P = 0.6479 for females). On the other hand, differences between the 15% ointment and the pooled placebo groups in male and female patients were almost statistically significant (Fisher’s exact test, P = 0.0802 for males and P = 0.0678 for females). When the data for both gender were pooled, the complete clearance rates of 10% cream (46.8%) and placebo (37.3%) were still not significantly different (Cochran-Mantel-Haenszel test, P = 0.2290). In contrast, the complete clearance rate of the 15% ointment group (59.0%) was statistically significantly higher compared with placebo (Cochran-Mantel-Haenszel test, P = 0.0066; Table 1). During the treatment period, complete response rates increased gradually only in the 15% ointment group but raised considerably in the last 4 weeks of treatment in all treatment groups. At week 4, complete response rates were 2.6%, 0.0% and 3.6% for the 15% ointment, 10% cream and placebo groups, respectively. At week 8, 6.4%, 0.0% and 2.4%, and at week 12, 41.0%, 37.7% and 31.3% were achieved in these treatment groups.

A retrospective analysis of the complete clearance of all warts (baseline and new warts occurring during treatment) showed that 56.4% and 45.5% of patients of the 15% ointment and 10% cream groups were completely wart-free after 12 weeks of treatment compared to 37.5% and 37.2% of patients of the placebo ointment and cream groups, respectively. The difference between the 15% ointment and placebo ointment groups was almost statistically significant (Fisher’s exact test, P = 0.079).

**Efficacy analysis: secondary endpoints**

Complete clearance rates for the PP population were similar to those of the ITT population and also yielded statistically significant result for the 15% ointment over placebo with both gender combined (Cochran-Mantel-Haenszel test, P = 0.0195). This was not true for the 10% cream group.

No significant differences were found between the 10% cream and 15% ointment groups in terms of complete clearance, irrespective of whether the gender were compared separately or combined (P = 0.6514 for males, P = 0.1681 for females, P = 0.1339 for gender combined). Complete clearance rates seem to be influenced to some extend by circumcision in males: the comparison of 15% ointment to placebo for uncircumcised men was almost statistically significantly different (P = 0.0506) compared with P = 1.0000 for circumcised men. Mean time to complete clearance of all baseline warts was 10.6 ± 2.6 weeks and was comparable between gender and active treatment groups. Evaluation of baseline characteristics (baseline wart area, baseline number of warts and average daily dose) and patient compliance showed no significant effect on the complete clearance rates seen in treatment or gender groups.

Results for treatment success (75–100% clearance) are shown in Table 2. 15% ointment was statistically superior to placebo in both gender groups and for gender combined (P = 0.0102 for males, P = 0.0084 for females and P = 0.0001 for gender combined).

---

**Table 1** The number of patients with complete clearance rates (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>10% cream</th>
<th>15% ointment</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>53.8</td>
<td>25</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>39.5</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>46.8</td>
<td>46</td>
</tr>
</tbody>
</table>

*Clearance rates statistically significantly higher than in placebo-treated patients (P = 0.0066).

**Table 2** The number of patients with a 75% to 100% reduction of baseline wart area (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>10% cream</th>
<th>15% ointment</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>61.5</td>
<td>33</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>47.4</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>54.5</td>
<td>63</td>
</tr>
</tbody>
</table>

*Males and females significantly superior to placebo (P = 0.0102 and 0.0084, respectively) and for the combined sexes (P = 0.0001).
Total number of patients with recurring baseline warts during the treatment period was very low at 4.2% (10 patients). For both gender, the 15% ointment group had the highest number of patients with recurring baseline warts (4 males and 2 females).

Recurrence of baseline warts during the first 4 weeks of follow-up occurred only in 3 males (2.7%), 1 in the 10% Cream group and 2 in the 15% ointment group in both the ITT and the PP populations. From the first to the second follow-up visit (12 weeks after the end of treatment), recurrence occurred in only three male patients in each of the three treatment groups. There were no recurrences in female patients throughout the follow-up. Thus, overall recurrence rates for the 12-week follow-up period were 10.6%, 11.8% and 10.3% for the Polyphenon® E 15% ointment, the Polyphenon® E 10% cream and the pooled placebo groups, respectively.

Influence of prognostic factors

Complete response rate in the placebo group was surprisingly high (37.3%). Analyses were also done to assess the contribution of baseline characteristics of the warts to efficacy rates in the different treatment groups.

In addition, a logistic regression procedure was defined with the primary endpoint, complete clearance of all baseline warts, as the dependent variable vs. a set of related explanatory variables (treatment, pretreatment, age of patients, and wart characteristics at baseline) to identify relevant prognostic factors. With the present sample sizes and due to difficulties in satisfying the model assumptions (poor model fit), no parameters could be identified as relevant prognostic factors.

Local tolerability as assessed by the investigator and patient

At all visits, the blinded investigator assessed local skin signs and questioned the patient about local skin symptoms. An overview of the incidence of any local skin signs and/or symptoms during treatment is shown in fig. 2. Local skin symptoms were present at the baseline visit in 25 (31.3%) and 22 patients (27.8%) in the 15% ointment and 10% cream groups compared with 24 patients (28.0%) in the placebo group. At the same time, 10 (12.5%) and 9 patients (11.4%) in the 15% ointment and 10% cream groups had local skin signs compared to 14 patients (16.9%) in the placebo group. After start of treatment, the incidence of local reactions increased in all three treatment groups to a maximum in week 2 (overall 37.0% and 31.4% local skin signs and symptoms, respectively). Subsequently, all local reactions gradually declined through the treatment period in all three treatment groups to levels well below the ones before start of treatment.

A number of local signs and symptoms were most frequent in the 15% ointment group at all visits. The majority of local skin signs were of mild intensity, most local skin symptoms of mild to moderate intensity. The most frequently observed local skin sign was erythema, being most frequent at week 2 (52 patients [22.1%] with mild, 22 patients [9.4%] with moderate and 4 patients [1.7%] with severe erythema). Overall, burning and itching were the most frequent local skin symptoms with their maximum also at week 2. They were reported in 44 (18.7%) and 46 patients (19.6%) with mild, in 14 (6.0%) and 16 patients (6.8%) with moderate and in 2 (0.9%) and 3 patients (1.3%) with severe intensity, respectively.

At end of treatment, local signs were present in 13 (17.1%) and 6 patients (7.9%) in the 15% ointment and 10% cream groups, respectively, compared with 7 patients (8.6%) in the placebo group, and local symptoms were reported for 10 (12.5%) and 5 patients (6.3%) in the 15% ointment and 10% cream groups, respectively, compared with 7 patients (8.4%) in the placebo group.

During the treatment-free 12-week follow-up, only 1 patient (2.2%) in the 15% ointment group had local reactions at the first follow-up visit (4 weeks after treatment);
in addition, 1 patient each in the 15% ointment and 10% cream groups had local skin symptoms at the second follow-up visit (12 weeks after treatment).

Complete responders had an increased number of local skin reactions (79 complete responders, 69.9%) when compared to non-responders (58 non-responders, 46.4%), proved by statistical significance (Fisher’s exact test, two-sided, \( P = 0.0002 \)). The difference in the complete responders group was mainly based on the difference between the Polyphenon® E 15% ointment group and the placebo group. In the 15% ointment group, 38 (82.6%) complete responders had (a) local reaction(s) compared with 15 (48.4%) complete responders in the placebo group (\( P = 0.0024 \)).

A similar statistically significant correlation with complete clearance was found when the local skin signs (\( P = 0.0112 \)) and local skin symptoms (\( P = 0.0067 \)) were assessed separately, for 15% ointment vs. placebo for both any local skin signs (\( P < 0.0001 \)) and any local skin symptoms (\( P = 0.0050 \)), and also for the 10% cream vs. placebo for any local skin signs (\( P < 0.0002 \)). However, when only severe local skin reactions, severe signs or severe symptoms were considered, no significant differences were found both in the comparison of complete responders vs. non-complete responders overall and in the comparison of the active treatment groups vs. placebo.

Time to first onset analysis of any local sign or symptom with an at least ‘moderate’ intensity yielded a significant result for the comparison between the two active formulations only in male patients (\( P = 0.0263 \)), indicating that such symptoms were to occur sooner in the 15% ointment group. For female patients, no statistically significant differences were found.

**AEs other than local reactions**

Throughout the study, there were no serious AEs, and no deaths occurred.

During the treatment period, 19 patients (7.9%) in the safety population (242 patients) had 21 AEs involving 7 patients (8.9%, 7 AEs) receiving 10% cream, 9 patients (11.3%, 10 AEs) receiving 15% ointment and 3 patients (3.6%, 4 AEs) receiving placebo. Only 6 of these patients (2.5%) had AEs that were considered possibly or probably related to study drug, with 2 patients in the 10% cream group (hyperkeratosis and skin discoloration) and 4 patients in the 15% ointment group (transient local necrosis [not otherwise specified], allergic dermatitis [2 patients], and pain in the foreskin). Of these 21 AEs, 8 were mild, 11 moderate and 2 were of severe intensity, with the latter being probably related to the study drug. Most frequent AEs, experienced by 9 patients (3.7%), were classified as ‘infections and infestations’, with ‘respiratory tract infection (not otherwise specified; 4 patients, 1.7%)’ being the most common, followed by ‘skin and subcutaneous tissue disorders’ (3 patients, 1.2%). The number of female patients (\( n = 5 \), 4.3%) with treatment-related AEs was higher than for male patients (\( n = 1 \), 0.8%).

Withdrawals due to AEs involved three patients in the 15% ointment group. One female patient developed (unproven) allergic dermatitis/vulvitis of severe intensity, which was assessed as probably related to the study drug. Another female patient developed allergic dermatitis of mild intensity and assessed as possibly related to the study drug. In both cases, allergic reactions were not confirmed because no retesting was done. One male patient developed severe itching and burning, assessed as probably study drug-related.

During the follow-up period, only 5 patients (2.1%) had a total number of 6 AEs. All AEs occurring during the follow-up period were assessed as not related to study treatment.

**Other safety assessments**

Regarding the laboratory values, mean values of laboratory parameters showed only negligible changes during the treatment period. No clinically significant abnormal laboratory values were reported.

Mean blood pressure, heart rate and body temperature were also generally within normal range at baseline and at the end of the study, hardly changing in between. Physical examinations revealed normal results in most of the system organ classes of all patients examined. No clinically significant changes were observed during the treatment period.

**Discussion**

The study has shown clearly that the 15% ointment preparation was more effective than the 10% cream formulation in significantly increasing the wart clearance rates compared with those of placebo. Following treatment with 15% ointment, complete clearance of baseline warts was observed in 59% of patients (vs. placebo \( P = 0.0066 \)), and a 75% to 100% reduction in wart area (therapeutic success) was seen in 80.8% of patients (vs. placebo \( P = 0.0001 \)). These significant effects were observed in both the ITT and the PP populations, and results were similar for both gender. Clearance rates for the 10% cream treatment group vs. placebo were not statistically significant: total clearance was achieved in 46.8% of patients vs. 37.3% for placebo, and 75% to 100% reduction in wart area was observed in 54.5% of patients vs. 51.8% for placebo. Complete clearance rate of placebo (37.3%) was higher than expected. However, in recent clinical
studies, rates of spontaneous healing have been reported to be as high as 40%.12,13 Thorough care and increased hygiene during the treatment period as well as known irritant base excipients might have contributed collaterally to the placebo effect.

In previous studies conducted in China (Cheng SJ, Beijing; see Introduction), tea polyphenols achieved an overall complete clearance of external genital warts in 57% of patients. In a number of clinical trials, 0.5% podofilox (marketed as Condylox® in Germany and USA and as Condyline® in Russia) gave rise to a 30% to 70% complete response rate but had a recurrence rate of approximately 33% to 91%.2,3,14 Another patient-applied modality, 5% imiquimod cream (marketed as Aldara®), gave a 30% to 62% response rate in men3,7,15,16 and a 60% to 80% response rate in women,3,4,15,16 with approximately 13% to 19% recurrence rates in both gender within 6 months after the last administration.3,4,16 It is worth noting that response rates for Polyphenon® E in our study were comparable for both gender. Complete clearance for 15% ointment was 61% for males and 56.8% for females. A 75% to 100% reduction (treatment success) was observed in 80.5% of male patients and in 81.1% of female patients. The relatively poor response to 5% imiquimod cream in males has been linked to greater keratinization of the skin, which influences drug penetration, particularly on the penile shaft, which is the most common location of warts in males. The lower degree of keratinization and the semiocclusive effect of the foreskin may result in discontinuation of treatment and reduced recurrence is frequent. Local therapy with podophyllin or trichloroacetic acid requires multiple applications done by the physician and often causes considerable problems associated with local skin reactions, such as burning, itching and scarring.2-8 Other topical treatments such as imiquimod and podofilox are proven to be effective, but podofilox showed high recurrence rates, and both are also frequently associated with application site reactions, which may result in discontinuation of treatment and reduced patient compliance, ultimately affecting overall efficacy.

Superiority of the 15% ointment over placebo was established in this study, but not for the 10% cream. Therefore, the 15% ointment will be used for further development. As more than two thirds of the patients had complete clearance relatively late, between 8 and 12 weeks of treatment, it is anticipated that partial responders at week 12 may achieve complete clearance if the maximum treatment period is extended to 16 weeks.

In conclusion, the results of this study suggest that Polyphenon® E is a favourable new self-applicable treatment for external genital warts with properties that differ from other treatments. In view of the beneficial efficacy and excellent safety profile of the 15% ointment, this formulation will be further evaluated in prospective clinical studies.
Acknowledgements

We are indebted to the investigators who participated in this study, and we gratefully acknowledge their contribution, in Germany [Prof. G Gross, Rostock; Dr. KG Meyer, Berlin; Dr. H Pres, Berlin; Dr. C Bayerl, Mannheim; Dr. R Ellringmann, Kirchzarten; Dr. HW Grimm, Gernsheim; Dr. K Ihm, Munich; Dr. H Lupp, Bruchsal; Dr. P Pierchalla, Recklinghausen; Dr. D Quast, Osnabrucken; Prof. E Stockfleth, Kiel (now Berlin); Dr. HG Weidenhammer, Freiburg; Dr. RN Bartelt, Frankfurt; Dr. MS El Tobgui, Frankfurt; Dr. N Fischer, Munich; Dr. HW Hanf, Rees; Dr. P Kirschner, Berlin; Dr. M Sebastian, Mahlow; Dr. J Tyagi, Muehlheim; Dr. E Zahn, Berlin] and in Russia [Dr. O Moryleva; Dr. M Umakhanova; Dr. V Krasnopolskiy; Dr. N Podzolkova; Dr. A Kubanova; Dr. V Prilepskaya, all Moscow]. The authors would like to thank Quintiles GmbH as the conducting CRO and Omnicare Clinical Research Ltd for medical writing support.

References