

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-902

MEDICAL REVIEW

DEPUTY DIRECTOR MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUGS
OFFICE OF DRUG EVALUATION III**

DATE: October 31, 2006
FROM: Daniel A. Shames, MD
Deputy Director (Actg.)

TO: NDA 21-902

USAN NAME: Kunecatechins
(Trade, nonproprietary)

TRADENAME Veregen™ 15% Ointment

INDICATION Veregen™ 15% ointment is indicated for topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

SUBJECT: Concurrence of Approval Action

Background

In this application, the Sponsor is seeking approval of Veregen, a botanical drug product, for the proposed indication of the treatment of external genital and perianal warts (*condyloma acuminata*) in male and female adults. The product is to be applied topically three times daily. Veregen contains an extract of dried green tea leaves. The botanical material is wholly obtained from tea farms in Hunan China. The drug substance is produced by [redacted] and contains a mixture of tea polyphenols, including a family of related flavinoids, particularly catechins. The drug substance is a botanical mixture consisting of 8 known catechins (85-95% by weight) as well as associated compounds, some of which are unidentified.

Catechins have been extensively studied for their pharmacologic properties and reportedly exert anti-oxidant activity. [redacted]

The active ingredient(s) in the drug substance are not known and the unidentified associated compounds may also contribute to the activities of the drug substance. To ensure the continued safety and efficacy of marketed batches of Veregen, botanical controls on the source of the green tea leaves and the tea cultivars have been established.

Anogenital warts (condyloma acuminata), non-malignant tumors caused by infections of the Human Papilloma Virus (HPV), are one of the most common sexually transmitted diseases in the U.S. The annual prevalence of genital warts is estimated to be 1% of the sexually active population 15–49 years of age.

Destructive treatment modalities of anogenital warts include cryotherapy, trichloroacetic acid, carbon dioxide laser, electrocautery. Surgical excision is also a treatment option. Cryotherapy is a frequently used first-line treatment for anogenital warts and reportedly has a high response rate. Both laser ablation and electrocautery can be associated with potentially infectious HPV particles in the smoke plume.

FDA-approved topical therapies include podophyllotoxin and imiquimod. Both are available for patient's home use. Podofilox (e.g., Condylox) is a purified podophyllotoxin that is antimitotic, cytotoxic. Imiquimod 5% cream (Aldara) induces interferon production and is a cell-mediated immune response modifier. Both podofilox and imiquimod can cause local reactions such as erythema, irritation, ulceration, edema, pain and burning. Both podofilox and imiquimod are available by prescription for self application by the patient and both are pregnancy class C.

None of these treatments is 100% effective. Patients remain at risk for recurrence, re-infection and/or local disfigurement as a result of the treatment, as well as possible progression to malignancy in both men and women. Treatment failures may be influenced by the presence of sub clinical lesions, missed or deep lesions, as well as host immunosuppression. However, clinically normal skin and mucosa in the vicinity of HPV-associated lesions often contain HPV and this reservoir is thought to explain the recurrence, which is estimated to be 20-50% after treatment of genital warts. Although currently available therapies for HPV-related lesions may reduce viral load in HPV infection, they probably do not eliminate infectiousness.

This is the first botanical drug product approved in the United States since issuance of the Botanical Guidance.

Clinical Data

Efficacy

The two phase III trials which provided substantial evidence of effectiveness were studies CT 1017 and CT 1018. The trials were similar in study design and sample size. Each trial consisted of a 16-week treatment period and a treatment free-period of 12-weeks to assess for recurring warts in those patients who had complete clearance of all warts.

The primary efficacy endpoint for both trials was the proportion of patients with complete clearance of all warts (baseline and new) by week 16. Treatment groups consisted of 15% Ointment, 10% Ointment and Vehicle in a randomization ratio of 2:2:1. Each of the two pivotal trials succeeded in demonstrating statistically significant treatment effect for both doses of active study drug compared with Vehicle. The efficacy results based on the primary efficacy endpoint are shown in table 1.

Table 1 Primary Endpoint Efficacy Results (ITT-LOCF) N (%)

	Study CT 1017			Study CT 1018		
	Vehicle N=103	10% Oint N=199	15% Oint N=201	Vehicle N=104	10% Oint N=202	15% Oint N=196
Success	38 (36.9)	99 (49.7)	102 (50.7)	35 (33.7)	111 (55.0)	111 (56.6)
Fail	65 (63.1)	100 (50.3)	99 (49.3)	69 (66.3)	91 (45.0)	85 (43.4)
p-value	-	0.0384	0.0284	-	<0.001	<0.001

Source: Statistical Reviewer's Analysis using Fisher's exact test.

There was a trend for higher treatment effect observed in the 15% dose group compared to 10% in both of these independent well-controlled clinical trials. The 15% dose was proposed for approval by the Sponsor. . Approximately 51% of patients treated with the 15% ointment in study CT1017 achieved success compared to 37% for vehicle, with statistical significance at 0.02. Approximately 57% of patients treated with 15% ointment in study CT1018 reached success compared to 34% for vehicle, with statistical significance at <0.001.

Safety

Treatment-emergent AEs were defined as events with onset dates on or after the date of the first application of study treatment and up to 10 days after the last application of study treatment. Pre-treatment AEs reported with increased intensity during treatment were counted as treatment-emergent.

Higher proportions of subjects in the active treatment groups were reported to have treatment-emergent AEs, 84-85% across active arms versus 70% in control.

The most frequent and important drug-related adverse events occurred in the region of the local application site or in the draining lymph nodes. These included the following adverse events which resulted in study drug discontinuation: burning/itching, allergic vulvitis, contact dermatitis, suspicion of allergic reaction, genital herpes, allergic reaction, inguinal adenitis, and phimosis.

Several of these adverse events were thought to be allergic in nature. The dermal safety studies in healthy volunteers showed a contact sensitization rate of 2.4%. It is not known whether patients experiencing vesicular local reactions had allergic contact dermatitis or some other cause of vesicles e.g., HSV infection. Laboratory evaluation for HSV in these cases would have been helpful, but were not done.

Chemistry Manufacturing and Controls (CMC)

This is the first botanical product approved in the US. As such, CMC issues were extremely important in the review of this application. Much credit should be given to CMC review team especially Dr. Rajiv Agarwal. The Botanical Guidance deals primarily with the early phases of development so this application required pro-active and

innovative thinking on the part of both the Office of New Drug Chemistry (ONDC) and Botanical teams. There were over twenty communications between the Agency and the Sponsor regarding CMC issues.

In addition, selection of United States Adopted Name (USAN) name required significant work and creative thinking on the part of the CMC group. The USAN council rarely creates names for chemical mixtures but "conjugated estrogens" is a notable exception. Kunecatechins was the name accepted by the USAN council. At the time of the writing of this memo, the sponsor was intending to dispute the USAN name.

Drug substance

Kunecatechins is a mixture of catechins (85 – 95% by weight). The major component is (-)-Epigallocatechin gallate (EGCg), which comprises _____ of the total. _____ catechins are identified and quantitated (_____ individual catechins and _____ as a group) in addition to EGCg they are (-)-Epigallocatechin (EGC), (-)-Epicatechin gallate (ECg), (-)-Epicatechin (EC), (-)-Gallocatechin gallate (GCg), (-)-Catechin gallate (Cg), (-)-Gallocatechin (GC), and (+)-Catechin (C). Kunecatechins also contains gallic acid, caffeine, and theobromine which together constitute about 2.5% of the drug substance. The remaining amount of the botanical drug substance contains undefined mixtures of catechin-related compounds, which is also controlled in the drug substance.

The _____ steps may epimerize or dimerize some active components into other active components. Since the activity of each individual catechins peak is not known, it must be assumed that each dimerized or epimerized component has activity. Based on the information provided by the NDA holder (lot # and amounts of each batch in a lot) and information provided on catechin components present in each batch, a virtual blending was performed by the FDA and an acceptance criteria of catechins in the drug substance was proposed based on the amounts contained in clinical batches which were determined to be efficacious. The Sponsor and the CMC group agreed that the acceptance criteria of Kunecatechins should be based on the $\pm 10\%$ of lower (efficacy) and higher amounts (safety) of each component present in the clinical batches.



Drug Product

The drug product is an ointment containing 15% (w/w) Kunecatechins drug substance suspended in a hydrocarbon base. Excipients are isopropyl myristate, white petrolatum, cera alba (white wax), propylene glycol palmitostearate (also known as propylene glycol monopalmitostearate), and oleyl alcohol. Oleyl alcohol is identified as a penetration enhancer in this formulation.

The drug substance is a mixture of chemical species (catechins and other related compounds) and activity is considered to be from the whole mixture and not from an individual component. It is not known if the total activity from individual catechin

components is additive or synergistic. Drug product specifications have an HPLC fingerprint test for all catechin components, but this test shows only their presence and not the amounts. Therefore, it was important to assure that these components are present at least at the levels which were seen in clinical batches to address efficacy, but not above those levels to address safety. Since it is assumed that each catechin may be active, to address the overall quality of the drug product, the minor catechin components in the drug product should also be controlled. Therefore, the acceptance criteria of catechins in the drug product, as with the drug substance, is based on the $\pm 10\%$ of lower (efficacy) and higher amounts (safety) of each component present in the clinical batches.

A total of 8 catechins are identified and quantitated in the drug product. The four major peaks (EGCg, EGC, EC and ECg) are controlled individually, while the four minor peaks (GCg, GC, Cg and C) are controlled as a group of four. The four minor peaks (as opposed to five in the drug substance) can result from epimerization of the major peaks.

The primary stability batches are used to establish the expiration date even though the assay values of catechins in these batches are different (lower or higher) than the acceptance criteria set based on clinical efficacy. When the stability characteristics of the catechins and ointment matrix is evaluated, it is found that catechins and ointment matrix is stable when stored at room temperature. At other ICH storage conditions, *phase separation* was seen and this resulted in a compromised content uniformity of catechins within a tube. Based on the stability characteristics of the drug product at intermediate and at accelerated conditions, it is deemed that prior to dispensing to the patient, the drug product should be stored refrigerated at 2°C to 8°C (36°F to 46°F). After dispensing, consumer should not store the drug product above 25°C (77°F). The stability data supports only 12 months of expiry dating when the ointment is stored below 25°C.

Clinical Pharmacology and Biopharmaceutics

The biopharmaceutics team concluded that the totality of the data provided (i.e. nonclinical findings, clinical pharmacology and clinical trial data) suggested that the systemic exposure of the four major catechins evaluated obtained following topical administration of Veregen Ointment, 15 % was minimal. Biopharmaceutics supported this conclusion with the observations that the clinical safety data indicated a low incidence of adverse events other than local reactions, and the nonclinical findings indicated that there were no apparent systemic toxicities noted in minipigs after topical treatment with the drug product.

The assessment of the systemic exposure relied on the nonclinical and clinical safety data because the results obtained in the pharmacokinetic study # CT 1007 on the systemic exposure of the four major catechins (EGCg, EGC, ECg and EC) in Veregen Ointment, 15 % could not be interpreted. This was an open label comparative assessment of the pharmacokinetics of repeated topical application of Veregen ointment, 15% (3 times daily for 3 weeks) with a single oral intake of 400mL of brewed green tea. The plasma samples were measured on day 1, 3, 14 and 21 in the topical arm. This study suggested that the systemic exposure to the four most abundant catechins in green tea extract may be minimal following topical application; however, the data were potentially flawed

because the samples were stored for an extended period of time before they were analyzed, and the plasma concentrations of the catechins may have degraded. Although the analytical method used to assay the four catechins in plasma was validated for sensitivity, accuracy, and precision, the long term stability evaluation to cover the period of sample collection to sample analyses (for the first patient) did not meet the acceptance criteria.

The deficiency of the long term analytical stability evaluation used to assay for the catechins in this pharmacokinetic study will be resolved via a Phase 4 study. This study agreed upon with the applicant on 26-Oct-06 is described below and is submitted in the Approval letter:

A phase 4 study comparing the pharmacokinetics of catechins following topical application of Veregen Ointment, 15%, with that obtained after oral administration of green tea solution. The two-arm study will be designed to enroll into one arm 20 evaluable patients ("completer") with external genital and perianal warts who will be treated 3 times daily for 7 days with Veregen Ointment, 15%, and into the second arm 20 evaluable healthy volunteers, who are to drink a green tea solution 3 times daily for 7 days. Blood samples for the analysis of catechin levels will be obtained prior to and at several sampling time points (over 12 hours) after oral intake of a green tea solution or topical application of Veregen Ointment, 15%, respectively, at Days 1 and 7. The study will be carried out with material from the final commercial source for API to be established in and fulfilling the FDA-defined specifications for the botanical drug substance and drug product. The timeline is as follows:

Protocol to be submitted by July 2007.

Study Start Date by January 2008.

Final Report Submission by January 2009.

Regulatory conclusion

I concur with DDDP's conclusion that NDA 21-902 (Veregen 15% Ointment) should be approved for the topical treatment of external genital and perianal warts (*Condylomata acuminata*) in immunocompetent patients 18 years and older.

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Deputy Director (Actg.)
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CDER/FDA

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/s/

Daniel A. Shames
10/31/2006 11:03:39 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21- 902
Submission Code	N - 000
Letter Date	September 23, 2005
Stamp Date	September 30, 2005
PDUFA Goal Date	October 31, 2006
Reviewer Name	Elektra J. Papadopoulos, M.D.
Review Completion Date	October 15, 2006
Established Name	Kunecatechins
Proposed Trade Name	Polyphenon® E 15% Ointment
Proposed Therapeutic Class	Immunomodulatory
Applicant	MediGene, Inc.
Priority Designation	S
Formulation	Ointment
Dosing Regimen	Topical, three times daily
Indication	treatment of external genital and perianal warts
Intended Population	Adult

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List of Abbreviations

AE	adverse event
CRF	Case report form
GCP	Good clinical practices
HPV	Human papilloma virus
ITT	Intention-to-treat
LOCF	Last observation carried forward
SAE	serious adverse event
Polyphenon E® 15% ointment	15% Ointment
Polyphenon E® 10% ointment	10% Ointment
Polyphenon E® 10% cream	10% Cream

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of the NDA with revised labeling and recommendations for post-marketing studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is recommended at this time.

1.2.2 Required Phase 4 Commitments

The following two phase 4 commitments are requested to inform labeling:

- 1) A study of PK to assess the systemic absorption of Polyphenon 15% Ointment after topical application under maximum use conditions. Oral intake of green tea should be used as a positive control; and
- 2) A study of Polyphenon 15% Ointment to evaluate the rate of recurrence of external genital and perianal warts for patients experiencing complete clearance.

1.2.3 Other Phase 4 Requests

The Agency is not requesting additional phase 4 studies for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The submission contains clinical data for the study of Polyphenon® E (Polyphenon) ointment applied topically, three times daily for the treatment of perianal and genital condyloma accuminata. The proposed mechanism of action is immunomodulatory. The clinical program included two pivotal phase 3 clinical trials, CT 1017 and CT 1018, and one phase 2/3 trial, CT 1005 (Table 3). The primary endpoint for studies CT 1017 and CT 1018 was complete clearance of all baseline and new genital and perianal warts by week 16 of treatment. For study CT 1005, the primary endpoint was complete clearance of all baseline warts by week 12 of treatment.

In study CT 1005, Polyphenon 10% Cream and 15% Ointment, were compared with matching placebo cream and ointment, respectively. The 10% Cream failed to prove superiority over placebo and the 15% ointment did not meet criteria for efficacy based on the prespecified analytic plan. The sponsor hypothesized that the response rate may improve with longer duration of treatment and, therefore, the two pivotal studies included a treatment period of up to 16 weeks. In both of the pivotal Phase 3 clinical studies, CT 1017 and CT 1018, two Polyphenon ointment strengths, 10% and 15%, were studied. In both studies, patients were randomized 2:2:1 to 10% Ointment, 15% Ointment and matching placebo ointment (Vehicle). CT 1017 included a total of 503 randomized patients and CT 1018 included 502 randomized patients. A total of 1,085 adult patients with external genital and perianal warts received Polyphenon ointment (either 10% or 15%) at a frequency of three times daily for up to 16 weeks in the clinical development program.

1.3.2 Efficacy

The two pivotal phase 3 trials were studies CT 1017 and CT 1018. Both trials were similar in study design and sample size. Each trial consisted of a 16-week treatment period and a treatment free-period of 12-weeks to assess for recurring warts for those patients who had complete clearance of all warts. Clinical response in each trial was defined as complete clearance of all warts, baseline and new, by week 16. Treatment groups consisted of 15% Ointment, 10% Ointment and Vehicle in a randomization ratio of 2:2:1 in both trials. The prespecified primary analysis method was also the same in both trials, Fisher's exact test imputing missing data as the last observation carried forward (LOCF). Each of the two pivotal trials succeeded in demonstrating statistically significant treatment effect for both doses of active study drug compared with Vehicle using the pre-specified primary endpoints and multiplicity adjustment (Hochberg procedure). The efficacy results based on the primary efficacy endpoint are shown in the following table.

Table 1 Primary Endpoint Efficacy Results (ITT-LOCF) N (%)

	Study CT 1017			Study CT 1018		
	Vehicle N=103	10% Oint N=199	15% Oint N=201	Vehicle N=104	10% Oint N=202	15% Oint N=196
Success	38 (36.9)	99 (49.7)	102 (50.7)	35 (33.7)	111 (55.0)	111 (56.6)
Fail	65 (63.1)	100 (50.3)	99 (49.3)	69 (66.3)	91 (45.0)	85 (43.4)
p-value	-	0.0384	0.0284	-	<0.001	<0.001

Source: Statistical Reviewer's Analysis using Fisher's exact test.

Both treatment groups had similar treatment effects that reached statistical significance by the protocol-defined primary analysis. Although there was a small trend in higher treatment effect observed in the 15% dose group, this trend is seemingly real as it has been observed in two independent well-controlled clinical trials.

A small minority of patients in the clinical development program were from the United States. Only study CT 1018 included U.S. centers. A total of 50 patients in study CT 1018 were from the United States; 9, 20, and 21 were randomized to Vehicle, 10% Ointment, 15% Ointment, respectively. As will be shown later in this review, there appeared to be variable response rates based upon geographic location. Although, response rates tended to be lower in U.S. population compared with the study results overall, a trend toward treatment effect was observed in the U.S. population.

The clinical efficacy observed in one of the two pivotal trials, CT 1017, was affected by a single large investigational site (Moscow, Russia; Site # 01). In a sensitivity analysis by the FDA statistical reviewer, the efficacy was evaluated without this site and the trial failed to achieve statistical significance. This investigational site was among the sites that were audited by FDA and no findings of significance were noted. The clinical efficacy observed in study CT 1018 was more robust and did not appear to be influenced by any single investigational site.

Given the possibility that anogenital warts may recur and new lesions may develop, data regarding recurrence rates as well as the safety and efficacy retreatment are useful to evaluate. None of the studies was designed to assess for the safety and efficacy of retreatment upon relapse. Although treatment responders in both pivotal phase 3 trials were to enter a 12-week follow-up period to assess for recurrence, the method of recording data in these studies made it impossible to estimate recurrence rates after treatment because the sponsor recorded both missing data and zero count data in the same way. As a result, it was not possible to distinguish whether a subject failed to appear for follow-up evaluation or did appear for the evaluation and had no warts.

1.3.3 Safety

Adverse events (AEs) occurring during the treatment period were those with onset dates up to 10 days after the last application of study treatment or *any* AE for subjects that did not enter a follow-up period. AEs occurring during the follow-up period were those with onset dates > 10 days after the date of the last application. With the exception of study CT 1007 in which there was no follow-up period, these follow-up periods were 12-week treatment-free periods. Treatment-emergent AEs were defined as events with onset dates on or after the date of the first application of study treatment and up to 10 days after the last application of study treatment. Pre-treatment AEs reported with increased intensity during treatment were counted as treatment-emergent.

An overview of AEs occurring during study treatment in studies of three times daily use of study ointment follows (see Table 2). This table includes Studies CT 1005, CT 1007, CT 1017, and CT 1018. Adverse events/local reactions with onset dates up to 10 days after the last application of study treatment were included in this table. AEs/local reactions with onset dates greater than 10 days after the last application of study treatment were also included if the patient did not enter the follow-up period. Of note, Studies CT 1005 and CT 1007 were of shorter duration than the pivotal phase 3 trials.

Table 2 Overview of All Adverse Events during Treatment [Number (%)]

	Placebo (N=247)	10% Oint (N=400)	15% Oint (N=515)
Men	N=137	N=212	N=266
Women	N=110	N=188	N=249
Treatment-Emergent AE			
Men	84 (61)	180 (85)	224 (84)
Women	90 (82)	161 (86)	209 (84)
Total	174 (70)	341 (85)	433 (84)
Serious AE			
Men	0	1 (<1)	0
Women	0	3 (2)	5 (2)
Total	0	4 (1)	5 (1)
Serious AERelated to Study Treatment			
Men	0	0	0
Women	0	1 (<1)	2 (1)
Total	0	1 (<1)	2 (<1)
Maximum Intensity of AE			
Mild			
Men	52 (38)	51 (24)	56 (21)
Women	35 (32)	40 (21)	67 (27)
Total	87 (35)	91 (23)	123 (24)
Moderate			
Men	33 (24)	88 (42)	116 (44)
Women	45 (41)	59 (31)	72 (29)
Total	78 (32)	147 (37)	188 (36)
Severe			
Men	3 (2)	44 (21)	55 (21)
Women	13 (12)	66 (35)	75 (30)
Total	16 (6)	110 (28)	130 (25)
Discontinued Treatment Due to AE*			
Men	0	1 (<1)	5 (2)
Women	1 (1)	3 (2)	8 (3)
Total	1 (<1)	4 (1)	13 (2)

*Includes those patients for whom the adverse event/local reaction was not the primary reason for discontinuation from the study.

Higher proportions of subjects in the active treatment groups were reported to have treatment-emergent AEs, 84-85% across active arms versus 70% in control. Nine serious AEs were observed and accounted for 1% of subjects in each of the active treatment arms compared with no reported serious AEs in the control group. Of these, three were deemed related to study drug. Serious AEs were observed more commonly among women. Eight women were reported to have serious AEs compared with one man. Of the nine serious AEs, three were considered related to study drug and all three occurred in women.

The distribution of AEs was such that a higher proportion of subjects had moderate and severe AEs in the active arms compared with control. This was true even though this group had the shortest exposure to treatment (Table 24). The percentage of subjects who discontinued study treatment in the active arms was also higher in the active treatment arms compared with control. The proportions were 2.5% in the 15% group, 1% in the 10% group and 0.4% in the control group.

1.3.4 Dosing Regimen and Administration

The dosing regimen is three times daily topical application. The maximum treatment period evaluated was 16-weeks. The product label should reflect that treatment beyond 16-weeks has not been studied.

1.3.5 Drug-Drug Interactions

Per protocol, the use of other concomitant topical therapies was prohibited. The clinical protocol of the pivotal trials were amended to allow the use of systemic antiviral therapy, e.g. acyclovir and related compounds. No specific drug-drug interaction studies were conducted, however.

1.3.6 Special Populations

The efficacy and safety of Polyphenon was evaluated in subgroups defined by age, gender and race. A higher incidence of serious adverse and severe events in women compared with men was observed and will be described in labeling under the adverse reactions section. No apparent differences in safety or clinical efficacy were observed in subgroups defined by race; however, the majority of subjects in the clinical studies were Caucasian or Hispanic with Asian and Black patients comprising a very small number of those studied. Pregnant and breast-feeding patients were excluded.

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2 INTRODUCTION AND BACKGROUND

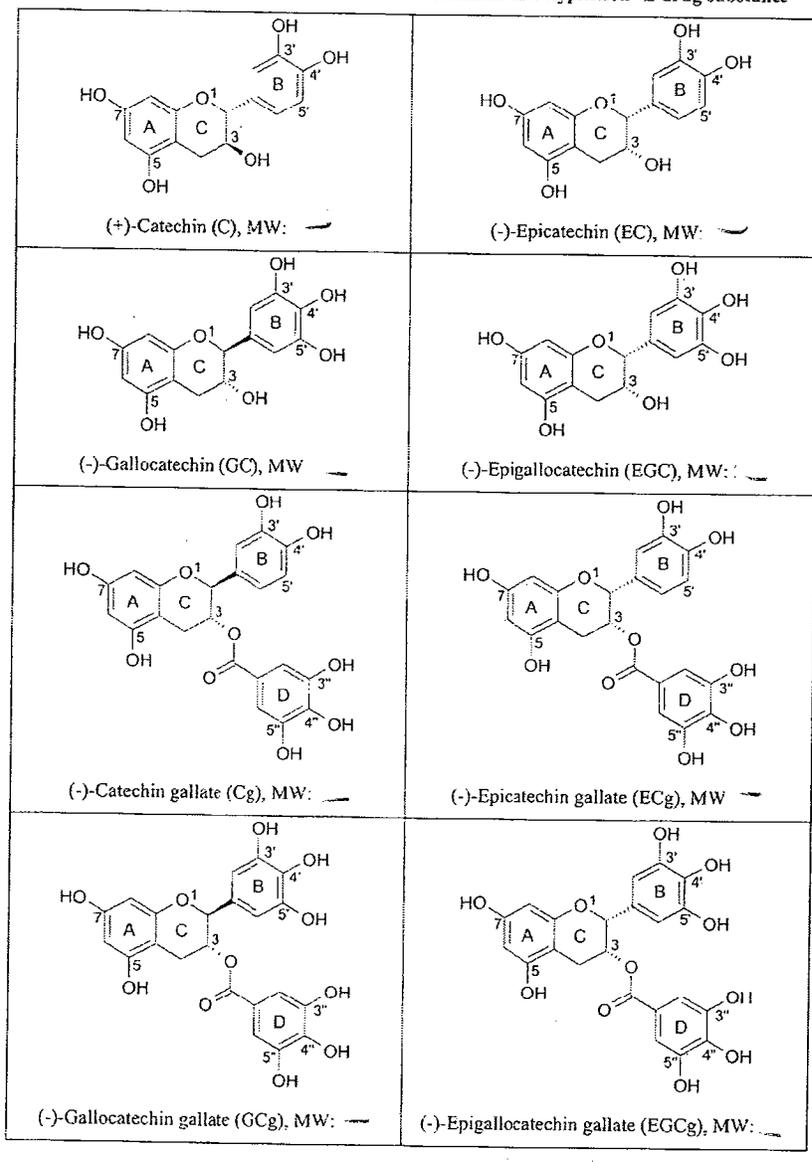
2.1 Product Information

Polyphenon E is a defined extract of dried green tea leaves of the species *Camellia sinensis* var. *sinensis* belonging to the Theaceae family. The botanical material is from tea farms in [redacted]. The extract is produced [redacted] and contains more than [redacted] of a mixture of tea polyphenols, including a family of related flavinoids, particularly catechins. The main catechin, in Polyphenon E, is (-)-epigallocatechin gallate (EGCg).

Polyphenon E drug substance is a botanical mixture consisting of 8 known catechins (85-95% by weight) as well as associated compounds, some of which are unidentified. Catechins have been extensively studied for their pharmacologic properties and reportedly exert antiviral as well as anti-oxidant activity and bind to some proteins. However, the active ingredient in the drug substance are not known and the unidentified associated compounds may also contribute to the activities of the drug substance. The structures and molecular weight of the 8 catechins are adapted from the NDA and given in the figure below. To ensure safety and efficacy of marketed batches of Polyphenon E, botanical controls on the source of the green tea leaves, the tea cultivars have been established (See Botanical Review by Dr. Jihui Dou).

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Figure 2.6.1-1: Chemical structure of catechins contained in Polyphenon® E drug substance



The drug product is a topical formulation consisting of the active ingredient, Polyphenon E 15%, and the following excipients: isopropyl myristate, white petroleum, cera alba (White wax), propylene glycol palmitostearate, and oleyl alcohol. Dosing is approximately 250 mg per application (three times per day). The final drug product is a yellow-brown ointment.

The clinical batches studied in the phase 3 pivotal studies are shown below. To ensure safety and efficacy of marketed batches of Polyphenon E 15%, the final product specifications and release criteria will include establishment of ranges based on the catechin components measured in the 15% Ointment batches evaluated in the phase 3 pivotal studies. See CMC Review by Dr. Rajiv Agarwal).

Study CT1018:

Manufacturer: _____

15% Ointment: Batch number: 000.00402; B000.10103

E 10% Ointment: Batch number: 000.38402; B000.09903

Placebo Ointment: Batch number: 000.09603

Study CT1017:

15% Ointment: Batch numbers: 000.00402 and 000.43902

10% Ointment: Batch number: 000.38402

Placebo Ointment: Batch number: 000.00302

2.2 Currently Available Treatment

Anogenital warts (condyloma acuminata), non-malignant tumors caused by infections of the Human Papilloma Virus (HPV), are one of the most common sexually transmitted diseases in the U.S. Condyloma acuminata are generally caused by HPV strains 6 and 11, whereas, HPV 16 and 18 are among the HPV strains associated with the development of cervical cancer. The annual prevalence of genital warts is estimated to be 1% of the sexually active population 15–49 years of age.

Destructive treatment modalities of anogenital warts include cryotherapy, trichloroacetic acid, carbon dioxide laser, electrocautery. Surgical excision is also a treatment option. Cryotherapy is a frequently used first-line treatment for anogenital warts and reportedly has a high response rate. Both laser ablation and electrocautery can be associated with potentially infectious HPV particles in the smoke plume.

FDA-approved topical therapies include podophyllotoxin and imiquimod. Both are available for patient's home use. Podofilox (e.g., Condylox) is a purified podophyllotoxin that is antimitotic, cytotoxic. Imiquimod 5% cream (Aldara) induces interferon production and is a cell-mediated immune response modifier. Both podofilox and imiquimod can cause local reactions such as erythema, irritation, ulceration, edema, pain and burning. Both podofilox and imiquimod are available by prescription for self application by the patient and both are pregnancy class C.

None of these treatments is 100% effective. Patients remain at risk for recurrence, re-infection, local disfigurement as a result of the treatment, as well as possible progression to malignancy in both men and women. Treatment failures may be influenced by the presence of subclinical lesions, missed or deep lesions, as well as host immunosuppression. However, clinically normal skin and mucosa in the vicinity of HPV-associated lesions often contain HPV and this reservoir is thought to explain the recurrence, which is estimated to be 20-50% after treatment of genital warts. Although currently available therapies for HPV-related lesions may reduce viral load in HPV infection, they probably do not eliminate infectiousness.

2.3 Availability of Proposed Active Ingredient in the United States

The product's active ingredient, or ingredients, have not been identified, but are thought to be the catechins derived from green tea. The drug substance in Polyphenon E® 15% ointment is considered a new molecular entity and is not currently marketed in the United States. If approved, this would be the first green tea-derived drug product to be approved by the FDA.

2.4 Important Issues with Pharmacologically Related Products

This is a new molecular entity. However, the study of other green-tea products is underway in various cancer chemoprevention trials. The drugs are green tea extracts, epigallocatechin gallate (EGCG) and polyphenon E, given orally in capsule form. Hepatotoxicity was noted in the pre-clinical trials done in dogs and some dogs died early or became moribund and were sacrificed in the middle and high dose groups of 500 or 1,000 mg/kg/day of polyphenon E. However, the data obtained from preclinical studies in dogs were with polyphenon E given orally, at relatively high doses and under fasting conditions, and these data do not raise a safety concern for hepatotoxicity with topically applied Polyphenon E for external genital and perianal warts. Please also refer to Section 3.2 regarding animal pharmacology/toxicology of this review.

2.5 Presubmission Regulatory Activity

The associated IND with this submission was IND 56,401. Meetings held with the sponsor included a Pre-NDA on January 24, 2005, an End of Phase 2 (EOP2) meeting on November 19, 2001 and a Guidance meeting held June 11, 2001. An SPA letter was also issued on June 12, 2002.

At the EOP2 meeting, the FDA's advice to the sponsor included the following considerations:

- (1) All warts, whether present at baseline or not, should be cleared in order to be considered for success. Patients who do not have complete clearance of all warts by the end of the treatment period, should be considered non-responders.
- (2) The product should demonstrate effectiveness in both genders combined, although stratification by gender should be provided.
- (3) Some discussions also took place about the possibility of isopropyl myristate (IPM) being an active ingredient in this product as well as polyphenon E. If IPM is considered active, then the product would be considered a fixed-combination drug, and a factorial design would be needed to determine the contribution of each of the active ingredients.
- (4) Dermal safety studies should be done with the to-be-marketed formulation.
- (5) The sponsor was to refer to ICH E5 Guidance regarding the acceptability of foreign data.
- (6) The Agency emphasized the importance of the data base of 300 to 600 patients treated with the final to be marketed formulation.

- (7) The FDA encouraged the sponsor to perform a dose ranging study for selection of the optimal dose prior to phase 3.
- (8) Phototoxicity studies and photoallergenicity studies could be waived since the product is to be used over covered areas.
- (9) FDA's comments regarding the phase 3 study, CT 1005, included the following:
 - (a) The study included a shorter treatment duration (12 weeks, instead of 16).
 - (b) The study failed to demonstrate efficacy under the criteria pre-specified in the protocol, especially when adjustments for multiplicity is taken into account.
 - (c) The placebo arms from the two dosage forms were combined in the analysis and it was not clear that adequate criteria for pooling the arms were pre-specified in the protocol.

2.6 Other Relevant Background Information

As stated earlier, there have been no green tea-derived products (either oral or topical) which have received FDA approval for this or any other indication.

Polyphenon® E ointment has not been approved for marketing in any other country. Two other topical medications are FDA approved for anogenital warts. Oclassen's Condylox solution (containing 0.5% podophilin) was approved in 1990, and 3M's Aldara ointment (containing 5% imiquimod) was approved in 1997. There is also a gel formulation of Condylox.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and Botanical

Please see CMC review by Dr. Rajiv Agarwal and Dr. Jinhui Dou. All of the botanical issues as well as the CMC issues have been adequately addressed by applicant. The issues that Dr. Dou has identified in his botanical review include the following.

- The applicant should properly identify the tea variety/cultivars as there are two varieties of *Camellia sinensis*. This item has been addressed by the applicant. The variety of the originating plant for the botanical raw material is *Camellia sinensis* (L.) O. Kuntze [Family: Theaceae]
- Established cultivars and tea farms that have been used during clinical development should be maintained. Any new varieties/cultivars as well as tea farm suppliers should be pre-approved by the Agency before mass production of marketing batches. The applicant has provided certificates of authenticity of ~ tea cultivars including names (both common and scientific names), descriptions (with photographs), and signature of the botanist who identified the tea cultivars.

- Bioassays used for comparing the similarity of different batches in the NDA should be further developed and validated to assist in the CMC of future marketing batches, or as a means to evaluate the comparability of new sources of botanical raw material to those already studied.

Dr. Agarwal has identified the following CMC issues:

The final product contains 90% catechins and a 10% unknown component by weight. Because it is not known which catechin component (or combination of catechins) is active, a reference range will need to be met for each of the main catechin components prior to lot release. The Agency will also have acceptance criteria for the 10% unknown component.

3.2 Animal Pharmacology/Toxicology

Please see animal pharmacology/toxicology review by Dr. Jiaquin Yao. A 13-week toxicity study in fasted dogs showed hepatotoxicity of polyphenon E with oral doses of purified EGCG of starting at 120 mg/kg/day. Three animals from the 120 mg/kg/day dose group and one animal from the 400 mg/kg/day dose group died or was sacrificed from a moribund condition (Isbrucker et al, 2006).

No hepatic toxicity was noted with topical use of 15% Ointment in a minipig study under this IND. Under conditions for anogenital warts, the amount of polyphenon E to be applied topically would be approximately 2 mg/kg/day. If one conservatively assumes 100% absorption, the safety margin is at least 50 fold from the dog study in fasting dogs to humans with topical use. It is, therefore, unlikely that hepatotoxicity would result with topical use in this indication.

This drug product induced minimal to severe local irritation including erythema, edema, and inflammatory reactions when topically applied to rats, rabbits, and mini-pigs. This drug product also caused severe local reactions in vaginal mucosa after vaginal application in female rats and mini-pigs. Three times daily vaginal administration of Polyphenon E 15% ointment for a total period of nine days resulted in substantially higher plasma concentrations and exposures for EGCG than those observed following topical administration. If licensed, product labeling will convey that the product is not for internal use. Local lymph node assay suggested that Polyphenon E Ointment had the potential to induced contact sensitization and it was a sensitizer in the guinea-pig. If licensed, sensitization potential will be described in labeling.

One carcinogenicity study conducted in a particular model (p53 mice) in which test substance was administered orally was negative. Based on the entire database, which included lack of concerning signals in the chronic minipig study, the Agency did not require a topical carcinogenicity study.

3.3 Clinical Pharmacology

Please see clinical pharmacology review by Dr. Adebowl. Studies of systemic absorption of polyphenon E in humans were not interpretable due to degradation of the catechins. The plasma

samples collected were tested outside of the window for stability, which was 7 days. Therefore, we do not know whether lack of detection of catechins was due to degradation or due to lack of absorption.

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4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data for the review included the trials conducted by the sponsor and submitted in the NDA application.

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4.2 Tables of Clinical Studies

Table 3 Listing of all Clinical Studies

<i>Type of Study;Phase</i>	<i>Study</i>	<i>Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dosage Regime</i>	<i>No. of Subjects</i>
PK--2	CT 1007	Comparative plasma concentrations and PK of topically applied 15% Oint. To condyloma and oral intake of green tea	Open-Label, Multi-Center	15% Oint: topical 3 x daily for 3 weeks; Green tea: single oral	38
Efficacy + Safety--2/3	CT 1005	Efficacy and safety in the treatment of external genital warts	Randomized, Double-Blind, Four-Arm Parallel-Group, Placebo-Controlled, Multi-Center	15% Oint.; Vehicle Oint.; 10% Cream; Vehicle Cream; 3 x daily topical for up to 12 weeks	272 (80, 40, 79, 43)
Efficacy + Safety--3 pivotal	CT 1017	Efficacy and safety in the treatment of external genital warts	Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled, Multi-Center	15% Oint.; 10% Oint.; Placebo Oint. 3 x daily topical for up to 16 weeks	503 (201,199, 103)
Efficacy + Safety--3 pivotal	CT 1018	Efficacy and safety in the treatment of external genital warts	Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled, Multi-Center	15% Oint.; 10% Oint.; Placebo Oint. 3 x daily topical for up to 16 weeks	502 (196,202, 104)
Dermal Tolerance-1	CT 1004	Suppression of UV-induced erythema	Randomized, Double-Blind, Vehicle- controlled	18 different Polyphenon E formulations / vehicles	42
Dermal Tolerance-1	CT 1016	Sensitization potential to intact skin	Randomized, Observer-Blind, Placebo- Controlled	15% Oint.; Vehicle Oint.	219
Dermal Tolerance-1	CT 1019	Local irritation on intact and scarified skin (back)	Randomized, Observer-Blind, Placebo- Controlled	15% Oint.; Vehicle Oint.; 0.2% SDS (positive control); 0.9% NaCl (negative control) Topical under occlusion for 22 hours	20
Proof of Concept--2	CT 1101	Safety and Efficacy in Actinic Keratosis	Randomized, Double-Blind, Two-Arm Placebo-Controlled, Multi-Center	15% Oint.; Placebo Oint.	6 (42, 20)

Table 3 Listing of all Clinical Studies (cont.)

<i>Type of Study;Phase</i>	<i>Study</i>	<i>Objective(s) of the Study</i>	<i>Study Design and Type of Control</i>	<i>Test Product(s); Dosage Regime</i>	<i>No. of Subjects</i>
Safety and Efficacy---2	CT 1008	Safety and Efficacy in Common warts	Randomized, Double-Blind, Two-Arm Parallel-Group, Placebo-Controlled, Multicen.	10% Cream Placebo Cream	60 (31, 29)
Safety and Efficacy---2	EPI-003	Tolerability in women vs. comparator products	Randomized, Observer-Blind, Active- Controlled, Multi-center	15% Oint.; Imiquimod 5% Cream; Podofilox 0.5% gel	81 (34, 35, 12)
Efficacy and Safety-1/2	EPI-004	Efficacy and tolerability in men	Randomized, Double-Blind, Placebo-Controlled, Multi-center	15% Oint.; Placebo	83 (52, 31)

4.3 Review Strategy

The two pivotal phase 3 trials, CT 1017 and CT 1018, were reviewed for clinical efficacy. All trials were reviewed for safety with primary focus on the trials in the target population with external genital and perianal condyloma as well as the dermal safety studies in healthy volunteers.

4.4 Data Quality and Integrity

Please also see statistical review by Dr. Mat Soukup for greater detail. The protocol defined primary analyses for both pivotal Phase 3 trials were to be based on the ITT population, all subjects randomized and dispensed drug product. However, the analyses provided in the sponsor's clinical study reports excluded patients who had baseline data only. Therefore, the FDAs efficacy results differ slightly from that of the sponsor.

The efficacy analyzable data sets contained imputed data without distinction between imputed values and those that were observed. This made it difficult for the FDA reviewers to determine which values were imputed and which were actual observations. Differences also were noted between raw datasets containing patient disposition data found in the isedern folder and that found in the issdern folder. The poor quality of the data sets led to the Agency's request for resubmission of the data sets on several occasions.

The FDA undertook one domestic and two foreign inspections. The sites investigated were from both Study 17 and Study 18 as follows:

Dr. Swinehart	Denver, CO	Site # 09
Dr. Santander	Santiago, Chile	Site # 04
Dr. Grigorian	Moscow, Russia	Site # 01

No findings of significance were noted at any of the sites. A list of observations was compiled for site #9. However, these observations were adequately addressed by the clinical investigator and no regulatory action was deemed necessary.

4.5 Compliance with Good Clinical Practices

In study CT 1005, a phase 2/3 trial, one investigational center was found by the applicant to have ICH/GCP violations. This was investigational site #45 in Moscow. The applicant has excluded this center from the efficacy and safety analysis of this study. The noncompliance issues observed were as follows:

- Study medication was not accurately dispensed to patients. In four cases, medication from one patient was given to another patient. As a result, study medication was missing for some patients and therefore could not be treated further.
- For 8 patients, study assessments (e.g. blood sampling) were performed before patients had signed the informed consent form.
- Laboratory results were incomplete for 11 patients.
- Drug accountability was incomplete and in some cases obscure.

The applicant noted no violations in adverse events and serious adverse event reporting at this site. Safety data from this site was reviewed by both the applicant as well as the FDA and was not deemed to have an influence on the overall study results.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators. None of the financial arrangements raised any questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Study CT 1007 was designed to investigate the plasma concentrations and pharmacokinetics (PK) of Polyphenon 15% Ointment administered over a 3-week period to subjects with

condyloma accuminata and to compare these data with plasma concentrations and PK of tea catechins following oral intake of green tea. A total of 38 patients were randomized into this study. Subjects had the option to continue study drug in a treatment phase up to a total exposure of 16 weeks. As stated previously in this review, this study was inconclusive as degradation of stored samples made it impossible to assess plasma drug levels. It is therefore, not possible to describe in detail the degree of absorption of polyphenon from topical use in patients with condyloma accuminata.

Reviewer's comment: This information is important for product labeling and it has been recommended that a new PK study be performed as a post-marketing commitment.

5.2 Pharmacodynamics

The mechanism of action of Polyphenon E is unknown and the sponsor has not identified any known accepted pharmacodynamic markers for activity.

5.3 Exposure-Response Relationships

Only two concentrations of Polyphenon E were evaluated in the phase 2 and phase 3 clinical studies, 10% and 15%. A small trend in higher efficacy, consisting of an absolute difference of 1-2% across the two phase 3 studies, was observed in the 15% polyphenon ointment group compared with 10% polyphenon ointment.

Reviewer's comment: This is not considered to be a complete dose-ranging as only two concentrations were studied and very little difference was deemed likely between these two concentrations.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

Two independent multicenter, multinational, randomized, double-blind, placebo-controlled phase 3 trials in immunocompetent men and women with genital and perianal condyloma were conducted. The study design was similar in both trials. In both studies, patients were randomized 2:2:1 to Polyphenon 10% , Polyphenon 15% or placebo three times daily topically. The primary endpoint was complete clinical (visual) clearance of all warts by 16 weeks of treatment. Biopsies for histology or viral typing were not performed. Patients who cleared at or before week 16 were to go into a follow-up period of up to 12 weeks where they were to be followed for relapse. Patient photography of the treatment area was optional in the clinical study.

6.1.2 General Discussion of Endpoints

The primary endpoint in both pivotal trials was complete clearance of all genital warts. At the end-of-phase 2 meeting, the Agency advised the sponsor that the primary efficacy variable should be the proportion of patients showing complete clearance of **all** warts (old and new) by Week 16, the end of treatment period, and those who do not have complete clearance of lesions should be considered nonresponders.

6.1.3 Study Design

Both pivotal trials were randomized, double-blind, vehicle-controlled clinical trial of a maximum of 16 weeks treatment duration. To maintain the blind, the vehicle control was prepared with matching color and consistency as the active study drug. Iron Oxide and Titanium Dioxide were added to placebo (Vehicle) to achieve the identical color.

6.1.4 Efficacy Findings

For both pivotal trials, the primary efficacy endpoint was defined as the proportion of patients who presented with clearance of all warts (baseline warts and new warts occurring during treatment) within a maximum treatment period of 16 weeks. A summary of the efficacy findings for the two studies is shown again in the following table.

Table 4 Primary Endpoint Efficacy Results (ITT-LOCF) N (%)

	Study CT 1017			Study CT 1018		
	Vehicle	10% Oint	15% Oint	Vehicle	10% Oint	15% Oint
Success	38 (36.9)	99 (49.7)	102 (50.7)	35 (33.7)	111 (55)	111 (56.6)
Fail	65 (63.1)	100 (50.3)	99 (49.3)	69 (66.3)	91 (45)	85 (43.4)
p-value	-	0.0384	0.0284	-	<0.001	<0.001

Source: Statistical Reviewer's Analysis using Fisher's exact test.

Fisher's exact test was used to assess the treatment effect of the 10% Ointment versus Vehicle and 15% Ointment versus Vehicle. Using the Hochberg procedure, both the 10% Ointment and the 15% Ointment show a statistically significant treatment effect in terms of the complete clearance rate of all warts (baseline and new) compared to placebo. The study indicated efficacy based upon the prespecified primary analysis. A small difference in response was observed between the 10% Ointment dose group and the 15% Ointment dose group in favor of the 15% Ointment.

The analysis differs from that of the sponsor which excluded some randomized patients with only baseline observations from the ITT population. The overall conclusions are similar, however.

Study CT 1018 was the phase 3 trial that included subjects from the United States. Clinical response by country in Study CT 1018 is shown in Table 5 below.

Table 5 Complete Clearance Rates of All Warts (Baseline and New) by Country

Country	10% Ointment (N=202)		15% Ointment (N=196)		Vehicle (N=104)	
	*n	%	*n	%	*n	%
Argentina	20	61	23	70	8	42
Chile	11	52	12	71	2	20
Colombia	17	46	23	56	3	14
Mexico	27	77	20	57	10	56
Peru	15	68	8	47	2	17
Romania	18	60	20	67	10	67
USA	3	15	5	24	0	0
Total	111	56	111	57	35	34

Modified from sponsor's study report for CT1018 (Table 11.22)

*n= number of subjects with complete wart clearance

Response rates vary among countries. Columbia, Chile, Peru and Argentina had the greatest numeric difference between active treatment and placebo among all of the countries studied. For the 15% Ointment group, for example, the differences were 42%, 51%, 30%, and 28% respectively. Mexico showed a difference from Vehicle of 20% in the 10% Ointment group but not a substantial difference for the 15% Ointment group. The Romanian subset had a higher response rate in the Vehicle group compared with the 10% Ointment group and no difference between Vehicle and the 15% group. In the U.S. subset, both active treatment groups showed

higher response rates compared with Vehicle. However, the overall response rate in U.S. patients was lower than any other country. U.S. response rates were 15%, 24% and 0% in the 10% ointment group, 15% ointment group and Vehicle group respectively. The U.S. figures are based upon a limited sample size, a total of 50 patients across all three treatment groups. The U.S. subgroup in Study CT 1018 had a relatively high discontinuation rate, 36% (18 out of 50 subjects discontinued early).

To further evaluate if U.S. or non-U.S. is important in predicting 100% wart clearance, the FDA statistical reviewer used a classification and regression tree. The following measures of baseline disease activity were analyzed for Study CT1018: country (U.S. or non U.S.), treatment arm, race, gender, age, BMI, wart location, time from diagnosis, number of previous episodes, baseline number of warts, baseline area of warts. The following is a summary from the FDA statistical review; for further details please refer to the statistical review.

Of these measures of baseline disease activity, two prognostic factors which may have an impact on efficacy were found. The first factor was the number of days from date of first diagnosis. The other factor is the number of warts present at baseline. Patients with more days from date of first diagnosis had lower response rate (with algorithm node selection of 447 days). More than 60% of U.S. subjects were diagnosed more than 447 days prior to treatment, possibly explaining the reason for lower response rate in the U.S. subgroup.

Most of the men recruited in the United States were circumcised (33/36). It is not clear what role circumcision has in predicting treatment success.

Reviewer's comment: It is possible that subjects with fewer anogenital warts are easier to treat than those with a large number of warts, and that subjects with a longer history of warts have warts which are more recalcitrant to treatment or resolution.

The subset of subjects with perianal warts was also provided and the results show treatment effect (absolute difference active-vehicle) in this subset of subjects. Treatment effect was observed in both 10% and 15% ointment. The sponsor also provided similar data for other anatomic locations (e.g., vulva in females, penis and scrotum in males and inguinal and perineal sites in both genders) which showed similar trends of treatment effect. Altogether, these data demonstrate efficacy for the indication of both external genital and external perianal warts.

Table 6 Complete Clearance of All Perianal Warts (Baseline and New) During Treatment by Visit – LOCF All Patients With Perianal Warts ITT Population

	Vehicle Ointment N=51	Polyphenon 15% Oint N=108	Polyphenon 10% Oint N=74
End of Treatment@ Complete Clearance	20 (39%)	57 (53%)	49 (67%)
No Complete Clearance	31 (61%)	51 (47%)	24 (33%)
Missing*	0	0	1

CT1005, CT1017 and CT1018

@ Based on a patient's status at Week 12 in study CT1005 and at Week 16 in studies CT1017 and CT1018.

Source Table 8.7.1.1 ISE

6.1.5 Clinical Microbiology

No HPV typing was performed in the pivotal clinical trials. For the phase 2 study, CT 1005, HPV typing was optional and performed at selected investigational sites.

6.1.6 Efficacy Conclusions

Both pivotal studies met their primary endpoints using the protocol-specified primary endpoint of complete visual clearance of all genital and perianal warts. Treatment effect was demonstrated in both men and women. There was little apparent difference in treatment effect between the 10% and the 15% concentration, but the trend in both pivotal studies was toward a slightly higher absolute difference from Vehicle in the 15% dose compared with the 10% dose. In study CT1018, the subset of subjects from the United States had lower response rates than the overall study population. However, a trend of treatment effect (active-vehicle) was noted in the U.S. subgroup. The proportion of Black and Asian subjects in the clinical studies was relatively low.

A limitation of both studies is that photography was optional and not a requirement to document complete clearance of condylomata. We cannot exclude that potentially unblinding side effects of the active study medication may have led to bias in the investigator's assessments of complete wart clearance. Documentation of wart clearance with clinical photography would have been useful.

The high response rate in the Vehicle arm also suggests the possibility of clinical activity of Vehicle alone. At the end-of-phase 2 meeting there was discussion regarding the possibility that IPM has clinical activity. However, the possible contribution of isopropyl myristate (IPM) has not been established through the use of appropriately designed clinical studies. It is unclear on what basis IPM might have activity in treatment of condyloma.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported during any of the studies.

7.1.2 Other Serious Adverse Events

A total of 1085 patients with condyloma received a formulation of Polyphenon, either cream or ointment. This number does not include 30 subjects who were all from one investigational center in Study CT 1005 due to findings of GCP non-compliance at this center. Of the 1085 patients, 479 were treated with Polyphenon 10% ointment or cream and 606 patients were treated with polyphenon 15% ointment. Another 47 patients were treated with an active comparator and 322 were treated with placebo. The safety data from the investigational center that was excluded from the sponsor's analysis will be evaluated separately in this review. The safety population (subjects randomized and received at least one treatment) in the combined phase 3 clinical studies included 397 subjects in the 15% Ointment group, 400 in the 10% Ointment group and 207 in the Vehicle group.

Six patients in the Polyphenon 15% Ointment group and four subjects in the Polyphenon 10% group (Cream and Ointment) presented with serious adverse events (SAEs). Two of the six patients in the Polyphenon 15% ointment group and one of the four subjects in the Polyphenon 10% group, a total of three subjects, had serious adverse events that were considered related to study treatment and were all local reactions at the application site. None of the SAEs in the active comparator or Vehicle groups were considered related to study treatment. Three patients with SAEs that were considered related to study drug are summarized below.

- A 41-year-old woman (subject 2311 in Study CT 1017) assigned to the 15% ointment dose group had severe local symptoms 11 days after her baseline visit resulting in withdrawal from study treatment and hospitalization. The subject was hospitalized for one week and completely recovered. A probable causal relationship to the study medication was assessed by the investigator.
- A 31-year-old woman (subject 0328 in Study CT 1018) assigned to the 10% ointment dose group, suffered from vulvovaginitis of severe intensity 35 days after the baseline visit. The event was described as a severe inguinal adenitis and severe pustular vulvovaginitis and resulted in interruption of study medication. The investigator considered the vulvovaginitis to be an SAE as the patient could not work for 3 days or have sexual intercourse for a month. The adenitis resolved without sequelae within 12 days and the vulvovaginitis by 1 month. The study drug was reintroduced. The investigator assessed the event as having a

possible causal relationship to the study medication. The sponsor’s assessment was that the subject suffered from a bacterial superinfection.

- A 22-year-old woman (subject 0304 in Study CT 1018) assigned to the 15% Ointment dose group suffered from application site pain, application site vesicles and erythema, all of moderate intensity 12 days after the baseline visit and received medication. This AE resulted in interruption of study treatment after the patient recovered she continued the study medication. A probable causal relationship to the study medication was assessed by the investigator.

Each of these serious adverse events occurred in women. Two out of three occurred in the 15% dose group.

Reviewer’s comment: This raises a question about a possible difference in the safety of the drug in women compared with men.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The overall pattern of dropouts including reasons for discontinuation in the phase 2 and phase 3 studies in which study drug was applied three times daily is shown in the following table.

Table 7 Patient Disposition of Target Studies (Studies CT 1005*, CT 1007, CT 1017, CT 1018)

Patient Status	Vehicle (N=247)	15% Ointment (N=515)	10% Ointment (N=401)
Number (%) of Patients in Safety Population [#]	247	515	400
Number (%) Patients Withdrawn from Study	50 (20)	84 (16)	69 (17)
Primary Reason for Withdrawal from Study			
Adverse Event	1 (<1)	10 (2)	0
Warts Requiring Treatment [~]	0	1 (<1)	3 (1)
Non-compliance of Study Treatment	4 (2)	10 (2)	11 (3)
Lost to Follow-up	8 (3)	9 (2)	6 (2)
Patient Withdrew Consent	14 (6)	30 (6)	25 (6)
Protocol Violation/Pregnancy	1 (<1)	7 (1)	3 (1)
Lack of Efficacy/Treatment Failure	14 (6)	10 (2)	10 (2)
Administrative Reasons	0	1 (<1)	0
Investigator’s Decision	0	2 (<1)	1 (<1)
Other	8 (3)	4 (1)	10 (2)
*: In Study CT 1005, a total of 30 patients at 1 site were excluded from all analyses due to GCP non-compliance at the site.			
#: Patients randomized who received at least 1 application of study treatment.			
Source sponsor’s ISS table 9			

From this table, at least 10 patients (2%) in the 15% Ointment group discontinued for adverse events compared to none in the active comparator and in the 10% Ointment group. From the table below, it appears that all are local reactions or local adverse events. The most common cause of discontinuation was due to “patient withdrew consent”.

Reviewer's comment: The classification of "withdrawal of consent" is a nebulous term, as it does not provide underlying reasons for withdrawal of consent. Withdrawal of consent where the underlying reason is unknown may not be a random occurrence in that subjects who experience AEs or lack of efficacy may be more likely to be lost to follow-up.

7.1.3.2 Adverse events associated with dropouts

AEs associated with dropouts in all target population studies (studies CT 1005, CT 1017, CT 1018 and EPI-003) are shown below.

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Table 8 Listing of Patients Who Discontinued Due to Adverse Events Including Local Reactions in Polyphenon E treated subjects or Vehicle

Study/Subject #	Gender	Onset Day*	Resolved Day*	Adverse Events	Severity	Relationship
Primary reason for discontinuation						
Vehicle ointment						
CT 1017/2243	Female	49	Resolving	Allergy	Severe	Probable
15% ointment						
CT 1005/1119	Male	10	51	Burning/itching	Severe	Probable
CT 1005/8095	Female	3	Resolving	Allergic vulvitis	Severe	Probable
CT 1005/8142	Female	54	71	Allergic reaction	Mild	Possible
CT 1017/2051	Male	31	Resolving	Toxic irritant reaction to medication	Severe	Probable
CT 1017/2055	Male	2	18	Genital herpes	Severe	Probable
CT 1017/2244	Female	44	Resolving	Allergy	Severe	Probable
CT 1017/2260	Male	12	Continuous	Right inguinal lymphadenitis	Mild	Probable
		12	Continuous	Phimosis	Severe	Probable
CT 1017/2311	Female	12	19	Strong local symptoms, redness, edema, burning, pain	Severe	Probable
CT 1017/2498	Female	86	Not resolved	Suspicion of allergic reaction to study drug	Moderate	Possible
CT 1018/0296	Female	16	18	Vulvitis	Severe	Possible
EPI004/4078	Male	9	13	Rash on wart area being treated	Severe	Probable
EPI004/4084	Male	-42	22	Burning on scrotum	Severe	Probable
				Swelling on scrotum	Severe	Probable
				Redness on scrotum	Severe	Probable
EPI004/4086	Male	25	33	Swelling on penis shaft and scrotum/contact dermatitis	Moderate	Probable
Secondary reason for discontinuation						
15% ointment						
CT 1018/0103	Male	5	Not resolved	Erosion with crust in urethral meatus	Severe	Probable
CT 1018/0330	Female	41	Not resolved	Pregnancy	Severe	Not related
CT 1018/1005	Female	75	93	Genital herpes	Moderate	Not related
10% ointment						
CT 1017/2702	Male	28	28	Surgery for scrotal cyst	Moderate	Not related
CT 1018/0163	Female	-13	229	Pregnancy	Severe	Not related
CT 1018/0166	Female	68	127	Pregnancy	Severe	Not related
CT 1018/0991	Female	43	47	Perineal burning sensation	Moderate	Possible
		43	47	Perineal pain	Moderate	Possible
		43	47	Perineal itching	Severe	Possible

Source: Table 44 of ISS (AEs/local reactions were either the primary or secondary reason for discontinuation.)

A total of 25 patients across treatment groups experienced AEs leading to withdrawal from the study: 1 patient assigned to vehicle, 4 assigned to 10% ointment, 16 assigned to 15% ointment patients. Active comparator patients from trial EPI- 003 accounted for the remaining 4 of the 25

patients who discontinued due to AEs (data not shown); the reasons were due to local inflammation in two subjects and the other two the subjects withdrew for unrelated events.

Adverse local reactions were recorded as a primary reason for discontinuation in 13 patients (6 women and 7 men) in the 15% ointment group compared with none in the 10% ointment group. Relationship was assessed as probably related in all but one of these patients, patient 8142 in study CT 1005, in which possible relationship to study drug was indicated by the investigator. The majority of these 13 patients had a local reaction rated severe in intensity; 10 patients had a severe reaction, 2 patients had a moderate reaction and 1 had a mild reaction. In all, adverse reactions as primary reason for discontinuation were more common in the 15% group compared with the 10% group (13 vs. 0), each of these occurred locally and the majority were severe.

7.1.4 Other Search Strategies

This reviewer use JMP software to evaluate the ISS dataset using the following SOC terms: “General Disorders/Administration site conditions”, “Skin/Subcutaneous Disorders”, “Reproductive/Breast Disorders”, “Blood and Lymphatic” and “Renal and Urinary”. The following table shows the overall incidence of adverse events in these categories. Each event is counted only once per subject.

Table 9 Search by Selected SOC terms (CT1017 and CT1018) N (%)

	Vehicle N=207		Ointment 15% N=397	
General Disorders/ Administration site conditions	136	(66)	341	(86)
Skin/Subcutaneous Disorders	19	(9)	97	(24)
Reproductive/Breast do	7	(3)	21	(5)
Blood and Lymphatic	2	(1)	16	(4)
Renal, Urinary	2	(1)	5	(1)

The incidence rate of General Disorders/Administration site conditions was higher in the active group (86%) compared with vehicle (66%). The overall incidence was lower for skin and subcutaneous disorders, reproductive and breast disorders, blood and lymphatic disorders and renal and urinary disorders.

General Disorders and Administration Site Conditions and ‘Skin and Subcutaneous Disorders’

The SOC terms “General disorders and Administration site conditions” and “Skin and Subcutaneous disorders” were evaluated for adverse events occurring at the application site (or probably related to study drug) and the results are shown below.

Table 10 Application Site Conditions (Study CT1018 and CT1017)

	Vehicle Gel		Ointment 15%	
	n=207	%	N=397	%
Erythema	67	32	276	70
Pruritus	94	45	272	69
Burning	65	31	265	67
Pain/discomfort	30	14	224	56
*Ulcer	20	10	194	49
Edema	23	11	178	45
Induration	23	11	138	35
Rash vesicular	13	6	78	20
Desquamation	1	<1	20	5
Discharge	1	<1	12	3
Bleeding	1	<1	8	2
Reaction	0	0	6	2
Scar	0	0	5	1
Irritation	0	0	3	1
Rash	0	0	3	1
Pigmentation changes	0	0	2	<1
Dryness	1	<1	2	<1
Eczema	0	0	1	<1
Hyperaesthesia	0	0	1	<1
Necrosis	0	0	1	<1
Papules	0	0	1	<1
Discoloration	1	<1	1	<1

Includes ulcer captured under SOC skin and subcutaneous disorders and general and administration site disorders.

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Skin ulcer occurred in 49% of subjects. This includes a subject (CT1018 ARG-01 00103) described as having severe erosion and crust involving the urethral meatus and resulted in discontinuation from the study. The outcome of the event is unknown. The most common events in the 15% ointment group were ‘erythema’ in 70%, ‘pruritus’ in 69%, ‘burning’ in 67% and ‘pain’ in 56% of subjects, respectively. Other common events were ulcer, edema, induration, vesicular rash and desquamation.

Blood and Lymphatic Disorders

The SOC term “Blood and lymphatic disorders” was summarized with the focus on “lymphadenitis” (also included tender adenopathy) and “lymphadenopathy” (not specified). Lymphadenitis occurred in 4% (14/397) and lymphadenopathy in <1% (2/397) in the 15% ointment group at a rate that was higher compared with vehicle. The lymphadenitis was described in subjects with concomitant adverse events at the application site and some subjects were treated with analgesics. In at least four subjects, the event resulted in treatment suspension or discontinuation. Eleven of the 14 cases of lymphadenitis were from a single investigational site, COL-02 and one of the remaining cases was from RUS-08 (subject 2260). For the latter subject, the lymphadenitis was associated with severe phimosis and these events resulted in discontinuation (see section 7.1.3).

Table 11 Lymphadenopathy (CT1017 and CT1018)

	Vehicle		15%Oint	
	n	%	n	%
Lymphadenitis	2	1	13	3
Lymphadenopathy	0	0	2	<1

Lymphadenitis occurred in 3% (13/397) and lymphadenopathy in <1% (2/397) in the 15% ointment group, at rates that were higher compared with vehicle. The cases of lymphadenitis were described in subjects with concomitant adverse events at the application site and some subjects were treated with analgesics. In at least four subjects, the event resulted in treatment suspension or discontinuation. Eleven of the 14 cases of lymphadenitis were from a single investigational site, COL-02 and one of the remaining cases was from RUS-08 (subject 2260). For the latter subject, the lymphadenitis was associated with severe phimosis and these events resulted in discontinuation (see section 7.1.3). A line listing of subjects with lymphadenitis follows.

Table 12 Line Listings of Lymphadenopathy and Adenitis in 15% Ointment Group (CT1017 and CT1018)

CT1017 RUS-08 02260	Right Inguinal Lymphadenitis	mild
CT1017 ZAF-09 02527	Inguinal Lymph Glands Right Side	mild
CT1018 ARG-07 00119	Tender Adenopathy-Inguinal	moderate
CT1018 COL-02 00162	Lymphadenitis	severe
CT1018 COL-02 00164	Lymphadenitis-Inguinal	severe
CT1018 COL-02 00167	Lymphadenitis	severe
CT1018 COL-02 00170	Lymphadenitis-Inguinal	moderate
CT1018 COL-02 00187	Lymphadenitis	moderate
CT1018 COL-02 00188	Lymphadenitis	severe
CT1018 COL-02 00203	Lymphadenitis	moderate
CT1018 COL-02 00295	Lymphadenitis	mild
CT1018 COL-02 00343	Lymphadenitis-Inguinal	severe
CT1018 COL-02 00344	Lymphadenitis-Inguinal	severe
CT1018 ROM-06 00798	Lymphadenitis-Inguinal	mild
CT1018 USA-06 00508	Lymphadenopathy- Inguinal	mild

Reviewer's comments: The reasons for the seemingly disproportionate incidence of lymphadenitis from COL-02 is unknown. However, it possible that subjects from this site were more likely to continue treatment despite adverse reactions. Subjects from this site had multiple observations of lymphadenitis (up to 7 in one subject) compared with just one observation in the subjects from the remaining sites. In six subjects, all from this site, the adenitis was described as severe.

A limitation of the data is that seven subjects from the site COL-02 did not have the location of the lymphadenitis specified. This reviewer deems the location was most likely inguinal in cases where it was not specified.

Reviewer's comment: The potential for lymphadenopathy and lymphadenitis should be described in labeling.

In combined phase 3 studies, there were 4 events “pyoderma”: 3 were in the 15% ointment group and one was in the vehicle group. The three events described as ‘pyoderma’ in the active group were all treated with oral antibiotics. One was moderate in severity and ‘probably related’ to study drug but the location was not provided. The other two events were described as unrelated (one in gluteus, one in lumbar region). The incidence of pyoderma in 15% ointment was not higher than in vehicle.

Renal and Urinary Disorders

Under SOC renal and urinary disorders, there were four subjects with dysuria (3 moderate and 1 mild) in men with warts in the genital location treated with 15% ointment. An additional male subject (ARG-05 00112) had urethral meatal stenosis which resolved upon suspension of study drug. In the vehicle group, there were 2 subjects with dysuria, both women. Both events were mild in severity and did not result in treatment suspension.

Reviewer’s comment: The potential for dysuria and meatal stenosis should be described in labeling.

Reproductive/Breast Disorders

The incidence rates of adverse events in the SOC category Reproductive/Breast Disorders were summarized by gender and treatment group and the results are shown below.

Table 13 Genital disorders by Gender and Treatment Group (CT1017 and CT1018)

Vehicle			15% Ointment		
Male (n=108)	N	%	Male (n= 205)	N	%
#Phimosis	1	1	#Phimosis	5	3
Genital burning sensation	1	1	##Genital ulceration	2	1
			Balanitis	1	<1
			Erectile dysfunction	1	<1
Female (n=89)			Female (n=192)		
Vaginal discharge	3	3	Vaginal discharge	5	3
Dysmenorrhea	2	2	Dysmenorrhea	3	2
Amenorrhea	1	1	Pelvic pain	3	2
			Cervical dysplasia	1	<1
			Dysfunctional uterine bleeding	1	<1
			Genital discharge	1	<1
			Oligomenorrhea	1	<1
			Polymenorrhea	1	<1

uncircumcised men: vehicle=99; 15% ointment= 174

These two subjects were given benzathine penicilline, and may have had another sexually transmitted disease leading to genital ulceration.

The incidence of phimosis was 3% among uncircumcised men in 15% ointment compared to 1% in vehicle. The incidences of phimosis use only the numbers of uncircumcised men in the denominator, the subjects at risk for this adverse event.

Reviewer's comment: The incidence of common genital adverse events should be described in product labeling by gender.

In the two phase 3 trials, one woman was diagnosed with grade 3 cervical dysplasia during the trial. This illustrates the importance of regular gynecologic examination including careful monitoring and screening for cervical dysplasia. This should be included in labeling under Precautions.

This reviewer used JMP to search the adverse event database from Studies CT1017 and CT1018 for adverse events described as probably related by the investigator. A total of 266/ 397 (67%) of subjects in the Polyphenon, 15% group had either a moderate or a severe adverse event that was considered probably related and of these, 120 (30%) subjects had a severe event. Severe adverse events occurred in 37% (71/192) of women and in 24% (49/205) of men. These moderate and severe adverse events included (in the approximate order of frequency), pruritus, burning, erythema, pain, ulceration, edema as well as other adverse events. These data should be described in labeling in the Adverse Reactions section.

The following table shows the incidence rates of adverse events by baseline wart location. For the Polyphenon, 15% treatment group, the overall incidence of adverse events related to study treatment (definite, probable, possible, or unlikely) was 78% in subjects with genital and perianal warts, 85% in subjects with genital warts only, and 89% in subjects with perianal warts only. The incidence rates of severe related adverse events were: 30%, 24% and 34% in subjects with genital and perianal warts, genital warts only and perianal warts only, respectively. These numbers suggest a trend toward a higher rate of severe adverse events in subjects with genital and perianal warts as well as perianal warts alone.

This reviewer used JMP software and the dataset WARTLOCATION from ISE and found the total number of subjects in the two phase 3 trials with warts in the genital only location was 328, 45 with both genital and perianal locations and 23 with warts in perianal location only.

Using the adverse event database from ISS folder to describe results for studies CT1017 and CT1018 only, the number (%) of subjects with at least one severe adverse event was 86 (26%) for subjects with genital warts only, 19 (42%) in subjects with both genital and perianal warts and 11 (48%) of subjects with only perianal warts. These data should be described under "Adverse Reactions" in labeling.

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Table 14 Adverse Events Including Local Reactions During Treatment by Baseline Wart Location

	Vehicle Ointment	Polyphenon 15% Ointment	Polyphenon 10% Ointment
Genital and Perianal Area			
N	28	83	43
Number (%) of Patients with:			
Any Adverse Event	21 (75)	66 (80)	40 (93)
Treatment-Emergent Adverse Event	21 (75)	64 (77)	40 (93)
Adverse Event Related to Study Treatment	21 (75)	65 (78)	37 (86)
Serious Adverse Event	0	2 (2)	1 (2)
Serious Adverse Event Related to Study Treatment	0	0	0
Maximum Intensity of Adverse Event			
Mild	6 (21)	21 (25)	10 (23)
Moderate	9 (32)	20 (24)	14 (33)
Severe	6 (21)	25 (30)	16 (37)
None	7 (25)	17 (20)	3 (7)
Number (%) Subjects Discontinued Treatment Due to AE	0	2 (2.4)	2 (5)
Genital Area Only			
N	202	396	331
Number (%) of Patients with:			
Any Adverse Event	147 (73)	343 (87)	283 (86)
Treatment-Emergent Adverse Event	141 (70)	337 (85)	277 (84)
Adverse Event Related to Study Treatment	139 (69)	337 (85)	283 (86)
Serious Adverse Event	0	3 (1)	3 (1)
Serious Adverse Event Related to Study Treatment	0	2 (<1)	1 (<1)
Maximum Intensity of Adverse Event			
Mild	75 (37)	97 (24)	76 (23)
Moderate	63 (31)	153 (39)	119 (36)
Severe	9 (4)	93 (24)	88 (27)
None	55 (27)	53 (13)	48 (14)
Number (%) Subjects Discontinued Treatment Due to AE	0	10 (2)	2 (<1)
Perianal Area Only			
N	17	35	26
Number (%) of Patients with:			
Any Adverse Event	13 (76)	31 (89)	25 (96)
Treatment-Emergent Adverse Event	12 (71)	31 (89)	24 (92)
Adverse Event Related to Study Treatment	12 (71)	31 (89)	25 (96)
Serious Adverse Event	0	0	0
Serious Adverse Event Related to Study Treatment	0	0	0
Maximum Intensity of Adverse Event			
Mild	6 (35)	4 (11)	5 (19)
Moderate	6 (35)	15 (43)	14 (54)
Severe	1 (6)	12 (34)	6 (23)
None	4 (24)	4 (11)	1 (4)
Number (%) Subjects Discontinued Treatment Due to AE	1 (6)	1 (3)	0

Note: Target Population Studies (Ointment TID) included Studies CT 1005, CT 1007, CT 1017, and CT 1018.

Source: ISS table 61

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

For the pivotal phase 3 studies, AEs were elicited at each study visit during the treatment period, which took place every two weeks.

Clinical assessments and elicitation of AEs for study CT 1017 are as follows:

All laboratory data obtained during the course of the study, comprising both those assessments required by this protocol and any other clinical investigation, were reviewed.

Any abnormal value considered to be of clinical significance was reported as an AE as appropriate, unless this value was consistent with the subject's present condition, 'baseline' assessments during screening or was consistent with values obtained prior to entry into the study.

Local tolerability: The investigator assessed the local skin reaction at the wart sites. The solicited skin signs (erythema, edema, induration, vesicles, erosion/ulceration, and global reaction) were graded as none (0), mild (1), moderate (2) or severe (3). In the overall evaluation of the skin reaction, the investigator took all local signs into account.

Reviewer's comment: This scale does not contain any descriptions to guide the investigator in the rating of the local skin reactions.

Subject Reported Outcomes of Local Skin Symptoms: Subjects were asked to grade the worst intensity of solicited local skin symptoms (burning, itching, pain, other, and overall evaluation of skin symptoms) experienced since their previous visit as none, mild, moderate or severe. In the overall evaluation of the skin symptoms, the subject considered all the local symptoms he/she experienced.

The definitions for grading of local skin reactions are as follows (analogous to the definitions for the grading of adverse events):

- Mild: Local skin reactions which can be easily tolerated.
- Moderate: Local skin reactions which are associated with considerable discomfort, but do not prevent usual activity.
- Severe: Local skin reactions which substantially interfere with the subject's usual activity.

See Table 34 for the schedule of study assessments.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The preferred terms were compared to the terms used by investigators. Reasons for discontinuation were also compared to comments made by the clinical investigator. The

following observation is notable. Few AEs were noted from Russian site 1 in Study CT 1017 and this was a relatively large investigational site. Three AEs were noted in two patients and the clinical site studied a total of 25 patients in this trial.

The sponsor inappropriately included the active assessments in the tables describing adverse events in the submitted Integrated Summary of Safety document.

7.1.5.3 Incidence of common adverse events

The most common AEs, including those of severe intensity, in the Polyphenon groups compared with Vehicle Ointment and Cream, were application site reactions (local skin reactions), which included pruritus, erythema, burning, pain, ulcer, edema, and induration. Also common were vesicular skin reactions.

Reviewer's comment: Although a high proportion of patients were classified as having "vesicular reactions", it is not known whether this was influenced by the fact that this term was used in the sponsor's scale for the active assessment of local reactions. The definition of vesicular requires lesions to be fluid-filled. Vesicular lesions are seen in cases of HSV infection or reactivation and in acute allergic contact dermatitis. It is possible that the term "vesicular" was overused in the assessment of local reactions. A truly vesicular rash should prompt discontinuation of study treatment and evaluation for HSV; this was not done in most cases.

7.1.5.4 Common adverse event tables

Local signs were assessed during treatment and follow-up by the study investigator and defined as edema, erosion/ulceration, erythema, induration, vesicles, scaling, crusting irritation, and other.

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Table 15: Incidence of Local Signs During Treatment for All Patients and by Gender

	Vehicle Oint.+Cream	Active Comparators	15% Oint.	10% Oint. +10% Cream	Polyphenon Overall
All patients					
N	322	47	606	479	1085
Overall					
No Local Sign	189 (59)	6 (13)	167 (28)	121 (26)	288 (27)
Any Local Sign	131 (41)	41 (87)	427 (72)	348 (74)	775 (73)
At Least One Severe	5 (2)	5 (11)	59 (10)	40 (8)	99 (9)
Local Sign					
Missing*	2	0	12	10	22
95% CI for local sign rate	(0, 3)	(2, 20)	(8, 12)	(6, 11)	(8, 11)
Males					
N	192	0	322	253	575
Overall					
No Local Sign	115 (60)	0	78 (25)	67 (27)	145 (26)
Any Local Sign	75 (40)	0	236 (75)	181 (73)	417 (74)
At Least One Severe	2 (1)	0	27 (9)	22 (9)	49 (9)
Local Sign					
Missing*	2	0	4	5	13
95% CI for local sign rate	(0, 2)	NE	(5, 12)	(5, 12)	(6, 11)
Females					
N	130	47	284	226	510
Overall					
No Local Sign	74 (57)	6 (13)	89 (32)	54 (24)	143 (28)
Any Local Sign	56 (43)	41 (87)	191 (68)	167 (76)	358 (72)
At Least One Severe	3 (2)	5 (11)	32 (11)	18 (8)	50 (10)
Local Sign					
Missing*	0	0	4	5	9
95% CI for local sign rate	(0, 5)	(2, 20)	(8, 15)	(4.5, 11.8)	(7, 13)

NE = not estimable.

Note: All Target Population Studies included Studies EPI-003, EPI-004, CT 1005, CT 1007, CT 1017, and CT 1018.

In the 15% Ointment group, the incidence of severe local signs was numerically higher in women (11%) compared with men (9%). The opposite trend was noted in the 10% Ointment group.

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Local symptoms were assessed by the patient during treatment and follow-up and defined as burning, itching, pain, ulceration (assessed as both a local sign and symptom in studies EPI-003 and EPI-004), and other.

Table 16 Incidence of Local Symptoms During Treatment - All Target Population Studies

	Vehicle Oint+Cream	Active Comparators	15% Oint	10%Oint + 10%Cream	Polyphenon Overall
All Patients					
N	322	47	606	479	1085
Overall					
No Local Symptom	143 (45)	3 (6)	138 (23)	108 (23)	246 (23)
Any Local Symptom	177 (55)	44 (94)	456 (77)	361 (77)	817 (77)
At Least One Severe Local Symptom	9 (3)	15 (32)	120 (20)	105 (22)	225 (21)
Missing*	2	0	12	10	22
95% CI	(1, 5)	(19, 45)	(17, 23)	(19, 26)	(19, 24)
Males					
N	192	0	322	253	575
Overall					
No Local Symptom	96 (50)	0	76 (24)	58 (23)	134 (24)
Any Local Symptom	94 (50)	0	238 (76)	190 (77)	428 (76)
At Least One Severe Local Symptom	0	0	52 (17)	42 (17)	94 (17)
Missing*	2	0	8	5	13
95% CI for severe local	NE	NE	(12, 21)	(12, 22)	(14, 20)
Females					
N	130	47	284	226	510
Overall					
No Local Symptom	47 (36)	3 (6)	62 (22)	50 (23)	112 (22)
Any Local Symptom	83 (64)	44 (94)	218 (78)	171 (77)	389 (78)
At Least One Severe Local Symptom	9 (7)	15 (32)	68 (24)	63 (28)	131 (26)
Missing*	0	0	4	5	9
95% CI severe local symptom rate	(3, 11)	(19, 45)	(19, 29)	(23, 34)	(22, 30)

NE = Not estimable.

Note: All Target Population Studies included Studies EPI-003, EPI-004, CT 1005, CT 1007, CT 1017, and CT 1018.

The incidence of severe local symptoms was generally higher for women (24% and 28% in 15% Ointment and 10% Ointment, respectively) than men (17% across dose groups). The overall incidence of local symptoms was comparable between women and men. Of note, all 47 subjects on active comparator were women.

Table 17 Incidence of Adverse Events Related to Study Treatment Excluding Local Reactions During Treatment in $\geq 2\%$ in any Treatment Group [N (%)]

MedDRA Organ Class System/ Preferred Term	Vehicle (N=247)	15% Ointment (N=515)	10% Ointment (N=400)
TOTAL	5 (2)	61 (12)	28 (7)
Skin and subcutaneous tissue disorders	3 (1)	21 (4)	7 (2)
Pruritus	0	11 (2)	2 (<1)
Erythema	1 (<1)	11 (2)	1 (<1)
General disorders and administration site conditions	0	25 (5)	2 (<1)
Pain	0	11 (2)	1 (<1)

Note: Target Population Studies (Ointment TID) included Studies CT 1005, CT 1007, CT 1017, and CT 1018.

Source: Table 43 of ISS

It is unclear why these were not included on the local reactions. This may have resulted from mapping the active assessments to MedDRA terminology. However, these data are useful and indicate a dose response for such reactions as pruritus, erythema and pain. For example, pain was reported in 2% of patients in the 15% treatment group compared with <1% in the 10% treatment group and none in vehicle.

The sponsor was asked to provide separate safety tables using safety data from only the two pivotal studies for all subjects (men and women) as well as by gender. Since the duration of the two pivotal studies was 16 weeks and was longer than earlier studies, it was important to also evaluate rates from these studies separately. General disorders and administration site conditions from the sponsor's table are shown below.

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Table 18 Incidence of Adverse Events During Treatment at Application Site (SOC: General disorders and administration site conditions) - Studies CT1017 and CT1018

Application Site Adverse Events	Vehicle Ointment		Polyphenon 15% Ointment		Polyphenon 10% Ointment	
	(N=207)		(N=397)		(N=400)	
Total	147	(71%)	348	(88%)	344	(86%)
Pruritus	116	(56%)	302	(76%)	290	(72%)
Erythema	77	(37%)	289	(73%)	278	(70%)
Burning	77	(37%)	274	(69%)	267	(67%)
Pain	36	(17%)	224	(56%)	191	(48%)
Ulcer	23	(11%)	191	(48%)	185	(46%)
Edema	25	(12%)	177	(45%)	160	(40%)
Induration	27	(13%)	142	(36%)	115	(29%)
Desquamation	2	(1%)	20	(5%)	18	(4%)
Discharge	2	(1%)	12	(3%)	8	(2%)
Bleeding	2	(1%)	8	(2%)	11	(3%)
Scar	0		5	(1%)	3	(1%)
Reaction	0		6	(2%)	1	(<1%)
Irritation	0		4	(1%)	1	(<1%)
Pigmentation Changes	0		3	(1%)	1	(<1%)
Discomfort	0		2	(<1%)	1	(<1%)
Dryness	1	(<1%)	1	(<1%)	2	(<1%)
Papules	0		2	(<1%)	1	(<1%)
Rash	0		3	(1%)	0	
Discoloration	0		1	(<1%)	1	(<1%)
Hyperesthesia	0		1	(<1%)	1	(<1%)
Eczema	0		1	(<1%)	0	
Necrosis	0		1	(<1%)	0	
Pustules	0		0		1	(<1%)
Drug intolerance	0		1	(<1%)	0	
Granuloma	0		0		1	(<1%)

Source : Table 99.5.1 of submission 43

The most common adverse reactions in all treatment groups were application site pruritus, erythema, burning, pain, ulcer, edema and induration. The incidence rates of these reactions were numerically highest in the 15% ointment group followed by the 10% ointment group and these rates were lowest in Vehicle.

Reviewer's comment: Of note, there are two rows for "ulcer". The reasons are not clear.

7.1.5.5 Identifying common and drug-related adverse events

From these data, the adverse events of pruritus, erythema, pain can reasonably be identified as drug-related based on a higher incidence in patients treated with active vs. vehicle.

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events

The incidence of urological/genital adverse events including local reactions during treatment in ≥ 2 subjects in any treatment group in all target population studies is shown in the following table.

Table 19 Incidence of Urological/Genital Adverse Events* During Treatment in ≥ 2 Patients in any Treatment Group

MedDRA Preferred Term	Vehicle Ointment (TID) (N=247)	15% Ointment (TID) (N=515)	10% Ointment (TID) (N=400)
	Number (%) of Patients		
TOTAL	14 (5.7)	40 (7.8)	40 (10.0)
Urinary tract infection	1 (0.4)	4 (0.8)	6 (1.5)
Vaginal candidiasis	2 (0.8)	3 (0.6)	6 (1.5)
Dysuria	2 (0.8)	4 (0.8)	4 (1.0)
Phimosis	1 (0.4)	5 (1.0)	3 (0.8)
Vaginal discharge	3 (1.2)	5 (1.0)	4 (1.0)
Cystitis	1 (0.4)	0	4 (1.0)
Dysmenorrhea	2 (0.8)	3 (0.6)	1 (0.3)
Genital ulceration	0	2 (0.4)	1 (0.3)
Pelvic pain	0	3 (0.6)	0
Vulvitis	0	2 (0.4)	1 (0.3)
Pelvic inflammatory disease	0	0	2 (0.5)
Vaginitis	1 (0.4)	0	2 (0.5)
Vaginitis bacterial	1 (0.4)	2 (0.4)	0

Source: Table 47 of Sponsor's ISS
Note: Target Population Studies (Ointment TID) included Studies CT 1005, CT 1007, CT 1017, and CT 1018.

Although, the overall incidence of urogenital adverse events was highest (10%, 40/400) in the 10% Ointment group, there appeared to be a higher incidence of severe reactions as well as a higher incidence of related reactions in the 15% Ointment group. Six severe urological/genital adverse events in the Polyphenon 15% Ointment group (allergic vulvitis, phimosis, chemical vulvovaginitis, vulvitis, burning scrotum, and swelling on scrotum) were considered probably related to study medication and 1 severe urological/genital adverse event in the Polyphenon 15% Ointment group (vulvitis) was considered possibly related to study medication. Most urological/genital adverse events in the Polyphenon 10% Ointment and Cream group were mild or moderate in intensity and most were not related to study medication.

Phimosis was observed in 2% of males (5/266) in the 15% Ointment group, in 1% of males (3/212) in the 10% group and in <1% of (1/137) vehicle-treated male subjects. None of the patients in the active comparator group, who were all female, were at risk for phimosis. The higher incidence of phimosis in the active Polyphenon treatment groups (and apparent dose relationship) compared to vehicle is notable and should be included in product labeling.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In general, the following laboratory samples were obtained in accordance with the schedule of assessments:

Hematology: Erythrocytes, leukocytes with differential count, hemoglobin, hematocrit, platelets.

Biochemistry: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, potassium, sodium, calcium, serum creatinine, urea, glucose, albumin.

Urinalysis: Dipstick analysis for glucose, proteins, erythrocytes/blood, leukocytes. Microscopic analysis was performed in the case of cellular abnormality.

Pap smear: At screening, a Pap smear for cytologic examination was taken directly from the cervix of female patients in South Africa in Study CT 1017.

No drug concentration measurements were performed in either of the two phase 3 studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The phase 2 and 3 randomized placebo-controlled studies were selected to perform analyses of drug-control comparisons of laboratory values.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

See analyses under the appended clinical study reports.

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

The following table shows shifts from baseline to end of treatment in hematology and biochemistry values. Shifts to values deemed clinically significant (CS) are counted separately from those that were not deemed clinically significant (NCS). Tables include studies CT 1005, CT 1007, CT 1017, and CT 1018.

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Table 20 Shifts From Baseline to End of Treatment in Hematology Target Population Studies for Subjects with Normal Values at Baseline

Baseline Value	Vehicle (N=247)			10% Ointment (N=400)			15% Ointment (N=515)		
	Normal	Outside NCS	Outside CS	Normal	Outside NCS	Outside CS	Normal	Outside NCS	Outside CS
Neutrophils	168 (77)	25 (12)	0	259 (73)	48 (14)	0	353 (77)	33 (7)	1 (<1)
Eosinophils	162 (75)	19 (9)	2 (1)	268 (76)	22 (6)	2 (0.6)	343 (75)	35 (8)	0
Hg	181 (82)	22 (10)	1 (<1)	308 (86)	20 (6)	1 (0.3)	396 (85)	27 (6)	0
Hct	177 (81)	16 (7)	0	295 (83)	30 (8)	1 (0.3)	392 (85)	32 (7)	0

Table 21 Shifts From Baseline to End of Treatment in Biochemistry Laboratory Data for Subjects with Normal Values at Baseline [Number (%) Patients]

	Vehicle (N=247)			15% Ointment (N=515)			10% Ointment (N=400)		
	Normal	Outside, NCS	Outside, CS	Normal	Outside, NCS	Outside, CS	Normal	Outside, NCS	Outside, CS
Urea	200 (91)	13 (6)	0	426 (94)	8 (2)	0	315 (90)	11 (3)	1 (<1)
Blood Glucose	180 (81)	19 (9)	0	370 (80)	35 (8)	1 (<1)	310 (85)	23 (6)	0
SGOT (AST)	199 (89)	10 (4)	0	412 (88)	16 (3)	1 (<1)	320 (87)	16 (4)	0
SGPT (ALT)	198 (88)	10 (4)	0	391 (84)	25 (5)	0	294 (80)	26 (7)	1 (<1)
GGT	198 (90)	12 (6)	0	379 (86)	15 (3)	2 (<1)	301 (88)	13 (4)	0
Alkaline Phosphatase	209 (93)	6 (3)	0	418 (91)	18 (4)	0	324 (90)	14 (4)	1 (<1)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

No patient discontinued treatment for laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

Additional analyses of liver function test results in the individual studies are described in appended reviews of CT 1017 and CT 1018. These analyses did not reveal any signals for hepatotoxicity related to three times daily topical use of Polyphenon E at any of the dose levels studied.

7.1.7.5 Special assessments

No other special assessments for laboratory abnormalities were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were assessed at baseline and at the end of treatment visit in both phase 3 studies.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The two phase 3 studies were selected for overall drug-control comparisons.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean blood pressure (both systolic and diastolic) and heart rate measurements were comparable among treatment groups at both baseline and final treatment visit and did not substantially change over time in either of the two pivotal trials. A mean increase from baseline in body temperature was noted in the 10% ointment group in study CT1017 (0.05 °C). However, no changes in mean body temperature were noted in any treatment group in study CT1018.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

No analyses focused on outliers or shifts from normal to abnormal were performed.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No patients discontinued for vital sign abnormalities.

7.1.9 Electrocardiograms (ECGs)

Electrocardiogram testing was not performed as part of the drug development program.

7.1.10 Immunogenicity

Immunogenicity testing was not conducted as part of the drug development program.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not deemed necessary.

7.1.12 Special Safety Studies

In addition to the two phase 3 studies, dermal safety studies were performed. Dermal safety studies in healthy human volunteers were CT 1004, CT 1016 and CT 1019.

From the sponsor's integrated summary of safety.

Table 22 Incidence of Local Reactions in Intact (Normal) Skin For All Subjects and by Gender During Treatment - Healthy Volunteer Studies – Safety Population

	15% Ointment
All Subjects	
N	239
No Local Reaction	15 (6)
Any Local Reaction	223 (94)
Missing	1
Male Subjects	
N	92
No Local Reaction	8 (9)
Any Local Reaction	84 (91)
Missing	0
Female Subjects	
N	147
No Local Reaction	7 (5)
Any Local Reaction	139 (95)
Missing	1

Note: Local reactions in scarified skin in Study CT 1019 and subjects in Study CT 1004 who had UV-induced erythema were not included in this table.

From the healthy volunteer studies in which intact skin was assessed (CT 1016 and CT 1019) the majority (94%) of subjects experienced a local reaction. The incidence of local reactions was similar between females and males.

In Study CT 1004, 10 subjects in Group I (occlusive treatment) experienced adverse reactions in the test fields which were probably related to study preparations. The reactions ranged from slight erythema to erythema with papules, pustules, or edema, all of which regressed following cessation of treatment. In Group II (semi-occlusive treatment), there were no adverse reactions related to the study preparations.

In Study CT 1019, Polyphenon 15% Ointment showed relatively little irritant potential on intact skin. On the scarified skin fields, a relevant interference with healing of superficial scratches was found for the Polyphenon 15% Ointment group. Due to intense skin reactions (up to score 5) the treatment with Polyphenon 15% Ointment was discontinued in 12 of the 20 subjects before the last scheduled treatment.

Reviewer's comment: Based on results of this study, the dermal tolerance of Polyphenon Ointment on scarified skin was poor compared to that on intact skin. The dermal tolerance was better on scarified skin treated with vehicle free of active ingredient.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. Withdrawal and abuse potential is not suggested by the proposed mechanism of action of this drug.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. It is unknown whether systemic exposure to catechins following topical administration of Polyphenon Ointment in humans occurs.

Reviewer's comment: Another PK study would be needed to evaluate the systemic exposure following topical application in humans. In the PK study that has already been done, samples were tested outside the stability window and degradation of samples occurred.

7.1.15 Assessment of Effect on Growth

No studies were conducted in pediatric subjects. The sponsor applied for and received a waiver for the pediatric patient population.

7.1.16 Overdose Experience

No overdose was noted in clinical development.

7.1.17 Postmarketing Experience

No postmarketing experience is available, as this drug has not been previously approved in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Safety evaluation was done in both healthy volunteers on intact, normal skin as part of the dermal safety study evaluation as well as in the patient population with anogenital warts. Dermal safety studies included irritancy and sensitization studies as well as studies of scarified skin. The types of dermal safety studies as well as numbers of patients enrolled were deemed adequate.

As stated earlier in this review, a total of 1085 patients with condyloma received a formulation of Polyphenon E, either cream or ointment. Of the 1085 patients, 479 were treated with Polyphenon 10% ointment or cream and 606 patients were treated with polyphenon 15% ointment. Another 47 patients were treated with an active comparator and 322 were treated with placebo. The safety population of the phase 2 and 3 randomized, placebo-controlled clinical studies of polyphenon ointment three times daily included 400 patients receiving polyphenon 10% ointment, 515 patients receiving polyphenon 15% ointment and 247 patients receiving placebo.

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7.2.1.2 Demographics

Table 23 Demographic and Baseline Characteristics in Safety Population

Characteristic	Vehicle (N=247)	10% Ointment (N=400)	15% Ointment (N=515)
Gender [n (%)]			
Male	137 (56)	212 (53)	266 (52)
Female	110 (44)	188 (47)	249 (48)
Age (years)			
<18	0	2 (<1)	1 (<1)
18-30	143 (58)	245 (61)	301 (58)
31-45	64 (26)	109 (27)	147 (28)
46-65	35 (14)	41 (10)	59 (12)
>65	5 (2)	3 (1)	7 (1)
Mean	32	31	31
Median	28	28	28
Min, Max	18, 73	16, 98	17, 90
Race [n (%)]			
Caucasian	166 (67)	255 (64)	366 (71)
African (Black)	6 (2)	9 (2)	11 (2)
Hispanic	72 (29)	131 (33)	135 (26)
Asian	1 (<1)	2 (<1)	1 (<1)
Other	2 (0.8)	3 (1)	2 (<1)
Weight (kg)			
N	247	400	514
Mean	71	70	71
Median	69	68	69
Min, Max	44, 126	41, 159	44, 138
Women of Childbearing Potential			
Yes	95 (86)	158 (84)	189 (82)
No	15 (14)	30 (16)	41 (18)
Circumcised Men			
Yes	21 (15)	30 (14)	39 (16)
No	116 (85)	182 (86)	208 (84)

Note: Target Population Studies (Ointment T1D) included Studies CT 1005, CT 1007, CT 1017, and CT 1018.

Demographic and baseline characteristics were similar across the 3 treatment groups. A higher percentage of male subjects were enrolled overall. Among all subjects who received polyphenon E 15%, the male to female ratio was 53: 47. The median age ranged was 28 years for all subjects receiving polyphenon E 15%. Few geriatric subjects were enrolled; subjects over the age of 65 comprised 1% (7/515) of the study population receiving polyphenon E 15%. Also, few Black subjects were included 2% (11/515 subjects) receiving Polyphenon 15%, as well as few Asian subjects (1%).

Reviewer’s comment: The relatively low proportion of some non-White racial groups in these studies was because they were conducted in Europe and South America. This probably does not represent the U.S. population with genital and perianal warts where Black patients would be seen more commonly. In a previously conducted study in the United States and Canada for approval of another drug for the treatment of condyloma acuminata, Black patients made up 13-17% of patients and White patients made up 81-83% of patients. Most of the subjects in the studies who received Polyphenon 15% were uncircumcised (84%). This is unlikely to be the case in the U.S. population where circumcision is more common.

7.2.1.3 Extent of exposure (dose/duration)

The duration of study treatment (excluding treatment interruptions) is shown below.

Table 24 Duration of Study Treatment - Safety Population

Duration (days)	Vehicle (N=247)	10% Ointment (N=400)	15% Ointment (N=515)
Mean	92	91	83
Median	106	111	90
Min, Max	1, 142	1, 157	1, 206

The median duration of study treatment ranged from 90 days in the high dose group to 111 days in the low dose group. Duration in the Vehicle group was intermediate, 106 days. Of note the maximum duration of treatment that was allowed was 16 weeks, 112 days.

Reviewer’s comment: The shorter duration of treatment in the high dose group may reflect subjects who withdrew early due to adverse events and also early discontinuation due to resolution of all warts prior to the end of the 16 week treatment period. The maximum duration of treatment exceeded 112 days in all three treatment groups. This suggests that some evaluations occurred outside the scheduled window.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Not applicable. No studies were reviewed outside of the NDA application and none were referred to by the applicant.

7.2.2.2 Postmarketing experience

There is no postmarketing experience since this drug has not been marketed in any country.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience overall appeared to be adequate. However, the clinical data obtained from U.S. investigational sites was very limited. Response rates were lower in U.S. population compared to the overall study population, although, treatment effect was also observed in the U.S. population. Follow up for recurrence of anogenital condyloma accuminata was conducted; however, the data were difficult to interpret (see below).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal testing appeared to be adequate. See animal toxicology review by Dr. Jiaquin Yao.

7.2.5 Adequacy of Routine Clinical Testing

The methods and the frequency of routine clinical testing of study subjects, including monitoring of laboratory parameters, vital signs, and efforts to elicit adverse event data were considered adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The clinical pharmacology study was inadequate in that plasma samples from patients were tested outside the appropriate window for stability. This made it difficult to assess for the degree of possible systemic absorption from topical use.

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7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The method of assessing local reactions was suboptimal in that the clinical scale used to evaluate local reactions did not contain adequate descriptions, definitions and subjects with vesicular reactions did not have evaluation for HSV infection. However, the local assessments were deemed acceptable and are described in product labeling.

7.2.8 Assessment of Quality and Completeness of Data

The preponderance of the safety data were complete. Some exceptions exist, however. There were many patients who were lost to follow-up in study CT1005 after a clinical site was closed for non-compliance with GCP. Some patients with severe local reactions, did not appear to have follow-up data after the treatment period. See appended clinical review for studies CT 1017 and CT 1018.

7.2.9 Additional Submissions, Including Safety Update

The sponsor has submitted a safety update. No new safety concerns were noted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The most frequent and important drug-related adverse events occurred in the region of local application or in the draining lymph nodes. These included the following adverse events which resulted in study drug discontinuation: burning/itching, allergic vulvitis, contact dermatitis, suspicion of allergic reaction, genital herpes, allergic reaction, inguinal adenitis, and phimosis.

In sum, several of these adverse events were thought to be allergic in nature. The dermal safety studies in healthy volunteers showed a contact sensitization rate of 2.4%. However, the data are limited as the study was not considered conducted in a blind manner as the investigators could have access to the CRF during their assessments.

It is not known whether patients experiencing vesicular local reactions had allergic contact dermatitis or some other cause of vesicles e.g., HSV infection. Laboratory evaluation for HSV in these cases would have been helpful, but were not done.

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7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The integrated safety analysis (ISS) was done in the ISS ITT population of all studies using the ointment formulation for 16 weeks. Pooling of data was done to yield a larger patient database from which a safety analysis could be done.

Clinical studies presented in sponsor's ISS were based on 4 different formulations of Polyphenon E: 3 ointments (10% and 2 different 15% formulations [EPI-studies versus MediGene-studies]) and 1 cream. Polyphenon E 15% Ointment administered 3 times daily was the to-be-marketed formulation used in the pivotal studies. The ISS included the pooled safety data from nine Phase 1 and 3 studies of varying study populations and study designs related to the indication external genital and perianal warts and also included tables pooling only those studies 3 times daily use of the 15% Ointment formulation,

7.4.1.2 Combining data

In pooling data, the numerator events and denominators for the selected studies were simply combined. The FDA also requested that the sponsor present tables of all patients (men and women) and by gender (men alone and women alone) for the phase 3 pivotal studies of 16-week duration only.

Reviewer's comment: The information from the phase 3 pivotal studies, is the information that should be presented in labeling because some of the earlier studies were based upon 12-week treatment period.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

To evaluate for dose dependency for adverse findings, the incidence of severe adverse events including local reactions that occurred during treatment in $\geq 2\%$ of patients in any treatment group (excluding active comparator) was evaluated.

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Table 25 Incidence of All Severe Adverse Events Including Local Reactions During Treatment in $\geq 2\%$ of Patients All Target Population Studies [N(%)]

MedDRA Organ Class System/Preferred Term	Vehicle	Active	15% Ointment	10% Ointment+Cream	Polyphenon Overall
	Ointment+ Cream (N=322)	Comparators (N=47)	(N=606)	(N=479)	(N=1085)
TOTAL	19 (6)	17 (36)	139 (23)	118 (25)	257(24)
General disorders and administration site conditions					
Application site pruritus	12 (4)	4 (8)	83 (14)	81 (17)	164 (15)
Application site erythema	3 (1)	4 (8)	43 (7)	29 (6)	72 (7)
Application site burning	7 (2)	9 (19)	79 (13)	65 (14)	144 (13)
Application site pain	1 (<1)	6 (13)	68 (11)	46 (10)	114 (10)
Application site ulcer*	0	0	29 (5)	20 (4)	49 (4)
Application site edema	1 (<1)	1 (2)	27 (4)	18 (4)	45 (4)
Induration	3 (1)	0	21 (4)	10 (2)	31 (3)
Application site ulcer	0	3 (6)	3 (0.5)	0	3 (<1)
Application site irritation	0	1 (2)	2 (<1)	0	2 (<1)
Skin and subcutaneous tissue disorders					
Rash vesicular	0	0	16 (3)	8 (2)	24 (2)

Source: table 31 of sponsor's ISS

Note: All Target Population Studies included Studies EPI-003, EPI-004, CT 1005, CT 1007, CT 1017, and CT 1018.

Using the combined database of all target population studies, there was no apparent dose response for the following severe adverse events: pruritus and burning. There was a numerically higher frequency of erythema, pain, ulcer, edema, induration, irritation and vesicular rash in the 15% ointment group compared with the 10% ointment group.

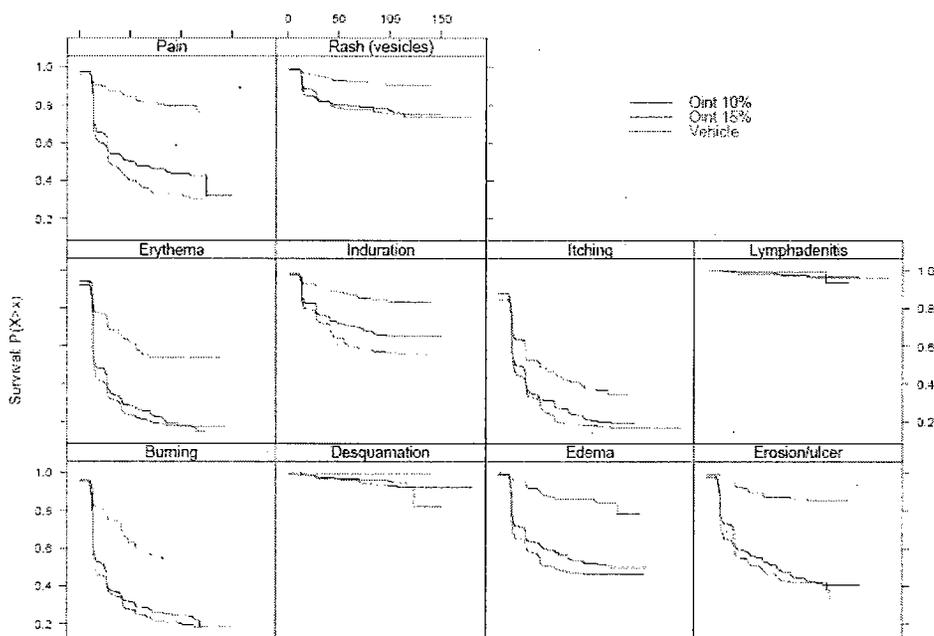
Reviewer's comment: Of note, ulceration, induration and vesicular rashes were not observed in the active comparator arm. It is possible that these reactions are related to the sensitization potential of Polyphenon E. Alternatively, the term "vesicular" could have been overused to describe local reactions because the term was included in the assessment tool for active assessments used by investigators to grade local tolerability without adequate description, or definition.

7.4.2.2 Explorations for time dependency for adverse findings

At all study visits, signs and symptoms of adverse local reactions were sought. The FDA statistical reviewer analyzed the time to first event for the 10 most frequent application site reactions reported and showed that the time- to -first event for the two active arms appears to be faster than the vehicle arm. Both 10% Ointment and 15% Ointment have higher rates of treatment emergent AE's than the vehicle arm (see Table 26).

Reviewer's comment: Of concern is that the rate of onset and higher incidence of local adverse reactions may have led to unblinding. It would also be helpful to know whether these events resolved over time with continued use or required permanent discontinuation of study drug.

Figure 1 Time to First Event for Local Reactions



7.4.2.3 Explorations for drug-demographic interactions

The following table contains a summary of local reactions broken down by gender.

Table 26 Application Site Reactions as Assessed by the Investigator or Subject (Percent of Subjects)

	Women			Men		
	Vehicle (N=110)	10% Oint (N=188)	15% Oint (N=249)	Vehicle (N=137)	10% Oint (N=212)	15% Oint (N=266)
Erythema	36%	69%	63%	31%	70%	71%
Edema	12%	38%	32%	11%	42%	46%
Induration	11%	30%	24%	10%	31%	34%
Vesicles	6%	21%	15%	5%	18%	20%
Erosion/Ulceration	11%	52%	38%	10%	42%	47%
Other Signs	2%	10%	10%	2%	11%	14%
Burning	38%	72%	61%	27%	61%	66%
Itching	56%	73%	70%	39%	67%	70%
Pain	16%	51%	50%	11%	44%	50%
Other Symptoms	6%	7%	11%	1%	7%	7%

Includes data from Studies 1005, 1017 and 1018.

For both men and women, signs and symptoms of erythema, edema, vesicles, erosions, burning, itching, pain were higher in both active treatment groups compared to placebo. A higher proportion of men than women experienced induration and/or edema. Up to 46% of men experienced edema compared with 38% of women and up to 34% of men had induration compared to 30% of women across the active treatment groups. No clear trends were noted for the signs of erosion/ulceration and vesiculation, overall.

Table 27 Severe Application Site Reactions

	Women			Men		
	Vehicle (N=110)	10% Oint (N=188)	15% Oint (N=249)	Vehicle (N=137)	10% Oint (N=212)	15% Oint (N=266)
Erythema	2%	7%	8%	1%	9%	8%
Edema	1%	3%	5%	0	6%	5%
Induration	2%	3%	4%	1%	6%	4%
Vesicles	0	2%	4%	0	2%	3%
Erosion/Ulceration	0	6%	7%	0	5%	5%
Other Signs	0	<1%	2%	0	1%	1%
Burning	4%	25%	17%	0	8%	12%
Itching	6%	26%	20%	0	14%	12%
Pain	1%	18%	18%	0	6%	9%
Other Symptom	0	<1%	2%	0	2%	2%

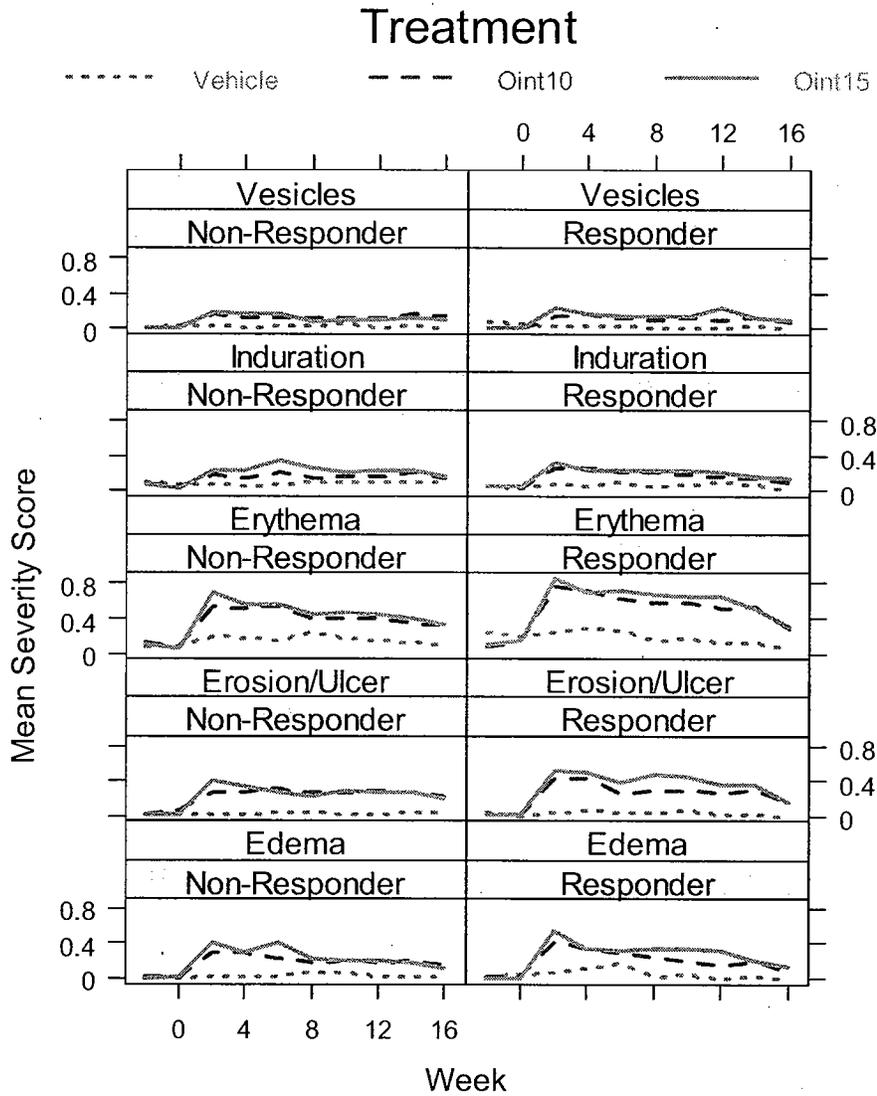
The incidence of some signs and symptoms rated as severe showed differing trends by gender. There was a trend toward a higher proportion of women with severe erosion/ulceration (7% women vs. 5% men), burning (17% women vs. 12% men) and itching (20% women vs. 12% men) and pain (18% women vs. 9% men). For patients receiving vehicle, a higher proportion of women than men experienced burning and itching.

7.4.2.4 Explorations for drug-disease interactions

The FDA statistical reviewer explored local reactions by responder status and results are shown in the following figure.

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Figure 2 Local Reactions by Clinical Response



The mean severity score in the responders appeared somewhat higher in the responder group for erythema as well as for erosion/ulcer compared with non-responders. The clinical relevance of this finding is unclear. Although there was a modest decline in mean severity after the peak during the first month, there did not appear to be substantial decline in mean severity until after the 12-week treatment period.

Reviewer's comment: Some of the decrease in mean severity in certain signs and symptoms that was observed was likely related to withdrawal of the most severely affected subjects.

7.4.2.5 Explorations for drug-drug interactions

Not done as part of the clinical investigation as concomitant topical medications were prohibited.

7.4.3 Causality Determination

The vehicle controlled studies show a higher incidence of local signs and symptoms of study treatment in the active treatment arms compared with vehicle alone supporting a causal relationship between local signs and symptoms and the drug substance. In the pooled phase 2 and phase 3 studies, phimosis was observed in 2% of males (5/266) in the 15% Ointment group, in 1% of males (3/212) in the 10% group and in <1% of (1/137) vehicle-treated male subjects. Although the numbers are small, these data suggest a possible dose relationship and causal association for phimosis. Lymphadenitis was also observed in some subjects, likely as a result of local reactions due to study drug, either immune mediated or due to irritation.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Polyphenon E ointment was studied in patients who applied study treatment three times daily for 16 weeks in the pivotal clinical trials. The 16 week study duration that was chosen, because the phase 2-3 clinical trial suggested that a higher proportion of patients may have wart clearance with longer treatment duration. Retreatment upon relapse was not evaluated as part of this development program. Treatment durations of longer than 16 weeks were not evaluated.

8.2 Drug-Drug Interactions

Drug-drug interaction studies were not conducted for this NDA, and no drug-drug interactions observed during the clinical trials.

8.3 Special Populations

Polyphenon E ointment was studied in adults men and women age ≥ 18 years and, if approved, would be indicated for this population. Pregnant and breast-feeding subjects were excluded from the study and if approved, Polyphenon E ointment would have a Pregnancy Category C.

8.4 Pediatrics

The sponsor requested a pediatric waiver and a full waiver was granted by the Agency. Polyphenon E ointment offers no meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients. Condyloma accuminata is a sexually transmittable viral disease; therefore, the number of pediatric patients is limited. As a

therapeutic alternative, Aldara (imiquimod) is available in the U.S. market for the age group 12 years and above.

8.5 Advisory Committee Meeting

No advisory committee meeting was held for this application.

8.6 Literature Review

Literature related to the application is referenced in the body of the review as needed.

8.7 Postmarketing Risk Management Plan

The sponsor has not submitted a postmarketing risk management plan. For Agency recommendations for postmarketing risk management, see section 9.3.1.

8.8 Other Relevant Materials

A consultation from the Division of Drug Marketing, Advertising, and Communication (DDMAC) was received. DDMAC has made suggestions regarding product package insert as well as the patient package insert. For details, please see the review by Dr. Suzanne Berkman.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

Two independent phase 3 studies of similar design and have demonstrated statistically significant differences in the primary endpoint for both doses of Polyphenon E ointment compared with Vehicle in complete clearance of external genital and perianal condyloma by 16 weeks of treatment. In both phase 3 studies, the 15% ointment showed a slightly higher response rate than the 10% ointment (Table 4). Although the response rates in the U.S. population was lower than the overall response rates in the phase 3 pivotal studies, the number of subjects from the United States was limited and a similar magnitude of treatment effect (active-vehicle) was also observed for the U.S. subset as for the overall study population.

To further evaluate if U.S. or non-U.S. is important in predicting 100% wart clearance, the FDA statistical reviewer used a classification and regression tree. Two prognostic factors which may have an impact on efficacy were identified, the number of days from date of first diagnosis and the number of warts present at baseline. Patients with more days from date of first diagnosis had lower response rate (with algorithm node selection of 447 days). More than 60% of U.S. subjects were diagnosed more than 447 days prior to treatment, possibly explaining the reason for lower response rate in the U.S. subgroup.

The applicant has not provided data to allow assessment of relapse rate of condyloma in subjects who had complete clearance in the 16-week treatment period. Although the protocol allowed for a 12-week follow-up period for responders, the data did not distinguish between subjects who appeared for a follow-up visit and had no recurrence and those who did not appear for a follow-up visit. The Agency does not agree with the applicant's conclusions regarding the relapse data. As a result, the Agency will request a phase 4 study to assess relapse in those subjects who demonstrate complete visual clearance of external condyloma.

Safety

In the three times daily safety database (Studies CT 1005, CT 1007, CT 1017, and CT 1018) there were 9 serious adverse events and of these, 3 were considered related to study drug by the investigator (see Table 2). Each of the 3 related SAEs occurred in women and consisted of local reactions. One resulted in hospitalization. It is possible that women are at higher risk of serious local events with treatment compared with men.

Adverse reactions as primary reason for discontinuation were more common in the 15% group compared with the 10% group (13 vs. 0), each of these occurred locally and the majority were severe (see Table 8). A total of 25 patients across treatment groups experienced AEs leading to withdrawal from the study (either primary or secondary reason): 1 patient assigned to vehicle, 4 assigned to 10% ointment, 16 assigned to 15% ointment patients.

As stated above, it is possible that women are at higher risk of serious local events with treatment compared with men. The incidence of some signs and symptoms rated as severe also showed differing trends by gender. There was a trend toward a higher proportion of women with severe erosion/ulceration, burning, itching and pain (see Table 27).

Other clinically significant events resulting in discontinuation of some male subjects included phimosis. Phimosis was observed in 2% of males in the 15% Ointment group, in 1% of males in the 10% group and in <1% of vehicle-treated male subjects. The risk of phimosis in male patients should be described in product labeling.

The time course of adverse events was such that the peak in mean severity was by week 2 of treatment and a modest decrease in mean severity was noted over time with continued treatment. Substantial decrease in local reaction severity did not occur until after the treatment period.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of the 15% Ointment with revisions to proposed labeling.

A phase 4 randomized, vehicle-controlled trial of Polyphenon Ointment to evaluate efficacy and safety anogenital warts including the objective of evaluation of recurrence in responders is suggested in the U.S. population with external genital and perianal condyloma.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The sponsor should submit post-marketing safety data according to regulations.

9.3.2 Required Phase 4 Commitments

A study of PK to assess the systemic absorption of Polyphenon Ointment after topical application under maximum use conditions. Oral intake of green tea should be used as a positive control.

A study of the safety of retreatment of anogenital condyloma accuminata upon relapse for patients experiencing complete clearance.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are being made.

9.4 Labeling Review

There is insufficient information to accurately assess recurrence rates in Polyphenon Ointment and Vehicle recipients and the sponsor's current data regarding recurrence rates should be removed from product labeling. The data regarding systemic absorption of study drug has also not been adequately characterized and should be removed from product labeling.

This reviewer recommends inclusion of the following precautions. The label should state that Polyphenon ointment is not a cure for external genital and perianal warts and that the effects on transmission are unknown. Women with external genital and perianal condyloma should have gynecologic examination and undergo cervical cancer screening per standard of care.

Please refer to the appended line-by-line labeling review for details.

9.5 Comments to Applicant

Suggested letter comments to applicant with regard to phase 4 studies are as follows:

1. A clinical study of VeregenTM 15% Ointment in adult men and women with external genital and perianal warts to assess for the incidence rate of relapse in subjects who respond by complete visual clearance of all warts during the treatment period (16 weeks). Please include a follow-up period of at least 12 weeks for assessment of relapse.
2. A Relative Bioavailability Study to assess the pharmacokinetics of topically applied VeregenTM Ointment compared to oral intake of green tea solution, following

single and repeated administration to patients with external genital and perianal warts. The study should be conducted under maximal use conditions (e.g. maximum total body surface area consistent with the approved labeling and dosage regimen) and designed, as a parallel group study with at least 20 completers in each treatment arm (Minimum Total N = 40). The concentrations of the catechins in the plasma should be determined using an adequately validated analytical method that has an acceptable performance based on its accuracy, precision, selectivity, sensitivity, reproducibility and stability.

Protocol to be submitted by May 2007.

Study Start Date by October 2007

Final Report Submission by October 2008.

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10 APPENDICES

10.1 Study CT 1005: A Randomized, Double-Blind, Four-Arm Parallel-Group, Placebo-Controlled Phase III Study To Investigate The Clinical Efficacy Of Two Galenic Formulations Of Polyphenon™ E In The Treatment Of External Genital Warts (Vol. 15)

10.1.1 Protocol

This section describes the study protocol as originally written. Protocol amendments are discussed separately.

Date of Protocol: 25 October 25, 2000

Study Dates: December 27, 2000 to November 18, 2001

Study Design: randomized, double-blind, placebo-controlled, multicenter, study

Study Objectives: To investigate the clinical efficacy of Polyphenon™ E cream (Formulation A) and ointment (Formulation B) in the treatment of external genital warts in male and female patients.

No. patients: 272 randomized; 242 treated

No. centers: 28 (Germany and Russia)

Study duration: 11 months

10.1.2 Study Population

Adult men and women age 18 and older with external anogenital warts (also included perineal and inguinal). Patients should have wart number of at least 2 but no more than 30 and a total wart area of between 12 mm² and 600 mm² (length x width). Pregnant and lactating women were excluded, and both a negative pregnancy test and adequate contraception during the study treatment was required for all women of child-bearing potential.

10.1.3 Study Treatment

Study medication was to be topically applied to all external genital warts, baseline and new, three times daily. Patients were treated for a maximum of 12 weeks.

The active ingredient was Polyphenon E with two formulations and dosages, a 10% Cream and a 15% Ointment.

10% cream (Batch no.: 000.38700, 000.38800; Manufacturer: _____)
Additional ingredients: Isopropyl Myristate, _____

15% ointment (Batch no.: 592, 601; Manufacturer: _____)
Additional ingredients: Isopropyl Myristate, Oleyl Alcohol, White Petrolatum, White Wax, Propylene Glycol Monostearate.

Placebo for Polyphenon™ E, 10% cream (Batch no.: 000.38900; _____, Germany) was prepared in identical color and consistency matched to 10% cream.

Placebo for Polyphenon™ E, 15% ointment (Batch no.: 591; _____) was prepared in identical color and consistency matched to 15% ointment.

Treatment allocation: Patients were randomly allocated to one of the treatment groups in a 2:1 active:placebo ratio. Randomization was performed using randomized permuted blocks and was stratified by gender.

Treatment groups: 4 arms (10% cream, placebo cream, 15% ointment, placebo ointment)

10.1.4 Endpoints

Primary Endpoint: Proportion of patients with complete clearance of all baseline warts within a maximum of 12 weeks.

Reviewer's comment: Note that this is different from the two pivotal trials in which complete clearance of all warts (baseline and new) was the primary efficacy endpoint.

10.1.5 Study Assessments

Assessments included wart measurements, local tolerability parameters, adverse events and concomitant medication use on weeks 2, 4, 6, 8 and 12 of treatment period and at 4 weeks and 12 weeks after wart clearance for those patients who had complete clearance of all baseline warts. Hematology, blood chemistry, urinalysis and pregnancy testing were done at baseline and final visit. The following assessments/procedures were optional: biopsies for confirmation of the diagnosis; HPV typing (selected centers); and clinical photography.

Reviewer's comment: HPV typing was not conducted in the pivotal trials.

10.1.6 Study Results

A total number of 272 patients were randomized for the study. Of the 272 patients randomized, 242 patients were treated and included in the safety population. Thirty patients were excluded by sponsor from one center because this center did not conduct the study in accordance with ICH / GCP guidelines.

The study site excluded from CT 1005 analysis was Site # 45.

Principle Investigator – Prof. Dr. Yuri Skripkin

Department of Skin & Venereal Diseases of the Russian Medical University

Mosfilmovskaya Street, 6

Moscow, Russian Federation

A total number of 221 patients were study completers; 21 patients did not complete the study according to the protocol.

Table 28 Safety Population

	Safety population			ITT-population		
	Male	Female	Total	Male	Female	Total
10% cream	41	38	79	39	38	77
15% ointment	42	38	80	41	37	78
Vehicle	42	41	83	42	41	83
Total	125	117	242	122	116	238

The safety population consisted of 242 patients and the ITT-population consisted of 238 patients. A description of the disposition of patients by treatment group is presented in the following table.

Table 29 Number of Patients who Discontinued and Reasons for Discontinuation

Reason for discontinuation	Placebo	10% Cream	15% Ointment
Lost to follow-up	2	2	2
Adverse event	0	0	3
Lack of efficacy/treatment failure	2	0	1
Non-compliance with study procedures	1	2	0
Subject withdrew consent	1	1	0
Investigator's decision	0	0	1
Other	1	2	0
Total	7	7	7

A total number of 21 patients discontinued the study prematurely; seven patients in each treatment group. Six patients were lost to follow-up, three patients (all in the 15% ointment group) had an AE (allergic reaction, hypersensitivity/allergic vulvitis, severe itching and burning), and three patients each discontinued due to lack of efficacy, non-compliance with study procedures, and other reasons, respectively; two subjects withdrew their consent and one patient was withdrawn by the investigator.

The three treatment groups were comparable with respect to their baseline characteristics. About half of the patient population was male and half was female. Total mean age was 33 years, mean weight 72 kg (data not shown).

Analysis of Clinical Efficacy: The primary analysis was defined as the proportion of patients experiencing complete clearance of all baseline warts within a maximum of 12 weeks. The following table shows rates of complete clearance in the ITT population.

Table 30 Complete Clearance of all Baseline Warts

Male						
	10% Cream		15% Oint		Vehicle	
	N =39	%	N =41	%	N =42	%
Yes	21	53.8	25	61.0	17	40.5
No	18	46.2	16	39.0	25	59.5
Female						
	10% cream		15% Oint		Vehicle	
	N=38	%	N =37	%	N =41	%
Yes	15	39.5	21	56.8	14	34.1
No	23	60.5	16	43.2	27	65.9
Total						
	10% cream		15% ointment		Vehicle	
	N = 77	%	N =78	%	N =83	%
Yes	36	46.8	46	59.0	31	37.3
No	41	53.2	32	41.0	52	62.7

Source: Sponsor's table 11.9

Trends towards higher number of patients showing complete clearance were seen in the 10% cream group compared with placebo, but these differences failed to show statistical significance. The differences between the 15% ointment group and placebo were more robust. Overall, the median time to clearance was 10.6 weeks and was comparable between the treatment groups. (Data not shown)

Reviewer's comment: Of note, responders were defined as those patients with complete clearance of all baseline warts. The most clinically meaningful endpoint would be complete clearance of all warts.

Reviewer's comment: This study is not considered a pivotal efficacy study and the review of further efficacy endpoints are not discussed here.

Safety: AEs that are noteworthy are discussed below. The following table describes patients for who adverse events were considered related to study treatment in Study CT 1005.

Table 31 Adverse Events Considered Drug-Related by the Investigator

Adverse event [reported term (MedDRA term)]	Intensity	Treatment received	Gender	Patient No.
Allergic reaction at the wart site (Allergic dermatitis)	mild	15% ointment	female	F-8142
Fingers painted black from cream (Skin discoloration)	mild	10% cream	female	F-8087
Local necrosis (Necrosis)	moderate	15% ointment	female	F-8221
Pain in the foreskin (Penile pain)	moderate	15% ointment	male	M-1155
Something like hyperkeratosis on the labias (Hyperkeratosis)	severe	10% cream	female	F-8043
Allergic vulvitis (Allergic dermatitis)	severe	15% ointment	female	F-8095

Six patients had six AEs during the treatment period which were considered to be related to the study drug, 2 patients in the group receiving 10% cream and 4 patients in the group receiving 15% ointment. In the group receiving 10% cream, these AEs were skin discoloration of mild intensity (fingers painted black from cream) and hyperkeratosis of severe intensity. In the group receiving 15% ointment, these AEs were necrosis of moderate intensity, allergic dermatitis (two patients, one with mild and one with severe intensity), and penile pain of moderate intensity.

In study CT 1005, the number of patients with related AEs was higher in women compared with men [male: one patient (0.8%); female: 5 patients (4.3%)]. From Table 31, all of the related AEs occurred in the active treatment groups compared with no related AEs reported in Vehicle.

Three withdrawals for adverse events occurred in the group receiving 15% Ointment compared with none in either of the other two treatment groups. These are described as follows.

- Patient F-8095, a female patient, developed an allergic dermatitis two days after starting study medication. The AE was classified as non-serious, but severe in intensity. The AE was assessed to be probably related to the study drug treatment and resulted in the discontinuation of the study drug. The patient was treated locally with betamethasone cream.
- Patient F-8142, a female patient, also developed allergic dermatitis. The AE was classified as non-serious, mild in intensity and possibly related to the study drug. The AE resolved without sequelae after discontinuation of the study drug.
- Patient M-1119, a male patient, developed severe itching and burning, which resulted in the discontinuation of the study drug and was assessed to be probably study-drug related. The AE resolved without sequelae after discontinuation of study drug.

There were no deaths and no SAEs in the safety population. One patient excluded from the safety population due to GCP violations was hospitalized due to worsening diabetes mellitus. The serious AE was not deemed related to study drug and the patient was assigned to the placebo group.

Safety data from the excluded investigational site was also examined by the applicant and this reviewer and was not found to raise any additional safety concerns. Of note, many patients

discontinued early as this investigational center was closed during the ongoing study and post-treatment follow-up was not reported for these patients.

10.1.7 Study Summary and Discussion

The study consisted of 272 randomized patients of who 242 were treated. Thirty patients were excluded from one clinical investigational site which was discontinued due to GCP violations.

Treatment effect with regard to complete clearance of all baseline warts was observed in the 15% ointment group: 59% active compared with 37% vehicle. A trend toward treatment effect was observed in the 10% cream group: 47% active compared with 37% vehicle.

No serious AE's occurred in the safety population. A higher number of patients had treatment-related AEs in the active treatment arms compared with control. The number of treatment-related AEs was highest in the 15% Ointment group, 4 patients compared with 2 patients in the 10% cream group and none in vehicle. Two patients, both women in the 15% Ointment group, developed an allergic dermatitis resulting in discontinuation of study treatment compared. There was no allergic dermatitis reported in either of the other two treatment arms.

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10.2 Study CT 1019: Assessment of dermal tolerance of a topical Polyphenon E preparation in healthy subjects on intact and scarified skin following repetitive occlusive application

10.2.1 Protocol

Study Design: The study was observer blind for the study preparations and the controls with random assignment of the treatments to the test fields in each patient, all of whom received the same treatments. Seven test fields on the back were examined; in three of the fields the skin was damaged by scarification and in four the skin was left intact. The test fields were treated once daily on days 1 to 4. Visual assessment was done on days 2 to 5.

Study Objectives: Assessments of dermal tolerance

No. Patients: 21

Study Duration: Duration of treatment 4 consecutive days.

10.2.2 Study Population

Main inclusion criteria are as follows.

Male or female, age 18-50 years

Healthy subjects with skin color that allows assessment of reddening (e.g. Fitzpatrick skin type \geq III)

No known hypersensitivity to the ingredients of the study preparation.

10.2.3 Study Treatment

Study Preparation 1: Polyphenon E 15% ointment Batch #: 000.00402

Study Preparation 2: Active Ingredient free vehicle, Batch #: 000.00302

Negative Control: 0.9 % SDS (scarified and intact skin) Batch #: 2265A71

Positive Control: 0.2 % SDS (intact skin only) Batch #: L169260

Treatments were applied by a staff member and the subjects removed the adhesive bandages themselves at specified times and were to record these times in a patient diary.

Scarification was done on study day 1 in the method of Frosch and Kligman. Six criss-cross scratches (3 in one direction and 3 in another) each approximately 1 cm in length, were made in the test field with a sterile needle.

Treatment allocation: All patients received the same treatments with random assignment of the treatments to the test fields in each patient. There was a distance of at least 2 cm between test fields

10.2.4 Endpoints

Primary Endpoint: assessment score used to evaluate dermal tolerance

Dermal Reactions in fields of intact skin were graded according to the following scales:

Erythema:

0= no reaction

1= slight diffuse, partial or follicular erythema

2= clear, sharply demarcated erythema

3= severe erythema with induration

4= severe erythema with induration and/or epidermal defect (blister, blebs, erosions)

Scaling:

0= negative

1= fine scaling

2= intermediate scaling

3= severe scaling

Dermal reactions on scarified (scratched skin):

0= scratches healing normally or already healed

1= scratches erythematous or broadened

2= scarification as in 1, in addition erythematous in the spaces between the scratches

3= scarification as in 2, in addition erythema extends beyond the boundaries of the scarified field

4= scarification as in 3, in addition palpable induration

5= scarification as in 4, in addition papules, vesicles, or epithelial defect.

Individual treatments were discontinued in the event of assessment with a score for erythema greater than 2 on intact skin or a score greater than 3 in scarified skin. Treatments in the other fields were continued. On the last day a final examination was performed.

Statistical methods: Descriptive

10.2.5 Study Results

Disposition:

A total of 21 patients were enrolled in this study (9 women and 11 men). One subject was withdrawn because the participation of this subject was not consistent with GCP and this subject was replaced. Twenty subjects completed the study as planned.

Reviewer's comment: It is not clear how investigator could be blinded to treatment group as the investigator is applying the treatments and these have differences in color and other properties.

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Analysis of Dermal Tolerance:

Intact skin:

Table 32 Visual Assessment Scores for Erythema on Intact Skin

		Day 2	Day 3	Day 4	Day 5
		N=20	N=20	N=20	N=20
15% Ointment	Median	0	0	0	1
	# reactions > 0	2	6	9	14
	Score sum	2	7	12	17
	# score 0	18	14	11	6
	# score 1	2	5	7	12
	# score 2	0	1	1	1
	# score 3	0	0	1	1
	# score 4	0	0	0	0
Vehicle	Median	0	0	0	0
	# reactions > 0	1	3	2	5
	Score sum	2	3	3	5
	# score 0	19	17	18	15
	# score 1	0	3	1	5
	# score 2	1	0	1	0
	# score 3	0	0	0	0
	# score 4	0	0	0	0
NaCl 0.9%	Median	0	0	0	0
	# reactions > 0	1	4	3	4
	Score sum	1	4	3	4
	# score 0	19	16	17	16
	# score 1	1	4	3	4
	# score 2	0	0	0	0
	# score 3	0	0	0	0
	# score 4	0	0	0	0
SDS 0.2%	Median	0	0	2	2
	# reactions > 0	2	3	16	19
	Score sum	2	3	31	34
	# score 0	18	17	4	1
	# score 1	2	3	3	5
	# score 2	0	0	11	13
	# score 3	0	0	2	1
	# score 4	0	0	0	0

Table 33 Dermal Tolerance in Scarified Skin

		Day 2	Day 3	Day 4	Day 5
		N=20	N=20	N=20	N=20
15% Ointment	Median	2	3	4	4
	# reactions > 0	19	19	19	19
	Score sum	42	58	68	70
	# score 0	1	1	1	1
	# score 1	3	2	0	0
	# score 2	9	4	1	3
	# score 3	7	4	6	2
	# score 4	0	9	12	12
	# score 5	0	0	0	2
Vehicle	Median	1	1	1	1
	# reactions > 0	19	18	19	17
	Score sum	24	26	26	21
	# score 0	1	2	1	3
	# score 1	14	12	13	13
	# score 2	5	4	5	4
	# score 3	0	2	1	0
	# score 4	0	0	0	0
	# score 5	0	0	0	0
NaCl 0.9%	Median	0	0	0	0
	# reactions > 0	2	0	0	1
	Score sum	2	0	0	1
	# score 0	18	20	20	19
	# score 1	2	0	0	1
	# score 2	0	0	0	0
	# score 3	0	0	0	0
	# score 4	0	0	0	0
	# score 5	0	0	0	0

The results of the dermal tolerance study indicated that Polyphenon E 15% ointment is poorly tolerated on scarified skin. The median score for scarification reached 4 by day 3 of treatment. A score of 4 indicates that erythema extends beyond the boundaries of the scarification field, and there is palpable induration. A couple of patients had scores of 5 meaning that in addition, papules vesicles or epithelial defect was noted.

10.3 Study CT 1016: Assessment of sensitization potential of a topical Polyphenon E preparation in a predictive repeated insult patch test in 200 healthy volunteers

10.3.1 Protocol

Study Design:

The trial was an observer-blind study with intraindividual comparison in 220 healthy subjects, 200 evaluable. Three test fields were examined for the sensitization potential: 1) substance-treated field; 2) a vehicle-treated field; 3) a untreated control field.

The design was based upon the methods of described by Shelanski and Draize. There were three parts to the sensitization testing.

Induction phase: 250 mg of the active formulation or the vehicle were applied under occlusion on the respective test fields for 24 hours three times weekly for 3 weeks. The untreated field had only the occlusive dressing.

Resting phase: This was a treatment-free resting phase of 10-17 days after the last application

Challenge phase: New test fields are marked.

- Active formulation under occlusion for 20-30 minutes
- Active formulation for 24 hours
- Vehicle for 24 hours
- Left untreated but not occluded.

Visual assessments: immediately, 24, 48, and 72 hours after removal of the occlusion.

Retesting was done for patients who developed a positive reaction.

Study Objectives: To assess the sensitization potential of Polyphenon E ointment following repeated application to intact skin.

No. Patients: 200 at a single investigational center

10.3.2 Study Population

- Healthy men and women aged 18-50 with
- Healthy skin in the test fields,
- Fitzpatrick skin type I-II
- Sexually active women of childbearing potential had to use a reliable form of contraception (pregnant or nursing women were excluded).

10.3.3 Study Treatment

Study preparation 1: 15 % Ointment 250 mg each application (batch 000.00402)

Study preparation 2: active ingredient-free vehicle ointment, 250 mg each application (batch 000.00302)

Given that the observer could have access to the CRF during the observation, the study cannot formally be regarded as observer-blind. According to the sponsor, however, the study was conducted in the “spirit of observer-blind.” See section 9.4.6 of the clinical study report.

Reviewer’s comment: It is not clear that the agency can rely on the results of this study. The codes were entered in the respective application scheme on page 6 of all CRFs.

10.3.4 Study Assessments

0 = no dermatitis

0.5 = equivocal erythema, did not cover the test field

1 = erythema which covered the test field

2 = erythema and induration which covered the test field

3 = erythema, induration and vesicles covering the field

4 = erythema, induration, vesicles and bullae covering the test field.

10.3.5 Study Results

A total of 219 subjects were enrolled in the study and 209 subjects completed the study as planned. The re-test was performed in 5 subjects. Nine subjects dropped out of the study.

Demographics were as follows: 138 women and 81 men were enrolled. Ages ranged from 18-50 years and the mean age was 32 years.

Analysis of Sensitization:

In one subject (no. 42), the treatment was discontinued on study day 5 due to symptoms of acute contact dermatitis. This subject was included in the retest.

Reviewer's comment: The time course of this reaction suggests previous sensitization to components of the polyphenon formulation, either active or inactive.

In 153 subjects, localized follicular papules were observed during the induction phase. These reactions were not covered by the scoring system. In 142 subjects such a skin reaction was observed in the fields treated with Polyphenon E ointment and in 27 of the subjects reactions were additionally noted in the fields treated with the vehicle and/or negative control.

Analysis of Challenge:

Five of the 209 subjects (subjects 22, 36, 82, 99, and 202) were sensitized and showed an allergic contact dermatitis against Polyphenon Ointment during the challenge phase of the study (2.4% of subjects) and one patient (42) showed allergic contact dermatitis during the induction phase most likely due to prior exposure to one of the formulation components. The vehicle and untreated control sites were negative in all study subjects. Retesting was undertaken to determine which of the ingredients of the Polyphenon ointment resulted in the allergic reactions. Type IV sensitization to the active ingredient was identified in four subjects, including subject 42. In one subject (99), sensitization to neither the complete formulation nor to any of the components could be verified at that timepoint and another one of the five subjects (36) who showed a positive reaction during the challenge phase was lost to follow-up and did not have re-testing.

No dermal reactions were noted on the urticaria evaluation test in any of the 209 patients.

Safety:

There were no deaths or serious AEs observed. Three subjects discontinued study participation due to an AE; plaster dermatitis (day 8), pityriasis rosea (day 36), leucocyturia (day 1) were observed in one subject each. Two AEs were recorded in two subjects in the retest, both common cold, and were considered unrelated or unlikely related to study preparations.

10.3.6 Study Summary and Discussion

Six of the 209 subjects showed an allergic reaction at some point during the study. Five of the 6 were sensitized during the induction phase and showed an allergic reaction during the challenge phase and one patient who presumably had already been sensitized, showed an allergic reaction during the induction phase. Retesting confirmed allergy to the active ingredient of the Polyphenon ointment in 4 of these subjects, one subject was lost to follow-up, and retesting was negative in another subject. In conclusion, the active ingredient in the Polyphenon ointment was shown to be sensitizing (type IV hypersensitivity) in 2.4% of subjects (N=209). This study was performed on the backs of healthy volunteers. It is unclear how these results translate into the patient population with genital warts where application is on a thin mucosal environment.

10.4 Study CT 1017: A Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled Phase 3 Trial to Investigate the Clinical Efficacy and Safety of Polyphenon® E in the Treatment of External Genital Warts

Protocol Number: CT 1017

Study Design: randomized, double-blind, placebo-controlled, multicenter, study

Study Objectives: The primary objectives were:

- to investigate the clinical efficacy of the 10% Ointment and of the 15% Ointment as compared to placebo in the treatment of external genital warts in male and female patients; and
- to assess the safety and tolerability of the 10% Ointment and of the 15% Ointment in comparison to placebo when applied for a maximum of 16 weeks.

No. patients: Four hundred and eighty (480) randomized patients were planned to be enrolled at approximately 50 sites in Europe

Duration of Treatment: Patients were to remain in the study up to a maximum of 16 weeks of treatment unless a complete clearance of all warts is observed earlier. Patients experiencing a complete clearance of all warts were to enter a treatment-free follow-up period of up to 12 weeks.

10.4.1 Study Population

Main inclusion criteria: Male or female patients, 18 years of age or older at the time of enrollment and all of the following:

- Clinical diagnosis of external genital warts which can be located:
 - in men, over the glans penis, penis shaft, scrotum and foreskin,
 - in women, on the vulva,
 - in both sexes, in the inguinal, perineal, and perianal areas.
- At least two, but not more than 30 external genital warts.
- A total wart area between 12 and 600 mm².
- For women of child-bearing potential: negative pregnancy test and willingness to use effective contraception;
- For partners of male patients who are of child-bearing potential: use of effective contraception during the treatment period

Exclusion criteria:

- Participation in an investigational trial within 30 days prior to enrollment.
- Previous participation in a trial investigating Polyphenon® E in the treatment of external genital warts.
- Treatment of external genital warts within 30 days prior to enrollment.
- Systemic intake of virostatics within 30 days prior to enrollment and for the whole study duration.
- Systemic intake of immunosuppressive or immunomodulatory medication within 30 days prior to enrollment and for the whole study duration.
- *Systemic intake of virostatics within 30 days prior to the patient's randomization and for the whole study duration, with the exception of systemic acyclovir and the related drugs famcyclovir and valcyclovir. (Topical application of these drugs in the anogenital area remained excluded.)
- Any current and/or recurrent pathologically relevant genital infections other than genital warts.
- Current known acute or chronic infection with HBV or HCV.
- Known human immunodeficiency virus (HIV) infection.
- Any current uncontrolled infection.
- Organ allograft.
- For female patients: pregnancy or lactation.
- Known allergies against any of the ingredients of the treatments.
- Any chronic or acute skin condition susceptible of interfering with the evaluation of the drug effect.
- Any chronic condition susceptible, in the opinion of the investigator, of interfering with the conduct of the study.
- Internal (vaginal or rectal) warts requiring treatment.

*This exclusion criteria was modified in protocol amendment 2. The exclusion in the original protocol read as follows: Current infection with Herpes genitalis or history of Herpes genitalis infection within the last 3 months.

Reviewer's comment: The effect was to allow use of systemic (but not topical) acyclovir and related drugs.

Treatment allocation: A total of 480 patients were to be randomized as follows to one of the three treatments:

- 40% to 10% Ointment (192 patients)
- 40% to 15% Ointment (192 patients)
- 20% to matching placebo (96 patients)

10.4.2 Study Treatment

Study medication was to be applied three times a day topically for a maximum of 16 weeks.

Dosing was anticipated by sponsor to be < 250 milligrams of study medication per application. Two tubes were to be provided every four weeks each containing 15 g of ointment.

10.4.3 Endpoints

Primary Efficacy Endpoint: The primary efficacy endpoint was complete clearance of all external genital warts after a maximum of 16 weeks of treatment and was to be analyzed using the ITT population.

Each active ointment was to be compared to the placebo group with regard to the response rate using Fisher's exact test (1-sided, $\alpha=2.5\%$), and the overall significance kept at 5%.

Amendment 2 to the clinical protocol further clarified the primary endpoint as follows: Proportion of patients experiencing complete clearance of all warts (baseline warts and new warts occurring during treatment) (i. e. clinical response), within a maximum of 16 weeks treatment.

Major Secondary Endpoints:

- Time to complete clearance of all warts (baseline warts and new warts occurring during treatment), time to complete clearance of all baseline warts, and of all new (post-baseline) warts.
- Proportion of patients with complete clearance of all baseline warts within a maximum of 16 weeks treatment.
- Proportion of patients experiencing a certain level of wart clearance (partial clearance of all baseline warts and new warts occurring during treatment) at the end of treatment.
- Proportion of patients experiencing a certain level of baseline wart clearance (partial clearance of all baseline warts) at the end of treatment.
- Proportion of patients with complete clearance of all warts or only all baseline warts experiencing recurrence of any cleared wart (baseline warts and new warts or only baseline warts occurring during treatment) during the 12-week follow-up period.

10.4.4 Study Assessments

The schedule of study assessments is shown in the following table.

Table 34 Schedule of Study Assessments (Study CT 1017)

	SCREEN	TREATMENT PERIOD									FOLLOW-UP	
	Day -14 to -1	Visit 1 (Baseline) Day 0	Visit 2 Wk 2	Visit 3 Wk 4	Visit 4 Wk 6	Visit 5 Wk 8	Visit 6 Wk 10	Visit 7 Wk 12	Visit 8 Wk 14	Visit 9 (Final) Wk 16	Visit 10 Wk 20	Visit 11 Wk 28
Informed consent	X											
Eligibility criteria	X	X										
Disease history	X											
Medical history	X											
Demographic data	X											
Pap smear test	X											
Wart measurements	X	X	X	X	X	X	X	X	X	X	X	X
Photography (optional)		X								X		
Local tolerability parameters	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination and vital signs	X	X								X		
Laboratory assessments	X									X		
Pregnancy test	X									X		
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Patient randomization		X										
Dispense study medication		X		X		X		X				
Start of study medication application		X										
Collect unused study medication				X		X		X		X		
Drug compliance check			X	X	X	X	X	X	X	X		

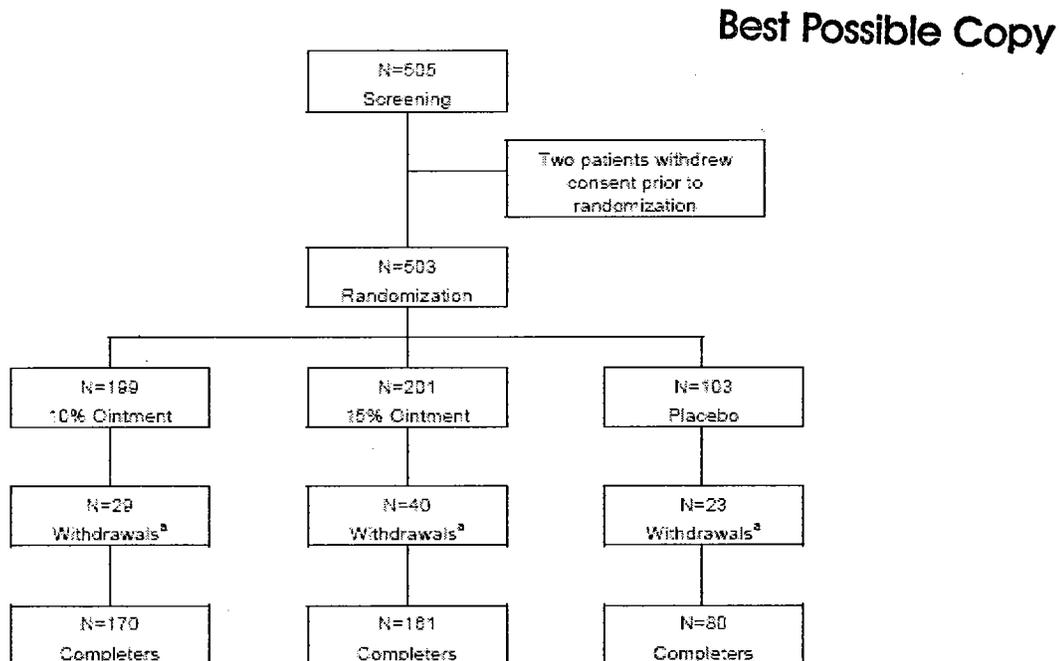
Only patients with a complete clearance of all external genital warts were to be followed up for four weeks and, if no recurrence of any cleared wart or occurrence of any new warts were

observed within these four weeks, for up to 12 weeks after treatment completion in order to obtain data on the recurrence rate. Patient photography was optional.

10.4.5 Study Results

The patient disposition is shown in the following figure.

Figure 3 Study 17-Patient Disposition



The reasons for premature discontinuation as provided in the sponsor’s study report are shown in the following table. This reviewer noted some differences from this table as discussed below.

Appears This Way
On Original

Table 35 Reasons for Premature Discontinuation at Any Time N (%) (Study CT 1017)

Reason for discontinuation	10% Ointment (N=199)		15% Ointment (N=201)		Vehicle (N=103)	
	N	%	N	%	N	%
Patient withdrew consent	10	34	16	40	9	39
Non-compliance with study procedures	7	24	6	15	2	9
Lack of efficacy/treatment failure	6	21	2	5	6	26
Adverse event	0	0	6	15	1	4
Protocol violation/pregnancy	1	3	4	10	1	4
Lost to follow-up	0	0	3	8	2	9
Other	5	17	3	8	2	9
Total	29	100	40	100	23	100

Source: Table 10.3 on p. 57 of Sponsor's Study Report (N=number of patients; Percentages calculated relative to the number of patients who discontinued.)

Overall, 92 subjects (18%) discontinued the study prematurely. "Withdrawal of consent" was listed as the most common reason for premature discontinuation. The study report does not state reasons for "withdrawal of consent." The second most common reason given for premature discontinuation was "non-compliance with study procedures." A total of 7 subjects were classified as having withdrawn for adverse events, of these 6 subjects were assigned to the 15% ointment treatment group.

Reviewer's comment: The actual number of patients who withdrew for adverse events was 9. An additional two patients withdrew for reasons described as "other" but were experiencing local reactions. See table 28 below.

For 10 subjects who were classified under "Other" the investigator comments are included below. Two of these patients (15% oint) appear to have discontinued for local skin reactions.

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On Original

Table 36 Reasons for Treatment Discontinuation for Select Patients as Reported in Datasets

Patient number	Other investigator comments	Treatment
02536	Patient decision to finalize	Vehicle
02187	Girlfriend confirmed the patient do not participate any longer in the study	Vehicle
02188	Mother confirmed patient has left the country	15% oint
02184	Out of visit-timeline	10% oint
02661	Strong local skin reaction	15% oint
02664	Because of exclusion criteria	10% oint
02702	Surgery of the warts	10% oint
02193	Personal reason	10% oint
02021	Too young, under age of 18.	10% oint
02011	Local symptoms	15% oint

Source: Sponsor's dataset: DISP.XPT issdern folder

Protocol deviations are summarized in the following table.

Table 37 Protocol Deviations (Study CT 1017)

	Vehicle (N=103)		10% Ointment (N=199)		15% Ointment (N=201)	
	N	%	N	%	N	%
Inclusion criteria not met	0	0	2	1	0	0
Exclusion criteria met	0	0	1	<1	1	<1
Time schedule violated	1	1	3	2	3	2
Treatment schedule violated	3	3	5	2	4	2
Excluded concomitant medication	2	2	6	3	3	2
Poor compliance	0	0	1	<1	0	0
No wart measurements/safety measurements up to Visit 3	4	4	4	2	12	6
Combination of reasons listed	0	0	3	2	7	4
Total	10	10	25	13	30	15

Source: Table 10.4 on p. 58 of Sponsor's Study Report

Protocol violations occurred in 10%, 13% and 15% in the placebo, low dose and high dose, respectively. A higher proportion of subjects, 6%, in the high dose group had poor compliance with wart measurements and safety measurements compared with the other two treatment groups, which were 4% and 2% for the placebo and low dose group, respectively. Overall, these protocol deviations are not deemed to have influence study results.

Baseline characteristics: The following table shows the baseline demographics of the study population.

Table 38 Baseline Characteristics (Study CT 1017)

		Vehicle	10% Ointment	15% Ointment
Gender				
Total	N (%)	103 (100%)	199 (100%)	201 (100%)
Male		62 (60%)	110 (55%)	105 (52%)
Female		41 (40%)	89 (45%)	96 (48%)
Ethnic group				
Total	N (%)	103 (100%)	199 (100%)	201 (100%)
African		4 (4%)	6 (3%)	6 (3%)
Asian		1 (1%)	1 (<1%)	1 (<1%)
Caucasian		97 (94%)	189 (95%)	191 (95%)
Hispanic		0 (0%)	0 (0%)	1 (0.5%)
Other		1 (1%)	3 (2%)	2 (1%)
Age (years)				
	Mean	30	31	31
	Median			
	Range	18-60	16-98	17-69
Body weight (kg)				
	Mean	71	72	70
	Range	44-105	47-133	46-115
Body mass index (kg/m²)				
	Mean	23	24	23
	Range	17-37	17-44	16-39
Circumcision (male subjects only)				
No	N (%)	56 (90%)	97 (88%)	98 (93%)
Yes	N (%)	6 (10%)	13 (12%)	7 (7%)
Childbearing Potential (female subjects only)				
No	N (%)	4 (10)	10 (11)	11 (11)
Yes	N (%)	37 (90)	79 (89)	85 (89)

Source: Table 11.3 on page 62 of sponsor's study report

The vast majority of subjects were Caucasian, 94-95% across treatment groups. Across the three treatment arms, a higher number of men (52-60%) were enrolled compared to women (40-48%). A higher proportion of men were assigned to placebo (60%) compared to active treatment (55% and 52% in the low and high dose groups, respectively). The mean age ranged from 30-31 across treatment groups. Of note some adolescent subjects down to age 16 were enrolled into the study. The mean body weight was comparable across treatment groups (ranging from 70-72 kg) as was body mass index (ranging from 23-24 kg/m²). Across treatment groups, 89-90% of female subjects were of childbearing potential.

Baseline disease history and characteristics:

Table 39 Time (Weeks) between First Diagnosis, Current Episode and Study Visit 1 (Study CT 1017)

	Vehicle (N=103)	10% Ointment (N=199)	15% Ointment (N=201)
Time from first diagnosis to Visit 1			
Mean	89	44	42
Median	11	9	7
Range	0-1193	0-723.9	0-933
Time from start of the current episode to Visit 1			
Mean	34	32	30
Median	10	10	12
Range	0-1193	0-1297	(-16.7)-724
Time from first diagnosis to start of the current episode			
Mean	55	12	12
Median	0	0	0
Range	(-76)-841	(-783)-678	(-221)-730

The median time in weeks between the time of first diagnosis and study baseline was 11, 9, and 7 in the placebo group, low dose and high dose groups, respectively. There was a marked difference in the mean duration in the placebo group (89 weeks) compared to either active arm (42-44 weeks across groups). This is likely due to in large part the influence of outliers in the placebo treatment group.

The median number of warts per subject in the ITT population was the same in each of the treatment groups and was 6 warts per subject. The median baseline wart area was also comparable across the treatment groups: 10% Ointment: 51.0 mm²; 15% Ointment: 50.5 mm²; and Vehicle: 51.5 mm².

Efficacy: The primary efficacy endpoint was defined as the proportion of patients who presented with clearance of all warts (baseline warts and new warts occurring during treatment)

within a maximum treatment period of 16 weeks. The primary analysis was based upon the ITT population, which consisted of 503 subjects.

Table 40 Primary Endpoint Efficacy Results (ITT-LOCF)

	Vehicle N= 103	10% Ointment N=199	15% Ointment N=201
Fail n (%)	65 (63.1)	100 (50.3)	99 (49.3)
Success n (%)	38 (36.9)	99 (49.7)	102 (50.7)
p-value		0.0384	0.0284

Source: FDA Statistical Reviewer's Analysis using Fisher's exact test.

Fisher's exact test was used to assess the treatment effect of the Polyphenon E 10% Ointment versus placebo and Polyphenon E 15% Ointment versus placebo Ointment. Using the Hochberg procedure, both Polyphenon E 10% Ointment (p=0.0384) and Polyphenon E 15% Ointment (p=0.0284) show a statistically significant treatment effect in terms of the complete clearance rate of all warts (baseline and new) compared to placebo. The treatment effect was 12.8% for the low dose group and 13.8% for the high dose group (active – placebo). There was only a 1% difference in treatment effect between the 10% dose group and the 15% dose group. The study demonstrated efficacy in both active arms based upon the prespecified primary analysis.

From the FDA statistical reviewer's analysis, the median *time- to- complete clearance* for those who cleared (rounded to whole number) was 16 weeks (10% oint), 16 weeks (15% oint) and 15 weeks (placebo).

A decrease in the total median number of warts per patient was observed in all three treatment groups from a baseline value of 6 across all treatment groups to the following values by the end of treatment: 0 warts in the 10% Ointment, 0 warts in the 15% Ointment group and 3 warts in the Vehicle group.

The area of warts at baseline and at end of treatment is shown in the following table.

Table 41 Wart Area at Baseline and End-of-Treatment

	10% Ointment	15% Ointment	Vehicle
N	195	194	102
Baseline			
Mean (mm ²)	100	94	76
Median	51	50	52
Q25/Q75	28 /112	24 /113	26 /92
Range (mm ²)	13 -572	12 -591	12 -490
Visit 9			
Mean (mm ²)	29	27	41
Median	0	0	15
Q25/Q75	0 /22	0 /20.0	0 /55
Range (mm ²)	0 -728	0 -424	0 -401

Source: Table 11.38 on page 129 of the clinical study report.

The median wart area decreased to 0 mm² in both active treatment groups and to 15 mm² in the placebo group from a baseline of 51 mm² across all groups.

The following table includes analyses done by the FDA statistical reviewer to better understand the impact of the Russian site (Rus-1) on the overall efficacy results for CT 1017.

Table 42 Sensitivity Analysis of Russian Site

	10% Ointment	15% Ointment	Vehicle
Overall			
X/n (%)	99/199 (49.7)	102/201(50.7)	38/103 (36.9)
Treatment Effect ²	12.8	13.8	--
p-value ¹	0.0384	0.0284	--
Exclude RUS-01			
X/n (%)	92/189 (48.7)	93/191 (48.7)	38/98 (38.8) -
Treatment Effect ²	9.9	9.9	-
p-value ¹	0.1335	0.1341	-
Imputed RUS-01			
X/n (%)	97/199 (48.7)	98/201 (48.8)	40/103 (38.8)
Treatment Effect ²	9.9	10	--
p-value ¹	0.1136	0.1141	--
1 Fisher's Exact Test.			
2 Response for active minus response for vehicle.			
Source: FDA statistical reviewer's analysis.			

The following table shows the response rates and treatment effect by gender for Study 17.

Table 43 Study 17: Primary Endpoint- Complete Clearance of All Warts (Baseline and New) by Gender

Gender	Vehicle			10% Ointment				15% Ointment			
	N	Cleared	Rate	N	Cleared	Rate	TE*	N	Cleared	Rate	TE*
Female	41	17	41%	89	52	58%	17	96	54	56%	15
Male	62	21	34%	110	47	43%	9	105	48	46%	12
Total	103	38	37%	199	99	50%		201	102	51%	

*TE=treatment effect (active-placebo)

Treatment effect was seen in both men and women in both dose groups. Women tended to have a higher treatment effect than men in Study CT 1017. The treatment effect for women was 17% and 15% and for men was 9% and 12% (10%-oint and 15%-oint groups, respectively). Differences in treatment effect between men and women were more pronounced in the 10%-ointment group in this study compared with 15%-ointment. In general, women tended to have higher efficacy rates than men in all treatment arms in the study.

Clinical response by subgroups defined by age quartile is shown in the following table.

Table 44 Clinical Efficacy by Age: Mean Percent Clear by Week 16

Age (yrs) Quartile	Vehicle		10% Ointment		15% Ointment	
[16,24)	41	N=39	60	N=51	49	N=59
[24,29)	21	N=19	47	N=58	55	N=47
[29,37)	50	N=20	35	N=42	50	N=50
[37,98]	32	N=25	54	N=48	49	N=45

Source: FDA statistician

The overall trend was toward treatment effect in both younger and older age groups. Treatment effect was observed in each of the age quartiles with the exception of the 29-37 year quartile for the 10% ointment group. However, this appears to have been by chance as all the other quartiles including the fourth quartile for age showed treatment effect. The numbers of subjects the geriatric age group, age 64 and older, were too small to make any inference regarding efficacy; there were a total of 4 subjects in this group (3 in the 15% ointment group and 1 in the 10% vehicle group).

Table 45 Complete Clearance of all Warts by Country

Country	Vehicle (N=102)		10% Ointment (N=195)		15% Ointment (N=194)	
	N	%	N	%	N	%
SCAN, CZE, ZAF	4	(29%)	8	(27%)	9	(32%)
POL	4	(36%)	13	(62%)	12	(57%)
DEU	8	(33%)	18	(43%)	17	(42.5%)
ROM	15	(50%)	30	(54%)	36	(62%)
RUS	7	(30%)	30	(65%)	28	(60%)
Total	38	(37%)	99	(51%)	102	(53%)
p-value			0.0218		0.0117	

The countries with the highest difference between treatment groups were Poland (delta=21) and Russia (delta=30) for the high dose group.

The clinical reviewer could not confirm the sponsor's figures regarding recurrence rate. The following data from the sponsor's study report could not be confirmed by the clinical reviewer because the method of data recording in the datasets submitted to the Agency did not distinguish between missing observations and zero wart counts. The values in Table 40 below that were submitted by the sponsor are likely to be an underestimate of the recurrence rate, because they are based on the assumption that patients with missing data did not have recurrence.

Table 46 Sponsor's Analysis of Patients with Recurrence during Either visit 10 or 11 of the Follow-up Period

	10% Ointment		15% Ointment		Vehicle	
	<i>(Nf=51, Nm=47)</i>		<i>(Nf=54, Nm=47)</i>		<i>(Nf=17, Nm=21)</i>	
	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>	<i>N</i>	<i>%</i>
<i>Female</i>	3	3.1	2	2.0	1	2.6
<i>Male</i>	1	1.0	4	4.0	0	0.0
Total	4	4.1	6	5.9	1	2.6
<i>95% confidence interval for recurrence rate</i>	<i>[1.1%, 10.3%]</i>		<i>[2.2%, 12.6%]</i>		<i>[0.1%, 14.2%]</i>	

Source: Table 11.45 of clinical study report

Reviewer's comment: This reviewer does not support allowing any labeling statements regarding recurrence rate on the basis of these data.

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Safety

A total of 8 subjects suffered adverse events leading to withdrawal from the study. One of the 8 subjects (subject 2702) had a scrotal cystectomy that was considered not related to study medication by the clinical investigator. Five subjects had severe local reactions assessed by the investigator as probably related to study medication. Four of these were in the high dose group and one was in the placebo group. Two subjects withdrew due to moderate hypersensitivity reactions, both in the high dose group. In some of these cases, there was inadequate subject follow-up for assessment of AE resolution as in the following case history.

Case history: A 19-year-old male presented with genital warts and was enrolled in the study and was randomized to Polyphenon 15% Ointment. On day 11, he presented with phimosis and right inguinal lymphadenitis. The investigator considered these events to be probably related to the study medication and discontinued the administration of the study medication. The patient was withdrawn from the study. The event had not resolved at the time of the final visit on day 12 and the outcome is unknown. The investigator considered the overall local tolerability to be severe, with severe erythema and edema.

Reviewer's comment: The final study visit was the day after the subject presented with the adverse event. The follow-up for this subject was insufficient.

Reviewer's comment: The high dose appears to be poorly tolerated in some subjects. The difference in treatment effect between the low dose and high dose of this product in this study was modest and not deemed to be clinically significant.

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Table 47 Adverse Events Resulting in Discontinuation of Study Drug (Study CT 1017)

Patient	Adverse Event	LLT decode derived from MEDDRA	Action Taken	Serious	Severity	Outcome	Relationship	Study Drug Batch / Dose group
10% oint group								
2702	Surgery of a scrotal cyst	Scrotal cystectomy		No	Moderate	Resolved without sequelae	Not related	38,402/ 10% oint
15% oint group								
2311	Strong local symptoms: redness, edema, burning, pain	Application site reaction	Hospitalization and operation	Yes	Severe	Resolved without sequelae	Probable	402/ 15% oint
2498	Suspicion of allergic reaction to study drug, differential diagnosis: psoriasis	Allergic reaction		No	Moderate	Not resolved	Possible	402/ 15% oint
2051	Toxic irritant reaction to medication	Toxic reaction (nos)	Treatment bactroban ointment	No	Severe	Resolving	Probable	402/ 15% oint
2055	Genital herpes	Genital herpes	Zelitrex tabl. 1 g twice daily for 7 days	No	Severe	Resolved without sequelae	Probable	402/ 15% oint
2244	Allergy	Allergy	Concomitant medication	No	Severe	Resolving	Probable	402/ 15% oint
2260	Phimosis	Phimosis		No	Severe	Unknown/lost to follow-up	Probable	402/ 15% oint
	Right inguinal lymphadenitis	Lymphadenitis		No	Mild	Unknown/lost to follow-up	Probable	
Vehicle Group								
2243	Allergy	Allergy	Concomitant medication	No	Severe	Resolving	Probable	302/ Vehicle oint

Source : ModifiedTable 12.26 of Sponsor's CSR

Of the 8 patients with AEs resulting in discontinuation of treatment, 6 were classified as having a probable relationship to study drug and 5 of these were assigned to the 15% ointment. One patient was hospitalized for the adverse event. One subject assigned to the 10% group had a

scrotal cystectomy that was considered unrelated to study drug and one patient assigned to placebo had suspected hypersensitivity was considered probably related to study drug. One patient had two AEs, phimosis and lymphadenitis. Six of the 8 patients were assigned to the 15% ointment group (Batch 402).

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Table 48 Mean Biochemical Values Over Time (Study CT 1017)

Variable [unit] Treatment	Visit 1 (Baseline)		Last reported		Change	
	N	Mean	N	Mean	N	Mean
Sodium [mmol/L]						
10% Ointment	195	140.05	176	139.93	174	-0.17
15% Ointment	197	140.18	174	140.05	171	-0.21
Vehicle	102	140.54	92	140.10	92	-0.49
Potassium [mmol/L]						
10% Ointment	195	4.53	175	4.47	173	-0.08
15% Ointment	196	4.46	172	4.45	169	0.02
Vehicle	101	4.47	92	4.39	91	-0.03
Calcium [mmol/L]						
10% Ointment	193	2.30	166	2.33	165	0.06
15% Ointment	198	2.30	164	2.36	162	0.08
Vehicle	102	2.31	90	2.29	90	0.01
Urea [mmol/L]						
10% Ointment	186	4.58	173	4.59	167	-0.07
15% Ointment	194	4.51	171	4.72	170	0.16
Placebo	99	4.63	91	4.81	91	0.24
Creatinine [µmol/L]						
10% Ointment	195	75.36	178	77.87	175	2.54
15% Ointment	193	78.28	175	78.39	171	0.67
Vehicle	101	77.35	93	79.13	92	1.72
Blood glucose [mmol/L]						
10% Ointment	198	4.76	180	4.70	180	-0.09
15% Ointment	199	4.90	174	4.82	173	-0.11
Vehicle	101	4.87	93	5.14	92	0.26
Aspartate aminotransferase (AST) [U/L]						
10% Ointment	197	24.04	181	24.89	180	1.06
15% Ointment	200	25.86	175	25.72	175	0.27
Vehicle	101	23.06	93	25.58	92	2.81
Alanine aminotransferase (ALT) [U/L]						
10% Ointment	197	26.24	181	25.63	181	-0.06
15% Ointment	201	26.00	175	24.10	175	-1.54
Vehicle	101	24.57	93	23.51	93	-0.40

Table 46 Mean Biochemical Values Over Time (Study CT 1017) (cont.)

Variable [unit] Treatment	Visit 1 (Baseline)		Last reported		Change	
	N	Mean	N	Mean	N	Mean
Gamma glutamyl transferase (GGT) [U/L]						
10% Ointment	192	26.54	177	27.34	176	0.63
15% Ointment	192	25.05	172	26.21	168	0.95
Vehicle	99	26.77	91	26.40	91	0.57
Alkaline phosphatase [U/L]						
10% Ointment	197	107.91	178	112.08	178	1.86
15% Ointment	199	106.83	173	104.07	173	-3.88
Vehicle	102	106.19	93	103.54	93	-0.68
Albumin [g/L]						
10% Ointment	157	44.93	145	45.03	139	-0.21
15% Ointment	163	44.92	140	44.15	137	-0.70
Vehicle	81	45.06	77	44.13	74	-0.86

The mean creatinine increased in the 10% treatment group (+2.5mmol/L). This was not observed in the 15% treatment group or in the vehicle arm. Shift tables are a more sensitive way of analyzing the data. No clinically significant trends were noted in AST, ALT and alkaline phosphatase. Bilirubin was not measured.

Summary of Clinical Efficacy:

Prespecified Primary analysis: The study demonstrated efficacy in both active arms based upon the prespecified primary analysis. Both the 10% Ointment and the 15% Ointment show a statistically significant treatment effect in terms of the complete clearance rate of all warts (baseline and new) compared to placebo. The treatment effect was 12.8% for the 10% dose group and 13.8% for the 15% dose group (active – placebo). There was only a 1% difference in treatment effect between the 10% dose group and the 15% dose group and thus the study did not demonstrate a meaningful dose response for clinical efficacy.

Sensitivity analyses (summarized from FDA statistical review):

For the 10% dose group, the efficacy results were affected by some methods of imputation for missing data, but not to others. If all missing are imputed as success, the test would fail to reach statistical significance. If all missing are imputed as failures, the statistical significance is still achieved. The primary method of imputation, LOCF, did meet pre-specified criteria.

For the 15% dose group, the sensitivity analysis showed that statistical significance was reached for both extremes (i.e. if all missing are treated as success and if all are treated as failures).

A single large investigational site in this study appears to have influence the efficacy results. Analyzing the primary efficacy endpoint CT1017 without the large Russian site (Rus-01),

affected the overall efficacy results. This site was selected for investigation by the Division of Scientific Investigations.

Subgroup analyses: Treatment effect was demonstrated in subgroups defined by gender and age. Women tended to have higher response rates in all three treatment groups and also had higher treatment effect than men (active-placebo) for each of the two comparisons.

One study site in Romania, site 5, had efficacy findings reversed in both clinical studies with all patients receiving vehicle ointment (4 in each study) showing complete clearance of warts. The reason for this observation is unclear.

Secondary endpoints:

Included among the secondary endpoints was proportion of responders who experienced recurrence during the follow-up period. However, the clinical reviewer could not confirm the sponsor's figures regarding recurrence rate. The values that were submitted by the sponsor are likely to be an underestimate of the recurrence rate, because the method of data recording did not allow any distinction between those subjects who appeared for follow-up and remained wart-free (had zero wart counts) from those who did not appear for follow-up.

Safety:

- There were no patient deaths in this study.
- One SAE in the 15% dose group was described as an application site reaction with probable relationship to study medication that resolved with sequelae (Patient ID=2311). There were no serious AEs reported in the placebo group. One SAE in the 10% dose group was a knee injury and was deemed unrelated to study drug.
- AEs resulting in discontinuation of study drug were reported in nine patients. One of these was classified as unrelated (cystectomy). The other eight patients had local AEs in the site of study drug application; one was classified as possibly related (suspected hypersensitivity) and the remaining seven were classified as probably related.

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10.5 Study CT 1018: A Randomized, Double-Blind, Three-Arm Parallel-Group, Placebo-Controlled Phase 3 Trial to Investigate the Clinical Efficacy and Safety of Polyphenon E in the Treatment of External Genital Warts (vol 40)

10.5.1 Protocol

The study design of study CT 1018 was similar to that of study CT 1017. The trial took place from July 28, 2003 to August 16, 2004. In contrast to study CT1017 which took place in Europe, CT 1018 included sites in Central and South America as well as in the US.

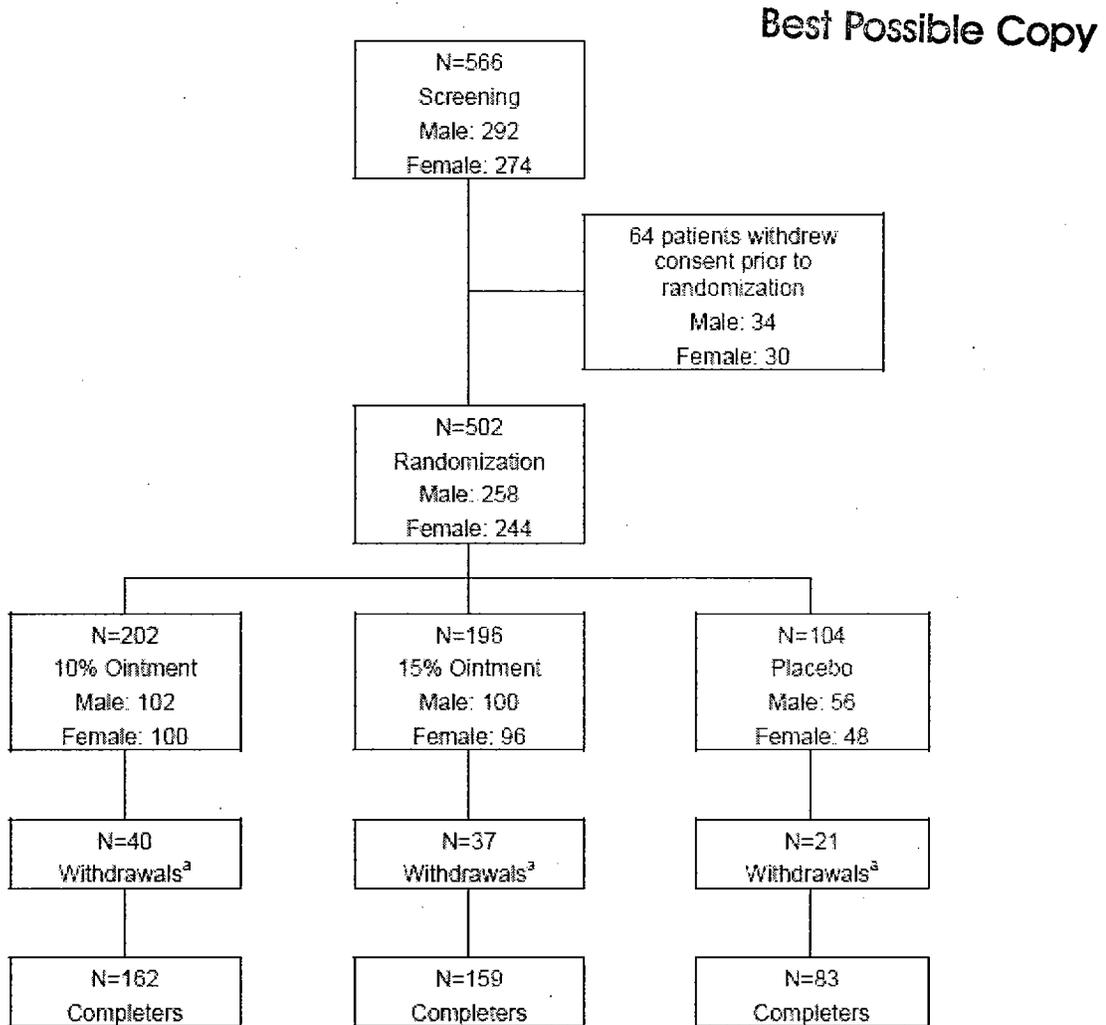
10.5.2 Study Results

The study was conducted at 50 centers throughout North, Central and South America, as well as Romania. All 50 centers enrolled patients. Patients were recruited and treated on an outpatient basis at gynecology, urology and dermatology centers.

The subject disposition is shown in the following figure.

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Figure 4 Study 18-Subject Disposition



Reviewer's comment: A high number of subjects (64) in study 18 withdrew consent prior to randomization. The reasons for withdrawal of consent are not discussed in the study report.

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Table 49 Reasons for Premature Discontinuation at any Time after Randomization

	Vehicle N=104	10% Ointment N=202	15% Ointment N=196
Total	21 (20%)	40 (20%)	37 (19%)
Subject withdrew consent	4 (4%)	15 (7%)	14 (7%)
Lack of efficacy/Treatment failure	6 (6%)	4 (2%)	7 (4%)
Lost to follow-up	4 (4%)	6 (3%)	4 (2%)
Non-compliance to study treatment	1 (1%)	4 (2%)	4 (2%)
Protocol violation/Pregnancy	0 (0%)	2 (1%)	3 (2%)
Warts requiring treatment	0 (0%)	3 (2%)	1 (<1%)
Investigator's decision	0 (0%)	1 (<1%)	1 (<1%)
Administrative reasons	0 (0%)	0 (0%)	1 (<1%)
Adverse event	0 (0%)	0 (0%)	1 (<1%)
Eligibility criteria no longer fulfilled	0 (0%)	0 (0%)	0 (0%)
Other	6 (5.8%)	5 (2.5%)	1 (<1%)

Source: Table 10.3, page 59 of clinical study report

Fewer subjects withdrew from the study prematurely due to adverse events in study CT 1018 compared with study CT 1017. Across treatment groups, 19-20% of patients withdrew early from study treatment. A higher proportion of patients in the active treatment arms withdrew consent compared to vehicle arm. The reasons for subject withdrawal of consent were not described. One subject in the high dose group withdrew due to adverse event in study CT 1018.

Similar to Study CT 1017, several patients were classified under "Other". Comments within the dataset helped to clarify the reasons for discontinuation. See the following table.

Table 50 Reasons for Treatment Discontinuation for Select Patients as Reported in Datasets

Patient ID no.	Comments
ARG-07 00144	Lack of compliance with visit schedule
CHL-03 00255	Unable to attend future visits for labor reasons
CHL-04 00256	Sponsor decision; patient received investigational product from another patient.
CHL-05 00756	Sponsor decision since blinded codes were lost at site
CHL-06 00277	Lack of efficacy/treatment failure
MEX-10 00421	Missing blinding code
MEX-12 00426	Site lost blinding codes 0426-0430.
PER-01 00581	Patient was lost after visit 4
PER-01 00649	Lost at visit 4, patient had poor protocol compliance and he did not return to site after that visit, although following visits were scheduled.
PER-03 00631	Patient refused to follow scheduled visits
PER-03 00632	Patient did not attend visit 11
USA-08 00472	Local signs + symptoms

Source: Sponsor's dataset: DISP.XPT issdern folder

The comments included statements concerning “missing blinding codes” in reference to the following patients: CHL-05 00756, MEX-10 00421, and MEX-12 00426. One patient (USA-08 00472) appeared to have discontinued for local adverse events.

Disposition for the subset of patients from the United States was also evaluated. Fifty patients from the United States were randomized and treated; 32 patients completed and 18 patients did not complete the study.

Reviewer’s comment: Of U.S. patients, 36% (18/50) did not complete the study. This percentage is higher than that when U.S. patients are excluded which was 18% (80/452).

The database for study CT 1018 provided was explored using JMP and reasons for discontinuation for U.S. patients provided below.

Table 51 Reasons for Discontinuation for U.S. Patients

Primary Reason for Discontinuation	Placebo (N= 9)	10% oint (N= 20)	15% oint (N= 21)
administrative reasons			1
at visit 9 or during follow-up		1	
lack of efficacy/ treatment failure	1		1
lost to follow up	2	2	
non-compliance			2***
protocol violation/ pregnancy			1
subject withdrew consent		4**	2*
other	1		
Total	4	7	7

* lack of efficacy;

** includes one subject who opted for cryotherapy; one with a side effect of itching; and one subject with symptoms of concurrent herpes.

*** includes one subject who had an AE of genital herpes

Source: Dataset DISP.XPT in CT 1018dn folder

Subject demographic characteristics in Study 18 are shown in the following table.

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Table 52 Patient Demographic Characteristics

		10% Ointment	15% Ointment	Vehicle
Gender				
Male	N (%)	102 (50.5%)	100 (51.0%)	56 (53.8%)
Female		100 (49.5%)	96 (49.0%)	48 (46.2%)
<i>Total</i>		<i>202 (100.0%)</i>	<i>196 (100.0%)</i>	<i>104 (100.0%)</i>
Race				
Caucasian	N (%)	67 (33.2%)	57 (29.1%)	29 (27.9%)
African		3 (1.5%)	5 (2.6%)	2 (1.9%)
Hispanic		131 (64.9%)	134 (68.4%)	72 (69.2%)
Asian		1 (0.5%)	0 (0.0%)	0 (0.0%)
Other		0 (0.0%)	0 (0.0%)	1 (1.0%)
<i>Total</i>		<i>202 (100.0%)</i>	<i>196 (100.0%)</i>	<i>104 (100.0%)</i>
Age (years)				
<18	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18 to 30		125 (61.9%)	120 (61.2%)	62 (59.6%)
31 to 45		53 (26.2%)	49 (25.0%)	24 (23.1%)
46 to 65		22 (10.9%)	23 (11.7%)	14 (13.5%)
>65		2 (1.0%)	4 (2.0%)	4 (3.8%)
	Mean	31.3	31.2	32.5
	Median	28.0	27.0	28.0
	Range	18-83	18-90	18-73
<i>Total</i>	<i>N (%)</i>	<i>202 (100.0%)</i>	<i>196 (100.0%)</i>	<i>104 (100.0%)</i>
Smoking Hx				
Non-smoker	N (%)	97 (48.0%)	101 (51.5%)	54 (51.9%)
Previous		17 (8.4%)	19 (9.7%)	8 (7.7%)
Current		88 (43.6%)	76 (38.8%)	42 (40.4%)
<i>Total</i>		<i>202 (100.0%)</i>	<i>196 (100.0%)</i>	<i>104 (100.0%)</i>
Childbearing potential (women only)				
Yes	N (%)	80 (80.0%)	76 (79.2%)	40 (83.3%)
No		20 (20.0%)	20 (20.8%)	8 (16.7%)
<i>Total</i>		<i>100 (100.0%)</i>	<i>96 (100.0%)</i>	<i>48 (100.0%)</i>
Circumcision (men only)				
Yes	N (%)	17 (16.7%)	24 (24.0%)	13 (23.2%)
No		85 (83.3%)	76 (76.0%)	43 (76.8%)
<i>Total</i>		<i>102 (100.0%)</i>	<i>100 (100.0%)</i>	<i>56 (100.0%)</i>

Source: Table 11.3 on page 66 of Sponsor's study report

The majority of subjects are Hispanic in this study, 65% to 69% across treatment groups, and Caucasian subjects consist of 28% to 33% across treatment groups. Overall, men make up 51% and women make up 49% of the study population. In the placebo group, men make up 54% and women make up 46%. The median age is 27 to 28 years across treatment groups. Women of childbearing potential make up 80% of all women patients. The majority of men are uncircumcised, 79% of all men.

Baseline disease history and characteristics:

The majority of patients, 82.5%, in the ITT population (82% to 84% across treatment groups) experienced their first episode of genital warts.

The median number of warts per subject in the ITT population was the similar across treatment groups and ranged from 6 to 7 across treatment groups. The median baseline wart area was as follows: 10% Ointment: 46 mm²; 15% Ointment: 50 mm²; and Vehicle: 58.5 mm². (See Tables 11.41 and 11.42 of sponsor's study report).

Baseline Wart Characteristics by Country

This reviewer use JMP software to summarize baseline wart area and wart number by country (source WART18 data set submitted March 5, 2006).

Table 53 Baseline Wart Number Per Subject

country	N	1st quartile	Median	3rd quartile
ARG	86	4	6.5	13
CHL	50	6	8.5	13
COL	99	3	6	9
MEX	90	4	5	8
PER	51	6	11	19
ROM	76	4	5	9
USA	50	3.75	6	10.25
TOTAL	502	4	6	11

Table 54 Baseline Wart Area (mm²)

country	N	1st quartile	Median	3rd quartile
ARG	86	24.5	48.5	112.5
CHL	50	50.5	105	150.5
COL	99	26	50	115
MEX	90	19.25	30	76
PER	51	47	93	196
ROM	76	20.25	30	49.75
USA	50	27	63	162.5
TOTAL	502	24	50	114

The two countries with the fewest warts and smallest wart area at baseline were Mexico and Romania; each had a median of 5 warts and wart area of 30 mm². Chili was the country with the largest median baseline wart number (8.5) and area (105 mm²). For the U.S. subset, the median number of warts was 6 and the median wart area was 63 mm² at baseline.

Reviewer's comment: For the U.S. subgroup, the median wart number and area did not appear as either the highest or lowest when compared with all of the other countries. The U.S. subgroup appeared to be intermediate by these two measures of baseline wart severity.

Efficacy Study 18:

The protocol defined the ITT population as all subjects randomized and dispensed treatment. The results provided in the sponsor's study report do not completely follow this definition as several subjects with only baseline data were excluded from the results in the study report. Specifically, seven subjects from Study CT1018 were excluded from the analysis population in the study report. The FDA's primary efficacy endpoint results were including the entire ITT population and thus the response rates differ somewhat from that of the sponsor, but the p-values were <0.001 in both cases.

Table 55 Primary Endpoint Efficacy Results (ITT-LOCF)

	Vehicle	10% Ointment	15% Ointment
Fail	69 (66.3)	91 (45)	85 (43.4)
Success	35 (33.7)	111 (55)	111 (56.6)
p-value	-	<0.001	<0.001

Source FDA statistical review

Table 56 Sponsor's Analysis of Primary Endpoint

	10% Ointment		15% Ointment		Placebo	
	N	Rate	N	Rate	N	Rate
Men						
Patients with complete clearance	48	48.0%	49	50.0%	13	23.2%
Patients without complete clearance	52	52.0%	49	50.0%	43	76.8%
Analyzable patients	100		98		56	
Women						
Patients with complete clearance	63	64.9%	62	64.6%	22	45.8%
Patients without complete clearance	34	35.1%	34	35.4%	26	54.2%
Analyzable patients	97		96		48	
Total						
Patients with complete clearance	111	56.3%	111	57.2%	35	33.7%
Patients without complete clearance	86	43.7%	83	42.8%	69	66.3%
Analyzable patients	197		194		104	
p-value, odds ratio and confidence interval						
p-value (2-sided Fisher's exact test LOCF)		<0.001		<0.001		
Odds ratio and 95% CI		2.55 [1.55; 4.17]		2.64 [1.61; 4.33]		

Reviewer's comment: In the sponsor's study report, the ITT population was inappropriately defined as the analyzable population rather than the preferred definition of all randomized subjects.

Table 57 Clinical Efficacy Across Subgroups by Gender: Percent Clear by Week 16

	Vehicle	10% Ointment	15% Ointment
Female	45.8% (22/48)	63.0% (63/100)	64.6% (62/96)
Male	23.2% (13/56)	47.1% (48/102)	49.0% (49/100)

Source: FDA statistical review

A higher response rate was observed in women compared with men. Across the two active treatment groups, the response rate was 63-65% for women compared with 47-49% for men. Of note, the response rate in the vehicle arm was also higher among women compared with men, 46% and 23%, respectively. Treatment effect was observed in subgroups by gender and was slightly higher in men compared with women. For the 10% ointment group, the difference in proportion responding compared with vehicle was 24% for men compared with 14% for women. Recall that similar observations regarding the relative treatment effect in men and women were also noted in Study CT 1017.

Study CT 1018

Table 58 Clinical Efficacy by Age: Mean Percent Clear by Week 16 Study 18

Age Quartile	Vehicle		10% Ointment		15% Ointment	
[16,24)	38	N=29	65	N=55	69	N=59
[24,29)	44	N=25	57	N=49	61	N=46
[29,37)	36	N=22	50	N=52	50	N=48
[37,98]	18	N=28	46	N=46	42	N=43

Source: FDA statistical review

The overall trend was toward treatment effect in both younger and older age groups. Treatment effect was observed in each of the age quartiles. However, the overall responses were progressively lower with increasing age in all treatment groups including vehicle. The numbers of subjects the geriatric age group, age 64 and older, were too small to make any inference regarding efficacy; there were a total of subjects in this group (3 in the 15% ointment group and 1 in the 10% vehicle group).

Time to Complete Wart Clearance

From the sponsor's study report, the overall median actual time to complete wart clearance for the subset that cleared was 11.1 weeks in the 10% ointment group, 10.0 weeks in the 15% ointment group and 12.7 weeks in the vehicle group.

Reviewer's comment: This differed from study CT1017, where the time to complete clearance was shorter in the placebo group compared with the active groups.

Proportion that Relapse During Follow-up

Each subject that cleared was to return to the investigator at 4 weeks and 12 weeks after treatment clearance, visits 10 and 11, respectively. In this study, a total of 259 subjects achieved clear at during the treatment period, 36 in placebo, 112 in 10% ointment and 111 in 15%

ointment. Of these treatment responders, the vast majority of subjects had missing data during the follow-up period. Only 20 had non-missing data on visit 10 and even fewer, 11 subjects, had non-missing data on visit 11. Of subjects with non-missing data, a total of 4 were described as being clear on visit 10 or visit 11, i.e. the follow-up period (0 in placebo, 3 in 10% ointment, and 1 in 15% ointment). (Arg 3 110, Arg 7 236, Arg 7 239, Peru 7 618). Of these, 3 patients had missing values in between visits and one had warts in between visits that were assessed as clear (Peru 7 618). Therefore, these subjects were described as being clear on two non-consecutive visits. In the WART17 and WART18 data sets, unless a subject had warts present at the follow-up visits, the number of warts were recorded as missing. This method of data record-keeping makes it difficult to assess whether a subject had no warts at the visit or if the subject missed the visit. The majority of the data on wart counts was recored as “N/A” during the follow-up phase. In sum, the FDA was not able to calculate the relapse rate based on the submitted data. Please also see statistical review for greater detail.

Correlation of local reactions with treatment response.

It would be useful to evaluate to what subjects deemed “all clear” also experienced local reactions.

This reviewer has used JMP software to evaluate the percentage of treatment responders who also had ulceration. A total of four patients discontinued after the first two visits (253, 272, 1023 and 775). These subjects are not included in the analysis.

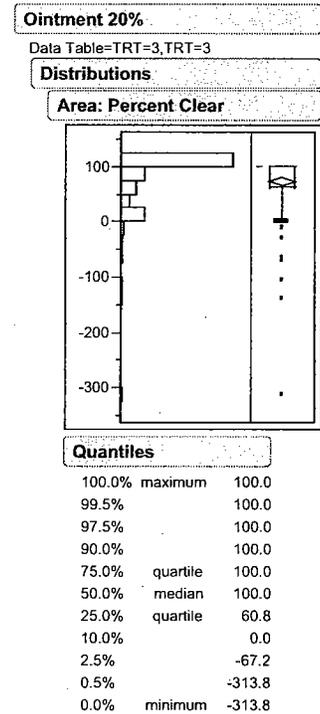
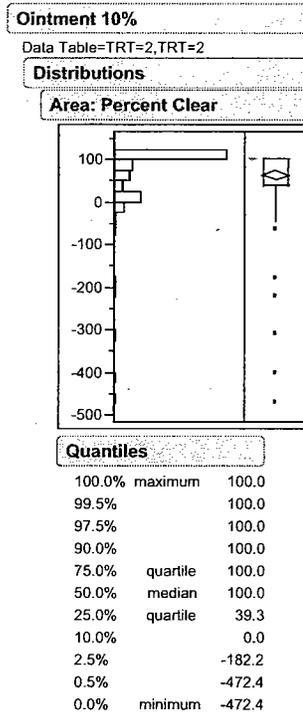
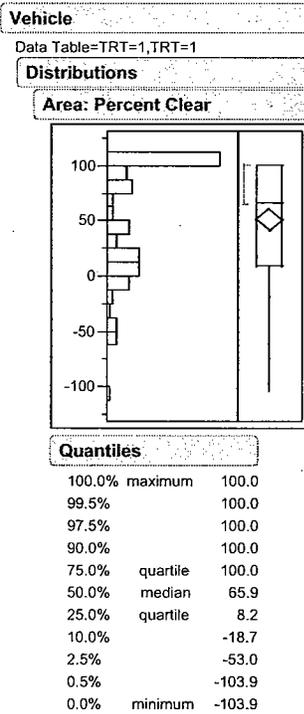
Table 59 Intensity of Ulceration at the Time of All Clear, Visit 9, Among Responders (N, %)

	Vehicle	10% Ointment	15% Ointment
Randomized	104	202	196
Clear of all warts	36	112	111
Degree of Ulceration			
None	35	90	86
Mild	1	16	18
Moderate	0	5	6
Severe	0	1	1

In cases of ulceration/erosion, wart virus may persist despite the disappearance of the gross skin lesion. It is therefore useful to evaluate subjects who achieved “of all clear” in the absence of ulceration. Ulceration among responders was more common in the active treatment groups, 22/112 (20%) in the 10% treatment group, 25/111 (23%) in the 10% treatment group and only 1/35 (3%) in the vehicle group. The proportions of randomized patients who cleared and had no ulceration at the time of assessment remained higher in the active treatment arms compared with vehicle and were 34%, 45%, and 44% in vehicle, 10% oint and 15% oint, respectively.

This reviewer used JMP software to evaluate the distribution of percentage change in wart area from baseline to last visit for the ITT population. The results are as follows.

Figure 5 Percentage Change in Wart Area From Baseline: Last Visit, ITT



The distribution favors treatment effect among the active groups compared with vehicle. The median subjects in the active groups achieved 100% wart clearance compared with 66% wart clearance in the vehicle group. The 25% quartile of the active groups achieved 39% wart clearance in the 10% dose group, 60% wart clearance in the 15% group compared with 8% wart clearance in the vehicle group. Of note, there were a certain proportion of subjects in all treatment groups with worsening of warts compared with baseline. The proportion who worsened was less than 10% in the active treatment groups and was higher, between 10-25%, in the vehicle group.

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Safety

The safety population consisted of 502 patients who were randomized and who received at least one application of the study medication. The distribution of patients included in the safety population was as follows: 104 patients in the Vehicle group, 202 patients in the Polyphenon 10% Ointment group, 196 patients in the Polyphenon 15% Ointment group. The mean duration of treatment in the safety population was 84 days in the Polyphenon 10% Ointment group, 80 days in the Polyphenon 15% Ointment group, and 95 days in the Vehicle group.

No patients died during the study. Serious adverse events are described below.

There were four serious adverse events, other than pregnancy, reported in 4 subjects. One of the four was considered probably related to study medication and the others were considered unrelated. These events are described below.

A 22-year-old woman (0304) in the 15% dose group, suffered from application site pain, vesicles and erythema, all of moderate intensity 12 days after the Baseline visit and received symptomatic treatment with acetaminophen. The patient recovered after 6 days. She restarted the study medication and was able to tolerate the study medication without recurrence of the AE. A probable causal relationship to the study medication was assessed by the investigator. The sponsor was of the opinion that the AE was caused by first occurrence of genital herpes infection based on the description of the clinical signs and symptoms and the negative re-challenge.

Reviewer's comment: Again, as in Study CT1017 the serious adverse event was observed in a woman assigned to the 15% dose group. It does not appear that a Tzank smear or herpes culture was done to evaluate for herpes infection. The close temporal relationship to the onset of polyphenon treatment suggests a possible contribution of the study drug, even if HSV was the primary cause of the adverse events.

In the remaining three serious adverse events a relationship to study medication was excluded by the investigator. A 23-year-old woman in the 15% dose group, suffered from diabetic ketoacidosis 70 days after the Baseline visit and was hospitalized. The patient recovered and continued the study treatment. The investigator assessed the diabetic ketoacidosis to be secondary to a brown recluse spider bite. In two reports of serious adverse events, the event involved injury. One was a knee injury during the follow-up period in a 53-year-old woman and the other was a lower limb fracture in a 32-year-old man. Both patients were assigned to the 10% ointment.

Three subjects were found to be pregnant during the study period.

- A 28-year-old woman (10% dose group) was found to be pregnant 13 days before the Baseline visit. The application of study medication was discontinued. The subject gave birth by C-section to a healthy male infant weighing 3120 g.
- A 37-year-old woman (10% dose group) was found to be pregnant 85 days of study treatment. She reported that she experienced a spontaneous abortion after a fall. The subject had not received prenatal care and the fetus was not examined.

- A 19-year-old woman (15% dose group), was found to be pregnant 41 days after the Baseline visit. The application of study medication was discontinued. The spontaneous abortion was 12 weeks after her last menstrual period and 4 weeks after the diagnosis of pregnancy. No pathology report is available and no congenital abnormality was reported.

Severe local skin signs during the treatment period according to the assessment of the investigator occurred in a total of 57 patients (11.4%) with a distribution by treatment group as follows,

- 10% Ointment: 28 patients (14.2%);
- 15% Ointment: 28 patients (14.4%); and
- Vehicle Ointment: one patient (1.0%).

Reviewer's comment: By this measure, no difference was detected in local tolerability between the 10% and the 15% dose groups. In both cases, severe local skin reactions during the treatment period occurred in 14% of patients compared with 1% in placebo. This does not, however, negate the positive findings in terms of patients who discontinued early and serious adverse events.

All severe local reactions at anytime during the study (not including Screening only) through Week 16 are summarized below.

Table 60 Frequencies of Patients with Severe Local Skin Signs (Investigator Assessment) during Treatment

	10% Ointment (N=202)		15% Ointment (N=196)		Placebo (N=104)	
	N	%	N	%	N	%
Number of patients	202	100.0	196	100.0	104	100.0
Erythema	22	11.2	19	9.7	0	0.0
Edema	14	7.1	14	7.2	0	0.0
Induration	9	4.6	14	7.2	1	1.0
Vesicles	7	3.6	10	5.1	0	0.0
Erosion/Ulceration	15	7.6	18	9.2	0	0.0
Other	3	1.5	6	3.1	0	0.0
Overall evaluation of skin signs	21	10.7	22	11.3	1	1.0
Missings	5	2.5	1	0.5	0	0.0
Any severe local skin signs	28	14.2	28	14.4	1	1.0

Source: Table 12.4 of Clinical Study Report

A total of 33 subjects experienced severe erosion/ulceration during the treatment phase. None of the vehicle-treated subjects experienced severe ulceration/erosion. 7.6% of subjects in the 10% Ointment group and 9.2% of the 15% Ointment group experienced severe ulceration/erosion during the treatment phase compared with no patients in the vehicle arm. Thus, it appears that severe ulceration may be dose-related. Of note, one subject (166) had assessment of severe ulceration from study visit 4 through study visit 9 and another subject (169) had assessment of severe ulceration from study visit 2-9. No follow-up data is available for these subjects beyond visit 9.

Reviewer's comment: Follow-up for safety should have been done for subjects with severe local reactions.

Similarly, there appears to be a dose relationship for appearance of vesicles: none vehicle; 3.6% in the 10% ointment group and 5.1% in the 15% ointment group. Twice as many patients in 15% ointment group had other local reactions (most commonly described as lymphadenitis) compared with the 10% ointment group (1.5% vs. 3.1%, respectively). Severe induration was also described more commonly in the 15% ointment group compared with the 10% Ointment group.

Reviewer's comment: It is possible that the 15% dose is related to greater sensitization potential compared with the 10% dose. This is one explanation for the higher frequency of vesicles and erosions in the high dose group compared with the low dose group.

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The proportion of subjects with severe local reactions at any time by gender is shown in the following table.

Table 61 Frequencies of Patients with Severe Local Skin Signs (Investigator Assessment) during Treatment

Local skin sign	10% Ointment (N=202)		15% Ointment (N=196)		Placebo (N=104)	
	N	%	N	%	N	%
Male						
Number of males	102	100.0	100	100.0	56	100.0
Erythema	11	11.0	6	6.1	0	0.0
Edema	10	10.0	5	5.1	0	0.0
Induration	4	4.0	5	5.1	0	0.0
Vesicles	4	4.0	3	3.0	0	0.0
Erosion/Ulceration	7	7.0	5	5.1	0	0.0
Other	2	2.0	2	2.0	0	0.0
Overall evaluation of skin signs	11	11.0	5	5.1	0	0.0
Missings	2	2.0	1	1.0	0	0.0
Any severe local skin signs	14	14.0	9	9.1	0	0.0
Female						
Number of females	100	100.0	96	100.0	48	100.0
Erythema	11	11.3	13	13.5	0	0.0
Edema	4	4.1	9	9.4	0	0.0
Induration	5	5.2	9	9.4	1	2.1
Vesicles	3	3.1	7	7.3	0	0.0
Erosion/Ulceration	8	8.2	13	13.5	0	0.0
Other	1	1.0	4	4.2	0	0.0
Overall evaluation of skin signs	10	10.3	17	17.7	1	2.1
Missings	3	3.0	0	0.0	0	0.0
Any severe local skin signs	14	14.4	19	19.8	1	2.1

Source: Table 12.4 of Clinical Study Report

A higher proportion of female patients compared with male patients experienced severe local signs of any kind during the treatment period in the 15% Ointment group. 20% of women in the high dose group experienced severe local signs compared with 14% in the low dose group and 2% in the vehicle arm. By contrast, 9% of males assigned to the high dose group had severe local signs compared with 14% in the low dose group and 0% in the vehicle group. Severe Erythema and Erosion/Ulceration were most common, each seen in 13.5% of women.

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Table 62 Frequencies of Patients with Severe Local Skin Signs (Investigator Assessment) by Visit

Local skin sign	10% Ointment (N=202)		15% Ointment (N=196)		Placebo (N=104)	
	N	%	N	%	N	%
Overall evaluation of skin signs						
Visit 1	0	0.0	1	0.5	0	0.0
Visit 2	8	4.1	11	5.8	1	1.0
Visit 3	8	4.3	6	3.3	0	0.0
Visit 4	8	4.7	9	5.6	0	0.0
Visit 5	7	4.8	5	3.5	0	0.0
Visit 6	5	3.7	9	7.6	0	0.0
Visit 7	5	4.2	7	6.4	0	0.0
Visit 8	5	5.0	5	5.2	0	0.0
Visit 9	4	4.1	3	3.7	0	0.0

For the investigator's overall evaluation of severe local skin signs, there did not appear to be a trend towards decreasing incidence with continued use over time.

Laboratory Data:

Table 63 Alkaline Phosphatase: Normal at Baseline to High at Visit 9 (CT 1018)

Patient	Baseline	Visit 9	Site	Normal Range	Treatment Group
167	100	120	COL02	26-117	15% Oint
187	110	119	COL02	26-117	15% Oint
230	247	286	ARG05	65-280	10% Oint
305	115	149	COL08	26-117	10% Oint
311	104	121	COL02	26-117	10% Oint
326	105	130	COL02	26-117	Vehicle
411	64	93	MEX04	32-92	15% Oint
613	248	319	PER05	65-306	10% Oint
681	243	310	ARG10	90-280	10% Oint
772	78	130	ROM01	42-128	15% Oint
822	96	109	ROM06	45-104	10% Oint

A total of 464 patients had both baseline and post-treatment values, and of these 426 were normal for alkaline phosphatase at baseline. Eleven patients (1 placebo, 6 Polyphenon 10%, and 4 Polyphenon 15 %) had shifts from normal at baseline to high post-treatment. In all cases, the change was less than a two-fold elevation of alkaline phosphatase from the patient's baseline and the degree of elevation was not deemed to be clinically significant by the investigator. See Table 63.

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Of the 464 patients had both baseline and post-treatment values for ALT, 408 subjects were within the upper limit of normal at baseline. Of these subjects, there were no differences between treatment groups in the distribution of ratio of post-treatment ALT to upper limit of normal. With the exception of a single outlier in the Polyphenon 15%, the distribution of ratio of post-treatment to pre-treatment values were similar among all three treatment groups.

Of the 420 subjects with normal baseline AST, there were no differences between treatment groups in distribution of ratio of AST to ULN or Post-treatment to Baseline value, with the exception of a single outlier (subject 776) in the Polyphenon 15%. There were 15 subjects with higher than 1 fold upper limit of normal post-treatment AST, of these 6 had ≥ 1.5 fold upper limit of normal (1 placebo, 2 Polyphenon 10% and 3 Polyphenon 15%). The outlying observation for AST, Subject 776, had an AST of 262 (ULN 32) this subject also had a shift to high for ALT, but not alkaline phosphatase or GGT. The clinical investigator deemed these changes to be of no clinical significance.

In summary based upon findings of ALT, AST and alkaline phosphatase analyses of distributions of ratio to patient baseline and ratio to upper limit of normal, little to no difference were seen between treatment groups.

10.5.3 Study Summary and Discussion

Summary of Clinical Efficacy:

- The study met its primary endpoint of complete clearance of all baseline and new warts by 16 weeks of therapy. The percentage of responders was 56.6% in the 15% ointment group, 55% in the 10% ointment group compared with 33.7% in the Vehicle group (P <0.001 for both comparisons).
- The sponsor's analysis of relapse rates for treatment responders could not be verified by the Agency because patients with zero wart counts and those with missing data were not distinguishable in the sponsor's datasets. The majority of the data on wart counts was recored as "N/A" during the follow-up phase.
- Women had higher response rates than men for all treatment groups. For women, 65% in both the 10% ointment and 15% ointment group had complete wart clearance compared with 46% of women treated with vehicle. For men, 48% to 50% across active treatment groups had a complete clearance compared with 23% in Vehicle. Treatment effect was observed in both men and women.
- Treatment effect was observed in each of the subgroups (quartiles) defined by age. However, the overall response rate in the upper age quartile (age 37-98) was numerically lower compared with the younger age groups. The highest response rates and also the largest treatment effect was observed in the lowest age quartile, the 16 to 24 year age group.

Summary of Safety:

- The safety population for this study consisted of 502 patients: 104 in Vehicle, 202 in the 10% Ointment group and 196 in the 15% Ointment group.

- There were four serious AEs, other than pregnancy, reported in 4 patients. One of the four patients had application site pain, vesicles and erythema that was temporally related to study medication. The remaining serious AEs were unrelated to study medication.
- Three subjects were found to be pregnant during the study. One patient gave birth to a healthy infant and two patients had a spontaneous abortions. In neither case was the fetus examined.
- Severe local reactions occurred at a higher rate in the active treatment groups compared to vehicle. In both active treatment groups, 14% of patients experienced severe local reactions compared to 1% of patients in the vehicle group. Overall, a higher frequency of induration, vesicles and Erosion/Ulceration was observed in the 15% dose group compared with the 10% dose group. However, in women each of the severe local reactions was more frequent in the 15% dose group compared with the 10% dose group, suggesting a dose-response for these findings. 20% of women in the high dose group experienced severe local signs compared with 14% in the low dose group and 2% in the vehicle arm. Collectively, the data regarding erosions and vesiculation suggest that the 15% dose may have greater sensitization potential compared with the 10% dose.

10.6 Line-by-Line Labeling Review

The draft package insert follows. For the FDA-approved package insert, please refer to the approval letter.

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9 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 8 § 552(b)(4) Draft Labeling

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