CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-902

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA Number	21-902
Letter Date(s)	September 23rd, 2005, January 6th, 2006, and April 20th and 25th, 2006
Proposed Brand Name	Polyphenon® E Ointment, 15%
Reviewer	Abimbola Adebowale Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DCP3
OND Division	OND-540
Applicant	Medigene Inc.CA
Related IND(s)	56,401
Submission Type; Code	Original NDA (NME);1S
Formulation	Ointment
Indication	Treatment of external genital warts and perianal warts (*condyloma acuminata*)

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1 Executive Summary

In this application, the applicant is seeking approval of Polyphenon® E Ointment, 15 %, a botanical drug product for topical use that contains Polyphenon® E as its active ingredient. Polyphenon® E is a green tea extract derived from a species of green tea, *Camellia sinesis*

containing more than 85 % of tea polyphenols including a family of related flavonoids, particularly catechins. Polyphenon E drug substance also contains other tea associated compounds including caffeine, theobromine and gallic acid. The proposed indication is for the topical treatment of external genital and perianal warts (*condyloma acuminata*) in male and female adults. It is intended to be applied three times daily.

The applicant did not provide any information in this NDA submission on what compounds in Polyphenon E contribute to the safety and/or efficacy of Polyphenon ® E Ointment, 15 %. The applicant included one vivo bioavailability study (CT 1007) comparing the systemic exposure obtained following topical treatment with Polyphenon ® E ointment and oral intake of green tea in patients with external genital and perianal warts. In this study, the applicant identified and measured the four most abundant catechins (Epigallocatechin gallate (EGCg), Epicatechin gallate (ECg), Epigallocatechin (EGC) and Epicatechin (EC)) in green tea extract. It is currently unknown as to whether these four catechins are the actual active moieties and/or their relative contributions to the safety and efficacy of Polyphenon ® E Ointment, 15 %.

1.1 Recommendations

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 Polyphenon ® E Ointment, 15 % was minimal. This is further supported by the observation that the clinical safety data indicated that the incidence of adverse events other than local reactions was low and, the nonclinical findings indicated that there was no apparent systemic toxicity noted in minipigs after topical treatment with Polyphenon ® E Ointment, 15 %.

The assessment of the systemic exposure had to also rely 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 Polyphenon ® E Ointment, 15 % could not be interpreted. This was because the long term analytical stability evaluation did not meet the acceptance criteria of—— recovery after sample storage (to cover the period from sample collection to the end of analyses).

Therefore based on the totality of the data provided (i.e. nonclinical findings, clinical pharmacology and clinical safety data) the clinical pharmacology data is acceptable. However, the applicant needs to address the deficiency of their long term analytical stability evaluation used to assay for the catechins in their pharmacokinetic study through a Phase 4 commitment (see Section 1.2 below).

1.2 Phase IV Commitments:

2. Conduct another pharmacokinetic study to assess the comparative pharmacokinetics of Polyphenon ® E Ointment, 15 % versus oral intake of green tea solution, following single and repeated administration to patients with genital and perianal warts. The study should be conducted under maximal use conditions (e.g. maximum total body surface area and dosage regimen) and designed, as a parallel group study with at least 20 completers in each treatment arm (Total N = 40). In addition, the concentrations of the catechins in the plasma should be determined within the storage time period that has been adequately validated for your assay method.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings:

The clinical development program for Polyphenon ® E Ointment, 15 % included one in vivo bioavailability study (CT 1007), two phase 3 clinical trials (CT 1017 and CT 1018), and one phase 2/3 trial (CT 1005).

Pharmacokinetics:
The results of the pharmacokinetic study #CT 1007, a comparative assessment of the pharmacokinetics of repeated topical application of Polyphenon® E ointment, 15 % (3 weeks) with a single oral intake of green tea suggested that the systemic exposure to the four most abundant catechins (Epigallocatechin gallate (EGCg), the main catechin, and other catechins, Epicatechin (EC), Epigallaocatechin (EGC), Epicatechin gallate (ECg)) in green tea extract, may be minimal following topical application. This study was an open-label, multi-dose, multi-centre Phase 2 trial in 24 Caucasian patients with external genital and perianal warts. The data obtained from this study should be interpreted with caution because the plasma concentrations of the catechins could have been degraded during storage as indicated by the failed stability data obtained from the assay method (see comment 1 and 2 in section 1.2 above.) Thus the plasma concentrations determined in this study cannot be relied upon as accurate measurements of the systemic exposure of the catechins following oral intake of Green Tea and topical administration of Polyphenon® E ointment, 15 %.

Analytical Method and Validation:

Plasma concentrations of 4 catechins (Epigallocatechin gallate (EGCg), the main catechin, and other catechins, Epicatechin (EC), Epigallaocatechin (EGC), Epicatechin gallate (ECg)) , which are also the most abundant catechins in green tea extracts, were measured in human plasma using an HPLC/MS method. 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 from sample collection (117 days for the last to 354 days for the first patient) to

the end of sample analyses did not meet the acceptance criteria of — recovery after sample storage. Also the stability data obtained after 5 days (for ECg) and 34 days (for EGC and EC) storage did not meet the acceptance criteria.

General Biopharmaceutics:
The drug product used in the PK studies and Phase 3 clinical trials was manufactured by —— . The proposed commercial manufacturer is C.P.M. Contract Pharma. The applicant stated that this will result in a change in the pharmacopoeial grade of the white petrolatum, cera alba and oleyl alcohol from USP and NF to EP. It will also result in a change in some of the manufacturing process parameters (such as tighter control of temperature during the preparation of the — phase). The applicant provided in vitro release data that demonstrated that —— and C.P.M. are comparable based on their in vitro release rates as described in the SUPAC-SS Guidance. Preliminary evaluation of this data by this reviewer indicates that the , respectively) were within the required % confidence interval limits of . For the in vitro release data the chemistry reviewer (Dr. R. Agarwal) concurs with the preliminary evaluation of this reviewer.

The applicant also provided additional data that evaluated the physicochemical properties (e.g. viscosity, consistency and particle size) to further support appropriate comparability of processes from both sites. The chemistry reviewer is currently conducting an in depth review of this additional data.

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2. QBR

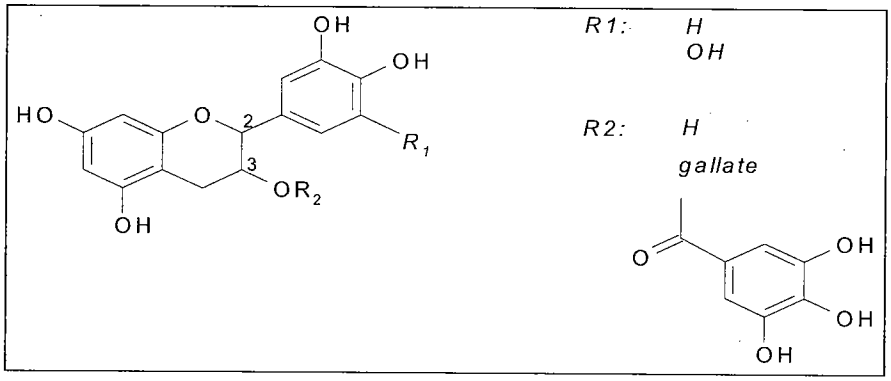
2.1 General Attributes

Physicochemical Properties of the Drug Substance:
Polyphenon® drug substance is a green tea extract containing 85-95% total catechin compounds by weight and other tea-associated compounds including caffeine, theobromine, and gallic acid. The main component of Polyphenon® E drug substance is (-) –Epigallocatechin gallate (EGCg), which comprises 55- —% of the extract. Chemical structures, molecular formulas and weight of

the eight catechins used as markers in Polyphenon ® E drug substance are as follows:

	Catechin	Molecular Formula	Molecular Weight
1	(-)-Epigallocatechin gallate (EGCg)	$C_{22}H_{18}O_{11}$	
2	(-)-Epigallocatechin (EGC)	$C_{15}H_{14}O_7$	
3	(-)-Epicatechin gallate (ECg)	$C_{22}H_{18}O_{10}$	
4	(-)-Epicatechin (EC)	$C_{15}H_{14}O_6$	
5	(-)-Gallocatechin gallate (GCg)	$C_{22}H_{18}O_{11}$	
6	(-)-Catechin gallate (Cg)	$C_{22}H_{18}O_{10}$	
7	(-)-Gallocatechin (GC)	$C_{15}H_{14}O_7$	
8	(+)-Catechin (C)	$C_{15}H_{14}O_6$	

General Structure of the Catechins:



Therapeutic Indication (s):

The proposed indication for Polyphenon ® E Ointment, 15 % is for the topical treatment of external genital and perianal warts (*condylomata acuminate*) in male and female adults.

Mechanism of Action:

External genital warts are non-malignant tumors believed to be caused by infections of the Human Papilloma Virus (HPV) strains 6 and 11. Current treatments include cryotherapy with liquid nitrogen, trichloroacetic acid, LASER vaporization, electrocautery, podophyllotoxin and imiquimod 5 % cream. Although the precise mode of action of Polyphenon® E Ointment, 15 % on the clearance of genital warts is not known, it is suggested that Polyphenon® E Ointment, 15 % exerts its activity through the activation of immune mechanisms, inhibition of cell growth and antiviral action. The proposed underlying mechanisms are promotion of cytokine release from different cell types, interference with cell cycle regulators, inhibition of cell signaling pathways and anti-oxidative activity. The proposed pharmacological class is immuno-modulatory.

Proposed Dosage and Route of Administration:

The ointment is intended to be applied three times per day to all external genital and perianal warts.

2.2 General Clinical Pharmacology

Q. What were the design features of the clinical pharmacology and clinical studies used to support efficacy and safety?

Efficacy: The design features of the pharmacokinetics study and the pivotal clinical studies are reproduced in the table below:

Study #	Type of Study (Phase)	Objective of the Study	Study Design	Test Product (s); Dosage Regimen [# of subjects]
CT 1007	PK (II)	Comparison of plasma concentrations and pharmacokinetics of topically applied Polyphenon ® E Ointment, 15 % and oral intake of green tea	Open-label multi-center study (3 centers in Germany, Estonia and Poland) in 38 subjects (24 completed PK study)	15 % topical ointment TID for 3 weeks, and Green tea: single oral dose [38]
CT 1017 (exclusively outside US)	Efficacy + Safety III pivotal	Efficacy and Safety in the treatment of external genital warts	Randomized, double-blind, 3-arm parallel group, placebo-controlled, multi-center study (48 centers in Europe, Russia, Romania and South Africa)	15 % topical ointment TID 10 % topical ointment TID Placebo topical ointment TID [503 (201, 199, 103)]
CT 1018 (included only ~ 10 % of patients from US sites)	Efficacy + Safety III pivotal	Efficacy and Safety in the treatment of external genital warts	Randomized, double-blind, 3-arm parallel group, placebo-controlled, multi-center study (50 centers in United States (10 %), South America, Mexico and Romania	15 % topical ointment TID 10 % topical ointment TID Placebo topical ointment TID [502 (196, 202, 104)]

Safety:

The safety assessment of Polyphenon ® E ointment, 15 % was based on the data collected from nine studies evaluating several Polyphenon® E formulations and schedules against matching placebo and active comparators (e.g. Imiquimod®) in patients and healthy volunteers and additional safety data from two studies conducted in other dermatological indications. The nine studies included 6 Phase II and III efficacy and safety studies (CT 1005, CT 1007, CT 1017, CT 1018, EPI-003 and EPI-004) and, 3 Healthy volunteer Phase I dermal tolerance studies for skin sensitization potential (CT 1016), skin irritation potential (CT 1019) and suppression of UV-induced erythema (CT 1004). The additional two studies were a safety and efficacy study in actinic keratosis (CT 1101) and safety and efficacy in common warts (CT 1008).

Q. What were the response endpoints, i.e. clinical or pharmacodynamic and, how were they measured in the clinical studies?

The primary efficacy endpoint in each of the two pivotal clinical studies (CT 1017 and CT 1018) was defined as complete clearance of all (baseline and new warts occurring during treatment) external genital and perianal warts, by week 16 (end of treatment). Responders (or success) were the proportion of patients showing complete clearance of all warts by week 16, and those who do not have complete clearance of all warts were considered non-responders (or failure). Each active ointment was to be compared to the placebo group with regard to the response rate using Fisher's exact test (1-sided, α=2.5%), and the overall significance kept at 5 %. In these two studies there was also a treatment free-period of 12-weeks to assess for recurring warts for those patients who had complete clearance of all warts.

Q. What are the characteristics of the exposure-response relationships for efficacy or safety?

A clinically meaningful dose-response relationship for efficacy was not observed in the two pivotal clinical studies evaluated. However, it appeared that the 15 % ointment was less well tolerated from the safety standpoint than the 10 % ointment.

Efficacy: In the two clinical pivotal trials (CT 1017 and CT 1018), two different strengths (10 % and 15 %) of Polyphenon ® E ointment were evaluated and compared with placebo. Inserted below is a table generated by the medical reviewer (Dr. E. Papadopoulos) based on the primary efficacy endpoint.

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

	Study CT 1017			**Study CT 1018**		
	Vehicle	Oint 10	Oint 15	Vehicle	Oint 10	Oint 15
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.

Reviewer's Comment: Based on the data in the table above, the medical reviewer concluded that there was little to no difference in efficacy between the 10 % and the 15% dose group observed suggesting that there was no dose-response relationship. Both treatment groups had similar treatment effects that reached statistical significance ($p < 0.05$) by the pre-specified primary endpoint. This analysis however differs from that of the sponsor (see clinical review for further details).

Safety:

Inserted below is a table showing the treatment emergent AEs observed in the two pivotal clinical studies (CT 1017 and CT 1018):

Table 4: Treatment Emergent AEs

Adverse Event	Oint 10% (N = 392)	Oint 15% (N = 388)	Vehicle (N = 206)
erythema	269 (68.6)	273 (70.4)	67 (32.5)
itching	260 (66.3)	269 (69.3)	94 (45.6)
burning	253 (64.5)	260 (67)	65 (31.6)
pain	185 (47.2)	216 (55.7)	30 (14.6)
erosion/ulceration	183 (46.7)	185 (47.7)	20 (9.7)
edema	159 (40.6)	173 (44.6)	23 (11.2)
induration	109 (27.8)	136 (35.1)	23 (11.2)
vesicles	75 (19.1)	78 (20.1)	13 (6.3)
headache	23 (5.9)	10 (2.6)	9 (4.4)
lymphadenitis	8 (2)	10 (2.6)	2 (1)
crusts	5 (1.3)	7 (1.8)	0 (0)
gastritis	2 (0.5)	7 (1.8)	3 (1.5)
bleeding	4 (1)	6 (1.5)	0 (0)
desquamation	5 (1.3)	6 (1.5)	0 (0)
scaling	1 (0.3)	6 (1.5)	0 (0)
yellow secretion	5 (1.3)	6 (1.5)	0 (0)
pharyngitis	2 (0.5)	5 (1.3)	1 (0.5)

Reviewer's Comments: Data in the table above indicates that a higher number of treatment emergent adverse events were observed in the 15 % treatment group compared to the 10 % treatment group suggesting a dose-response relationship for safety.

For the integrated safety review, there were 1085 patients with genital warts that 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 with polyphenon 15 % ointment. Six patients (10%) in the polyphenon 15 % ointment group and 4 patients (8.3 %) in the polyphenon 10 % group (cream and ointment) presented with serious adverse events. Two of the six patients in the polyphenon 15 % ointment group and 1 of the 4 patients in the polyphenon 10 % ointment group had serious adverse events that were considered related to study treatment and were all local reactions at the application site that required hospitalization. None of the serious adverse events in the active comparator or placebo groups were considered related to study treatment.

Reviewer's Comments: All three patients who experienced the serious adverse events were all women, with two out of three occurring in the 15 % dose group further suggesting a dose-response relationship. In addition, the medical reviewer had a concern that the data may indicate that there might be a possible difference in the safety of the drug in women compared to men. Overall, the safety data indicates that the incidence of adverse events other than local reactions was low.

Q. Were the active moieties in plasma appropriately identified and measured to assess the pharmacokinetic parameters?

No, the active moieties in plasma were not appropriately identified and measured because the actual active moieties are unknown. However, the applicant did identify and measure the four most abundant catechins (Epigallocatechin gallate (EGCg), Epicatechin gallate (ECg), Epigallocatechin (EGC) and Epicatechin (EC)) in green tea extract. The applicant did not provide any information in this NDA submission on whether these four catechins contribute to the safety and/or efficacy of Polyphenon ® E Ointment, 15 %.

In addition, although the analytical method (HPLC/MS) used to assay the four catechins in plasma was validated for sensitivity, accuracy and precision, the long term stability evaluation to cover the period from sample collection (117 days for the last to 354 days for the first patient) to the end of sample analyses did not meet the acceptance criteria of → recovery after sample storage. Also the stability data obtained after 5 days (for ECg) and 34 days (for EGC and EC) storage did not meet the acceptance criteria as shown in the table below.

Table: Summary of Long Term Stability Data

Type of Catechin	Mean Percent Recovery after the storage of the sample @ -20 °C					
	5 days	**7 days**	**34 days**	**38 days**	**96 days**	**417 days**
EGCg	87.9 %	ND	84.9 %	94.9 %	47.2 %	34.9 %
ECg	73.9 %	ND	88.4 %	87.2 %	46.7 %	54.5 %
EGC	103.4 %	96.3 %	77.4 %	97.2 %	41.0 %	19.8 %
EC	101.4 %	94.1 %	76.4 %	85.9 %	44.3 %	20.9 %

Reviewer's Comments: The failure of the long term stability evaluation to cover the period of sample storage and the inconsistency in the stability data obtained for shorter periods of storage makes it difficult to interpret any data obtained from stored plasma samples using this assay method.

Q. What are the PK characteristics of the drug product?

The results of the pharmacokinetic study, CT 1007 suggests that the systemic exposure of the catechins following topical application may be minimal. Study CT 1007 was a multi-center trial in which, plasma concentration versus time profiles of the four most abundant catechins (EC, EGC, ECg and EGCg) were determined following a single oral intake of 400 mLs of green tea solution (corresponding to approximately 320 mg of mean total catechin) and a single (250 mg) as well as repeated topical treatment with Polyphenon ® E ointment three times daily (corresponding to approximately ≥ 100 mg catechins daily) for 21 days. Pharmacokinetic assessments were performed at Visit 1 after oral intake of 400 mLs of green tea, after the first topical application of Polyphenon® E Ointment, 15 %, 3 days later, and on Days 3, 14 and 21 following study drug administration.

Following topical application of Polyphenon ® E 15 % ointment, plasma concentrations of the four catechins were below the LOQ (———) for most of the patients. Four patients had quantifiable plasma concentrations of two of the catechins (EGCg or EGC) at Visit 4 (Day 14) and/or 5 (Day 21). The applicant was unable to quantify the other two catechins (EC and ECG) in the plasma samples following topical application. The plasma concentrations and time and visit at which it was obtained are reproduced in the table below.

Type of Catechin	Patient No.	Plasma Concentration (ng/mL)	Time (hr)	Visit No.
Epigallocatechin gallate (EGCg)	2001	13.7	2	4
		9.89	4	4
	2009	6.8	8	5
		7.88	10	5
		6.0	12	5
	2030	11.4	0	4
		8.37	4	4
		6.02	1	5
		7.04	2	5
		6.64	3	5
		7.10	4	5
Epigallocatechin (EGC)	2010	5.37	0	5
		5.15	3	5

Reviewer's Comments: Although the data suggests that a maximum plasma concentration of 13.7 ng/mL was obtained for EGCg and about 5.4 ng/mL for EGC, this should be interpreted with caution considering that majority of the plasma concentrations of the catechins would have degraded during storage based on the results of the failed long term stability evaluation in plasma obtained for the four catechins. At best the provided data is not sufficient to draw any conclusions beyond relative comparisons between the catechins as to their abundance.

Q. How does the systemic exposure of the catechins following topical application compare to that obtained following oral intake?

The results of study CT 1007 suggest that the systemic exposure of three of the catechins (EGCg, EGC and ECg) after repeated topical application are similar to those obtained after an oral intake of 400 mLs of green tea. The plasma concentration of the fourth catechin (EC) was below the LOQ irrespective of whether it was administered orally or topically. Reproduced in the table below is a comparison of the maximum plasma concentrations obtained and the time at which it was obtained following topical and oral administration.

Catechin Type	Topical (N=24)	Dose ~ 100 mg catechins daily	Oral (N=24)	Dose ~ 320 mg catechins
	Cmax (ng/mL)	Tmax (hr)	Cmax (ng/mL)	Tmax (hr)
EGCg	13.7	2	181	1
EGC	5.4	0 (Day 14)	27.2	2
ECG	<LOQ	NA	45.9	1
EC	<LOQ	NA	<LOQ	NA

LOQ= Limit of Quantitation; NA = Not applicable

Reviewer's Comments: Although the data as presented suggests a higher systemic exposure (~5-13 fold) following oral intake of green tea compared to topical administration of Polyphenon ® E ointment, this may not actually reflect the actual relative systemic exposure because of the

difference in the dose of catechins administered and, the lack of stability of the catechins in plasma under the conditions of storage.

Q. Was there any other information provided to support the systemic exposure of the catechins?

The applicant provided some general toxicology data that indicated that the systemic exposure to Polyphenon E was minimal. This was reviewed by the Pharm/Tox reviewer (Dr. J. Yao) and the conclusions from his review were as follows:

> General toxicology: Polyphenon E 15% Ointment or Polyphenon E drug substance was tested for up to 3 months orally or topically in rats and dogs and for up to 9 months topically in mini-pigs. Gastrointestinal tract, liver, pancreas and lymphoid tissues were primarily affected in rats following oral administration. No apparent systemic toxicity was noted in mini-pigs after topical treatment of Polyphenon E 15% Ointment for 9 months. Polyphenon E Ointment induced minimal to severe local irritation including erythema, edema, and inflammatory reactions when topically applied to rats, rabbits, and mini-pigs. Polyphenon E Ointment caused strong local irritation to vaginal mucosa after vaginal application in female rats and mini-pigs.

Reviewer's Comments: In these studies it appears that the main catechin that was determined by the applicant was epigallocatechin gallate (EGCG). However, it appears that in some selected samples the catechins epicatechin gallate (ECG) and epicatechin (EC) were also determined following repeated dermal and intravaginal application to female minipigs (see pharm/tox review for further details). Therefore the catechins (although epigallocatechin (EGC) was omitted) that were measured in the pharm/tox studies were similar to those determined in the in vivo bioavailability study in humans.

2.3 Intrinsic Factors

Q. How does the systemic exposure change with various intrinsic factors?

Gender

The applicant stated that systemic absorption after topical application appears to vary according to gender and to the infected area therefore in the pharmacokinetic study (CT 1007), the patients were stratified by gender and location of diseased skin into four groups as follows:
M1: male patients, warts on penis; M2: male patients, warts on anogenital region; F1: female patients, warts on the vulva and F2: female patients, warts on anogenital region.

Following topical application of Polyphenon ® E 15 %, Ointment, the applicant was only able to evaluate this difference in gender in two patients who had quantifiable concentrations of Epigallocatechin gallate (EGCG). The applicant stated that the there plasma concentrations (mean for Males = 1.1 ng/mL and for females = 1.3 ng/mL) did not show any remarkable differences between the sexes.

Reviewer's Comments: The number of subjects with quantifiable concentrations of catechins was insufficient to determine whether males have a different systemic exposure when compared to females. Furthermore the accuracy of the systemic exposure data is questionable due to the failed

stability evaluation of the assay method. At best the sponsors conclusions are only speculative and not hypothesis generating.

2.4 Extrinsic Factors

This was not evaluated since systemic exposure was found to be minimal.

2.5 General Biopharmaceutics

Q. What is the relationship between the formulation of the drug product used in the pharmacokinetic study and that used in the pivotal clinical trials?

The formulations (Batch No. B000.10103 manufactured by) used in the pharmacokinetic study (CT 1007) and the clinical trials (CT 1016, 1017, 1018 and 1019) were the same. See tables below for the quantitative and qualitative composition of Polyphenon E ® 15% Ointment

Quantitative composition:

Component	% (w/w)	mg/g	mg/unit (tube)
Drug Substance			
Polyphenon® E			
Excipients			
Isopropyl Myristate			
White Petrolatum			
Cera Alba (white wax)			
Propylene Glycol Palmitostearate			
Oleyl Alcohol			

(1) Quantity of drug substance added during ointment formulation is variable and calculated in the table based on dry weight; adjustment is performed related to the water content (up to → maximum). To maintain total target batch size, the quantity of white petrolatum is adjusted accordingly to accommodate the water-adjusted drug substance quantity. Refer to Section 3.2.P.3.2, Vol. 3, for additional details.

Qualitative composition:

Component	Quality Standard	Function
Drug Substance		
Polyphenon® E	In-house standard and DMF holder's standard	Active ingredient
Excipients		
Isopropyl Myristate	NF	
White Petrolatum	EP	
Cera Alba (white wax)	EP	
Propylene Glycol Palmitostearate	EP	
Oleyl Alcohol	EP	

The proposed specification/ranges for the catechin content in Polyphenon E ® 15 % ointment are as follows:

Catechin	Specification/Proposed Range (mg/g)	Specification/Proposed Range (%)
EGCg		
EC		
ECg		
EGC		
Sum of four catechins (GCG, Cg, GC, C)		
Total Catechins		

Q. Are there any differences between the to-be-marketed drug product formulation and the formulation used in the pharmacokinetic study and the pivotal clinical trials?

Yes, there are differences. The drug product used in the Pharmacokinetic studies and the Phase 3 clinical trials were manufactured by ———. The proposed commercial manufacturer is C.P.M Contract Pharma. The applicant stated that the technical transfer —— to C.P.M will result in a change in the pharmacopoeial grade of the white petrolatum, cera alba (beeswax) and oleyl alcohol from USP or NF to EP. It will also result in a change in some of the manufacturing parameters (such as tighter control of temperature possible during preparation of the — phase).

The applicant provided in vitro release data that demonstrated that the ——— C.P.M. are comparable based on their in vitro release rates as described in the Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS). Although the chemistry reviewer has already conducted an in depth review of this data, preliminary evaluation of this data by this reviewer indicates that the ——— points were within the acceptance criteria for the 90 % confidence interval limits of ——. For the in vitro release data the chemistry reviewer (Dr. R. Agarwal) concurs with the preliminary evaluation by this reviewer.

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6 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

The applicant also provided additional evaluation of data of physicochemical properties (e.g. viscosity, consistency and particle size) to further support appropriate comparability of processes from both sites. The chemistry reviewer is currently conducting an in depth review of this additional data.

Reviewer's Comment: Currently, the clinical division is proposing an approvable action for this application at this time and one of the proposals is for the applicant to conduct another efficacy trial using the commercial formulation, and the actual impact of these differences in the formulation may then be definitively determined. In addition due to the deficiency of the long term analytical method stability evaluation, we will also be proposing that the sponsor conduct another PK study.

2.6 Analytical

Q. Were the analytical methods used for the determination of the four major catechins in biological fluids validated?

No, the stability data for the time period of storage of the samples was not acceptable.

Compound	Epicatechin (EC)	(-) Epicatechin gallate (ECg)
Internal Standard	Stavudine	Stavudine
Matrix	Plasma	Plasma
Accuracy ***Within-Day*** ***Between-Day***		
Precision (CV %) ***Within-Day*** ***Between-Day***		
Standard curve range	5-1000 ng/mL (r > 0.996, n = 6)	5-1000 ng/mL (r > 0.997, n = 7)
Sensitivity (LOQ)	for N = 36)	for N = 42)
Selectivity	No quantitative interference was observed for any of the catechins at the retention times of interest	
Mean Recovery % (%CV)	96.7-102.5 % (IS = 83.8 %)	58.3 – 66.3 % (IS = 83.8%)
Stability	Long term stability (not acceptable degradation).	Long term stability not acceptable (degradation)

Compound	Epigallocatechin (EGC)	(-) Epigallocatechin gallate (EGCg)
Internal Standard	Stavudine	Stavudine
Matrix	Plasma	Plasma
Accuracy ***Within-Day*** ***Between-Day***		

Precision (CV %) *Within-Day* *Between-Day*		
Standard curve range	5-1000 ng/mL (r > 0.999, n = 3)	5-1000 ng/mL (r > 0.996, n = 6)
Sensitivity (LOQ)	N = 18)	N = 36)
Selectivity		
Mean Recovery % (%CV)	105.6-132.9 % (83.8 % for IS)	80.5-92.3 % (83.8 % for IS)
Stability	Long term stability) not acceptable degradation).	Long term stability not acceptable).

3 **Labeling Comments:** The clinical division intends to make this application approvable due to inadequate efficacy data in the US population. In light of this decision, clinical pharmacology labeling comments are deferred until the application is approved.

4 Appendix

4.1 Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.

4.2

9 Page(s) Withheld

8 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

4.3 Individual Study Reviews:

Study # CT 1007

Title of Study: An Open-Label, Multi-Center Phase 2 Study to Assess the Pharmacokinetic Profile of Topically Applied Polyphenon® E 15% Ointment in Patients with External Genital Warts Compared to Oral Intake of Drinkable Green Tea

Investigators:

Studied period (years):
Date of first patient enrolment: 09 December 2002
Date of last patient completed: 30 September 2003

Phase of development: II

Objectives: The objective of this study was to obtain information on the plasma concentration and pharmacokinetics of topically applied Polyphenon® E 15% Ointment in patients with external anogenital warts stratified by gender and location of diseased skin and to compare these data with plasma concentrations and pharmacokinetics of tea catechins and their conjugates following oral intake of green tea. Furthermore an inter- and intra-individual comparison of plasma levels of catechins via stratification of patients by gender and location of diseased skin was to be made.

Methodology: An open-label, multiple-dose, multi-center Phase 2 study to assess the pharmacokinetic profile of topically applied Polyphenon® E 15% Ointment as compared to the pharmacokinetic profile of tea catechins following oral intake of drinkable green tea in patients with external anogenital warts.

Number of patients: 38 male and female patients enrolled. Patients were stratified by gender and location of diseased area. Clinical diagnosis of external genital warts location of diseased area was as follows:

In men, on the penis (M1) or on the rest of the anogenital region (M2)
In women, on the vulva (F1) or on the rest of the anogenital region (F2)

The total wart area in the stratified region was at least 200 mm^2. Only warts in the stratified region (be they baseline, recurrent, or new warts having occurred after the start of the study at each application time point) was to be treated.

Test and Reference Product, Dose and Mode of Administration, Batch Number:

Test: Polyphenon® E 15% Ointment, ≥ 250 mg three times per day on stratified wart area, label batch no.: 1007-1, product batch no.:B000.43902/000.43902 ***(same batch used in # CT 1017)***

Reviewer's Comments: Mean daily dose of ointment used was 0.95g (range= 0.54 to 1.81 g).

Reference (Comparator): Green tea prepared from raw tea leaves *(Camellia sinensis O. Ktze,* [redacted], single intake of 400 mL tea, batch no.: GTL020608

Duration of treatment: Green tea: Oral intake of 400 mL (2 cups) within 15 minutes on Day -3 (Visit 1) followed by PK sampling. Afterwards the study continued with Polyphenon® E 15% Ointment: 3 weeks topical application, three times per day (morning, noon and evening). Exception (PK sampling days): on Day 0 (Visit 2, baseline) and Day 20/21 (Visit 5) only two applications (morning and evening dose) were made. Then patients had the option to continue the treatment for an additional 13 weeks topical application, three times per day (thus participating in supportive efficacy evaluation with no PK data being obtained).

All ointment applications were to be made using cotton swabs. When washing the treatment area or bathing, the ointment had to be applied afterwards.

Pharmacokinetic Sampling: Blood samples (10 mLs) were taken at 0 (prior to oral intake of green tea), 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours following the oral intake of green tea on Visit 1 (Day -3), or following the morning application of the Polyphenon ® E 15 % ointment on Visits 2 (Day 0) and 5 (day 20/21). On Visits 3 (day 3) and 4 (day 14), blood samples were taken at the time points 0, 2, and 4 hours following the application of the second daily dose of the study drug. Additionally, at Visit 1, a sample of the green tea was taken for analyses for its catechin content. The total amount of blood drawn was approximately 390 mLs per patient (PK = 360 mLs (36 x 10 mLs) and safety lab tests = 30 mLs (2 x 15 mls)).

Analytical Methods: High Performance liquid chromatography with mass spectrometric detection (HPLC/MS) for plasma and, UV detection for aqueous tea solutions.

Criteria for evaluation:

Pharmacokinetics: Cmax, tmax, $t_{1/2}$, AUC (0-tlast), AUC (0-∞) of Epicatechin (EC), Epigallocatechin (EGC), Epicatechin gallate (ECg) and Epigallocatechin gallate (EGCg) concentrations measured in stratified groups M1 (male patients, external genital warts on penis), M2 (male, warts on the rest of the anogenital region), F1 (female, warts on the vulva), and F2 (female, warts on the rest of the anogenital region).

Reviewer's Comments: Applicant stated that the catechins being measured, EC, EGC, ECg and EGCg were the most abundant catechins in green tea.

Safety: Occurrences of treatment-emergent adverse events, changes in vital signs (blood pressure/pulse rate), electrocardiographic examinations, physical examinations and clinical safety laboratory parameters

Supporting Efficacy Data:, Number of warts, wart longest diameter [mm], diameter perpendicular to longest diameter [mm] total wart area (sum of the area of the single warts i.e. product of its maximal length and maximal width mm^2) were assessed at Visits 1 (Day -3), 5 (Day 21) and 6 (~ Week 16)

Others: Trial completion, use of concomitant medication, compliance with trial medication, tea or wine consumption.

Statistical methods: The evaluations were carried out by means of descriptive statistics only. No method of statistical hypothesis testing was applied.

Results:

Demographics and other baseline characteristics:

Thirty-Eight (38) Caucasian patients completed the PK study, however only 24 were included in the data analysis. There was a protocol violation (overdosing) for 14 patients (2015-2028) in the Estonian center. These patients received an additional erroneous noon time treatment at Visit 2 and 5. These patients were excluded from the PK analysis. Although 12 additional patients were enrolled into the trial (Applicant stated that 2 further patients were already enrolled at that time), these patients were not included in the PK data set.

Table IV: Baseline Demographic Data (Safety Set, N = 38) (Section 10.4, Tables 10.4.1.1 to 10.4.1.17)

		F1	F2	M1	M2
Gender	Male	0 (0%)	0 (0%)	9 (100%)	10 (100%)
	Female	9 (100%)	10 (100%)	0 (0%)	0 (0%)
Race	Caucasian	9 (100%)	10 (100%)	9 (100%)	10 (100%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age	Mean	27.33	28.10	24.44	34.70
[years]	SD	11.82	9.86	1.94	9.42
	Median	21.00	25.00	24.00	35.50
	Minimum	18.00	18.00	21.00	20.00
	Maximum	47.00	48.00	27.00	46.00
Weight at Visit 1	Mean	59.62	66.75	80.12	85.51
[kg]	SD	9.33	11.80	5.74	13.52
	Median	58.00	62.10	80.00	82.60
	Minimum	45.10	56.00	73.00	67.00
	Maximum	80.00	89.90	90.00	108.20
Height	Mean	163.33	166.30	180.00	176.30
[cm]	SD	5.36	7.18	6.02	4.81
	Median	163.00	163.50	180.00	177.50
	Minimum	155.00	160.00	172.00	168.00
	Maximum	173.00	180.00	192.00	182.00

Reviewer's Comments: The inclusion of 24 patients instead of 38 patients in the PK data set is okay because this still meets number that was specified in the protocol to be eligible for enrolment. Consistent with previous observations the weight and height of males were higher than in females.

10.4.1.14: Total Wart Area [mm^2] - Sample Characteristics by Group, Gender and Visit

Visit Screening

Total wart area	Group				
	F1	F2	M1	M2	Total
N	9	10	9	10	38
N missing	0	0	0	0	0
Mean	368.67	303.40	259.22	479.10	354.63
Std. dev.	314.08	127.60	45.80	353.12	251.46
Minimum	204.00	204.00	203.00	205.00	203.00
Median	227.00	249.00	258.00	254.00	249.00
Maximum	1175.00	611.00	340.00	1050.00	1175.00

Reviewer's Comments: The data indicates that the total wart area of at least 200 mm^2 was obtained for the patients in each subgroup. For the pivotal clinical trials, the inclusion criterion was for a total wart area between 12 and 600 mm^2.

***Pharmacokinetics*:**

Analytical Method Validation

Sample Storage and Stability: Study, samples were stored from sample collection to the end of sample analysis at a nominal temperature of -20°C for a duration of 117 days (last patient) to 354 days (first patient).

Reviewer's Comments: It is not clear from this statement if the applicant analyzed any plasma samples that were stored for a short period of time i.e. < 117 days.

Applicant's Summary on Stability:

Study samples were analyzed without exceeding short term, freeze-thaw stability or processed sample integrity. The following evaluations have been conducted prior to sample analysis:

Stability Summary	
Long-term Stability	7 days at -20°C nominal for EC and EGC 38 days at -20°C nominal for EGCG and ECG
Short-term Stability	5.6 hours in an ice bath
Freeze-thaw Stability	3 cycles at -20°C nominal
Processed Sample Integrity	143.4 hours at 5°C nominal for EC. ECG and EGCG 56.6 hours at 5°C nominal for EGC

Long-term stability evaluation was performed after storage for 96 and 417 days which approximately covered the shortest and longest period from sample collection to sample analysis (storage periods were 117 days for the last to 354 days for the first patient). However, acceptance criteria of — recovery after sample storage were not met. The results are described in the

Applicant's Results

Table: Summary Table of Pharmacokinetic Evaluation of, EGC (Epigallocatechin), ECg (Epicatechin gallate) and EGCg (Epigallocatechin gallate) Plasma Concentrations over Time by Stratified Group (N = 24)

		Arithmetic Mean (SD) [Range]				**N = 24 (~6 per subgroup)**
Analyte	PK Parameter	F1	F2	M1	M2	Total
Epigallocatechin (EGC)						
Visit 1 (oral intake)	AUC (0-t) (ng.hr/mL)	48.291 (27.75) [23.1-93.49]	69.355 (70.25) [9.16-204.45]	30.600 (24.58) [1.46-67.17]	30.169 (21.82) [0-72.33]	44.60 (41.76) [0-204.45]
	AUC (0-inf) (ng.hr/mL) (N = 17)	72.411 (26.82) [49.58-112.03]	76.823 (21.44) [57.19-97.52]	82.285 (19.29) [67.32-104.05]	59.974 (53.43) [0-145.80]	71.534 (33.12) [0-145.80]
	Cmax (ng/mL)	18.00 (5.524) [10.1-27.2]	16.015 (7.044) [7.530-26.40]	12.010 (5.5570 [5.830-19.800]	11.283 (7.960) [0-21.8]	14.327 (6.781) [0-27.2]
Median	Tmax (hr) (N = 24)	1 [0.417-2.0]	1.983 (2.693) [1.0-8.08]	1 [0.5-2]	0.967 [0.5-1.0]	1.0 [1-8.08]
	$T_{1/2}$ (hr) (N = 16)	2.309 (0.835) [1.516-3.672]	3.120 (0.940) [2.098-4.127]	3.065 (0.922) [2.215-4.046]	4.032 (4.5) [1.149-10.67]	3.084 (2.229) [1.149-10.67]
Visit 5 (3 weeks of topical administration) (N = 23)	AUC (0-t) (ng.hr/mL)	0	0	0	0.653 (1.599) [0-3.918]	0.17 (0.817) [0-3.918]
	Cmax (ng/mL)	0	0	0	0.895 (2.192) [0-5.370]	0.233 (1.12) [0-5.370]
Epicatechin gallate (ECg)						
Visit 1 (oral intake)	AUC (0-t) (ng.hr/mL)	48.137 (22.192) [41.37-119.77]	75.847 (52.989) [70.124-237.644]	76.427 (62.634) [7.393-182.225]	42.955 (55.419) [10.0-154.8]	60.841 (49.856) [7.393-182.225]
	AUC (0-inf) (ng.hr/mL) (N = 17)	69.492 (29.934) [41.371-119.766]	143.623 (70.105) [70.124-237.644]	122.064 (71.568) [52.036-211.97]	226.595 (236.828) [59.132-394.057]	120.879 (92.22) [41.371-394.057]
	Cmax (ng/mL)	19.00 (9.06) [8.35-33.10]	21.08 (9.615) [11.5-37.5]	25.425 (14.98) [6.15-45.9]	13.632 (5.57) [7.49-23.4]	19.787 (10.594) [6.15-45.9]
Median	Tmax (hr) (N = 24)	1.5 [0.95-2.0]	1.483 [1.0-8.08]	1 [1.0-2.0]	1.0 [0.967-2.0]	1.0 [1-8.08]
	$T_{1/2}$ (hr) (N = 17)	2.252 (1.482) [1.073-4.991]	5.407 (2.038) [3.106-7.652]	2.300 (0.499) [1.626-2.703]	9.122 (9.651) [2.298-15.946]	3.816 (3.624) [1.073-15.946]
Epigallocatechin gallate(EGCg)						
Visit 1	AUC (0-t)	259.482	369.262	392.096	205.427	306.567

(oral intake)	(ng.hr/mL)	(80.191) [161.575-360.87]	(196.47) [166.367-594.25]	(284.121) [41.275-820.61]	(207.430) [50.532-618.85]	(207.057) [41.275-820.61]
	AUC (0-inf) (ng.hr/mL) (N = 22)	287.223 (87.402) [185.883-387.294]	382.369 (184.359) [225.427-581.315]	429.447 (283.272) [94.659-839.328]	407.909 (659.098) [63.589-1750.104]	376.225 (364.112) [63.589-1750.104]
	Cmax (ng/mL)	79.05 (32.47) [45.3-120.0]	88.72 (40.05) [45.8-154.0]	101.03 (59.23) [19.5-181]	56.67 (24.60) [26.3-95.8]	81.37 (41.805) [19-181]
Median	Tmax (hr) (N = 24)	1 [0.417-2.0]	1.983 (2.693) [1.0-8.08]	1 [0.5-2]	1 [0.5-1.0]	1.0 [1-8.08]
	$T_{1/2}$ (hr) (N = 22)	2.134 (0.637) [1.141-2.929]	1.851 (0.3260) [1.556-2.234]	3.351 (2.101) [1.621-6.739]	4.196 (6.652) [1.018-17.740]	2.977 (3.551) [1.018-17.740]
Visit 5 (3 weeks of topical administration) (N = 23)	AUC (0-t) (ng.hr/mL) N=2	0	3.67 (8.991) [0-22.02]	0	5.897 (14.44) [0-35.38]	2.39 (8.34) [0-35.38]
	Cmax (ng/mL) N=2	0	1.183 (2.899) [0-7.10]	0	1.313 (3.217) [0-7.88]	0.624 (2.118) [0-7.88]

M1-male, penis, M2-male, rest of the anogenital region, F1-female, vulva, F2-female, rest of anogenital region

Applicant's Conclusions: Following drinking of green tea, there were no remarkable differences found for tmax of EGC, ECg and EGCg between men and women although the intraindividual variability was large. The peak and extent of exposure of ECg and EGCg as characterized by Cmax and AUC0-t, were not remarkably different between men and women. Slightly lower AUC0-t of EGC was observed in men as compared to women. The terminal half lives were not remarkably different between men and women.

Reviewer's Comments: In light of the limitations of the assay method in terms of stability it is unlikely that these estimates are accurate.

Reviewer's Summary of PK Data

Following oral intake of green tea the applicant was only able to quantify the following three catechins Epigallocatechin (EGC), Epicatechin gallate (ECg) and Epigallocatechin gallate (EGCg) in plasma. Following the topical application of Polyphenon E ointment, the applicant was only able to quantify two of the catechins EGCg and ECG. The fourth catechin, Epicatechin (EC) was not detectable following both oral intake and topical administration. Based on this reviewer's observations of the raw data reproduced in the table below is the list of patients that had levels of catechins above LOQ following topical application (at visits 4, and 5). Table shows there were actually three patients with EGCg levels and not two as stated by the applicant. This data should be treated with caution, as they may not be accurate due to degradation during storage.

Patient No.	*Epigallocatechin gallate (EGCg) plasma concentrations (ng/mL)*	*Epigallocatechin (EGC)plasma concentrations (ng/mL)*
2001	*13.7 @ 2 hr (Visit 4)* *9.89 @ 4 hr (Visit 4)*	*NA*
2009	*6.8 @ 8 hr (Visit 5)* *7.88 @ 10 hr (Visit 5)* *6.02 @ 12 hr (Visit 5)*	*NA*
2010	*NA*	*5.37 @ 0 hr (Visit 5)* *5.15 @ 3hrs (Visit 5)*
2030	*11.4 @ 0 hr (Visit 4)* *8.37 @ 4 hrs (Visit 4)* *6.02 @ 1 hr (Visit 5)* *7.04 @ 2 hrs (Visit 5)* *6.64 @ 3 hrs (Visit 5)* *7.10 @ 4 hrs (Visit 5)*	*NA*

Concentrations of the catechins in aqueous green tea extract

Analytical Method Development and Validation: HPLC

Compound	EGCg, EC, EGC, ECG and GCG
Matrix	Green tea solutions
Accuracy	
Precision (CV %)	
Standard curve range	30-3000 mcg/mL ($r \geq 0.998$)
Sensitivity (LOQ)	
Selectivity	No quantitative interference was observed for any of the catechins at the retention times of interest

Table: Mean (SD) concentration of EGCG, EC, EGC, ECG and GCG in green tea solutions from study CT 1007 (date derived from table 4 above) (N = 38)

Green Tea Component	**Concentration (mcg/mL)**	**% of Total Catechins**	**Acceptance Criteria for Polyphenon E ointment**
EGCG			Not less than — and not more than
EC			Not less than — and not more than
EGC			Not less than — and not more than
ECG			Not less than — and not more than
GCG			Not less than — and not more than
Total			*Distribution of catechins in Green tea is comparable to Polyphenon E*

Reviewer's Comments: Data in table above supports applicants claim that EGCg, EGC, ECg and EC are the most abundant catechins in green tea extract solution.

Table 4 **Concentration determination of EGCG, EC, EGC, ECG and GCG in green tea solutions from study CT 1007**

Subject	Concentration [µg/mL]				
	EGCG	EC	EGC	ECG	GCG
2001					
2002					
2003					
2004					
2005					
2006					
2007					
2008					
2009					
2010					
2011					
2012					
2013					
2014					
2015					
2016					
2017					
2018					
2019					
2020					
2021					
2022					
2023					
2024					
2025					
2026					
2027					
2028					
2029					
2030					

Subject	Concentration [µg/mL]				
	EGCG	EC	EGC	ECG	GCG
2031					
2032					
2033					
2034					
2035					
2036					
2037					
2038					

Applicant's Safety results:

No deaths or serious adverse events (AEs) occurred during the course of this trial including the 3-weeks pharmacokinetic evaluation time and the optional 13 week treatment period. The dose of the trial medication was reduced in six patients during the 3-week pharmacokinetic period (patient No. 2016, 2018, 2019, 2020, 2021 and 2027). One patient was from group Ml (11.1%) ~ one from group M2 (10.0%) and two patients each were from groups F1 (22.2%) and F2 (20.0%). Furthermore, trial medication was interrupted in two patients during the optional 13-week treatment period (patient No. 2022 and 2025). One patient was from group M1 (11.1%) and one patient was from group F2 (10.0%).

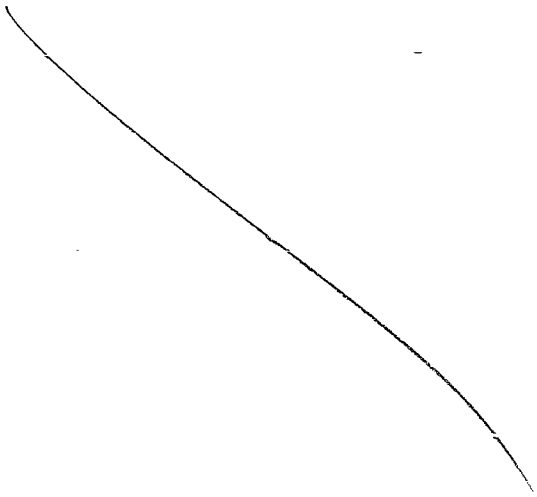
In total, 73 AEs were reported, 70 of which were treatment-emergent and drug-related AEs and occurred in 19 patients (50.0% of patients). Sixty-four AEs occurred during pharmacokinetic evaluation (in 17 patients; i.e. 44.7% of the total 38 patients) and 6 AEs occurred during the optional treatment period (in 2 patients; i.e. 8.3% of the total 24 patients in this part).
In group Fl, 55.6% of patients experienced an AE, in group F2 60.0%, in group M1 44.4% and in group M2 40.0% of patients experienced an AE. The percentage of patients affected by an AE was higher in females than in males. In total 11 females (57.9%) and 8 males (42.1%) were affected by 35 treatment-emergent AEs out of a total of 73 AEs.

Two patients (patient No. 2022 and 2025) suffered from severe AEs (each of these two patients had 3 cases of severe AEs). For all 6 severe AEs a relationship to trial medication was assessed as definite since they were located at the application site. One AE occurred on the first treatment day. No patient was withdrawn from the trial due to an AE, and no concomitant medication for the treatment of any AE was necessary in any of the four stratified groups Fl, F2, M1, and M2. The majority of AEs was limited to the application site with only one exception. Patient No. 2021 from group M1, suffered from a skin irritation not related to the site of application.
No remarkable changes in ECG, body temperature, physical examination findings, clinical laboratory parameters, and vital signs were observed from baseline to last study visit.

Applicant's Conclusions

The systemic absorption of green tea catechins EGC, ECg and EGCg after repeated topical application of Polyphenon® E 15% Ointment was very low as compared to the oral intake of 400 mL green tea. The plasma concentration of EC was below the LOQ whether it was administered orally (green tea) or topically (Polyphenon® E 15% Ointment). Under the conditions evaluated, a systemic distribution of catechins was not proved following topical application of Polyphenon® E ointment. An accumulation of the ingredients of the study drug in plasma was not seen. The majority of adverse events that occurred during the trial were mild and limited to the application site.

In Vitro Release Data



1 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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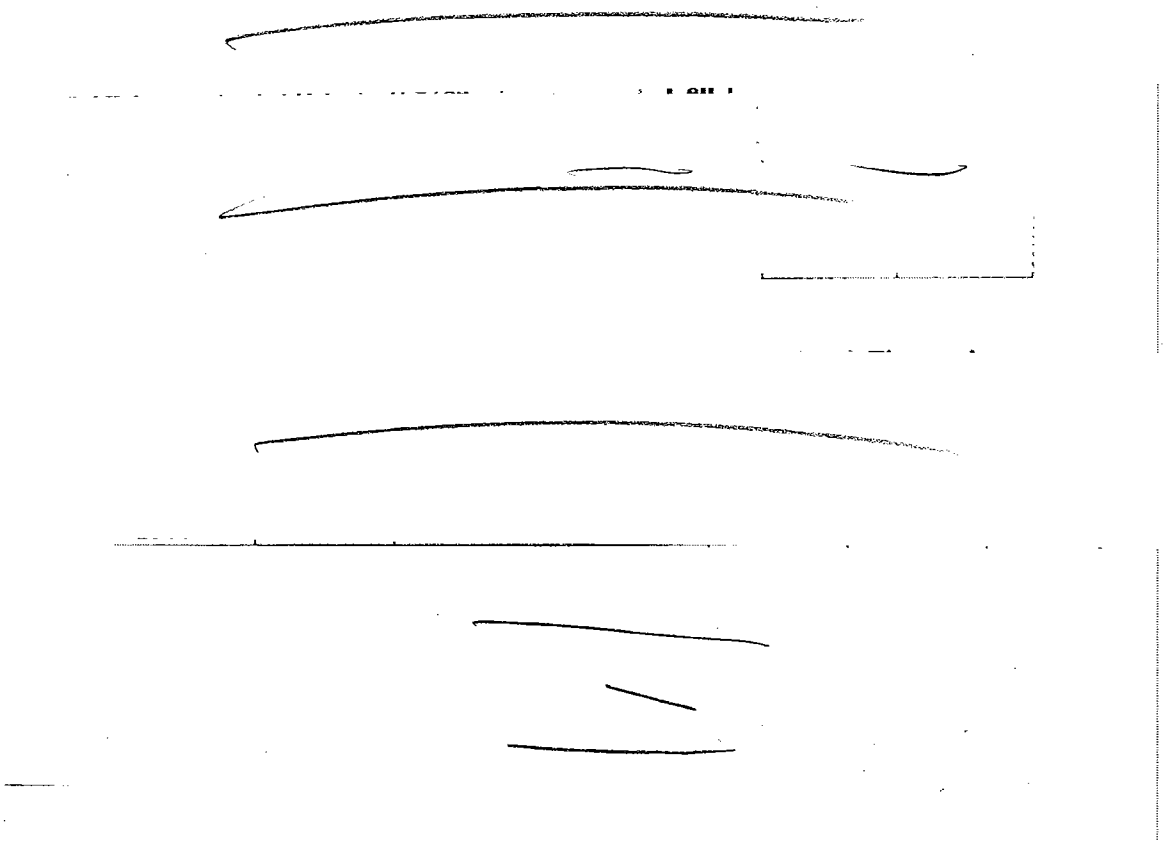

4.4 OCPB Filing Form:

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21-902	**Brand Name**	Polyphenon ® E Ointment, 15 %
OCPB Division (I, II, III)	DCPB3	**Generic Name**	Polyphenon E, Green Tea Extract
Medical Division	HFD-540	**Drug Class**	Immuno-Modulatory
OCPB Reviewer	Abi Adebowale	**Indication(s)**	Treatment of external genital and perianal warts in adult patients
OCPB Team Leader	Dennis Bashaw	**Dosage Form**	Ointment
		Dosing Regimen	To be applied three times per day to all external genital and perianal warts
Date of Submission **Internal Filing Date**	23rd September, 2005 14th November, 2005	**Route of Administration**	Topical

Estimated Due Date of OCPB Review	30th May, 2006	**Sponsor**	Medigene, Inc, San Diego, CA
PDUFA Due Date	**23rd July, 2006**	**Priority Classification**	NME, 1S
Division Due Date	**23rd June, 2006**	**IND Number**	56, 401

Clin. Pharm. and Biopharm. Information

Background and Introduction: Polyphenon E is a green tea extract containing 85-95 % total catechins by weight. Catechins are polyphenols, a family of flavonoids found in the tea leaves of *Camellia sinensis*. [redacted] The drug substance also contains other tea associated compounds including caffeine, theobromine and gallic acid. The most abundant catechins in Polyphenon ® E are (-)-epigallocatechin gallate (EGCg), (-)-epicatechin (EC), (-)-epigallocatechin (EGC).

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		Study No. CT 1007 (phase 2 maximal usage absorption study comparing ointment to oral intake of green tea)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan	**X**			Sponsor included a request for a waiver
Literature References	X	1		PK of green tea polyphenols after MD admin of Polyphenon E to healthy individuals
Total Number of Studies		2		

Filability and QBR comments

	"X" if yes	
	X	Comments Applicant provided information on ADME in the non clinical section with a few literature references on metabolism of the orally administered tea/or the drug substance in humans. These studies will be referred to and used as supportive information for the clinical pharmacology review as needed.
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**No**	Comment to be sent to the firm is as follows: For study # CT 1007, we noticed that the Binomial Scientific Name of the plant (Camellia sinensis O. Ktze) used for the brewed green tea "control" treatment arm is different from that used as the botanical raw material (Camellia sinensis (L.) O. Kuntze) for the Polyphenon E ointment, 15 % used in the same study. Please clarify whether this difference in names means that they are from different sources.
QBR questions (key issues to be considered)	What is the systemic exposure of Polyphenon E? What is the exposure –response relationship for safety and efficacy of Polyphenon E? How was the dose selected? What is the ADME of Polyphenon E?	

Other comments or information not included above	The formulation used in the clinical pharmacology studies manufactured by [redacted] is the same as that used in the clinical trials CT1017 (Pivotal Phase 3 trial), CT 1016 ([redacted] and CT 1019 [redacted]. However, the applicant stated that [redacted] will not be the manufacturer for the commercial product. The new manufacturer will be CPM. The applicant provided in vitro release data and stability data to support this change in manufacturer. This in vitro release data will be reviewed by the chemists (based on the directives provided as of Nov 1st, 2005). OCPB only reviews biowaivers and IVIVC.
Primary reviewer Signature and Date	**Abi Adebowale 11/10/05**
Secondary reviewer Signature and Date	**Dennis Bashaw**

CC: NDA 21-902, HFD-850 (P.Lee), HFD-540 (M.Wright), DCP3 (D. Bashaw, J.Hunt)

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/s/

Abi Adebowale
6/30/2006 05:25:06 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/3/2006 11:24:26 AM
BIOPHARMACEUTICS