CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-907

CHEMISTRY REVIEW(S)

MARKOW

SEP 29 1998

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
HFD-580

Review of Chemistry, Manufacturing, and Controls

NDA 20-907 **CHEM.REVIEW:** #1 **REVIEW DATE:** 7/30/98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	20 Nov 1997	13 Nov 1997	27 Mar 1998
BC Amendment	19 Mar 1998	20 Mar 1998	17 Jun 1998
BC Amendment	08 Jul 1998	17 Jul 1998	20 Jul 1998

NAME & ADDRESS OF APPLICANT:
Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

DRUG PRODUCT NAME

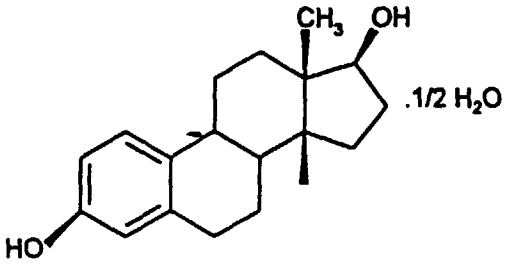
Proprietary:	Activelle (Previously Stelest Nuvera™)
Nonproprietary/USAN:	Estradiol/Norethindrone
Code Name/#:	Kliogest Low Dose
Chem.Type/Ther.Class:	For relief of estrogen deficiency symptoms during menopause . Type 4.
CAS-number:	50-28-2

Patent Status: There are no patents held by Novo Nordisk which claim Nuvera (1mg Estradiol and 0.5 mg Norethindrone acetate) or which claim a method of using Nuvera with respect to which a claim of patent infringement could reasonably be asserted against a non-licensed person.

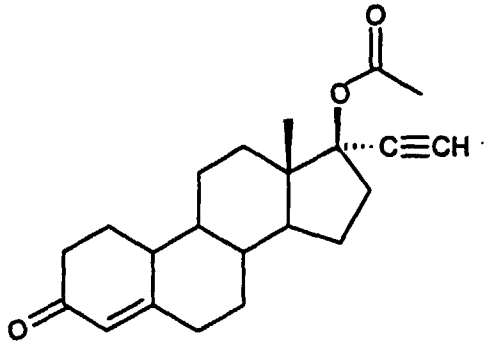
Foreign Marketing History: A Nuvera (1mg E_2/0.5mg Norethindrone Acetate) application has been submitted to the EU on September 26,1997. Nuvera is not currently marketed in any country.

PHARMACOL.CATEGORY/INDICATION: Combined oral hormone replacement therapy treatment of moderate to severe vasomotor symptoms associated with menopause and in the treatment of vulvar and vaginal athrophy, on women with an intact uterus.

DOSAGE FORM:	Tablets
STRENGTHS:	1 mg Estradiol/ 0.5 mg Norethindrone Acetate
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	Rx



Estradiol, USP
Estradiol hemihydrate, Ph.Eur



Norethindrone acetate, USP
Norethindrone acetate, Ph.Eur

SUPPORTING DOCUMENTS:

TYPE/NUMBER	SUBJECT	HOLDER	STATUS	REVIEW DATE	LETTER DATE
IND					
DMF	Estradiol		Adequate (Dr. A.Mitra) HFD-580)	9/12/97	N/A
DMF	Norethindrone Acetate Povidone		Adequate (Dr,Srinivas achar) HFD-180 Information provided in the NDA Vol. 1.3 page 351.	11/5/97	N/A
DMF	Resin		Adequate (Dr.LNg HFD-155)	8/15/95	NA
DMF	Norethindrone Acetate		Adequate (Dr.Mitra) HFD-580	7/31/98	N/A
DMF	Polystyrol		Information provided in the NDA.		
DMF	Estradiol		Adequate (Dr. Trimmer)	5/29/97	N/A
DMF	Dyeing pigment PE 192183		Information provided in the NDA Vol.1.3 page 493		

RELATED DOCUMENTS (if applicable): None
CONSULTS: Consults were sent to the Labeling and Nomenclature Committee for trade name, Activelle and the name were considered acceptable.
REMARKS/COMMENTS:
The BC amendment dated March 19, 1998 provided the requested 12 month interim stability data.
The BC amendment dated July 8, 1998 was a clarification with regard to the responsibilities of the site; the company indicated that the microbiological testing on the finished product is done at this site

Activelle (previously Nuvera), 1 mg E_2/0.5 mg Norethindrone Acetate is not currently marketed in any country.

The stability information provided for 12 months at 25°C/60% RH and 40°C/75% supports the two year expiry data proposed by the company.

Since the use of the active ingredients by the applicant for drug products will not exceed the combined total EIC of 1 ppb the request for categorical exclusion may be granted.

After corrective actions and commitments, the Novo Nordisk plants in Gentofte, Soeberg, and Maaloev in Denmark have been classified as acceptable by the Office of Compliance.
CONCLUSIONS & RECOMMENDATIONS:
The Novo Nordisk plants have corrected the deficiencies and received an acceptable evaluation from the inspection of the manufacturing and testing plants.
From the point of view of chemistry this application is APPROVABLE pending the resolution of some chemistry issues stated in the deficiency letter.

/S/ 9/28/98
Maria Elena Ysern, Msc
Review Chemist, HFD-180

/S/ 9/29/98
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

cc:
Orig. NDA 20-907
HFD-580/Division File
DISTRICT OFFICE
HFD-180/MYsern
HFD-580/MJRhee
HFD580/LPauls
R/D Init by: MJRhee
MY/dob **F/T 9-25-98**/Word: n:\wordfiles\chem\N\20907809.2MY

Division of Reproductive and Urologic Drug Products
HFD-580
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-907 **CHEM REVIEW #: 2** **REVIEW DATE:** 11/4/98

SUBMISSION TYPE

	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
BC Amendment	October 14, 1998	October 15, 1998	October 26, 1998
BC Amendment	November 3, 1998	November 4, 1998	November 4, 1998

NAME & ADDRESS OF APPLICANT:
Novo Nordisk Pharmaceuticals Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

DRUG PRODUCT NAME:

Proprietary:	Activelle (Previously Stelest Nuvera ™)
Nonproprietary/USAN:	Estradiol/Norethindrone
Code Name/#:	Kliogest Low Dose
Chem.Type/Ther.Class:	For relief of estrogen deficiency symptoms during menopause. Type 4.

PHARMACOLOGICAL CATEGORY/INDICATION: Combined oral hormone replacement therapy treatment of moderate to severe vasomotor symptoms associated with menopause and in the treatment of vulvar and vaginal athrophy, on women with an intact uterus

DOSAGE FORM: Tablets

STRENGTH: 1 mg estradiol/0.5 mg Norethindrone Acetate

ROUTE OF ADMINISTRATION: ORAL

HOW DISPENSED: Rx _
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Review #1.
SUPPORTING DOCUMENTS: See Review #1

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

REMARKS/COMMENTS: This amendment is in response to the CMC Review comments of October 1, 1998. The company is also amending the CMC section for several items that required changes for clarification purposes as well as in response to PAI observations.

CONCLUSIONS & RECOMMENDATIONS: From the standpoint of chemistry this NDA may be approved.

/S/ 11/5/98

Maria Elena Ysem, MSc
Review Chemist, HFD-180

/S/ 11/5/98

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, HFD-580

cc:
NDA # 20-907
HFD-580/Division File
HFD-180/MYsem
HFD-580/MJRhee
HFD-580//LPauls
R/D Init by:MJRhee
MY/dob **F/T 11/5/98/Word:n:\wordfiles\chem\n\20907890.3MY**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-907

PHARMACOLOGY REVIEW(S)

DEC 23 1997

NDA 20-907 12/23/97

Novo Nordisk Pharm

Submission: November 7, 1997

Pharmacology Review of NDA

Drug: Norethindrone Acetate (1 mg) and Estradiol (0.5 mg).

Indication: Relief of menopausal symptoms and the prevention of osteoporosis.

Both norethindrone acetate and estradiol are approved drugs. A high dose combination of 2 mg norethindrone acetate and 1 mg estradiol has been marketed outside the US for 13 yrs.

The sponsors conducted several preclinical studies including three single dose studies with the combination in rat and monkey which resulted in no unusual toxicity.

Toxicity study by oral (gavage) administration to CD rats for four weeks.
Novo Nordisk study no. 940265, 1997.

Groups of 20 female CD (Sprague-Dawley) rats received a combination of estradiol and norethindrone acetate by gavage daily for 4 weeks. There were two sets of doses; four or two parts E2 to one part NETA. Doses selected were 0.02+0.005 or 0.02+0.01 mg/kg/day for the low dose; 0.2+0.05 or 0.2+0.1 mg/kg/day for the mid-dose and 2.0+0.5 or 2.0+1.0 mg/kg/day for the high dose.

Mortality: None

Clinical signs: transient salivation after dosing in MD and HD and from wk 3, piloerection in the HD.

Body weight: Decrease bw gain in both HD gps.

Ophthalmoscopy: No effects.

Hematology: Prolonged prothrombin times in animals treated with either combination at the MD and HD. There was prolonged activated 0partial thromboplastin times and low mean cell volumes in both HD gps and slightly low packed cell vol in the HD receiving 2.0+1.0 mg/kg.

Clinical chemistry: No toxicological significant changes.

Urinalysis: Low urinary sodium and low specific gravity compared to controls in MD and HD.

Organ weights: Increased liver wts in both HD gps. Low thymus and ovary wts and high adrenal wts were seen in some HD animals. Rel kidney wts were increased in HD.

Gross pathology: No effects.

Histopathology: Effects seen only in the HD included centriacinar glycogenic vacuolation of the liver, acinar hyperplasia of the mammary gland, ovarian atrophy and luteal cysts, hyperplasia and focal squamous metaplasia of the uterine epithelium, and in a few animals, vacuolation of the vaginal epithelium.

Conclusion: This 4 week toxicity study in rats did not reveal any unexpected toxicities of the combination of norethindrone acetate and estradiol.

Labeling: Satisfactory.

Conclusion: Pharmacology recommends approval of norethindrone acetate and estradiol for treatment of menopausal symptoms.

/S/ 12/23

Alex Jordan, PhD

NDA 20-907
HFD-580

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-907

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA No:	20-907	OCT 16 1998
Applicant:	Novo Nordisk Pharmaceuticals, Inc.	
Name of Drug:	Nuvera™ (1 mg Estradiol (E_2) / 0.5 mg Norethrindrone Acetate (NETA) Tablets)	
Indications:	Treatment of moderate to severe vasomotor symptoms	
Medical Reviewer:	Phill H. Price, M.D.	
Statistical Reviewer:	Moh-Jee Ng, M.S.	
Documents Reviewed:	Vols 1.1, 1.2, 1.28, 1.29, 1,30, 1.39, 1.99, 1.128, 3.1	
45-Day filing Date:	July 14, 1997	
User Fee Due Date:	Dec. 19, 1998	

I. Introduction

Nuvera™ is a continuous combined oral hormone replacement therapy (HRT) product intended for the treatment of moderate to severe vasomotor symptoms associated with menopause and the treatment of vulvar and vaginal atrophy. Doses were administrated orally, once daily at bedtime, and swallowed without crushing, with 8 oz. of water.

This NDA includes four clinical trials. Three of these trials support the indication of moderate to severe vasomotor symptoms. The other trial supports prevention of endometrial hyperplasia. Table 1 summarizes these four studies:

Table 1
Summary of Randomized, Controlled Studies

Study Number (KLIM/PD/) Start/End Date	Treatment Daily Dose	No. Women Entered Per Group	Number of Centers	Site	Design	Duration	Efficacy variables (Primary)
Vasomotor Symptoms							
8/USA 11/93-12/94	 Placebo 0.25 mg E_2 0.5 mg E_2 1 mg E_2 2 mg E_2	333[a] 66 68 64 67 68 280[b]	15	United States	Multicenter Double-Blind Placebo Controlled Randomized Parallel-group	3 lunnar months	Hot Flushes (number, severity, weekly weighted score)
9/USA 2/95 - 11/96	 Placebo 1 mg E_2 1mg E_2 + 0.5 mg NETA	92[a] 34 29 29 90[b]	7	United State	Multicenter Double-Blind Placebo-Controlled Randomized Parallel-group	3 lunnar months	Hot Flushes (number, severity, weekly weighted score)
ı/N 1/93 - 1/96	 Placebo 1mg E_2 + 0.25 mg NETA 1mg E_2 + 0.5 mg NETA	119[a] 41 38 40 108[b]	5	Norway	Multicenter Double-Blind Placebo-Controlled Randomized Parallel-group	3 lunnar months	Hot Flushes (number, severity, weekly weighted score)
Endometrial Protection							
7/USA 9/94 – 8/96	 1mg E_2 1mg E_2 + 0.1 mg NETA 1mg E_2 + 0.25 mg NETA 1mgE_2 + 0.5 mg NETA	1176[a] 296 294 291 295 925[b]	40	United States	Multicenter Double-Blind Randomized Parallel-group	12 lunnar months	Incidence of endometrial hyperplasia

- a ; number of subjects were randomized in the study.
- b; number of subjects completed in the study.

Efficacy With Respect To Treatment of Vasomotor Symptoms

The sponsor submitted three multicenter, double-blind, randomized, parallel-group, placebo-controlled trials to support the efficacy and safety of E_2 with and without NETA for treatment of vasomotor symptoms (KLIM/PD/8/USA, KLIM/PD/9/USA and KLIM/PD/1/N). These studies had a 2-week screening period following by a 12-week treatment period. The two US trials (KLIM/PD/8/USA, KLIM/PD/9/USA) enrolled menopausal women with a minimum of at least 56 moderate to severe hot flushes per week. The European trial (KLIM/PD/1/N) enrolled menopausal women with a minimum of 20 moderate to severe hot flushes per week; this is not the FDA standard criterion of 56 moderate to severe hot flushes per week.

KLIM/PD/8/USA was an E_2 dose-ranging trial designed to identify the lowest effective dose of E_2 for vasomotor system relief. KLIM/PD/9/USA and KLIM/PD/1/N were designed to study the combination of 1 mg E_2 with different doses of NETA.

A. Demographics

All study subjects were healthy menopausal women years of age with mean age from 50.6 to 52.1 years in the various treatment groups. The majority of patients were Caucasian. The mean elapse time from menopause to inclusion in the trial ranged from 2.1 to 3.4 years in the different treatment groups. Approximately 30% of the women in the US and 40% in the European trial had been amenorrheic for less than 1 year at trial start. Treatment groups were fairly well balanced on age, age at menopause, and time since menopause for each study. There was no significant difference between the treatment groups in any of the studies. Demographic characteristics for treatment of vasomotor symptoms are summarized in Table 2.

Table 2
Demographic Characteristics for Treatment of Vasomotor Symptoms

KLIM/PD/8/USA	Placebo N=66	0.25 mg E_2	0.5 mg E_2	1.0 mg E_2	2.0 mg E_2
		N= 68	N=64	N=67	N=68
Race: %					
Caucasian	91%	91%	95%	85%	91%
Black	4.5%	4.4%	3.1%	7.5%	1.5%
Other	4.5%	4.4%	1.6%	7.5%	7.3%
BMI (kg/m^2)					
Mean (SD)	25.1 (3.7)	25.3 (3.3)	24.8 (3.4)	25.2 (4.2)	24.9 (3.7)
Age (years)					
Mean (SD)	52.1 (4.6)	50.9 (4.3)	51.2 (3.7)	50.8 (4.1)	50.6 (4.0)
Range					
Age at Menopause (years)					
Mean (SD)	48.8 (4.9)	48.3 (4.7)	47.8 (4.4)	48.2 (4.3)	47.9 (4.4)
Time since Menopause					
Mean (SD)	3.2 (3.4)	2.5 (2.2)	3.4 (3.1)	2.6 (2.7)	2.6 (2.5)

KLIM/PD/9/USA	Placebo N=34	1.0 mg E_2 N= 29	1mg E_2 + 0.5 mg NETA N=29
Race: n (%)			
Caucasian	34 (100%)	28 (97%)	27 (93%)
Black	0 (0%)	0 (0%)	2 (6.9%)
Other	0 (0%)	1 (3.4%)	0 (0%)
BMI (kg/m^2)			
Mean (SD)	25.3 (3.6)	25.3 (3.2)	24.9 (3.3)
Age (years)			
Mean (SD)	51.1 (3.7)	51.0 (4.0)	51.0 (4.6)
Range			
Age at Menopause (years)			
Mean (SD)	48.1 (3.7)	48.4 (3.4)	47.5 (4.1)
Time since Menopause			
Mean (SD)	2.9 (3.1)	2.5 (2.1)	3.4 (2.4)

KLIM/PD/1/N	Placebo N=41	1mg E_2 + 0.25 mg NETA N=38	1mg E_2 + 0.5 mg NETA N=40
BMI (kg/m^2)			
Mean (SD)	24.6 (3.8)	25.6 (4.6)	24.8 (3.8)
Age (years)			
Mean (SD)	51.9 (4.3)	51.3 (3.6)	51.1 (3.1)
Range			
Age at Menopause (years)			
Mean (SD)	42.9 (3.7)	48.6 (3.3)	48.9 (3.1)
Time since Menopause			
Mean (SD)	2.7 (3.4)	2.6 (3.2)	2.1 (2.1)

Source: Vol 1.2 – Tables 5-6, 5-26 and 5-35
Vol 1.27 – End-of-Text-Table, Tables 1, 23 and 29

Discontinuation

The most common reason for trial discontinuation was adverse events. In the KLIM/PD/8/USA trial, women in the 2 mg E_2 group were twice as likely to experience adverse events as those in the placebo group, 16% as opposed to 8%. Bleeding and breast pain were reported most frequently in the 2 mg E_2 group. In the KLIM/PD/9/USA, only two women discontinued from the trial, neither of them due to adverse events. In the KLIM/PD/1/N, no women in the 1 mg E_2 + 0.5 mg NETA group dropped out due to adverse events. The discontinuation disposition is summarized in Table 3.

Table 3
Discontinuation Disposition for Treatment of Vasomotor Symptoms

KLIM/PD/8/USA	Placebo N=66	0.25 mg E_2 N=68	0.5 mg E_2 N=64	1.0 mg E_2 N=67	2.0 mg E_2 N=68
Prematurely Discontinued due to					
Adverse Event	5 (8%)	1 (1%)	3 (5%)	6 (9%)	11 (16%)
Ineffective therapy	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other	4 (6%)	8 (12%)	4 (6%)	6 (9%)	3 (4%)
Did Not Complete Study	11 (17%)	9 (13%)	7 (11%)	12 (18%)	14 (20%)
Completed	55 (83%)	59 (87%)	57 (89%)	55 (82%)	54 (80%)

KLIM/PD/9/USA	Placebo N=34	1.0 mg E_2 N=29	1mg E_2 + 0.5 mg NETA N=29
Prematurely Discontinued due to			
Adverse Event	0 (0%)	0 (0%)	0 (0%)
Ineffective therapy	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	1 (3%)	1 (3%)
Did Not Complete Study	0 (0%)	1(3%)	1 (3%)
Completed	34 (100%)	28 (97%)	28 (97%)

KLIM/PD/1/N	Placebo N=41	1mg E_2 + 0.25 mg NETA N=38	1mg E_2 + 0.5 mg NETA N=40
Prematurely Discontinued due to			
Adverse Event	2 (5%)	3 (8%)	0 (0%)
Ineffective therapy	3 (7%)	0 (0%)	0 (0%)
Other	2 (5%)	1 (3%)	0 (0%)
Did Not Complete Study	7 (17%)	4 (11%)	0 (0%)
Completed	34 (83%)	34 (89%)	40 (100%)

Source: Vol 1.27, Table 7.1

C. Efficacy Variables

The primary efficacy variable was hot flushes. Subjects recorded the number and severity of hot ıshes in their daily diaries. Hot flushes were rated as mild, moderate, or severe. In the original submission, ..e sponsor analyzed the hot flush weekly weighted score. In a teleconference on December 12, 1997, the

FDA requested that primary analysis should be based on the mean change from baseline in the number of moderate to severe hot flushes per week rather than hot flush weekly weighted score. This reviewer only considers the additional primary analysis of the mean change from baseline in the number of moderate to severe hot flushes per week.

The mean change from baseline in the number of moderate to severe hot flushes at week 4 was the primary endpoint. The secondary endpoints were the mean change from baseline in the number of moderate to severe hot flushes at weeks 8, and 12 and the percent change from baseline in the number of moderate to severe hot flushes per week. All efficacy variables used in these analyses were based on an intent-to-treat population, with last observation carried forward (LOCF). The intent-to-treat population included all women who received one dose of trial study medication, and who had both baseline and at least one post-baseline observation.

D. Sponsor's Results for Treatment of Vasomotor Symptoms

The sponsor performed pairwise comparisons to show that there was a difference between each of the active treatment groups and the placebo based on analysis of variance, with treatment and center included as fixed effects. The sponsor concluded that there was a significant difference between the placebo group and the 1 mg E_2 + 0.5 mg NETA group in the mean change in number of moderate to severe hot flushes at weeks 4, 8 and 12.

1 KLIM/PD/8/USA

At week 4, the mean changes from baseline for the 1mg E_2 and 2 mg E_2 groups were statistically different from the placebo group, but the mean changes from baseline in the 0.25 and 0.5 mg E_2 groups were not (Table 4). At weeks 8 and 12, the mean changes from baseline in the 0.5 mg E_2 group, the 1 mg E_2 and 2 mg E_2 groups differed significantly from the placebo. The 0.25 mg E_2 treatment group never differed significantly from the placebo.

2. KLIM/PD/9/USA

At weeks 4, 8 and 12, the mean changes from baseline of moderate to severe hot flushes for the 1 mg E_2 + 0.5 mg NETA group and in the 1 mg E_2 were statistically significantly different from the placebo group ($p < 0.001$) (Table 4).

3. KLIM/PD/1/N

For KLIM/PD/1/N study, the sponsor did not provide results for the primary efficacy analysis, viz. the mean change from baseline.

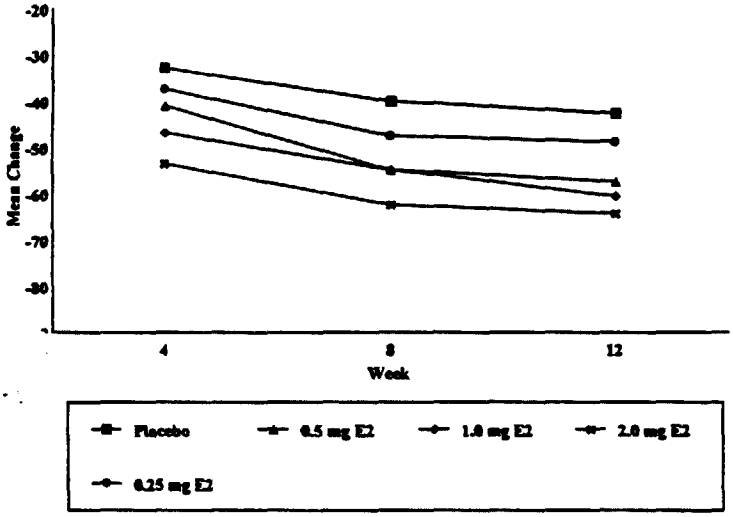
Reviewer's Analysis Results for Treatment of Vasomotor Symptoms

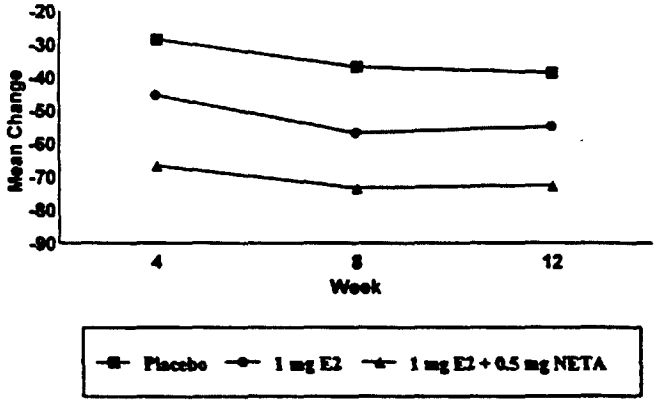
For studies KLIM/PD/8/USA and KLIM/PD/9/USA, this reviewer's analysis of the mean changes from baseline in number of moderate to severe hot flushes for weeks 4, 8 and 12 agrees with the sponsor's analysis (Table 4).

For KLIM/PD/1/N, there was no statistically significant difference between these two active treatment groups and placebo at weeks 4, 8 and 12. The results are summarized in Figure 1 and Table 4.

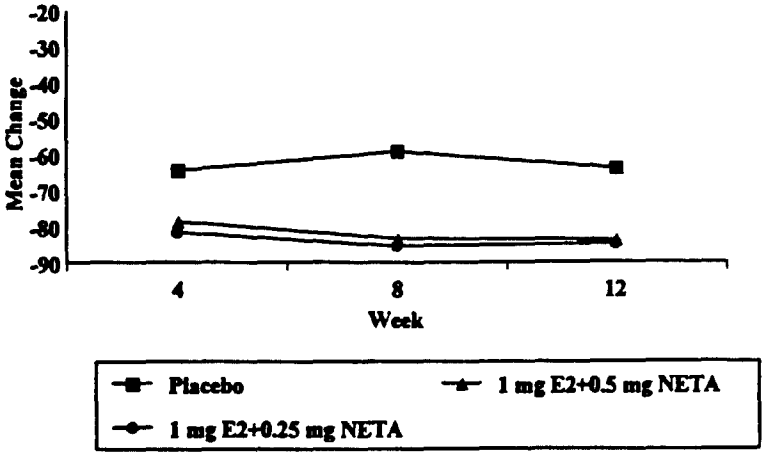
Figure 1

KLIM/PD/8/U





KLIM/PD/9/USA



KLIM/PD/1/N

Table 4
Reviewer's Analyses
Mean Change from Baseline in number of Moderate to Severe Hot Flushes per week
Last Observation Carried Forward (LOCF) – ITT Population
Treatment of Vasomotor Symptoms

KLIM/PD/8/USA	Placebo N=63	0.25 mg E_2 N= 66	0.5 mg E_2 N=61	1.0 mg E_2 N=65	2.0 mg E_2 N=68
Baseline- Actual Mean (SD)	72.3 (21.8)	74.4 (25.2)	73.4(23)	69.6 (17.1)	70.1 (19.2)
Week 4 - Actual Mean (SD)	39.6 (29.2)	37.1 (27.2)	32.5 (30.9)	22.9 (29.8)	16.9 (23.9)
Mean change from Baseline (SD of mean change)	-32.8 (29.2)	-37.3 (27.6)	-40.9 (30.9)	-46.7 (29.8)	-53.5 (23.8)
Range	-89:21	-140:24	-123:30	-102:33	-102:22
P-value (vs. placebo)		0.397	0.122	**0.005**	**< 0.001**
Week 8 - Actual Mean (SD)	32.3 (29.)	26.9 (26)	18.5 (25.8)	14.8 (22.9)	7.8 (21.3)
Mean change from Baseline (SD of mean change)	-40.0 (29.6)	-47.5 (26.0)	-54.8 (25.7)	-54.9 (22.9)	-62.4 (21.3)
Range	-121:19	-155:5	-123:15	-119:16	-147:22
P-value (vs. placebo)		0.163	**0.004**	**0.002**	**< 0.001**
Week 12 - Actual Mean (SD)	29.7 (30.4)	25.6 (25.8)	16.1 (27.8)	9.2 (22.1)	5.9 (21.7)
Mean change from Baseline (SD of mean change)	-42.6 (30.3)	-48.7 (25.8)	-57.3 (27.8)	-60.5 (22.1)	-64.2 (20.7)
Range	-140:23	-149:1	-123:20	-100:0	-100:16
P-value (vs. placebo)		0.242	**0.007**	**< 0.001**	**<0.001**

KLIM/PD/9/USA	Placebo N=34	1.0 mg E_2 N= 28	1mg E_2 + 0.5 mg NETA N=29
Baseline - Mean (SD)	68.6 (8.1)	67.1 (18)	75.3 (36.8)
Week 4 - Actual Mean (SD)	40.0 (31.4)	21.9 (25.5)	8.6 (17.7)
Mean change from Baseline (SD of mean change)	-28.6 (29.5)	-45.4 (30.9)	-66.6 (36.9)
Range	-91:51	-138:1	-220:-1
P-value (vs. placebo)		**0.0468**	**0.0001**
Week 8 - Actual Mean	32.5 (25.6)	10.4 (18.5)	2.1 (5.4)
Mean change from Baseline (SD of mean change)	-36.8 (21.0)	-56.8 (22.4)	-73.4 (34.8)
Range	-81:9	-131:-14	-231:-42
P-value (vs. placebo)		**0.0049**	**0.0001**
Week 12 - Actual Mean	29.9 (27.7)	12.2 (20.7)	2.8 (7.6)
Mean change from Baseline (SD of mean change)	-38.7(20.5)-	-55.0 (26.2)	-72.7 (35.3)
Range	68:9	-138:1	-231:-42
P-value (vs. placebo)		**0.0247**	**0.0001**

KLIM/PD/1/N	Placebo N=37	1mg E_2 + 0.25 mg NETA N=36	1mg E_2 + 0.5 mg NETA N=40
Baseline - Mean (SD)	91.4 (46.8)	87.8 (52.7)	85.2 (75)
Week 4 - Actual Mean	26.9 (26.5)	6.2 (12.5)	6.6 (110.1)
Mean change from Baseline (SD of mean change)	-64.4 (36.6)	-81.6 (49.3)	-78.6 (71)
Range	-158:-10	-204:1	-348:-14
P-value (vs. placebo)		0.1823	0.2582
Week 8 - Actual Mean	32.2 (28.8)	2.4 (5.5)	1.8 (4.8)
Mean change from Baseline (SD of mean change)	-59.1 (36)	-85.4 (50.8)	-83.3 (73.7)
Range	-151:-9	-200:-10	-348:-14
P-value (vs. placebo)		0.0721	0.0904
Week 12 - Actual Mean	27.5 (30.9)	3.0 (7.8)	1.4 (3.5)
Mean change from Baseline (SD of mean change)	-63.9 (38)	-84.8 (48.6)	-83.8 (74)
Range	-158:-7	-183:-10	-384:-14
P-value (vs. placebo)		0.1902	0.1922

This reviewer analyzed the percent change from baseline in the number of moderate to severe hot flashes per week. It produced similar results to that of the sponsor analysis as just described.

The reviewer also performed multiple comparisons using Dunnett's method to compare each dose to placebo for each study at the four-weekly time points. The intent-to-treat patient population, with last observation carried forward (LOCF), was used for this analysis. Table 5 presents the reviewer's adjusted 95% confidence intervals for treatment of vasomotor symptoms at weeks 4, 8, and 12. Note that each confidence interval followed by the asterisk does not contain zero, indicating a significant treatment effect.

Table 5
Reviewer's Analyses
Multiple Comparisons of Vasomotor Symptoms
Last Observation Carried Forward (LOCF) – ITT Population

	Mean Change from Baseline vs Placebo (Adjusted 95% CI)			
KLIM/PD/8/USA	**0.25 mg N=66**	**0.5 mg E_2 N=61**	**1.0 mg E_2 N=65**	**2.0 mg E_2 N=68**
Week 4	-37.3 (-15.8, 7.37)	-40.9 (-19.8,3.7)	-46.7 (-25.6,-2.3) **	-53.5 (-32.6,-9.5)**
Week 8	-47.5 (-16.9,4.8)	-54.8 (-24.1,-2.2)**	-54.9 (-24.1,-2.3) **	-62.4 (-33.8,-12.3)**
Week 12	-48.7 (-18,4.05)	-57.3 (-27.2,-5.1)**	-60.5 (-30.6,-8.5) **	-64.2 (-36.2,-13.9)**
KLIM/PD/9/USA	**1.0 mg E_2 N=34**		**1 mg E_2 + 0.5 mg NETA N=29**	
Week 4	-45.4 (-36,2.3)		-66.6 (-55.3,-16.9)**	
Week 8	-56.8 (-35.7,-4.2) **		-73.4 (-50.5,-19.3)**	
Week 12	-55.0 (-32.1.8)		-72.7(-47.4,-13.6) **	
KLIM/PD/1/N	**1 mg E_2 + 0.25 mg NETA N=36**		**1 mg E_2 + 0.5 mg NETA N=40**	
Week 4	-81.6 (-46.12,11.71)		-78.6 (-42.37,13.98)	
Week 8	-85.4 (-56.05,3.33)		-83.3 (-53.17,4.73)	
Week 12	-84.8 (-50.69,8.75)		-83.8 (-50.69,8.75)	

** Confidence Intervals are adjusted for multiple pairwise comparison within each time point using Dunnett's method. A confidence interval which excludes the value zero indicates the treatment group is significantly different from placebo at the .05 α-level.

This reviewer then further examined the mean change from baseline in the number of moderate to severe hot flushes for the 1 mg E_2+0.5 mg NETA group to determine why there was a lack of significance at weeks 4, 8 and 12 for KLIM/PD/1/N study. This was a European study, which accepted menopausal women with fewer than 56 moderate to severe hot flushes per week. This reviewer then analyzed the data for the subset of women with 56 or more moderate to severe hot flushes per week, the condition required in the two US trials. For this subset, there was statistically significant at week 4 (Table 6). This reviewer also found significance at weeks 8 and 12. No significant differences were seen for the women with baseline hot flushes less than 56.

Table 6
Subset of Mean Change from Baseline
Last Observation Carried Forward (LOCF) – ITT Population

KLIM/PD/1/N at week 4	1 mg E_2 + 0.25 mg NETA N=36	1 mg E_2 + 0.5 mg NETA N=40
Baseline number of moderate to severe hot flushes <56	N= 13	N=18
Mean change from baseline (SD of mean change)	-34.4 (14.6)	-31.7 (10.4)
P values (vs Placebo)	0.9218	0.4995
Baseline number of moderate to severe hot flushes ≥ 56	N=23	N=22
Mean change from baseline (SD of mean change)	-108.3 (41.2)	-117 (76.4)
P values (vs Placebo)	**0.0042 ****	**0.0156****

** significantly different from placebo at the 0.05 α-level.

F. Conclusion for treatment of vasomotor symptoms

The reviewer's analyses of mean change from baseline in the number of moderate to severe hot flushes at weeks 4, 8 and 12, and her multiple comparison analyses are in support of the sponsor's claims that 1 mg E_2 was the lowest effective dose for vasomotor symptoms relief, and 1mg E_2 + 0.5 mg NETA was the most effective combination dose with respect to vasomotor symptoms relief when compared with the placebo.

III. Efficacy With Respect to Endometrial Hyperplasia

The efficacy with respect to endometrial protection was investigated in study KLIM/PD/7/USA. This study was designed to determine the lowest dose of NETA in combination with 1 mg E_2 that will substantially reduce the incidence of endometrial hyperplasia when compared with 1 mg E_2 alone treatment. KLIM/PD/7/USA was a multi-center, double-blind, active controlled, randomized trail. Subjects underwent a 4-week screening period followed by 12 continuous lunar months active treatment. This trial included 1176 postmenopausal women with an intact uterus.

A. Demographics

All study subjects were healthy menopausal women years of age with mean age of 55.5 to 55.9 years in the 4 different treatment groups. A total of ninety six percent women were older than 65 years of age at trial start. The mean elapse time from menopause to inclusion in the trial ranged from 6.9 to 7.4 years in the different treatment groups. Treatment groups were fairly well balanced on race, BMI, age, age at menopause and time since menopause (Table 7). There was no significant difference between the treatment groups.

Table 7
Demographic Characteristics for KLIM/PD/7/USA

KLIM/PD/7/USA	1 mg E_2 N=296	E_2 + NETA 1+0.1 mg N=294	1+0.25 mg N=291	1+0.5 mg N=295
Race: N (%)				
Caucasian	280 (95%)	278 (95%)	277 (95%)	278 (94%)
Other	16 (5.4%)	16 (5.4%)	14 (4.8%)	17 (5.8%)
BMI (kg/m^2)				
Mean (SD)	25.7 (3.6)	25.8 (3.7)	25.8 (3.6)	25.5 (4.0)
Age (years)				
Mean (SD)	55. (6.2)	55.5 (6.3)	55.5 (6.3)	55.9 (6.4)
Range				
Age at Menopause (years)				
Mean (SD)	48.5 (4.7)	48.5 (4.6)	48.1 (5)	48.5 (4.7)
Time since Menopause				
Mean (SD)	6.9 (5.8)	7 (6.6)	7.4 (6.9)	7.4 (6.8)

Source: Vol 1.1, End-of-Text Synposes (page 245)

B. Discontinuation

The most common reason for discontinuation was adverse events. The primary adverse event leading discontinuation was bleeding. Discontinuation due to adverse events were similar among the three E_2/NETA combination groups, ranging from 9 to 12%; but for the 1 mg E_2 group, it was 18%. Table 8 summarizes the discontinuation disposition for KLIM/PD/7/USA.

Table 8
Discontinuation Disposition for KLIM/PD/7/USA

KLIM/PD/7/USA	1 mg E_2 N=296	1 mg E_2+0.1 mg NETA N=294	1 mg E_2+0.25 mg NETA N=291	1 mg E_2+0.5 mg NETA N=295
Prematurely Discontinued due to				
Adverse Event	53 (18%)	29 (10%)	27 (9%)	34 (12%)
Ineffective therapy	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)
Intercurrent Medical Problems	0 (0%)	0 (0%)	1 (0.3%)	3 (1%)
Non-compliance with Protocol	16 (5.4%)	20 (6.8%)	14 (5%)	11 (4%)
Other	15 (5%)	8 (3%)	6 (2%)	13 (4%)
Did Not Completed Study	84 (28%)	57 (19%)	49 (17%)	61 (21%)
Completed	212 (72%)	237 (81%)	242 (83%)	234 (79%)

Source: Vol 1.2, Table 5-13

C. Efficacy Variables

The primary efficacy variable was the incidence of endometrial hyperplasia at the end of the study for the intent-to-treat population. The intent-to-treat population included all women who received one dose of study product and who had a biopsy at the screening visit or at the end of the study.

Incidence of hyperplasia was based on readings of biopsies by 2 independent pathologists with a third pathologist adjudicating discordant results. The incidence rate for each treatment group was based upon the total number of biopsies available at the end of study.

D. Sponsor 's Results for the Incidence of Hyperplasia

The sponsor performed analyses to investigate the difference in the incidence rates of endometrial hyperplasia between 1 mg E_2 alone group and each of the combination groups. Pairwise comparisons based on Fisher Exact test were used. The sponsor concluded that these results indicate a significant reduction in the incidence of hyperplasia for the 1 mg E_2 + 0.5 mg NETA.

E. Reviewer's Results for the Incidence of Hyperplasia

The incidence of hyperplasia at the end of the study was 13.8% in the unopposed 1 mg E_2 group whereas in all the E2/NETA combination groups the incidence of hyperplasia was less than 1%. There was a statistically significant reduction in the incidence of endometrial hyperplasia for all E2/NETA combination compared with unopposed 1 mg E_2. Table 9 summarizes the incidence of Endometrial Hyperplasia at End of Trial, and Table 10 presents the 1 sample binomial 95% confidence intervals of E2/NETA combination groups for the incidence of endometrial hyperplasia.

Table 9
Incidence of Endometrial Hyperplasia

KLIM/PD/7/USA	1 mg E_2 N=247	1 mg E_2+0.1 mg NETA N=249	1 mg E_2+0.25mg NETA N=251	1 mg E_2+0.5 mg NETA N=241
Incidence of Hyperplasia	**34 (13.8%)**	**2 (0.8%)**	**1 (0.4%)**	**1 (0.4%)**
P-value (vs. 1 mg E_2)		**<0.001**	**<0.001**	**<0.001**
Histological Diagnosis				
Simple hyperplasis without Atypia	28 (11.3%)	1 (0.4%)	0 (0%)	1 (0.4%)
Complex hyperplasis without Atypia	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)
Simple hyperplasis with Atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Complex hyperplasis with Atypia	2 (0.8%)	1 (0.4%)	1 (0.4%)	0 (0%)

Source: Vol 1.2, Table 5-15

Table 10
95% Confident Interval for Incidence of Endometrial Hyperplasia

Incidence of Hyperplasia (95% CI)	1 mg E_2+0.1 mg NETA N=249	1 mg E_2+0.25mg NETA N=251	1 mg E_2+0.5 mg NETA N=241
	0.8% (.097%,2.8%)	0.4 % (.01%,2.3%)	0.4% (.01%,2.2%)

F. Conclusion for the Incidence of Hyperplasia

This reviewer's analyses show that the incidence of hyperplasia was less than 1% in all E_2/NETA combination groups and 13.8% in the 1 mg E_2 group. This analysis also shows that the 95% upper confidence interval for the incidence of endometrial hyperplasis was less than 4% in all E_2/NETA combination treatment groups.

The results support the conclusion that 1 mg E_2 + 0.5 mg NETA (the sponsor's combination dose of interest) provides protection from endometrial hyperplasis in women with an intact uterus, who are receiving E_2/NETA as estrogen-progestogen hormone replacement therapy.

IV. Overall Conclusion

The goal of the analyses for this NDA submission was to evaluate the effect of the 1 mg E_2 + 0.5 mg NETA combination with respect to vasomotor symptoms relief in menopausal women with moderate-severe symptomatology.

This reviewer concludes:

1. For studies KLIM/PD/8/USA and KLIM/PD/9/USA, there is a significant reduction in the mean change from baseline in the number of moderate to severe hot flushes at weeks 4, 8 and 12.
2. For study KLIM/PD/1/N, there is no significant mean change from baseline in the number of moderate to severe hot flushes at weeks 4, 8 and 12, however, there is a significant treatment effect in the subset of women with 56 or more moderate to severe hot flushes per week. A subgroup comparable to the patients studied in KLIM/PD/8/USA and KLIM/PD/9/USA.
3. There is a statistically significant reduction in the incidence of endometrial hyperplasia ($p<0.001$) for E2/NETA combination compared with unopposed 1 mg E_2.

These conclusions support the sponsor's claim that the 1 mg E_2 + 0.5 mg NETA is an effective combination dose with respect to vasomotor symptoms relief.

/S/

Moh-Jee Ng, M.S.
Mathematical Statistician

10/5/98

Concur: Joy Mele, M.S.

Ed Nevius, Ph.D. 10/16/98

cc: Original NDA 20-907
HFD-580/ Division file
HFD-580/JMarkow, PPrice, Mmann, LRarick
HFD-715/ENevius, JMele, Lkammerman, MNg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-907

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NOV 1 0 1998

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	20-907
Drug:	Estradiol/Norethindrone acetate tablets (Activelle®)
Sponsor:	Novo Nordisk
Date of Submission:	11/07/97
Type of Submission:	Original NDA
Reviewer:	Venkateswar R. Jarugula, Ph.D.

I. SYNOPSIS

NDA 20-907 for 1 mg estradiol(E_2)/0.5 mg norethindrone Acetate (NETA) tablets was submitted by Novo Nordisk for the relief of postmenopausal symptoms due to estrogen deficiency. This low dose continuous combined product has been developed for the United States and Europe. Novo Nordisk has also developed a high dose product (2mg E_2/ 1 mg NETA) which has been marketed outside US for over 13 years. The proposed dosage regimen for the low dose product is one tablet a day.

In total, 6 clinical pharmacology trials, including two supportive trials in Japanese women, were performed to provide information on single and multiple dose pharmacokinetics, relative bioavailability, food effect as well as bioequivalence of two different tablet formulations used in the clinical program. In addition, information on steady state plasma concentrations of E_2, estrone (E_1) and estrone sulfate (E_1S) were also available from two adequate and well controlled clinical trials (KLIM/PD/7/USA and KLIM/PD/8/USA).

The sponsor has adequately characterized the relative bioavailability, food effect, single dose and multiple dose pharmacokinetics of Activelle. However, the following comments/deficiencies are noted during the review of the NDA:

II. REVIEWER COMMENTS

1. From the biopharmaceutics perspective, the final clinical trials formulation (same as the to-be marketed formulation) is not bioequivalent to the formulation used in early clinical trials. ~~The 90~~% confidence intervals for $AUC_{0\text{-}72h}$ of NET and C_{max} of E_2 were

within 80 –125% limits while those for AUC_{0-72h} of E_2 and C_{max} of NET failed marginally (by 3%) and AUC of E_1 failed by (12%) a considerable margin. Upon reanalysis of the individual data by this reviewer, it was noted that one of the subjects was clearly an outlier because the ratios of AUC (Test Vs Reference) were 3.45 and 8.34 for E_2 and E_1, respectively. If this subject is omitted from the data for bioequivalence, the 90% CI for AUC of both E_2 and E_1 would be contained within 80 to 125%. However, the final copolyvidone formulation was used in the two adequate and well controlled pivotal US clinical trials (KLIM/PD/7/USA and KLIM/9/USA) which provided the main safety and efficacy data for the approval and labeling of Activelle. The study 7/USA was a dose finding trial for NETA in combination with 1mg E_2 and the study 9/USA was a confirmatory safety and efficacy trial for the combination. These two studies together with a dose ranging study for estradiol alone (KLIM/PD/8/USA) form the basis for the approval of this product. The earlier formulation was used in early Europian clinical trials which gave only the supporting information. Therefore, the bioequivalence of the two formulations is less of a concern as far as the approval of this product is concerned. The results of bioequivalence study were discussed with reviewing medical officer of HFD-580, Dr. Phil Price and he also felt that the marginal differences observed would not be clinically significant for hormone replacement therapy.

2. It should be noted that the information on lipids in the labeling has been derived from the study KLIM/PD/5/S, which used the old formulation. As noted in the above comment, the two formulations would be bioequivalent if the outlier subject were omitted. Therefore, from the clinical pharmacology perspective, it is acceptable to include the lipid beneficial effects in the labeling.

3. The presence of high fat meal did not significantly influence the pharmacokinetics of E_2 and E_1, although a significant increase (19%) in AUC of NET, which is not considered clinically significant, was observed. For the majority of the women, the observed peak concentrations of NET were in the first sample at 1 hour. Therefore, the true peak concentration and AUC may have been underestimated. Furthermore, in the pivotal clinical trials, the patients took Activelle without regard to food intake.

4. The proposed dissolution method for Activelle is USP paddle method with 100 rpm speed and % Since greater than % of E_2 and NETA are dissolved within minutes, the method does not provide adequate quality control.

5. The current proposed dissolution method could be accepted on interim basis until additional dissolution information as outlined in comment 4 is submitted for review. Based on the current dissolution data for both biobatches and stability batches, the

interim dissolution specifications should be modified as Q= % at minutes for both E_2 and NETA. Sponsor agreed to these interim specifications in a letter dated 11/3/98.

III. RECOMMENDATION

NDA 20907 for Activelle tablets meets the Clinical Pharmacology and Biopharmaceutics requirements and is recommended for approval. The sponsor should revise the labeling according to labeling comments listed on pages 17 through 20 of this review, and commit to submit additional dissolution data (as outlined in Reviewer Comment 4) for review with in six months from the date of approval.

Please convey the Recommendation and Reviewer Comments 4 to the sponsor as appropriate.

/S/ 11/10/98

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D. AP 10/13/98

FT initialed by Ameeta Parekh, Ph.D. /S/ 11/10/98

cc: NDA 20-907, HFD–580 (Price, Mercier), HFD-870 (M.Chen, Parekh, Jarugula), CDR (B.Murphy for Drug).

TABLE OF CONTENTS

IV. BACKGROUND

Estradiol among estrogens is the primary sex hormone responsible for the growth and maintenance of female sex characteristics. Estradiol is synthesized predominantly by the ovaries in premenopausal women. All women experience ovarian failure, mostly between ages of 45 and 55 years. This is characterized by a marked decline, then cessation of ovarian follicular activity and a consequent major decline in estrogen production. Although many women pass through the menopause without troublesome symptoms, some women experience postmenopausal symptoms such as vasomotor symptoms (hot flushes and night sweats) and urogenital atrophy which may involve vaginal (itching, dryness, dyspareunia) and urinary symptoms (frequency, recurrent urinary tract infection, incontinence).

Estrogen replacement therapy has been used for over 30 years in the treatment of postmenopausal symptoms. However, it has been known that the use of unopposed estrogen replacement in women with intact uterus has been associated with an increased risk of endometrial cancer. Concomitant use of progestin significantly reduces the risk of endometrial cancer. Currently, a lot of drug products are available in the market for hormone replacement therapy in postmenopausal women e.g., oral tablets such as Premarin, Prempro, transdermal patches such as Estraderm, Climara, Allora, Vivelle, Esclim etc. Transdermal patches have an advantage of by passing the first-pass metabolism of estradiol, thereby resulting in lower circulating serum levels of estrone (less potent) and estrone conjugates.

Activelle was developed to provide an optimized therapy for menopausal women who suffer from symptoms of estrogen deficiency and it consists of 1mg estradiol + 0.5 mg of norethindrone acetate in a tablet. The recommended dose is one tablet per day. The primary efficacy parameter in clinical studies for the estrogen component was reduction in the number and severity of hot flushes. The efficacy parameters selected for the progestin component were prevention of the increased risk of endometrial hyperplasia induced by unopposed estrogen treatment, and minimization of the bleeding often associated with continuous combined HRT.

V. ASSAY METHODOLOGY:

Reviewer Comment:

- The assay validation parameters for E_2, E_1, E_1S an NETA are within reasonable range and are acceptable except for the slightly high CV observed for low concentrations of E_2 and E_1 at which was used only for the multiple dose study KLIM/3/US. Since this was a multiple dose study, only the low serum levels of E_2 and E_1 (less potent metabolite) during early absorption phase after the first dose will be effected. Therefore, the observed slightly high CV (23%) of low concentrations of

E_2 and E_1 is not likely to affect the overall conclusions for the multiple dose administration of Activelle.

- It should be noted that following oral administration, NETA is rapdily converted to norethindrone (NET) by first-pass metabolism. Consequently the serum levels of NET were measured following oral administration of Activelle and serum levels of NETA could not be measured.

VI. FORMULATION

The composition of the tablet formulations used in clinical trails and the to be marketed formulation is summarized below in Table 2.

Table 2. Composition of the tablet formulations of Activelle.

Ingredients	Function	Formulation A (early clinical) (mg/tablet)	Formulation B (clinical & commercial) (mg/tablet)
Active ingredients			
Estradiol			
Norethindrone acetate	Active substance		
Other ingredients			
Lactose monohydrate	Filler		
starch	Disintegrant/Filler		
Copolyvidone	Binder		
Talc	Glidant/Lubricant		
Magnesium stearate	Lubricant		
Film-coating			
Talc*	Lubricant		
Triacetin	Plasticiser		

*Added as lubricant at the end of film-coating process. Adsorbed amount is not quantified.

During the clinical development of Activelle, the formulation has been changed once. Formulation A, which was used in early supporting clinical trials consisted of as a Formulation B, which was used in the two adequate and well controlled pivotal clinical trials for safety and efficacy, consisted of copolyvidone as the binder. According to the sponsor, the change in binder was made to prolong the shelf-life of NETA. It should be noted that Formulation B is the to-be marketed formulation. A bioequivalence study was conducted to test the bioequivalence between Formulations A and B (please refer to Bioequivalence study results in Section VIII B).

VII. *IN VITRO* DISSOLUTION

The sponsor's proposed *in vitro* dissolution method and specifications are given below:

Apparatus: USP 2
Media: %.
Volume: 500 ± 5 ml
Speed: 100 ± 2 rpm

Proposed specifications:

Table 3. Dissolution data for biobatches.

Trial ID	Formulation	Batch No.	Time	Mean% (CV) E_2	Mean% (CV) NETA	Range E_2	Range NETA
KLIM/PD/ 24/D	Formulation B	631702		93(2.4) 97(2.3) 99(1.5)	94(1.8) 98(3.1) 98(1.8)		
KLIM/PD/ 24/D	Formulation B	631701		96(3.5) 100(2.4) 101(2.4)	97(4.3) 100(3.0) 101(3.7)		
KLIM/PD/ 25/USA	Formulation B	517785		96(1.9) 100(1.9) 101(1.9)	94(2.1) 97(1.5) 98(1.1)		
KLIM/PD/ 25/USA	Formulation A	504083		91(3.5) 97(2.0) 98(1.8)	93(2.9) 97(1.9) 98(2.5)		

Reviewer Comments:

- It should be noted that the proposed dissolution method and dissolution medium and conditions were the same as those used in USP for estradiol tablets. However, the sponsor did not provide any methods validation information on dissolution in media without and with different conditions (speed, different media with and without surfactant etc).

- The proposed dissolution method for Activelle is USP paddle method with 100 rpm speed and %. Since greater than % of E_2 and NETA are dissolved within minutes, the method does not provide adequate quality control.

- The current proposed dissolution method could be accepted on interim basis until additional dissolution information as outlined in comment 4 is submitted for review. Based on the current dissolution data for both biobatches and stability batches, the interim dissolution specifications should be modified as Q % at minutes for both E_2 and NETA. Sponsor agreed to these interim specifications in a letter dated 11/3/98.

VIII. PHARMACOKINETICS

VIII A. Relative Bioavailability

A three period cross over study was conducted to determine the relative bioavailability of two dosage strengths, 1 mg E_2 + 0.25 mg NETA and 1 mg E_2 + 0.5 mg NETA tablets of same formulation versus an oral solution containing 1 mg E_2 + 0.5 mg NETA. Two dosage strengths were included in this study because the dose finding trial for NETA in combinations with 1 mg E_2 was not completed at the time.

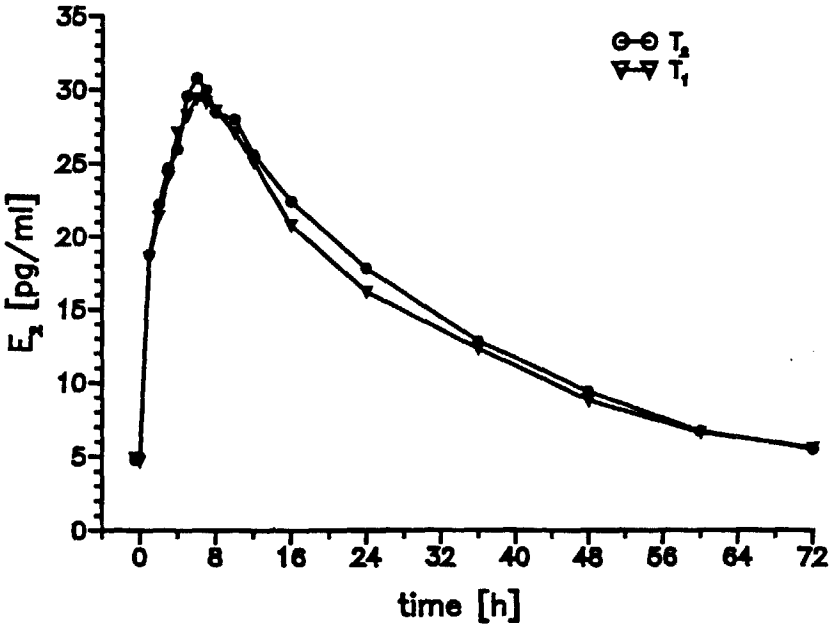


Fig 1. Mean plasma estradiol levels following single dose oral administration of 1 mg E_2 + 0.25 mg NETA (T_1) and 1 mg E_2 + 0.5 mg NETA (T_2)

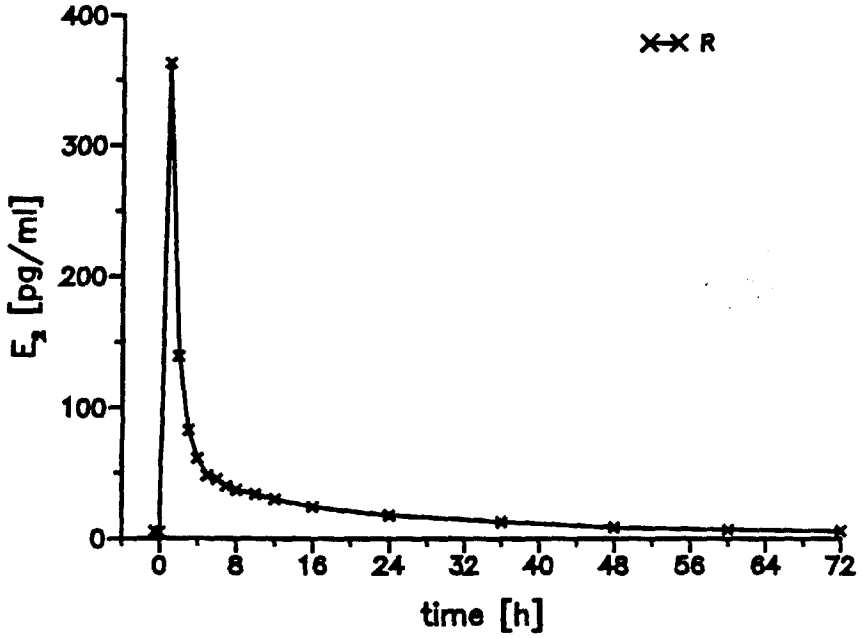


Fig 2. Mean plasma estradiol levels following single oral administration of 1 mg E_2 + 0.5 mg NETA solution.

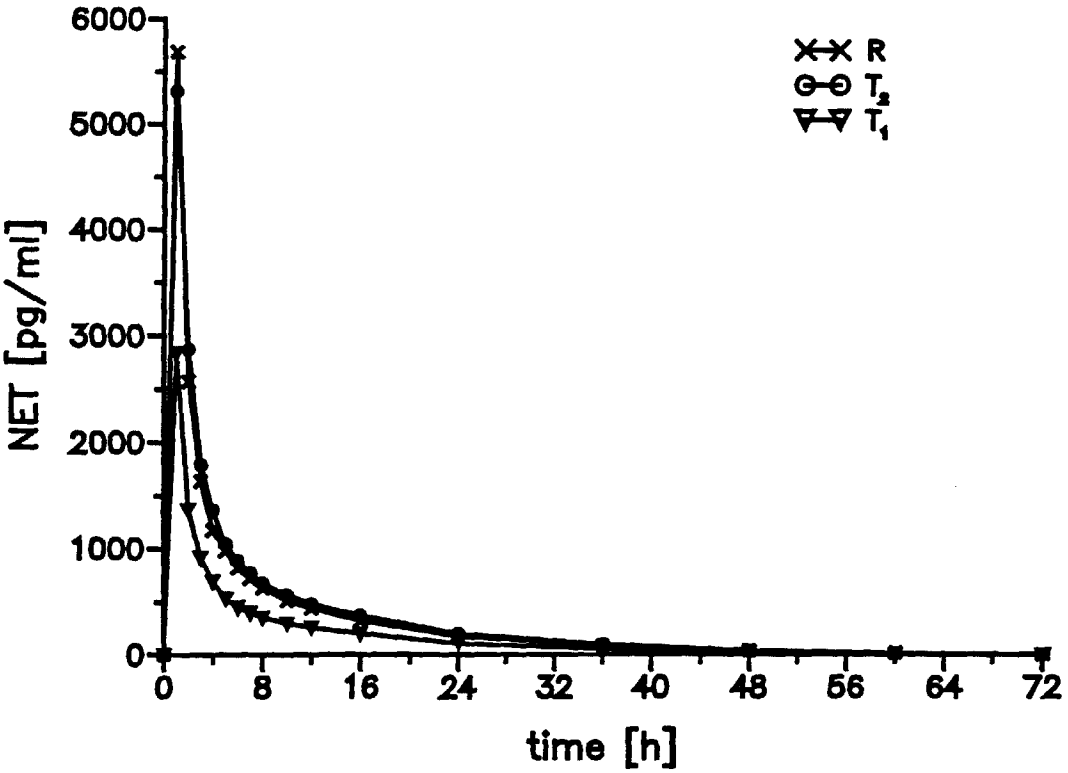


Fig 3. Mean serum profiles of NET following single dose of administration of 1 mg E_2 + 0.25 mg NETA tablet (T_1), 1 mg E_2 + 0.5 mg NETA tablet (T_2) and 1 mg E_2 + 0.5 mg NETA solution (R).

Table 4. Mean (SD) pharmacokinetic parameters and relative bioavailability

Parameter	1mg E_2 + 0.25 mg NETA (Tablet)	1mg E_2 + 0.50 mg NETA (Tablet)	1 mg E_2 + 0.5 mg oral solution
E_2[a]			
AUC_{0-72h} (pg/ml*h)	664 (234)	706 (252)	1326 (266)
$AUC_{0-\infty}$ (pg/ml*h)	697 (245)	759 (235)	1348 (267)
C_{max} (pg/ml)	28.2 (7.9)	29.7 (9.4)	358 (121)
T_{max} (h)	6.0 (1.7)	6.8 (2.9)	1.0 (0.0)
$T_{1/2}$ (h)	14.1 (4.0)	13.2 (4.7)	12.3 (3.6)
F (%) (T_2 vs R)		53 (48-59)[b]	
F(%) (T_1 vs T_2)	92 (83-102)		
E_1			
AUC_{0-72h} (pg/ml*h)	3713 (1586)	3741 (1446)	3721 (1321)
$AUC_{0-\infty}$ (pg/ml*h)	3831 (1634)	3851 (1462)	3796 (1342)
C_{max} (pg/ml)	236 (98)	230 (89)	235 (73)
T_{max} (h)	5.6 (1.0)	5.7 (1.4)	4.8 (2.0)
$T_{1/2}$ (h)	12.6 (5.7)	12.2 (4.6)	11.4 (3.7)
NET			
AUC_{0-72h} (pg/ml*h)	12210 (4420)	23681 (9023)	22184 (6824)
$AUC_{0-\infty}$ (pg/ml*h)	13143 (4243)	24115 (8935)	22659 (6863)
C_{max} (pg/ml)	2831 (1311)	5308 (1510)	5684 (1551)
T_{max} (h)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)
$T_{1/2}$ (h)	11.9 (3.2)	11.4 (2.7)	11.9 (2.8)
F (%) (T_2 vs R)		102 (98-107)[b]	
F (%) (T_1 vs T_2)[c]	110 (105-115)		

a baseline corrected
b 90% confidence intervals
c dose corrected with respect to NETA
F relative bioavailability

Reviewer Comments

- For the reference solution the maximum concentration of E_2 was observed in all subjects in the first sample after dosing at 1 hour. Therefore the true C_{max} might have been underestimated and occurred earlier (lower T_{max}).

- The relative bioavailability of estradiol from the tablet formulation is 53% while that of norethindrone is 100% when compared to the oral solution. The rate of absorption and extent of E_2 absorption are lower from the tablet when compared to the solution because of its poor water solubility.

- The peak concentrations of estradiol from tablet are only about 8% of that resulting from the solution probably in part because of the estradiol undergoes first pass effect and when given as solution, capacity for first pass metabolism is surpassed resulting in far higher C_{max}.

- Dose proportionality between 0.25 mg NETA and 0.5 mg NETA doses was observed indicating that 1 mg estradiol did not influence the bioavailability of norethindrone in the dose range tested.

VIII B. Bioequivalence

During the development of Activelle, there was a change in the tablet formulation from the early European trials to the late US trials using the final tablet formulation. The two tablet formulations differed only in the use of binder and in the admixing NETA as follows:

- with wet milling of NETA was used in the early formulation (Formulation A)
- Copolyvidone with dry admixing of NETA was used in the later formulation (Formulation B, to-be marketed)

Study KLIM/PD/25/USA was conducted to test the bioequivalence of the two formulations and the pharmacokinetic results from the study are summarized in Table 5.

Table 5. The mean pharmacokinetic parameters and bioequivalence of two Activelle formulations

Parameter	Formulation A (N=23)	Formulation B (N=23)	Ratio	90% CI
Estradiol[a]				
AUC_{0-72h} (pg/ml)	1378	1231	1.12	98 - 128
C_{max} (pg/ml)	37.5	35.4	1.06	**96 - 118**
t_{max} (h)	10.0	6.7		
Estrone[a]				
AUC_{0-72h} (pg/ml)	6126	5332	1.15	97 - 137
C_{max} (pg/ml)	248.7	225.9	1.10	95 - 128
t_{max} (h)	6.4	6.5		
Norethindrone				
AUC_{0-72h} (pg/ml)	17149	16660	1.03	**89 - 120**
C_{max} (pg/ml)	3917	4079	0.97	77 - 120
t_{max} (h)	1.2	1.2		

a not corrected for baseline

Bioequivalence was demonstrated for only AUC_{0-72h} of NET and for C_{max} of E_2 according to the Agency's 80-125% criterion. For all other pharmacokinetic parameters, 90% CI were marginally above 80-125% except for E_1.

Reviewer Comments:

- From the biopharmaceutics perspective, the final clinical trials formulation (same as the to-be marketed formulation) is not bioequivalent to the formulation used in early clinical trials. The 90% confidence intervals for AUC_{0-72h} of NET and C_{max} of E_2 were within 80 –125% limits while those for AUC_{0-72h} of E_2 and C_{max} of NET failed marginally (by 3%) and AUC of E_1 failed by (12%) a considerable margin. Upon reanalysis of the individual data by this reviewer, it was noted that one of the subjects was clearly an outlier because the ratios of AUC (Test Vs Reference) were 3.45 and 8.34 for E_2 and E_1, respectively. The plasma concentration profiles of this

subject show that E_2 and E_1 levels did not rise from the baseline after dosing with formulation B. This could have happened due to dosing error. If, this subject is omitted from the data for bioequivalence, the 90% CI for AUC of both E_2 and E_1 would be contained within 80 to 125%. Nevertheless, the final copolyvidone formulation was used in the two adequate and well controlled pivotal US clinical trials (KLIM/PD/7/USA and KLIM/9/USA) which provided the main safety and efficacy data for the approval and labeling. The study 7/USA was a dose finding trial for NETA in combination with 1mg E_2 and the study 9/USA was a confirmatory safety and efficacy trial for the combination. The earlier formulation was used in early Europian clinical trials, which gave only the supporting information. Therefore, the bioequivalence of the two formulations is less of a concern. The results of bioequivalence study were discussed with reviewing medical officer of HFD-580, Dr. Phil Price and he felt that the marginal differences observed would not be clinically significant for hormone replacement therapy.

- It should be noted that the information on lipids in the labeling has been derived from the study KLIM/PD/5/S, which used the old formulation. As noted in the above comment, the two formulations would be bioequivalent if the outlier subject were omitted. Therefore, from the clinical pharmacology perspective, it is acceptable to include the lipid beneficial effects in the labeling.
- It should be noted that serum estrone sulfate levels were not measured in this study as per the agreement reached with the FDA (see meeting minutes for IND

VIII C. Food Effect

The effect of a high-fat meal on the bioavailability and pharmacokinetics of Activelle tablets was investigated in 23 postmenopausal women in study KLIM/PD/26/USA using the final to be marketed formulation. The pharmacokinetic parameters from this study are summarized in Table 6.

Table 6. Mean PK parameters and 90% CI

Parameter	Fed N=23	Fasted N=23	Ratio fed/fasted	90% CI
Estradiol				
$AUC_{0\text{-}72h}$ (pg/ml.h)[a]	646.3	650.0	1.00	90 - 112
$AUC_{0\text{-}72h}$ (pg/ml.h)	1073	1064	1.01	96 - 106
C_{max} (pg/ml)	29.6	31.9	0.93	87 - 100
T_{max} (h)	8.0	7.7	--	---
Estrone				
$AUC_{0\text{-}72h}$ (pg/ml.h)[a]	3396	3199	1.07	94 - 122
$AUC_{0\text{-}72h}$ (pg/ml.h)	5164	4931	1.05	99 - 111
C_{max} (pg/ml)	211	209	1.01	92 - 111
T_{max} (h)	6.5	5.9	--	---
Norethindrone				
$AUC_{0\text{-}72h}$ (pg/ml.h)	24058	20137	1.19	114 - 126
C_{max} (pg/ml)	2837	4443	0.64	55 - 74
T_{max} (h)	2.6	1.1[b]	--	---

a - baseline corrected

b – C_{max} was observed in the first sample at 1 hour for majority of subjects.

Reviewer Comments:

- The presence food did not influence the bioavailability of estradiol and estrone. However, the bioavailability (AUC) of NET was increased by 19% and C_{max} decreased by 36% when given with high fat meal. For the majority of the women, the observed peak concentrations of NET were in the first sample at 1 hour. Therefore, the true peak concentration and AUC may have been underestimated. The change (19%) in AUC of NET is not likely to be clinically significant and the Cmax is not an important parameter for therapy like HRT for postmenopausal women. Furthermore, in the clinical trials, subjects took Activelle without regard to food intake. Therefore, in the labeling, Activelle is recommended to be given with or without food.
- Since higher strengths of norethindrone (upto 5 mg) are on the market, higher C_{max} for norethindrone observed in fasting conditions is not a concern.

VIII D. Single Dose Pharmacokinetics

The pharmacokinetics of Activelle following single dose administration was investigated in studies KLIM/PD/3/S, KLIM/PD/24/D, KLIM/25/USA, and KLIM/PD/26/USA, and also in the supportive Japanese trial KLIM/PD/12/J (not shown here, see synopsis on p34). The mean pharmacokinetic parameters estimated from these studies are summarized in the following Table 7.

Table 7. Mean pharmacokinetic parameters of Activelle following single dose administration.

Trial ID	Dosage Form	No.of subjects	$AUC_{0\text{-}72h}$ (pg*h/ml)	Cmax (pg/ml)	tmax (h)	t1/2 (h)
Estradiol						
3/S[a]	gelatin	24	1216[b]	70.4	5.5	--
24/D	copolyv	25	1053	34.6	6.8	13.2
25/USA	gelatin	23	1378	37.5	10	--
	copolyv	23	1231	35.4	6.7	--
26/USA	coployv					
	fasted	23	1064	31.9	7.7	--
	fed	23	1073	29.6	8.0	--
Norethindrone[c]						
3/S[a]	gelatin	24	33.8	7.39	0.9	8.8
24/D	copolyv	25	23.7	5.31	1.0	11.4
25/USA	gelatin	23	17.2	3.92	1.2	--
	copolyv	23	16.7	4.08	1.2	--
26/USA	copolyv					
	fasted	23	20.1	4.44	1.1	--
	fed	23	24.1	2.84	2.6	--

a method used in this trial had higher cross reactivity compared that used in other trials.
b 0-24 h c C_{max} (ng/ml), AUC (ng.h/ml)

Peak concentrations of estradiol of about 30-40 pg/ml were reached at 5-8 hrs following single dose administration of 1 mg E_2 + 0.5 mg NETA and plasma levels E_2 were eliminated slowly with a terminal half-life of about 12 – 14 hours.

Norethindrone acetate was rapidly absorbed and converted immediately to norethindrone.

Peak concentrations of about 3 to 8 ng/ml were reached at 0.5 – 1.5 hours following single dose administration. The half-life of NET was about 8 to 11 hours.

Reviewer Comment:

In general, the pharmacokinetics after single dose is similar across studies except in Study 3/S possibly because the method used had higher cross reactivity compared to others studies.

VIII E. Multiple Dose Pharmacokinetics

The pharmacokinetics of Activelle following multiple dose oral administration (once daily) was investigated in study KLIM/PD/3/S (part II of the trial) and supportive Japanese trial, KLIM/PD/13/J (not shown here, see synopsis on p37). The mean steady state levels from this study are listed in Table 8.

Table 8. Mean (SD) steady-state (trough) concentrations of estrogens and norethindrone from KLIM/PD/3/S

Parameter	Baseline (N=24)	Day 14 (N=24)	Day 21 (N=24)	Day 28 (N=24)
[a]E_2 (pg/ml)	35.4 (25.6)	59.8 (23.1)[b]	57.1 (25.3)	57.1 (19.9)
E_1 (pg/ml)	54.0 (22.1)	246 (174)	232 (175)	240 (163)
E_1S (ng/ml)	1.09 (0.35)	8.83 (3.47)	7.82 (3.13)	8.15 (3.28)
NET (ng/ml)		0.60 (0.72)	0.49 (0.32)	0.53 (0.34)

a baseline uncorrected
b n=16
c n=23

Table 8.1

Parameter	Single dose Mean[b] (SD)	Multiple dose Mean[b] (SD)	Ratio (MD/SD)
E_2[a]			
AUC_{0-24h} (pg/ml*h)	1216 (473)	1621 (593)	1.33
C_{max} (pg/ml)	70.4 (25.3)	101 (40.8)	1.43
T_{max} (h)	5.5 (6.3)	3.2 (2.6)	
E_1[a]			
AUC_{0-24h} (pg/ml*h)	5454 (1539)	8451 (4455)	1.47
C_{max} (pg/ml)	323 (104)	493 (259)	1.47
T_{max} (h)	6.4 (2.7)	4.9 (2.1)	
E_1S[a]			
AUC_{0-24h} (ng/ml*h)	321 (102)	443 (151)	1.34
C_{max} (pg/ml)	56.2 (24.5)	66.7 (24.7)	1.21
T_{max} (h)	0.9 (0.7)	0.8 (0.6)	
NET			
AUC_{0-24h} (ng/ml*h)	33.8 (15.6)	47.7 (20.9)	1.44
C_{max} (pg/ml)	7.4 (3.6)	8.0 (3.2)	1.12
T_{max} (h)	0.9 (0.4)	0.8 (0.4)	
$T_{1/2}$ (h)[c]	8.8	10.1	

a baseline uncorrected
b arithmetic mean
c harmonic mean

As the baseline levels of estrogens could not be determined accurately because of assay sensitivity problems, the data was not baseline corrected. Steady state was reached within two weeks for both E_2 and NET as determined from predose levels on day 14, 28 and 56. The accumulation of both compounds was similar to that expected from their elimination half-lives and single dose data.

IX. Special populations:

As both E_2 and NETA are well known substances in contraceptive products, no specific trials were conducted in special populations. However, the use of Activelle is contraindicated for subjects with liver dysfunction or disease based on established knowledge of the metabolism and excretion of these substances.

Effect of Age:

The effect of age on plasma steady state levels of E_1S in study KLIM/PD/7/USA was evaluated and there were no differences between subjects aged above 65 and below 65 years. However, it should be noted that estradiol and norethindrone levels were not measured in this study. Therefore any definitive conclusions regarding the effect of age on pharmacokinetics cannot be made from this study.

Effect of Race:

Analysis of the effect of race on pharmacokinetics of Activelle has not been performed because of very low number of non-Caucasian women in clinical trials in US/EU.

Two pharmacokinetic trials were performed in Japanese women. The $t_{1/2}$ of E_2 as well as that of NET were similar in Japanese and Caucasian subjects. However, comparison of results across these trials should be interpreted with caution due to differences in design and analytical methods.

X. Drug Interactions:

No specific drug interaction studies were conducted using Activelle. However, based on known literature information, the labeling includes appropriate drug-drug interactions for this class of compounds.

X.A. Interaction of E_2 on NETA absorption:

Study KLIM/PD/3/S investigated the effect of E_2 on NETA absorption by comparing the single dose pharmacokinetics of 1 mg E_2 + 0.5 mg NETA to that of a 0.5 mg NETA tablet formulation. This study also determined the multiple dose (28 days) pharmacokinetics of Activelle. The comparison of the mean pharmacokinetic parameters from this interaction study is summarized in Table 9.

Table 9. Mean (SD) pharmacokinetic parameters of NET following single dose administration.

Parameter	1mg E_2 + 0.5 mg NETA	0.5 mg NETA	Ratio	90% CI
NET				
$AUC_{0-\infty}$ (ng/ml)	33.8 (15.6)	32.8 (15.4)	1.02	98-106
C_{max} (ng/ml)	7.4 (3.6)	6.6 (3.6)	1.16	108-124
T_{max} (h)	0.9 (0.4)	1.0 (0.4)	--	---
$T_{1/2}$ (h)	8.8	8.4		

Reviewer Comment:
The results indicate that the pharmacokinetics of NET is not affected by the presence of E_2. This is consistent with the previous information for these drug products. However it should be noted that the interaction was studied under single dose condition. Because clinical trials for vasomotor indication and endometrial protection were done with the combination tablet formulation, lack of drug interaction information at multiple dose is not relevant.

XI. LABELING

The Clinical Pharmacology section of the proposed labeling should be replaced with the following:

CLINICAL PHARMACOLOGY

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

XII. SYNOPSES OF INDIVIDUAL STUDIES

SYNOPSIS OF RELTIVE BIOAVAILABILITY STUDY (KLIM/PD/24/USA)

TITLE OF TRIAL
A three-period, open-label, randomised, cross-over trial in healthy postmenopausal women to investigate the bioavailability of two Kliogest Low Dose strengths when compared to an estradiol and norethindrone acetate solution

INVESTIGATORS

TRIAL CENTRE

PUBLICATIONS
None

TRIAL PERIOD	**DEVELOPMENT PHASE**
- first subject screened 17 January 1997 - last subject completed 07 April 1997	Phase I

OBJECTIVES
- to investigate the bioavailability of two dosage strengths of Kliogest Low Dose tablets manufactured using the same formulation, but different dose strengths of NETA when compared with an oral solution of estradiol and norethindrone acetate.

METHODOLOGY
- The trial was a single-center, randomised three period, six sequence, open-label, crossover single-dose trial. Healthy postmenopausal women received either one of the two Kliogest Low Dose tablets or the oral solution on three different occasions, each separated by a 14 day washout period. There were four visits; a screening visit (Visit 1) and three treatment visits (Visits 2, 3 and 4). The treatment visits lasted 3½ days each.
- Subjects were randomised in blocks of six (6) referring to the 6 sequences with randomisation numbers available from 1 to 30.
- 72-hour profiles of estradiol (E_2), estrone (E_1) and norethindrone (NET) were determined, the first sample taken 30 minutes prior to dosing.
- Safety parameters (adverse events, blood pressure, heart rate, body temperature, body weight, urine drug screen) were assessed at each visit. Laboratory variables, physical examination and ECG were performed at screening visit (Visit 1) and at the end of the trial (Visit 4).

NUMBER OF SUBJECTS (PLANNED AND ANALYSED)
- 27 subjects planned
- 44 subjects were screened
- 27 subjects were enrolled and randomised;
- 26 completed the trial (subject no. 26 was withdrawn from the trial due to an adverse event)
- 25 subjects were included in pharmacokinetic and statistical evaluation (data of subject no. 02 were excluded, due to unreliable results for estradiol and estrone)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
Healthy postmenopausal women with at least 1 year history of physiologic amenorrhea or oophorectomized women, with a level of $E_2 \leq 20$ pg/ml and FSH ≥ 40 IU/l, aged 50-70 years and body weight within ±20% of normal range for height and frame (1983 Metropolitan height and weight table on metric basis)

TRIAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
Tablets T_1: 1 mg E_2 + 0.25 mg NETA, batch no.: 631702 (corresponding to: 624986)
Tablets T_2: 1 mg E_2 + 0.5 mg NETA, batch no.: 631701 (corresponding to: 624988)
Oral Solution (R): 1 mg E_2 + 0.5 mg NETA in oral solution, batch no.: 701086

Oral single-dose administration under fasting conditions

DURATION OF TREATMENT
Single-dose on three occasions, separated by a 14 days washout period

CRITERIA FOR EVALUATION - PHARMACOKINETICS
Serum concentrations of E_2, E_1 and NET were tabulated and presented in graphs. For each individual a baseline level of E_2 and E_1 was calculated at each visit as a mean of the -0.5 and 0 hour

concentrations. This value was used for baseline correction.
The primary pharmacokinetic endpoints are the following parameters derived from concentration-time profiles of E_2, E_1 and NET.

- area under the curve (AUC) from time of trial product administration to last sampling time point (72h) = AUC_{0-72}, calculated by linear trapezoidal rule
- area under the curve extrapolated to infinity ($AUC_{0-\infty}$) - for E_2 and E_1 calculated only after baseline-correction
- maximal concentration (C_{max})

Further pharmacokinetic parameters calculated include t_{max}, λ_z and t½.

CRITERIA FOR EVALUATION - SAFETY

- Adverse events, laboratory safety parameters (hematology, biochemistry, urine drug screen), vital signs (blood pressure, heart rate, body temperature, body weight), physical examination and electrocardiogram (ECG).

STATISTICAL METHODS

The pharmacokinetic parameters AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} for E_2 and E_1 after baseline correction and for NET were evaluated by analysis of variance (ANOVA) after logarithmic pre-transformation, including sequence, subject within sequence, period, first-order carry-over and treatment effect. Since for E_2 and E_1 the carry-over was found to be insignificant ($p \geq 0.10$), a second analysis was performed without carry-over effects and the results of this analysis are cited below.
Statistical analyses performed on pharmacokinetic parameters of E_2 and E_1 without baseline correction are to be found in Appendix J but are not discussed here.
t_{max} was compared between pairs of treatments by Pratt-Wilcoxon test.

PHARMACOKINETIC RESULTS

Estimates of relative bioavailability derived from results for unconjugated estradiol (E_2) after baseline-correction, N=25, T_1 = tablet, 1 mg E_2 + 0.25 mg NETA, T_2 = tablet, 1 mg E_2 + 0.5 mg NETA, R = solution, 1 mg E_2 + 0.5 mg NETA

Parameter	Estimated Ratio (T_1/R)	90% Confidence Interval
ln (AUC_{0-72})	47.64%	42.80% to 53.01%
ln ($AUC_{0-\infty}$)	49.09%	44.29% to 54.41%
ln (C_{max})	8.06%	7.00% to 9.26%
	Estimated Ratio (T_2/R)	90% Confidence Interval
ln (AUC_{0-72})	50.75%	45.58% to 56.49%
ln ($AUC_{0-\infty}$)	53.26%	47.95% to 59.14%
ln (C_{max})	8.29%	7.20% to 9.54%
	Estimated Ratio (T_1/T_2)	90% Confidence Interval
ln (AUC_{0-72})	93.87%	84.30% to 104.52%
ln ($AUC_{0-\infty}$)	92.18%	82.97% to 102.40%
ln (C_{max})	97.14%	84.39% to 111.81%

Estimates of relative bioavailability derived from results for unconjugated estrone (E_1) after baseline-correction, N=25:

Parameter	Estimated Ratio (T_1/R)	90% Confidence Interval
ln (AUC_{0-72})	96.90%	90.62% to 103.61%
ln ($AUC_{0-\infty}$)	98.05%	91.58% to 104.97%
ln (C_{max})	96.65%	88.08% to 106.04%
	Estimated Ratio (T_2/R)	90% Confidence Interval
ln (AUC_{0-72})	99.37%	92.91% to 106.27%
ln ($AUC_{0-\infty}$)	100.27%	93.64% to 107.37%
ln (C_{max})	93.46%	85.16% to 102.56%
	Estimated Ratio (T_1/T_2)	90% Confidence Interval
ln (AUC_{0-72})	97.51%	91.16% to 104.30%
ln ($AUC_{0-\infty}$)	97.78%	91.30% to 104.72%
ln (C_{max})	103.41%	94.20% to 113.51%

Estimates of relative bioavailability derived from results for norethindrone (NET) after dose-correction for treatment T_1, N=25:

Parameter	Estimated Ratio (T_1/R)	90% Confidence Interval
ln (AUC_{0-72})	108.45%	103.82% to 113.28%
ln ($AUC_{0-\infty}$)	112.62%	107.18% to 118.34%

ln (C_{max})	97.60%	89.81% to 106.05%
	Estimated Ratio (T_2/R)	90% Confidence Interval
ln (AUC_{0-72})	102.42%	98.02% to 107.01%
ln ($AUC_{0-\infty}$)	102.41%	97.58% to 107.47%
ln (C_{max})	90.07%	82.84% to 97.92%
	Estimated Ratio (T_1/T_2)	90% Confidence Interval
ln (AUC_{0-72})	105.89%	101.20% to 110.78%
ln ($AUC_{0-\infty}$)	109.97%	104.71% to 115.49%
ln (C_{max})	108.36%	99.55% to 117.94%

SAFETY RESULTS

No serious adverse events were reported. One (1) subject was withdrawn from the trial due to an adverse event (influenza-like symptoms). A total of 18 adverse events were experienced after administration of the trial products by 11 of the 27 dosed subjects. Twelve (12) of the adverse events, i.e. headache (9), hot flushes (2) and dizziness (1) were classified as possibly trial product related. For all other adverse events the trial product relation was considered unlikely by the investigator. No abnormal findings with respect to laboratory safety parameters, vital signs, physical examination or ECG were considered clinically significant.

CONCLUSION

In comparison to the oral solution, the tablets showed a relative bioavailability of E_2, assessed by the $AUC_{0-\infty}$ after baseline correction, of 49% (1 mg E_2 + 0.25 mg NETA) and 53% (1 mg E_2 + 0.5 mg NETA). The C_{max} in the geometric mean was 8% of the maximum observed after administration of the oral solution. After administration of the tablets the maximum was achieved in the median at 6 h after dosing for both tablets whereas t_{max} for the oral solution was 1 h.

Based on E_1, both tablet preparations were very similar to the reference oral solution. The ratio of $AUC_{0-\infty}$ was assessed to be 98% and 100%, for the two tablets with 1 mg E_2 + 0.25 mg NETA and 1 mg E_2 + 0.5 mg NETA, respectively, and the mean ratio of C_{max} was 97% and 93%. Maximal concentrations were achieved with a median t_{max} of 5 h and 6 h for the two tablets and median t_{max} was 5 h for the oral solution.

The relative bioavailability of the NET component of the 1 mg E_2 + 0.25 mg NETA tablet compared to the oral solution was 113% for $AUC_{0-\infty}$, dose-corrected, with a corresponding ratio of 98% for C_{max}. Comparing the 1 mg E_2 + 0.5 mg NETA tablet and the oral solution the respective ratios were 102% for $AUC_{0-\infty}$ and 90% for C_{max}.

When comparing the two tablet treatments with respect to E_2 and E_1, all confidence intervals for ratios of AUC_{0-72}, $AUC_{0-\infty}$ and C_{max} were within 0.8 to 1.25. This shows that there is no relevant interaction of NET on the pharmacokinetics of E_2 and E_1 within the dose range investigated.

When comparing results for NET after dose correction, 90% confidence intervals of the ratios were within 0.8 - 1.25. This proves that the pharmacokinetics of NET are linear within the dose range investigated.

Kliogest Low Dose was well tolerated after administration of both tablets and the oral solution.

DATE OF FINAL REPORT

08 August 1997

Synopsis of Bioequivalence Study (KLIM/PD/25/USA)

TITLE OF TRIAL

A two-period, open-label, randomized, crossover study in healthy postmenopausal female subjects to demonstrate the bioequivalence between two Kliogest Low Dose formulations.

INVESTIGATOR

TRIAL CENTRE

PUBLICATIONS

None

TRIAL PERIOD	**DEVELOPMENT PHASE**
January 22, 1997 – February 14, 1997	I

OBJECTIVES

To demonstrate the bioequivalence of two formulations (gelatin vs povidone) of Kliogest Low Dose tablets

METHODOLOGY

This was a two-period, open-label, crossover, single dose study in healthy subjects. There was a 10-day washout period between each alternative dose administered following an overnight fast. Subjects were observed for 72 hours, post-dose. Blood samples were drawn 30 minutes before and immediately prior to the administration of Kliogest Low Dose, and then at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72 hours after each dose administration. Pharmacokinetic assays for estradiol, estrone, and norethindrone were performed at each sample time.

NUMBER OF SUBJECTS

Twenty-four subjects were planned to be enrolled. Twenty-four subjects were enrolled of the 63 who were screened; however, pharmacokinetic data for subject [redacted] were excluded from the analysis due to a violation of protocol inclusion criteria.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Postmenopausal women of 50 to 70 years of age with a minimum of one year history of amenorrhea or oopherectomized and in good health. Subjects had to be non-smokers for at least three months prior to study entry, exhibit a negative mammogram within six months prior to study entry, and a level of 17-β-estradiol (E_2) ≤20 pg/ml and FSH≥40 mg/ml.

Subject demographics are summarized below:

	Demographic Characteristics All Subjects (N= 24)	
	Mean	Std. Dev.
Age (yrs)	55.6	3.6
Height (cm)	158.1	6.4

Weight (kg)	65.9	12.1

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Kliogest Low Dose tablets taken orally, containing 1 mg 17-β-estradiol (E_2) and 0.5 mg norethindrone acetate (NETA), manufactured using two different formulations of NETA:
Tablet A – gelatin formulation with wet granulation of NETA. Batch number: 504083
Tablet B – povidone formulation with dry milling of NETA. Batch number: 517785

DURATION OF TREATMENT

Two single doses 10 days apart

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

N/A

CRITERIA FOR EVALUATION – PHARMACOKINETIC

Primary
AUC_{0-72}, and C_{max} of estradiol (E_2), estrone (E_1), and norethindrone

Secondary
T_{max} of estradiol (E_2), estrone (E_1) and norethindrone

CRITERIA FOR EVALUATION – SAFETY

Physical examination/vital signs, ECG, Pap smear, mammogram, adverse events, and routine laboratory observations (hematology, biochemistry.)

STATISTICAL METHODS

In this two-period, crossover study, data from 24 subjects were collected and analyzed to examine the bioequivalence of pharmacokinetic (PK) parameters of two formulations of Kliogest Low Dose administered under identical conditions and to assess safety. PK analyses used observed values of AUC_{0-72}, C_{max} and T_{max}. Bioequivalence, defined by a parameter ratio whose 90% confidence interval is completely contained within (0.8, 1.25), was tested by a general linear model implemented in SAS PROC GLM. T_{max} was not analyzed for bioequivalece. Parameter differences between formulations were also examined. Analyses of safety used paired methods, including shift tables, to compare clinical laboratory parameters between formulations. There were insufficient adverse events to require formal analyses.

PHARMACOKINETIC RESULTS

Tablet A and Tablet B of Kliogest Low Dose were non-bioequivalent according to regulatory guidelines. Bioequivalence was attained only for estradiol C_{max} and norethindrone AUC_{0-72}. The other pharmacokinetic variables were borderline. These findings could be due to outlier data skewing the results. For example, estradiol AUC_{0-72} ratio changes from 1.12 (90% CI: 98-128) to 1.07 (90% CI: 95-120) with the exclusion of outlier data. Pk data is summarized below:

Estradiol

	Tablet A	Tablet B	Ratio	CI (90%)
AUC(hrs.pg/ml)	1377.9	1230.7	1.12	0.98, 1.28
Cmax (pg/ml)	37.5	35.4	1.06	0.96, 1.18
Tmax (hrs)	10.0	6.7	----	----

Estrone

	Tablet A	Tablet B	Ratio	CI (90%)
AUC (hrs.pg/ml)	6126.1	5331.7	1.15	0.97, 1.37
Cmax (pg/ml)	248.7	225.9	1.10	0.95, 1.28
Tmax (hrs)	6.4	6.5	----	----

Norethindrone

	Tablet A	Tablet B	Ratio	CI (90%)
AUC (hrs.pg/ml)	17,148.8	16,660.0	1.03	0.89, 1.20
Cmax (pg/ml)	3916.7	4079.0	0.965	0.77, 1.20
Tmax (hrs)	1.2	1.2	----	----

SAFETY RESULTS

No serious adverse events or deaths were reported. No subjects were withdrawn or dropped out due to adverse events. Five subjects reported a total of 12 adverse events, nine of which were considered possibly related to trial drug. These were mild in severity and resolved spontaneously without sequelae. Three events, hypertension and a urinary tract infection, occurred six to eight days subsequent to treatment and were considered unrelated to trial drug. The majority of changes in clinical chemistry and hematology were not considered clinically significant or formulation related.

CONCLUSIONS

The two formulations of Kliogest Low Dose can be considered therapeutically equivalent in this study.

Strict bioequivalence was attained for estradiol Cmax and norethindrone AUC 0-72. C. I.'s for estradiol AUC and norethindrone Cmax were 0.03 outside the upper and lower bounds of strict bioequivalence, respectively. Estradiol confidence intervals were corrected to well within the strict limits bioequivalence by excluding an outlier (Subject

With respect to norethindrone, the tablets were bioequivalent based on the AUC parameter. The lower CI limit for Cmax was just below 0.80.

Synopsis of Food Effect Study (KLIM/PD/26/USA)

TITLE OF TRIAL A randomized, open-label, crossover study, to determine the effect of a fatty meal on the absorption of a single oral dose of Kliogest Low Dose.	
INVESTIGATOR	
TRIAL CENTRES	
PUBLICATIONS None	
TRIAL PERIOD September 27 – December 7, 1996	**DEVELOPMENT PHASE** I
OBJECTIVES To determine the effects of a fatty meal on the absorption of a single oral dose of Kliogest Low Dose.	
METHODOLOGY This was a single center, randomized, open-label, two-way crossover trial in subjects in a fed or fasted state. There was a 10-day washout period between each dose, administered to subjects in a fed-first or a fasted-first sequence. Blood samples were drawn 30 minutes before and immediately prior to the administration of Kliogest Low Dose, and then 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours after each dose administration. Pharmacokinetic assays for estradiol, estrone and norethindrone were performed at each sample time.	
NUMBER OF SUBJECTS Thirty-nine subjects were screened and twenty-four subjects were enrolled; however, pharmacokinetic data for Subject [redacted] were excluded from the analysis due to a violation of protocol inclusion criteria.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION Postmenopausal women of 50 to 70 years of age with a minimum of one year history of amenorrhea or oopherectomized and in good health. Subjects had to be non-smokers for at least three months prior to trial entry, exhibit a negative mammogram within six months prior to trial entry, and a level of 17-β-estradiol (E_2) ≤ 20 pg/ml and FSH≥ 40 mg/ml.	

Subject demographics are summarized below:

Demographic Characteristics

	All Subjects (N=24)	
	Mean	Std. Dev
Age (yrs)	56.3	6.6
Height (cm)	164.3	6.4
Weight (kg)	67.7	9.8

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Kliogest Low Dose as 1 mg 17-β-estradiol (E_2) and 0.5 mg norethindrone acetate (NETA), taken orally. Batch number: 517785

DURATION OF TREATMENT

Two single doses 10 days apart.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

N/A

CRITERIA FOR EVALUATION - PHARMACOKINETICS

Primary
Baseline adjusted AUC_{0-72}, and C_{max} of estradiol (E_2) and, estrone (E_1), along with $AUC_{0-72hrs}$ and C_{max} of norethindrone.
Secondary
T_{max} of estradiol (E_2), estrone (E_1), and norethindrone.

CRITERIA FOR EVALUATION - SAFETY

Physical examination/vital signs, ECG, PAP smear, mammogram, adverse events, and routine laboratory observations (hematology, biochemistry, and urinalysis).

STATISTICAL METHODS

In this two-period, crossover trial, data from 24 subjects were collected in the fed/fasting states and analyzed to examine the bioequivalence of pharmacokinetic (PK) parameters of Kliogest® Low Dose administered under both conditions and to assess safety. PK analyses used observed values of AUC_{0-72}, with and without baseline adjustment, C_{max}, and T_{max}. Bioequivalence, defined by a baseline adjusted parameter ratio in which the 90% confidence interval is completely contained within (0.8, 1.25), was tested by a general linear model implemented in . T_{max} was not analyzed for bioequivalence. Parameter differences between fed and fasting states were also examined. Analyses of safety used paired methods, including shift tables, to compare clinical laboratory parameters between fed and fasting states and between trial periods. There were insufficient adverse events to require formal analyses.

PHARMACOKINETIC RESULTS

Bioavailability of estradiol and estrone were the same in the fed or fasting states. Norethindrone is more bioavailable when administered with a fatty meal. This finding, with a CI of 114-128 however, appears to be related to inappropriate blood sampling times. Due to a T_{max} at the first blood sampling time after fasting, some area of the AUC of NET was not measured. The findings of a slightly higher absorption after a fatty meal appear to have no clinical relevance.

Estradiol				
	Fed	Fasted	Ratio	CI (90%)
Baseline Adjusted AUC_{0-72} (pg/ml·h)	646.3	650.0	1.00	90-112
C_{max} (pg/ml)	29.6	31.9	1.01	96-106
T_{max} (h)	8.0	7.7	-	-

Estrone				
	Fed	Fasted	Ratio	CI (90%)
Baseline Adjusted AUC_{0-72} (pg/ml·h)	3395.9	3198.9	1.07	94-122
C_{max} (pg/ml)	211.0	208.8	1.01	92-111
T_{max} (h)	6.5	5.9	-	-

Norethindrone				
	Fed	Fasted	Ratio	CI (90%)
Non-Baseline Adjusted AUC_{0-72} (pg/ml·h)	24,058.1	20,137.1	1.19	114-126
C_{max} (pg/ml)	2,837.0	4,443.5	.64	55-74
T_{max} (h)	2.6	1.1	-	-

SAFETY RESULTS

No serious adverse events or deaths were reported. No subjects were withdrawn or dropped out due to adverse events. Eleven subjects reported a total of eighteen adverse events, two of which were considered to be possibly/probably related to trial drug. All adverse events were mild in severity and resolved spontaneously. Changes in clinical laboratory data were not considered clinically significant. Kliogest Low Dose was well tolerated.

CONCLUSIONS

Under the conditions of trial, it was found that the estradiol component of Kliogest Low Dose is absorbed equally well in the fed state as in the fasting state. Further, its oxidation to estrone appears to be unaffected as suggested by the bioequivalence of both hormones.

The data also suggests that absorption of the norethindrone component of Kliogest Low Dose may be increased when taken with a meal. The 90% confidence interval of $AUC_{(0-72\ hrs)}$ for NET was being just outside the bioequivalence limit of Since the T_{max} of NET after fasting is 1.1 hour and is close to the first blood sampling time of 1 hour, compared to T_{max} of 2.6 hours after fed, a minor area of the $AUC_{(0-72\ hrs)}$ after fasting might be lost. The results of a reduction in NET absorption after fed compared to fasting might be similarly affected. Thus, the difference

noted is likely to be a consequence of the sampling scheme rather than a true food effect.

The differential effect upon absorption may be best related to the intrinsic rate of absorption (in the fasting state) which is faster for norethindrone than for estradiol. Thus, if first pass metabolism plays a significant role in the early phase of elimination of norethindrone, a slight delay and reduction in C_{max} will have a larger effect than with estradiol, the absorption of which does not peak until 5-6 hours, well after the effect of a meal. Thus, the food effect on absorption on estradiol, if there is one, is largely over prior to T_{max}, and thus food has little or no effect upon C_{max} or AUC.

Because of its once-a-day dosing, long half-life, and the fact that plasma levels are most probably in excess (i.e., not closely titrated to individual response), it is unlikely that consistently taking Kliogest Low Dose on an empty stomach would lead to under dosing, nor would consistently taking it with a meal lead to excessive accumulation. Under normal conditions of administration when no recommendation regarding food is given, the impact of occasionally taking Kliogest Low Dose with a meal should be minimal.

Synopsis of Multiple Dose Study (KLIM/PD/3/S)

TITLE OF TRIAL Bioavailability evaluation of an estradiol-NETA preparation and a NETA preparation in 18 healthy postmenopausal volunteers	
INVESTIGATORS	
TRIAL SITE	
PUBLICATIONS None	
TRIAL PERIOD 16 March 1993 - 25 March 1994	**DEVELOPMENT PHASE** Phase I
OBJECTIVES To determine bioavailability and pharmacokinetic parameters of a combined 1 mg estradiol (E_2) + 0.5 mg norethisterone acetate (NETA) tablet formulation (single and multiple dose) and a 0.5 mg NETA tablet formulation (single dose)	
METHODOLOGY - Part I of trial was an open labelled, randomised crossover trial. A single dose of either a combined 1 mg E_2 + 0.5 mg NETA tablet or a 0.5 mg NETA tablet was administered followed by a blood sampling period of 72 hours. After a washout period of 10 days a single dose of the alternative tablet was administered followed by a blood sampling period of 72 hours. - Part II of trial was an open labelled trial. The subjects completing Part I were after a washout period of at least 7 days allocated to one tablet daily of 1 mg E_2 + 0.5 mg NETA for one cycle (28 days). Following ingestion of the last tablet (day 28) blood was sampled for 72 hours. Furthermore, blood samples were taken prior to tablet administration on day 1, 14, 21, and 28. Plasma samples were analysed for E_2, estrone (E_1), estrone sulphate (ES), and norethisterone (NET).	
NUMBER OF SUBJECTS PLANNED/ANALYSED: - 18 subjects were planned - sample size was increased from 18 to 24 due to FDA requirements - 27 subjects were screened - 25 subjects were enrolled - 24 subjects completed	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy, postmenopausal women, aged 45-70, with menopause more than 3 years prior to inclusion, FSH > 40 IU/l and E_2 < 72 pmol/l (20 pg/ml).	
TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NO. Trial product A: 1 mg E_2 + 0.5 mg NETA, tablets, p.o., batch number 215345 Trial product B: 0.5 mg NETA, tablets, p.o., batch number 205050	
DURATION OF TREATMENT Part I of trial: 2 single doses Part II of trial: 28 days	
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NO. None	

CRITERIA FOR EVALUATION - PHARMACOKINETICS

Bioavailability: Pharmacokinetic parameters of NET for the 1 mg E_2 + 0.5 mg NETA tablet and for the 0.5 mg NETA tablet.

Single dosing (SD) versus multiple dosing (MD): Pharmacokinetic parameters of E_2, E_1, ES, and NET for the 1 mg E_2 + 0.5 mg NETA tablet, single dose and multiple dose.

CRITERIA FOR EVALUATION - SAFETY

Recording of vital signs and adverse events

STATISTICAL METHODS

Part I: The pharmacokinetic parameters (AUC, C_{max}, T_{max}, and λ_z) for NET and the logarithmically transformed parameters were analysed using analysis of variance (ANOVA) including sequence, subject nested within sequence period and trial product. For the logarithmically transformed data the difference of the two trial products and the corresponding 90% confidence interval were exponentially transformed.

Part II: The pharmacokinetic parameters for NET, E_2, E_1, and ES and the logarithmically transformed data were analysed using ANOVA including subject and single/multiple dosing. For the logarithmically transformed data the difference between the non-transformed data and the corresponding 95% confidence interval were exponentially transformed.

PHARMACOKINETIC RESULTS

Bioavailability:

As the 90% confidence interval was within the % range, the results of the analysis confirmed that the two trial products were bioequivalent with respect to the bioavailability of NETA.

Parameter	Estimated Ratio (A/B)	90% Confidence Interval
log(AUC)	1.021	0.982 to 1.063
log(C_{max})	1.159	1.083 to 1.241

SD versus MD (NET):

No significant differences in C_{max} or T_{max}, from single to multiple dosing of 1 mg E_2 + 0.5 mg NETA, were seen. AUC increased significantly following multiple dosing. A significant increase in $t_{½}$ was also seen. However, the elimination $t_{½}$ may not have been properly revealed following single dosing. The mean values (± S.D.) were:

The "PHARMACOKINETIC RESULTS" section continues on the next page.

Dose/ Trial Product	C_{max} (ng/ml)	T_{max} (h)	AUC (ng h/ml)	$t_{½}$ (h)
SD (NETA)	6.62 ± 3.61	1.0 ± 0.4	32.8 ± 15.4	8.4
SD (E_2+NETA)	7.39 ± 3.64	0.9 ± 0.4	33.8 ± 15.6	8.8
MD (E_2+NETA)	8.02 ± 3.22	0.8 ± 0.4	47.7 ± 20.9	10

Dose/ Trial Product	C_{max} (pmol/ml)	T_{max} (h)	AUC (pmol h/ml)	$t_{½}$ (h)
SD (NETA)	22.2 ± 12.2	1.0 ± 0.4	110.2 ± 51.7	8.4
SD (E_2+NETA)	24.8 ± 12.2	0.9 ± 0.4	113.3 ± 52.5	8.8
MD (E_2+NETA)	26.9 ± 10.8	0.8 ± 0.4	159.9 ± 70.3	10

SD versus MD (E_2, E_1, and ES):

Plasma AUC(0-24h) and C_{max} of E_2, E_1, and ES increased from single to multiple dosing. For E_1, T_{max} decreased. Large variations, but no statistical changes were observed for T_{max} of E_2 and ES. The mean values (± S.D.) were:

Substance	Dosing	C_{max} (pg/ml)	T_{max} (h)	AUC(0-24h) (pg h/ml)
E_2	SD	70.4 ± 25.3	5.5 ± 6.3	1,216 ± 473
	MD	101 ± 40.8	3.2 ± 2.6	1,621 ± 593
E_1	SD	323 ± 104	6.4 ± 2.7	5,454 ± 1,539
	MD	493 ± 259	4.9 ± 2.1	8,451 ± 4,455
		C_{max} (ng/ml)	T_{max} (h)	AUC(0-24h) (ng h/ml)
ES	SD	56.2 ± 24.5	0.9 ± 0.7	326 ± 102
	MD	66.7 ± 24.7	0.8 ± 0.6	443 ± 151

Substance	Dosing	C_{max} (pmol/ml)	T_{max} (h)	AUC(0-24h) (pmol h/ml)
E_2	SD	0.259 ± 0.093	5.5 ± 6.3	4.47 ± 1.74
	MD	0.372 ± 0.150	3.2 ± 2.6	5.96 ± 2.18
E_1	SD	1.198 ± 0.386	6.4 ± 2.7	20.2 ± 5.7
	MD	1.826 ± 0.960	4.9 ± 2.1	31.3 ± 16.5
ES	SD	160.5 ± 69.9	0.9 ± 0.7	930 ± 292
	MD	190.5 ± 70.6	0.8 ± 0.6	1267 ± 431

(The calculated values include the endogenous level of the three compounds.)

SAFETY RESULTS

No serious adverse events were reported. No subjects were withdrawn or dropped out due to adverse events. A total of eight subjects experienced 10 non-serious adverse events; all were considered to have no relation or unlikely relation to the trial products.

CONCLUSION

- 1 mg E_2 + 0.5 mg NETA and 0.5 mg NETA were bioequivalent with respect to bioavailability of NETA. That is, no indication of any impact on the bioavailability of NETA administered concomitantly with of E_2 was found. Thus, E_2 did not influence the pharmacokinetics of NET.
- The C_{max} of NET was unchanged from single to multiple dosing with 1 mg E_2 + 0.5 mg NETA, whereas AUC and $t_{½}$ increased. The increase in AUC was somewhat expected and is partially attributed to the elimination $t_{½}$ of NET not being properly revealed.
- The C_{max} and AUC of E_2, E_1, and ES all increased from single to multiple dosing.
- After 14 days of dosing with 1 mg E_2 + 0.5 mg NETA, the levels of E_2, E_1, ES, and NET increased; after this point no further increase was observed.

Ethics Committee approval and signed informed consent were obtained prior to starting the trial. The trial was completed and it was conducted in accordance with the Helsinki Declaration and with Good Clinical Practice.

Synopsis for KLIM/PD/12/J

Title of Trial Ascending Single Dose Tolerability, Safety And Pharmacokinetic Trial of 4 Doses of a Combination of 17β-Estradiol (E_2) and Norethisterone Acetate (NETA)
Investigators
Trial Site
In-country Caretaker
Publications None
Trial Period First subject treated July 1, 1994 Last subject completed August 30, 1994
Objectives The objective of this trial was to evaluate the tolerability, safety and pharmacokinetics of the combination of E_2 with NETA at four dose levels in healthy postmenopausal women.
Methodology Single center, single blind, placebo controlled trial according to a two-segment sequential plan with 14 subjects. Each subject was administered two doses. The two lower doses were studied in the first period with 6 subjects being randomized to one dose, 6 subjects to the other dose and 2 subjects to placebo. The two higher doses were studied in the second period after rerandomization, again 6 subjects to one dose, 6 subjects to another dose and 2 subjects to placebo. Treatments were separated by an interval of at least one week. Blood samples for determination of plasma concentrations of unconjugated 17β-estradiol (E_2), unconjugated estrone (E_1) and unconjugated norethisterone (NET) were collected up to 72 hours after dosing.
Number of Subjects 18 healthy postmenopausal women were enrolled and randomized. Four subjects were protocol violators (smokers) and they were replaced after the first period. 14 subjects completed the trial.
Diagnosis and Main Criteria for Inclusion The key inclusion criteria were: healthy Japanese women with at least 1 year of amenorrhea or 3 months of surgical menopause, normal gynecological examination, aged 40-70 years inclusive
Test Products, Dose and Mode of Administration, Batch Number A: 1 mg E_2 + 0.25 mg NETA, batch no.: 410951 B: 1 mg E_2 + 0.5 mg NETA (Kliogest Low Dose), batch no.: 215345 C: 2 mg E_2 + 1.0 mg NETA (Kliogest™), batch no.: 208750 D: 4 mg E_2 + 1.0 mg NETA, batch no.: 406401 Oral single dose administration, 1 tablet in the morning after an overnight fast.
Duration of Treatment Two single doses
Reference Therapy, Dose and Mode of Administration, Batch Number Placebo, batch no.: 313441. Oral single dose administration, 1 tablet in the morning after an overnight fast.

Criteria for Evaluation

Safety
Screening procedures included a gynecological examination, including Maturation Index, smear test and Papanicolaou smear test, palpatory and ultrasound breast examination and laboratory assessments of hematology, biochemistry and urinalysis. Except for the Maturation Index test and ultrasonic breast examination, these tests were repeated upon trial completion. Additional laboratory assessments were performed 72 hours after dosing tin the first period and preceding drug administration in the second period. Vital signs (blood pressure, pulse rate and body temperature) were measured at 12 time points after drug administration and once before leaving the hospital on the final day after the second dosing. Any adverse events, reported spontaneously by the subjects or observed by the investigator, were recorded.

Pharmacokinetics
$AUC_{0-\infty}$, C_{max}, t_{max} and $t\frac{1}{2}$ for E_2 and E_1 with and without baseline correction and for NET. For E_2 and E_1 furthermore AUC_{0-24} and AUC_{0-72}. Plasma concentrations of NET additionally were evaluated assuming a two-compartment model in order to derive estimates of $t\frac{1}{2}_{\alpha}$ and $t\frac{1}{2}_{\beta}$.

Statistical Methods
Clinical laboratory results predose and 72h postdose in each period were compared by Wilcoxon test for paired samples with statistical significance level of $p<0.05$.

Summary of Results

Safety Results
All four doses were well tolerated. In total six adverse events were reported. One subject had a positive pap smear, reported twice, at sreening and at final visit, and evaluated with no relationship to trial products. Four adverse events (AEs) were reported after drug administration, mild constipation (2 subjects) and decreased pulse rate (1 subject) after 1 mg E_2 + 0.5 mg NETA and moderate abdominal pain (1 subject) after 2 mg E_2 + 1 mg NETA.. The AEs resolved spontaneously. The AEs as well as any abnormal findings in vital signs, laboratory tests or gynecological examination, as far as those occurred, were evaluated by the investigator as without relationship to the trial products.

Pharmacokinetic Results

The major pharmacokinetic parameters are summarized as follows (means ± S.D.), for E_2 and E_1 after baseline correction. Results are based on data of N=6 subjects each.

Dose	1 mg E_2 + 0.25 mg NETA	1 mg E_2 + 0.5 mg NETA	2 mg E_2 + 1 mg NETA	4 mg E_2 + 1 mg NETA
E_2				
$AUC_{0-\infty}$ [pg/mL·h]	1301 ± 328*	1724 ± 640	2930 ± 743	5393 ± 1434
C_{max} [pg/mL]	36.4 ± 12.0	48.9 ± 18.8	89.6 ± 53.3	322.8 ± 306.7
t_{max} [h]	6.2 ± 3.8	7.1 ± 5.5	8.4 ± 4.7	7.2 ± 4.4
t½ [h]	16.7 ± 6.1*	18.0 ± 3.5	22.0 ± 8.8	19.0 ± 5.2
E_1				
$AUC_{0-\infty}$ [pg/mL·h]	4447 ± 1645	6820 ± 2273	8450 ± 2259	16266 ± 7281
C_{max} [pg/mL]	174.8 ± 49.3	253.3 ± 73.4	282.8 ± 75.5	597.5 ± 153.5
t_{max} [h]	8.0 ± 4.0	3.3 ± 1.5	4.2 ± 2.0	6.2 ± 2.6
t½ [h]	13.8 ± 5.8	17.3 ± 6.3	17.3 ± 2.5	16.5 ± 6.7
NET				
$AUC_{0-\infty}$ [ng/mL·h]	15.00 ± 4.44	22.87 ± 12.67	40.43 ± 15.35	48.46 ± 19.19
C_{max} [ng/mL]	3.94 ± 1.37	7.54 ± 3.33	8.81 ± 2.48	12.87 ± 4.03
t_{max} [h]	0.67 ± 0.26	0.75 ± 0.27	1.17 ± 0.41	1.00 ± 0.00
t½ [h]	8.0 ± 2.4	7.5 ± 2.0	8.6 ± 2.0	8.1 ± 1.8

* N=5

Concentrations of NET decreased in a bi-exponential manner. $t_{½\alpha}$ in the mean was 41 to 51 minutes.

CONCLUSION

Single doses of a combination of E_2 and NETA at four dose levels were well tolerated and no abnormal findings in any safety parameter were evaluated as drug related for any subject. No differences in safety profiles among the four doses were observed.

The mean t_{max} of E_2 after the four doses was in the range of 6.2 to 8.4 hours, whereas the corresponding values for NET ranged from hours.

Results indicated a dose proportionality for the $AUC_{0-\infty}$ and C_{max} of E_2 and NET in the dose ranges administered. No final conclusions can be made, however, referring to the low number of 6 subject per dose group.

The mean t½ of E_2 and E_1 were in the ranges of 16.7 to 22.0 hours and 13.8 to 17.3 hours, respectively. The mean t½ of NET was in the range of 7.5 to 8.6 hours.

Synopsis for KLIM/PD/13/J

Title of Trial A phase I, randomized, single blind, placebo controlled, parallel group multiple dose trial to evaluate the tolerability, safety and pharmacokinetics of two preparations of 17β-estradiol (E_2) combined with norethisterone acetate (NETA)	
Investigators	
Trial Site	
In-country Caretaker	
Publications None	
Trial Period First subject screened November 12, 1994 and Last subject completed December 12, 1994	**PHASE OF DEVELOPMENT** Phase I
Objectives The objective of this trial was to evaluate the tolerability, safety and pharmacokinetics of a E_2/NETA combination at two doses administered daily for 14 days in healthy postmenopausal women, both with respect to comparing the two doses to each other and comparing single dose pharmacokinetics with multiple dose pharmacokinetics.	
Methodology Single center, single blind, placebo controlled, parallel group trial in which each subject received either 14 single daily doses of Kliogest Low Dose with 1 mg 17β-estradiol (E_2) and 0.5 mg norethisterone acetate (norethindrone acetate, NETA) or 14 single daily doses of Kliogest with 2 mg E_2 and 1.0 mg NETA or 14 daily doses of Placebo. Assignment to the product was done by random, with eight subjects in each of the two dose groups, six of whom received active drug and two received placebo. Procedures for evaluation of tolerability included gynecological examinations and laboratory assessments of hematology, coagulation, biochemistry and urinalysis during screening and at completion of the trial, vital signs (blood pressure, pulse rate and body temperature) measured eleven times each on days 1 and 7 and thirteen times on day 14, and questioning for adverse events during the trial period. Blood samples for determination of plasma concentrations of E_2, E_1 and norethisterone (NET) were collected up to 24 hours after dosing on days 1 and 7 and up to 72 hours after dosing on day 14. The following main pharmacokinetic parameters were derived: Area under the curve (AUC), maximal concentration (C_{max}), time of maximal concentration (t_{max}) and terminal half-life ($t_{½}$) for all three compounds.	
Number of Subjects 17 healthy postmenopausal women were enrolled and randomized 16 completed the trial	
Diagnosis and Main Criteria for Inclusion The key inclusion criteria were: healthy Japanese women with at least 1 year of amenorrhea or 3 months of surgical menopause, normal gynecological examination, aged 40-70 years	

Test Product, Dose and Mode of Administration, Batch Number

Preparation 1: Kliogest Low Dose (1 mg E_2 + 0.5 mg NETA), batch no.: 215345

Preparation 2: Kliogest (2 mg E_2 + 1.0 mg NETA). Batch no.: 208750

Oral multiple dose administration, 1 tablet once daily in the morning.

Duration of Treatment

Multiple dosing once daily for 14 days

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo, batch no. 313441

Criteria for Evaluation

Safety

Screening procedures included a gynecological examination, including Maturation Index, smear test and Papanicolaou smear test, palpatory and ultrasound breast examination, and laboratory assessments of hematology, biochemistry and urinalysis. Except for the Maturation Index test and ultrasonic breast examination, these tests were repeated upon trial completion. Vital signs (blood pressure, pulse rate and body temperature) were measured repeatedly on days 1, 7 and 14. Any adverse events, reported spontaneously by the subjects or observed by the investigator, were recorded.

Pharmacokinetics

AUC_{0-24h}, C_{max} and t_{max} for unconjugated estradiol (E_2) and unconjugated estrone (E_1) after baseline-correction and for unconjugated norethindrone (NET), evaluated separately for days 1, 7 and 14. Terminal half-life (t½) on day 14. Also $AUC_{0-\infty}$ on day 1 and AUC_{0-72h} of unconjugated E_2 and E_1 on day 14.

Statistical Methods

Clinical laboratory results pre-trial and post-trial were compared by Wilcoxon test for paired samples.

Safety Results

Any abnormal findings in vital signs, laboratory tests or on gynecological examination, as far as those occurred, never were thought to be related to the trial drug for any subject for either of the two groups.

One serious adverse event of acute close angle glaucoma occurred in one subject on Day 6. The event was considered not to be related to trial product. The subject was withdrawn and replaced.

Several subjects reported vaginal bleeding (mostly after treatment), vaginal discharge and breast tenderness in both treatment groups. The severity was assigned as mild or moderate. No differences between the two doses in relation to the frequency and intensity of symptoms were seen.

Pharmacokinetic Results

Dose Proportionality

After multiple dosing the results of AUC_{0-72h} and C_{max} of E_2 and E_1 as well as AUC_{0-24h} of NET are in conformity with an assumption of dose proportionality whereas the C_{max} of NET was lower after the highest dose than expected.

MD vs. SD (E_2 and E_1)

Repeated oral dosing of 1 mg E_2 + 0.5 mg NETA for 14 days increased plasma E_2 concentrations, as assessed by the $AUC_{0\text{-}24h}$, by a factor of 1.9 when compared with the $AUC_{0\text{-}24h}$ after the first administration. The corresponding ratio with daily doses of 2 mg E_2 + 1 mg NETA was 1.7. Means of C_{max} and $AUC_{0\text{-}24h}$ were slightly higher on day 14 than on day 7. This however can be considered a chance effect due to variability of the data. t½ and $AUC_{0\text{-}\infty}$ could not be determined with sufficient reliability on day 1 and on day 7.

Generally, plasma levels of E_1 were higher than those measured for E_2. Although results for E_1 on day 14 also were slightly higher than on day 7, the differences in C_{max} and $AUC_{0\text{-}24h}$ of E_1 were much less pronounced than for E_2.

Kliogest Low Dose	Single Dose	Multiple Dose	
1 mg E_2 + 0.5 mg NETA (N = 6)	Day 1	Day 7	Day 14
E_2 (baseline corrected)			
C_{max} (pg/ml)	61.7±30.3	78.7±28.4	90.4±36.2
t_{max} (h)	3.6±2.7	4.3±3.8	4.5±3.7
t½ (h)	-	-	15.5±4.6
$AUC_{0\text{-}24h}$ (h·pg/ml)	812.6±312.6	1345.5±545.3	1501.7±716.4
$AUC_{0\text{-}72h}$ (h·pg/ml)	-	-	2398.9±1344.5
E_1 (baseline corrected)			
C_{max} (pg/ml)	144.3±25.1	203.2±38.3	243.8±48.5
t_{max} (h)	4.5±2.8	4.0±3.1	3.3±2.6
t½ (h)	-	-	16.8±6.9
$AUC_{0\text{-}24h}$ (h·pg/ml)	1973.5±385.6	2862.0±788.0	3028.1±791.0
$AUC_{0\text{-}72h}$ (h·pg/ml)	-	-	5406.03±1542.8

Kliogest	Single Dose	Multiple Dose	
2 mg E_2 + 1 mg NETA (N = 6)	Day 1	Day 7	Day 14
E_2 (baseline corrected)			
C_{max} (pg/ml)	83.3±14.3	142.5±37.8	151.0±36.3
t_{max} (h)	6.6 ± 3.6	4.2±1.9	3.2±1.0
t½ (h)	-	-	17.5±4.9
$AUC_{0\text{-}24h}$ (h·pg/ml)	1457.4±260.6	2190.7±274.4	2479.5±618.7
$AUC_{0\text{-}72h}$ (h·pg/ml)	-	-	4270.3±1302.9
E_1 (baseline corrected)			
C_{max} (pg/ml)	275.5±77.2	371.2±128.7	419.3±190.1
t_{max} (h)	6.3±2.9	6.0±2.4	5.0±2.8
t½ (h)	-	-	19.8±3.2
$AUC_{0\text{-}24h}$ (h·pg/ml)	4473.2±1251.7	6347.3±2151.7	6556.1±2676.9
$AUC_{0\text{-}72h}$ (h·pg/ml)	-	-	10992.1±4101.1

MD vs. SD (NET)

Repeated oral dosing of Kliogest for 14 days increased plasma NET levels (AUC_{0-24h}) to 1.4 and 1.7 times the levels seen after the initial dose of 1 mg E_2 + 0.5 mg NETA and 2 mg + 1 mg NETA, respectively. Differences in AUC_{0-24h} and C_{max} between days 7 and 14 did not allow a clear conclusion. t½ showed a small, irrelevant increasing trend.

Kliogest Low Dose 1 mg E_2 + 0.5 mg NETA	Single Dose Day 1	Multiple Dose Day 7	Day 14
C_{max} (ng/ml)	5.48±1.80	6.09±2.18	8.38±3.20
t_{max} (h)	0.7±0.3	0.8±0.3	0.5±0.0
t½ (h)	7.42±1.94	8.50±1.33	9.22±1.57
$AUC_{0-\infty}$ (h·ng/ml)	21.76±11.84	—	—
AUC_{0-24h} (h·ng/ml)	24.87±8.69	25.56±13.90	33.85±18.71
Kliogest 2 mg E_2 + 1 mg NETA	Single Dose Day 1	Multiple Dose Day 7	Day 14
C_{max} (ng/ml)	7.41±1.38	9.05±1.89	10.31±2.56
t_{max} (h)	1.3±0.5	1.2±0.4	1.0±0.0
t½ (h)	8.12±2.15	8.80±2.31	9.98±2.58
$AUC_{0-\infty}$ (h·ng/ml)	35.23±9.84	—	—
AUC_{0-24h} (h·ng/ml)	31.97±7.68	45.09±10.33	55.21±11.14

CONCLUSION

- No differences between the two dose levels in relation to safety parameters were seen.
- Observed pharmacokinetic parameters showed a large variability between subjects.
- Repeated oral dosing for 14 days appeared to increase bioavailability (AUC) around 1.7 times of levels seen after the initial dose.
- AUC-ratios Kliogest Low *Dose* (1 mg E_2 + 0.5 mg NETA) vs. Kliogest (2 mg E_2 + 1 mg NETA) were about 1:1.7 for E_2 and NET despite a ratio of 1:2 of doses administered. The corresponding ratio was 1:2.2 for E_1. Taken the number of subjects into consideration and the large variability of data, no clear conclusion with respect to dose proportionality can be drawn. Data however did not give any hints of a relevant deviation from proportionality except for C_{max} where this might be possible.
- The half-lifes t½ of the three compounds E_2, E_1 and NET were about 16, 18 and 9.5 hours, respectively, after 14 days of dosing.