CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-258

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MEMORANDUM

Clinical Pharmacology and Biopharmaceutics (CPB)
Resubmission of Climara Pro™

NDA 21-258

Proposed Tradename:	**Climara Pro™ (Estradiol and Levonorgestrel Matrix Transdermal System**
Sponsor:	**Berlex Laboratories, Inc. 340 Changebridge Road P.O. Box 1000 Montville, NJ 07045-1000**
Proposed Indication:	**Treatment of moderate to severe vasomotor symptoms associated with the menopause.**
Proposed Claim:	
Dosage/Form/Route:	**0.045 mg estradiol/0.15 mg levonorgestrel administered daily via a transdermal 22 cm^2 system in a continuous combined regimen. The transdermal system is intended to be applied once weekly for all four weeks of a 28-day cycle.**
Date of Class 1 Resubmission:	**September 19, 2003**
Original CPB NDA Review:	**June 1, 2001**
Original CPB Reviewer:	**Ron Kavanagh, Pharm.D., Ph.D.**
Reviewer of Resubmission:	**Ameeta Parekh, Ph.D.** Ameeta Parekh 11/20/03
Date of Review:	**November 20, 2003**

The original review for NDA 21-258 was completed by the Office of Clinical Pharmacology and Biopharmaceutics. The labeling was not finalized at this stage since a non-approval action was taken due to deficiencies in clinical data as determined by DSI. The current submission addresses the clinical efficacy data that were previously deemed deficient as well as the labeling of Climara Pro™.

Recommendation:
The label has been updated to include all recommendations provided by the Office of Clinical Pharmacology and Biopharmaceutics. The NDA is acceptable from OCPB perspective.

11/20/03

John Hunt
Deputy Division Director
DPE II/OCPB

NDA 21-258
Climara Pro™ transdermal system
(estradiol/levonorgestrel) 0.045/0.015, 0.045/0.030, and 0.045/0.040 mg/day
Berlex laboratories, Inc.

Biopharmaceutics Review

No Biopharmaceutics review was required for this review cycle 2.

Addendum to the Review, NDA 21258, Climara Pro

From: Ameeta Parekh, Ph.D.

Subject: NDA 21-258

This addendum addresses the outstanding issues from the Clincial Pharmacology and Biopharmaceutics Review, namely, adhesion, release specification and comments conveyed to the sponsor. The comments from the reviewer (Dr. Ron Kavanaugh) on p. 36 of the review were conveyed by the Project Manager (Diane Moore) on June 15, 2001.

Adhesion of the Climara Pro

Adhesion of the Climara Pro transdermal systems was reviewed; the following information should be included in the label:

In-vitro release data

In-vitro release data was submitted by the sponsor and was reviewed by the Chemist (Dr. Amit Mitra) who discussed this with the Clinical Pharmacology and Biopharmaceutics Team Leader (Ameeta Parekh). The release specifications (attached) are acceptable.

3 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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/s/

Ameeta Parekh
6/15/01 02:04:38 PM
BIOPHARMACEUTICS

John P. Hunt
6/15/01 02:10:03 PM
BIOPHARMACEUTICS

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review – Addendum I

NDAs:	21-258
Type of Submissions:	NDA 4/S
Generic Name:	Estradiol Levonorgestrel Adhesive Matrix Transdermal Delivery System
Strengths:	0.045 / 0.015 mg/day nominal delivery 22 cm^2 (45 / 15 µg/day) 0.045 / 0.030 mg/day nominal delivery 22 cm^2 (45 / 30 µg/day) 0.045 / 0.040 mg/day nominal delivery 30 cm^2 (45 / 40 µg/day)
Brand Names:	ClimaraPro™
Sponsor:	NJ Berlex Laboratories, Inc. Montville, NJ
Submission Date(s):	June 29, 2000 January 03, 2001 January 12, 2001 February 7, 2001
Related IND(s)	51,188
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

This addendum is to clarify a statement on the first page of the ClimaraPro™ review.

On the first page the product strengths are listed as nominally delivering 45 mg/day of estradiol. However, later on the same page the following is written:

> ***What are the products and the proposed indications?***
>
> *...Each formulation is intended to deliver — of estradiol and 15, 30 or 40 µg/day of levonorgestrel. ...*

The sponsor's original **intent** was to create a formulation that delivered —

. Consequently, the labeled delivery rate was changed to reflect this.

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/s/

Ron Kavanagh
6/1/01 03:58:55 PM
BIOPHARMACEUTICS

Ameeta Parekh
6/15/01 11:30:19 AM
BIOPHARMACEUTICS

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDAs:	21-258
Type of Submissions:	NDA 4/S
Generic Name:	Estradiol Levonorgestrel Adhesive Matrix Transdermal Delivery System
Formulation(s); **Strength(s);** **Route(s)**	Estradiol / Levonorgestrel Adhesive Matrix Transdermal Delivery System 0.045 / 0.015 mg/day nominal delivery 22 cm^2 (45 / 15 µg/day) 0.045 / 0.030 mg/day nominal delivery 22 cm^2 (45 / 30 µg/day) 0.045 / 0.040 mg/day nominal delivery 30 cm^2 (45 / 40 µg/day)
Brand Names:	ClimaraPro™
Sponsor:	Berlex Laboratories, Inc. Montville, NJ
Submission Date(s):	June 29, 2000 January 03, 2001 January 12, 2001 February 7, 2001
Related IND(s)	51,188
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Note to the FREEDOM OF INFORMATION OFFICE:

The chemistry section and APPENDIX 1 of the review contains proprietary information and must be redacted.

Please note that the product is produced by 3M Pharmaceuticals under contract to Berlex Laboratories, Inc.. Consequently, the chemistry section must be redacted prior to release of this review to Berlex Laboratories, Inc..

I. REVIEW ISSUES / QUESTIONS

What are the products and the proposed indications?

This is an adhesive matrix transdermal system containing two hormonal components, estradiol and a progestational agent, levonorgestrel, that is intended for use in post-menopausal women.

There are 3 proposed formulations with an intended application period of 1 week per system. Each formulation is intended to deliver [redacted] µg/day of estradiol and 15, 30 or 40 µg/day of levonorgestrel. The estradiol component is intended to alleviate symptoms associated with menopause and the levonorgestrel is intended to decrease the risk of endometrial hyperplasia due to the estrogen component.

The proposed indications are as follows:

In women with an intact uterus, CLIMARAPRO™ (estradiol/levonorgestrel transdermal delivery system) is indicated for the following:

- Treatment of moderate-to-severe vasomotor symptoms associated with menopause

Is the clinical trial formulation the same as the to-be-marketed formulation?

Yes, all batches used in pivotal clinical pharmacology, bioavailability and clinical efficacy studies had the same qualitative/quantitative composition and were manufactured at the same facility as the proposed to-be-marketed product.

** **Are the proposed drug product release methods and specifications acceptable?**

Currently, insufficient data has been submitted to assess the adequacy of the specifications and additional data has been requested.

What are the bioavailability and pharmacokinetic characteristics?

Four pharmacokinetic/bioavailability studies were performed. Two single dose studies that examined all 3 to-be-marketed formulations in comparison to a single dose of levonorgestrel 90 µg orally in combination with Climara®, or it's claimed European equivalent. Plus, two 4-week multiple dose studies that examined all 3 to-be-marketed formulations.

With a single dose, mean estradiol exposure appears to increase with levonorgestrel exposure. There's also less fluctuation and slightly lower exposures than observed with the estradiol only products (~90%).

Upon multiple dosing the exposure to estradiol decreases over time with an accumulation ratio of approximately 0.7 after 4 weeks. This decrease in exposure may be due to enhanced elimination secondary to levonorgestrel. In spite of this, the average reported 'Cmin' values at the end of 4 weeks of treatment are all approximately $\geq$ 27.5 pg/ml, which should be sufficient to provide a pharmacologic effect.

It was noticed that the reported 'Cmin' values are not the true Cmin values in at least one of the multiple dose studies. Instead they are the concentration at the end of the 4th patch wear period. In contrast, in a few cases the true Cmin values occurred in the middle of the dosing interval. Consequently, the true average Cmin min will be slightly lower. Although the true mean values should still be close enough to the reported values such that any conclusions should be the same. For labeling purposes the sponsor will need to provide the correct values.

A similar effect of levonorgestrel is also seen on estrone as is seen with estradiol, i.e. an inverse relationship between levonorgestrel dose and estrone exposure with single dosing and decreased estrone exposure over time. After 4 weeks of treatment, estrone to estradiol AUC ratios are approximately 1.0. The average estrone 'Cmin' after 4 weeks with the lowest levonorgestrel dose is almost double the concentration observed with the highest dose. However, this is due to a single outlier who may not have been postmenopausal, and when this subjects values are excluded Cmins are similar across doses.

A similar effect of levonorgestrel is also seen on estrone sulfate with single dosing. Estrone sulfate to estradiol AUC ratios range from 16 – 21 with single dosing. No data on estrone sulfate was provided for the lowest levonorgestrel dose upon multiple dosing. Consequently, there's insufficient data to discern any patterns upon multiple dosing.

For single doses of levonorgestrel the AUCs of the 3 formulations are roughly in a ratio of 1:2:3 in the order of the intended deliveries. For the lowest strength of levonorgestrel the AUC is approximately the

same as observed with 3 x 30 µg Microlut™ (levonorgestrel) tablets. Tmax increases as the levonorgestrel dose decreases (69, 77.5, 101 hours), consequently the Cmax ratio of the higher strengths relative to lower strengths are quite high and the Cav and 'Cmin' ratios are much lower. This is seen in the different degrees of fluctuation observed with the 3 formulations, (23.2%, 39.4% and 53.0% from the lowest to highest strengths).

Upon multiple dosing there's too much variability in levonorgestrel metrics to clearly discern any patterns, however, Tmax is at 2-3 days, and by inspection the increase in exposure appears to be less than dose proportional. Although the sponsor's statistical analysis does demonstrate proportionality. Removing the data from the outlier would improve the proportionality, but not by much.

Is the estradiol component of the lowest strength patch bioequivalent to the middle strength?

The lowest strength patch (E2/LVG 45/15) was not studied in a clinical efficacy trial. However, its' ability to prevent endometrial hyperplasia was examined in a prevention study. Consequently, the product needs to be comparable to one of the other strength formulations, that has been demonstrated to be efficacious, in order for clinical efficacy against menopausal and post-menopausal symptoms to be assumed.

Upon multiple dosing at 4 weeks, the lowest strength patch (E2/LVG 45/15) is bioequivalent to the middle strength system (E2/LVG 45/30), with the estradiol exposure to the lowest strength somewhat higher than with the middle strength system. However, the active metabolite estrone is not bioequivalent, with the estrone exposure with the lower dose approximately double that with the middle dose.

In spite of this, since the estradiol and estrone exposures are higher and not lower they should provide the same or better control of symptoms and should be comparable clinically so long as the incidence of side effects and the prevention of endometrial hyperplasia are acceptable to the medical reviewers.

When the data from the outlier is excluded, (the woman who may not have been post-menopausal) the average pharmacokinetic metrics for estradiol and estrone for the middle and lowest doses become almost identical, and it's apparent even without recalculations that estradiol bioequivalence would be easily met.

Is the product performance consistent across time?

There is insufficient data to determine product performance over time. However, there are no penetration enhancers in the product. The formulations used in the clinical efficacy trials ranged in age from 9 to 43 months old. Products in the pharmacokinetic studies were 22 months old with the exception of an 8 month old product in the bioequivalence study that showed lower bioavailability than the same formulation at 22 months in another study. In conclusion, there is no indication that there is a product performance problem over time.

Are the nominal transdermal delivery rates (TDR) accurate?

The nominal delivery rate for estradiol for Climarapro™ is based upon a comparison of AUCs with Climara® and Cerulla™, a product that the sponsor claims is approved in Europe and is the same as Climara®. The nominal transdermal delivery rates for levonorgestrel is based upon a comparison of AUCs with a 90 µg oral dose of levonorgestrel. The sponsor was originally informed that use of average steady-state concentrations and clearance was acceptable to estimate the transdermal delivery rate, however, subsequent to this the sponsor was requested to base TDR on system depletion data.

It's likely that those who prescribe Climara® would also be likely prescribe Climarapro™. Since the nominal delivery rates of various estradiol transdermal systems vary considerably from their actual

delivery rates, referencing Climarapro's TDR to the TDR of Climara based on AUC mean ratios appears acceptable; provided the sponsor can substantiate the equivalence of Cerulla™ to Climara®.

The referencing of levonorgestrel delivery rate to the exposure of levonorgestrel after an oral dose is based upon several explicit and implicit assumptions; including, systemic oral and transdermal bioavailabilities of 1.0, dose proportionality, and lack of a drug interaction with estradiol.

Data has not been provided by the sponsor to support these assumptions, however, since there are currently no transdermal levonorgestrel products, referencing a nominal transdermal delivery rate to systemic oral exposure appears acceptable. Provided the sponsor can provide acceptable support for the explicit and implicit assumptions.

Is there and *in vitro – in vivo* correlation?

The possibility of *in vitro – in vivo* correlations was not examined.

Were the patch handling, application and wear instructions consistent across studies?

Yes.

How well do the patches adhere?

In the 4 pivotal pharmacokinetic studies approximately 8% – 17.4% of patches demonstrated some lifting and 0.56% of patches were replaced. These studies were not adhesion studies and there is insufficient detailed data to determine the various degrees of adhesion and the duration of time patches were detached. There is presumably a separate adhesion study. However, the study report was unavailable to the reviewer. When the data is available an addendum to the review will be written.

What is the skin tolerability of the patches?

33% – 100% of subjects experienced application site reactions in the two single dose PK studies that were observed by health care professionals and application site reactions were recorded by 18% - 50% of subjects in diaries in the multiple dose PK studies. The incidence was always lowest with the lowest strength and size patch (E2/LVG 45/15 22 cm^2) and increased with dose or size. Two subjects in one of the single dose studies had severe and prolonged application site reactions. A separate tolerability study was submitted to section 8 of the NDA and should provide more complete data.

II. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA #21-258 submitted June 29, 2000, with supplementary submissions January 03, 2001 and January 12, 2001.

OCPB finds this application acceptable and recommends that the application be accepted provided that currently outstanding issues are adequately resolved.

Certain information has been requested either from the sponsor, or from internal FDA sources, but was not received in sufficient time to finalize the review. When these data are provided they will be reviewed and addenda to the review will be written. The requested information may be found in section IX, Information Requested – Addenda to Review to be written, on page 36.

Comments and labeling comments should be communicated to the sponsor as appropriate (see section X, Comments to the Sponsor, on page 36, and section XI, Labeling Comments, on page 36).

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B. List of Abbreviations

ANCOVA..... Analysis of Covariance
ANOVA..... Analysis of Variance
AUCτ..... AUC Under the Curve for the dosage interval
AUC0-t..... Area Under the Concentration time curve from time 0 to time t
AUC0-tlast..... Area Under the Concentration time curve from time 0 to last time drug is measurable
AUCt1-t2..... Area Under the Concentration time curve from time 1 to time 2
AUC(s)..... Area(s) Under the Concentration time curve(s)
BA..... Bioavailability
BE..... Bioequivalence
BMI..... Body Mass Index
Cav..... Average Concentration
CBG..... Cortisol Binding Globulin
CI..... Confidence Interval
cm^2..... Square Centimeters
Cmax..... Maximum Concentration
Cmin..... Minimum Concentration
Conc..... Concentration
cps..... counts per second
CTF..... Clinical Trial Formulation
DMF..... Drug Master File
E1..... Estrone
E1 SO4..... Estrone Sulfate
E2..... Estradiol
F..... Fraction of Dose Bioavailable
FI..... Fluctuation Index
FSH..... Follicle Stimulating Hormone
GC/MS..... Gas Chromatography / Mass Spectrometry
IVIVC..... *In vitro – in vivo* correlation
LC/MS/MS..... Liquid Chromatography / Mass Spectrometry / Mass Spectrometry
LLOQ..... Lower Limit of Quantitation
LNG..... Levonorgestrel
LS..... Least Squares
LVG..... Levonorgestrel
md or MD..... Multiple Dose
N/A or n/a..... Not Available or Not Applicable
ND..... Not Determined
NLT..... Not less than
NMT..... Not more than
NF..... National Formulary
nr or NR..... Not Reported
NS..... Nonsmoker
OCPB..... Office of Clinical Pharmacology and Biopharmaceutics
OTC..... Over the Counter (nonprescription) drug
Ph. EUR. ..... European Pharmacopeia
PD..... Pharmacodynamics
PK..... Pharmacokinetics
po..... per os (by mouth)
q..... quinque (every)
QC..... Quality Control or Quality Control Sample
QQ..... Qualitative/Quantitative Composition
Rand..... Randomized
RCF..... Relative Centrifugal Force
RIA..... Radioimmunoassay
RP HPLC..... Reverse Phase High Performance Liquid Chromatography
rpm..... Revolutions per minute
R..... Reference or Accumulation Ratio
RT..... Room Temperature
Rx..... Prescription Medication
SA..... Surface Area
sd or SD..... Standard Deviation or Single Dose
SHBG..... Serum Hormone Binding Globulin
SPE..... Solid Phase Extraction
STD..... Standard
Subj..... Subject
$t_{1/2}$..... Half-life
T..... Test
TBM..... To-Be-Marketed
TDR..... Transdermal Delivery Rate
TDS..... Transdermal Delivery System
Tmax..... Time to Maximum Concentration
USP..... United States Pharmacopoeia
UV..... Ultraviolet
w/w..... % weight in weight (gm per 100 grams)
°C..... Degrees Centigrade

IV. LISTS OF STUDIES, PERFORMED, PROVIDED, AND REVIEWED

The pivotal bioavailability, pharmacokinetic, bioequivalence studies that were provided in section 6 and that were reviewed are listed in Table 1.

Table 1 Pivotal Bioavailability / Pharmacokinetic Studies

Protocol Number	Report Number	Study Title	Comments
ME98046	AW78	Open-label, randomized, cross-over study to determine the average daily delivery of estradiol (E2) and levonorgestrel (LNG) after single transdermal administrations of two different patch formulations containing E2 and LNG (test 1,2) in comparison with a standard treatment (single transdermal administration of an E2 patch + oral administration of LNG) in 48 healthy postmenopausal women.	Pivotal SD study of 4.4/3.75 30 cm^2 and 4.4./2.75 22 cm^2 systems
303341	A00084	Open-label, randomized, cross-over study to determine the average daily delivery of estradiol (E2) and levonorgestrel (LNG) after single transdermal administrations of a patch formulation (SH P 604 FM) containing E2 and LNG (test) in comparison with a standard treatment (single transdermal administration of an E2 patch + oral administration of LNG) in 24 healthy postmenopausal women.	Pivotal SD study of 4.4/1.39 22 cm^2 system
ME99003	B819	An Open-Label, Parallel Group Study to Determine the Pharmacokinetic Properties of 17 β-Estradiol, Estrone, Estrone Sulfate and Levonorgestrel Following Repeated Weekly Application of Estradiol/Levonorgestrel 30 cm^2 or 22 cm^2 Transdermal Combination Patches for Four Consecutive Weeks in Healthy Postmenopausal Women.	Pivotal MD study of 4.4/3.75 30 cm^2 and 4.4./2.75 22 cm^2 systems
304180	6199	An Open-Label, Two Period Crossover Study To Compare The Absorption Of 17 β-Estradiol During The Fourth Consecutive Weekly Application of Two Patch Strengths Of An Estradiol/Levonorgestrel Transdermal Drug Delivery System in Healthy Postmenopausal Women.	Pivotal MD BE study between 4.4/2.75 and 4.4/1.39 22 cm^2 systems

An adhesion study appears to have been submitted to section 8 of the NDA and appears to be one of the studies in the following table (see Table 2). This reviewer has been unable to obtain this study in spite of repeated requests. When this data is obtained and reviewed, an addendum to this review will be written.

Table 2 Adhesion and Tolerability Studies

3M-1304-LEVO	B573	Modification Study of a Transdermal Adhesive Combination Patch Containing Estradiol and Levonorgestrel
3M-1303-LEVO	98185	Twenty-one day cumulative irritation study of a transdermal adhesive combination patch containing estradiol and levonorgestrel
3M-1309-PLAC	99010	Adhesion and irritation study of the combination patch transdermal delivery system (estradiol and levonorgestrel) using a 22 cm^2 placebo patch and a 25 cm^2 CLIMARA® patch system

Additional preliminary bioavailability and pharmacokinetic studies with development formulations that were mentioned but were not included in section 6 of the NDA submission are listed in Table 3. These studies were not reviewed.

Table 3 Non-pivotal Bioavailability / Pharmacokinetic / Clinical Pharmacology Studies of Development Formulations

Protocol Number	Report Number	Study Title	Comments
ME97067	B510	Relative bioavailability of 17β-estradiol, estrone, and levonorgestrel following application of two estradiol/levonorgestrel 22 cm^2 transdermal combination patches containing different adhesives in healthy postmenopausal women.	Preliminary formulation vs. TBM formulation 4 day application
ME96035	97031	Pilot bioequivalence study comparing 17β-estradiol from two 22 cm^2 estradiol and levonorgestrel transdermal systems, each containing 4.4 mg 17β-estradiol and 2.75 mg levonorgestrel, with 17β-estradiol from a 25 cm^2 CLIMARA® (estradiol transdermal system) patch containing 7.8 mg 17β-estradiol	Preliminary development formulation compared to CLIMARA®
ME96015	AM37	Pharmacokinetic characterization of three true combination patches containing levonorgestrel and estradiol	3 preliminary formulations made in
Other Studies			
97093	RR AZ11 AW92	SD x 4 days bioavailability study of 3 Development formulations SHP 604 EN, SHP 604 GN, SHP 604 HN, SHP 604 IN	Did not include TBM
97094	RR AW91	Skin sensitization study	Did not include TBM
97203	Report incomplete	SH P 604 EM 11 cm^2 and 22 cm^2 MD 28 day BA/PK study including safety, tolerability, and adhesion	

V. CHEMISTRY

A. Drug Master File

The transdermal system discussed is manufactured by 3M Pharmaceuticals under contract to Berlex Laboratories, Inc.. Chemistry information may be found in the following drug master file (DMF).

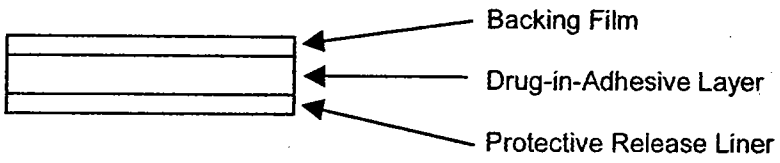
DMF —
Type II
Date of Submission
—
Estradiol/Levonorgestrel Transdermal Delivery System
Manufactured in Northridge, CA

B. Manufacturing, Packaging, Testing & Release Site

The following site will perform all manufacturing, as well as primary, secondary and tertiary packaging, in addition to product testing and release.

3M Pharmaceuticals
19901 Nordhoff
Northridge, CA

C. Schematic Diagram of Transdermal Delivery System



D. Qualitative / Quantitative Composition

Table 4 Qualitative / Quantitative Composition of To-Be-Marketed Formulations

Formulation Code	SH P 604 DM		SH P 604 EM		SH P 604 FM		Function
Surface Area	30 cm^2		22 cm^2		22 cm^2		
Proposed Nominal Delivery Rates E2 / LVG (mg/day)	0.045 / 0.040		0.045 / 0.030		0.045 / 0.015		
Component	Amount per System						
	(mg)	% (w/w)	(mg)	% (w/w)	(mg)	% (w/w)	
Estradiol Hemihydrate, Ph. Eur., Estradiol, USP	4.65		4.55		4.55		Active
Equivalent to: Estradiol Anhydrous	4.5		4.40		4.40		—
Levonorgestrel, Ph. Eur., Levonorgestrel, USP	3.75		2.75		1.39		Active
	246.8		179.9		181.2		Adhesive
	45.0		33.0		33.0		—
Film, Polyester, Clear, one-side silicon coated	≥30 cm^2		≥22 cm^2		≥22 cm^2		— Liner
Film, Polyester	—		—		—		Alternate — Liner
Film, Polyester one-side silicone coated	—		—		—		Alternate — Liner
Film, two side polyethylene	30 cm^2		22 cm^2		22 cm^2		Backing Film
	✓		✓		✓		Printing Ink for Backing
Total	300.2	100.0	220.2	100.0	220.14	100.0	
Additional Manufacturing Components that do not appear in the Final Product							

The 3 to-be-marketed formulations (TBM) are summarized in Table 5 with respect to their major identifying characteristics including: nominal transdermal delivery rate, surface area, and drug content/load.

Table 5 Summary of To-Be-Marketed Formulations

Formulation	Nominal Transdermal Delivery Rate E2/LVG (µg/day)	Surface Area (cm^2)	Estradiol		Levonorgestrel	
			Drug Content (mg)	Drug Load (%)	Drug Content (mg)	Drug Load (%)
SH P 604 DM	45 / 40	30	4.5		3.75	
SH P 604 EM	45 / 30	22	4.4		2.75	
SH P 604 FM	45 / 15	22	4.4		1.39	

A summary of all formulations used in all clinical trials can be found in APPENDIX 1.

E. Primary Packaging

The sponsor has submitted two different options for primary packaging. These packaging options differ only in their (see APPENDIX 1).

All batches used in the clinical trials were packaged in the Pouch (See Table 6

Table 6 Description of Primary Packaging Materials

	Pouch I	Pouch II	Function	
	Pouch	Pouch		

F. Batch Size

The batch size may be either —

For the — batch size, —

Theoretical and practical yields, assuming — are shown in Table 7 for a — batch, as per

Table 7 Theoretical and Practical Yields for a Batch

Formulation Code	Nominal Delivery Rate E2/LVG (µg/day)	Surface Area (cm^2)	Yield (# patches)	
			Theoretical	Practical[a]
SH P 604 DM	45 / 40	30		
SH P 604 EM	45 / 30	22		
SH P 604 FM	45 / 15	22		

G. Formulation Batches Used in Clinical Studies

1. Summary Information

A summary of the information on the formulations and batches used in clinical studies can be found in APPENDIX 1.

2. Age of Systems

It's noteworthy that all except 1 batch of systems used in the pivotal pharmacokinetic, clinical pharmacology and clinical efficacy / safety studies were 22 – 25 months old.

3. Packaging

All primary packaging for the systems used in the pivotal pharmacokinetic, clinical pharmacology, and clinical efficacy and safety studies was —

There was a — from manufacture until primary packaging.

H. Proposed Drug Release Methods and Specifications

1. Proposed Drug Release Methods

The proposed drug release methods are shown in Table 8. There are two different methods proposed. One for the 22 cm^2 patches (method 3557) and one for the 30 cm^2 patch (method 3558).

Table 8 Proposed Drug Release Methods for Estradiol and Levonorgestrel from 22 cm^2 and 30 cm^2 Transdermal Systems

Method Number	3557	3558
Patch Sizes Tested	22 cm^2 full patch	30 cm^2 full patch
Dissolution Apparatus		
Medium		
Volume		
Temperature		
Sampling Times		
Sample Volume		
Sample Preparation		
Analytic Method		

a Discussed with and will be clarified by chemistry reviewer

In contrast to analytic method 3305, the analytic method listed for content testing of estradiol and levonorgestrel is described as — it's claimed that equivalent results are obtained for content testing using —

2. Proposed Drug Release Specifications

a) Proposed Drug Release Specifications – Estradiol

Proposed drug release specifications for estradiol for both methods (all patch sizes) are shown in Table 9.

Table 9 Proposed Estradiol Drug Release Specifications for Methods 3557 and 3558

2 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

VI. BIOANALYTIC METHODS

A. Methods Used and Assay Validation

Estradiol, estrone, levonorgestrel, and SHBG were analyzed in each of the pivotal pharmacokinetic studies. Estrone sulfate was analyzed in all pivotal pharmacokinetic studies except for study 304180, the pivotal bioequivalence study for the E2 / LVG 45 / 15 µg per day formulation.

For each analyte, each study used the same methods and laboratories. A summary of these methods is shown in Table 11. Validation reports for the bioanalytic methods for drugs and metabolites were provided and were found to be acceptable. For estrone sulfate long term stability was not examined. A summary of the validation report assessments can be found in APPENDIX 2.

Table 11 Summary of Bioanalytic Methods Used

Analyte	Estradiol	Estrone	Estrone sulfate	Levonorgestrel	SHBG
Method	GC/MS	GC/MS	LC/MS/MS	RIA	Immunoassay
Biological Matrix	Serum	Serum	Serum	Serum	Serum
Limit of Quantification	5 pg/mL	10 pg/mL	50 pg/mL	8 pg/mL	
Where Performed					
Assay Validation Report #	CA429	CA429	27.1 Project OCE	RR B678	Not provided
Comments	Estradiol and Estrone analyzed simultaneously				kit used. Kits and controls were from various batches.

B. Sample Handling and Storage

Sample handling and storage as per the protocol for each of the pharmacokinetic studies was consistent with the assay validation (see Table 12).

Table 12 Sample Handling Procedures

Analytes	Study Report Number			
	AW78	A00084	B819	6199
Estradiol Estrone Estrone Sulfate Levonorgestrel SHBG	Blood allowed to stand approximately 30 minutes to allow clotting. Serum separated by centrifugation at 4000 RPM (~ 2000 RCF) x 10 minutes at room temperature Serum stored at –18 to –25 °C	Blood allowed to stand approximately 30 minutes to allow clotting. Serum separated by centrifugation at 4000 RPM (~ 2000 RCF) x 10 minutes at room temperature Serum stored at –18 to –25 °C	Blood allowed to stand for 20-30 minutes. Serum separated by centrifugation under refrigerated conditions. Serum stored at –20 °C	Blood allowed to stand for 20-30 minutes. Serum separated by centrifugation under refrigerated conditions. Serum stored at –20 °C

VII. PHARMACOKINETICS

n.b. Almost all values for pharmacokinetic metrics and statistics in this review are as presented by the sponsor without any recalculations, except as noted for the multiple dose PK metrics for report 6199.

A. Single Dose Pharmacokinetics

Single dose pharmacokinetics although not critical to the long-term clinical effects of this formulation. However, they do provide some insight into the formulation's behavior and are thus briefly described.

Two single dose crossover pharmacokinetic studies were performed, report numbers AW78 and A00084.

In the first study, AW78, the two formulations with the greater doses of levonorgestrel, [SH P 604 DM and SH P 604 EM; (E2/LVG 45/40 and 45/30)], were compared to an estradiol only formulation marketed in Europe, Cerulla™. The Cerulla™ was given in combination with a single oral dose of levonorgestrel 3 x 30 µg. The sponsor claimed that Cerulla™ is identical to the US FDA approved Climara™ 12.5 cm^2 system (E2 - 50 µg/day), except that it is made at a European facility. However, no data was provided to support this claim. The levonorgestrel was Microlut® which according to the European Drug Index 4th ed. is marketed in a number of European countries. It is not approved in the US.

In the second study, A00084, formulation SH P 604 FM (E2/LVG 45/15) was compared to a single dose of Climara™ 12. 5 cm^2 (E2 - 50 µg/day) in combination with a single oral dose of levonorgestrel 3 x 30 µg (Microlut®).

Only uncorrected data was reported for these studies and summary statistics as provided by the sponsor are included in APPENDIX 3, protocol design synopses are included APPENDIX 7, and subject demographic data is included in APPENDIX 8.

1. Estradiol

Bioavailability for estradiol appears to follow a rank order, with the formulation containing the highest amount of levonorgestrel exhibiting the highest estradiol bioavailability and the formulation containing the lowest amount of levonorgestrel exhibiting the lowest estradiol bioavailability. This pattern is seen with Cmax, AUC, Cav, and Cmin. However, there are no clear differences between the formulations because the variability observed is so high.

If there is a true difference, it's not possible to tell if it would be due to a drug interaction with levonorgestrel or if it would be due to formulation differences. For example the simultaneous variations in drug content and surface area could result in higher peaks and higher fluctuation with the highest levonorgestrel dosage formulation.

In study A00084 estradiol exposure and fluctuation is lower with both the combination product and with Climara™ compared to exposures in study AW78.

In general, Cmaxs are lower and Cmins are higher with the combination product than with the estradiol only formulations and this is reflected in the lower degree of fluctuation (Mean Fluctuation Index (FI) 70.5% - 94.0% vs. 106% - 126%).

2. Estrone

Similar patterns are seen with estrone. Estrone exposures are rank ordered with a lesser estrone exposure and lower degree of fluctuation seen with the lower levonorgestrel dosage combination formulations. Exposures and degree of fluctuation are also lower with the combination formulations than with Climara®. AUC ratios of estrone to estradiol range from ~88% to 108%.

3. Estrone Sulfate

Similar patterns are also seen with estrone sulfate. Estrone sulfate exposures are rank ordered with a lesser exposure and lower degree of fluctuation seen with the lower levonorgestrel dosage combination formulations. Exposures and degree of fluctuation are also lower with the combination formulations than with Climara®. AUC ratios of estrone sulfate to estradiol range from approximately 16 to 21.

4. Levonorgestrel

For levonorgestrel the AUCs of the 3 formulations are roughly in a ratio of 1:2:3 in the order of the intended deliveries. For the lowest strength, the AUC is approximately the same as observed with 3 x 30 µg Microlut™ (levonorgestrel) tablets.

Median Tmax increases as the levonorgestrel dose decreases (69, 77.5, and 101 hours for the 45/40, 45/30, and 45/15 µg/day formulations respectively). Consequently the Cmaxs of the higher strengths relative to lower strengths are quite high, and the Cav and Cmin ratios are much lower. This is reflected in the different degrees of fluctuation observed with the 3 formulations, (23.2%, 39.4% and 53.0% from the lowest to highest strengths).

B. Multiple Dose Pharmacokinetics

There were two multiple dose pharmacokinetic studies (Reports B819 and 6199) that reported both uncorrected and baseline corrected values. Estradiol, estrone and levonorgestrel concentrations were determined for both studies and metrics were calculated, but estrone sulfate was only measured in the first study (B819).

Study 99003 (report no. B819) examined the pharmacokinetics of the two highest strength levonorgestrel formulations, [SH P 604 DM and SH P 604 EM; (E2/LVG 45/40 and 45/30)], during the first and 4th weeks of application. Study 304180 (report no. 6199) was a bioequivalence study that examined the Cmin of the two lowest dose formulations at the end of each of the first 3 application periods and the complete pharmacokinetic profiles during the fourth application period.

The conclusions drawn from the uncorrected and baseline corrected data are identical. Consequently, the sponsor's uncorrected summary data is follows, and for completeness the sponsor's baseline corrected summary data is presented in APPENDIX 4.

1. Estradiol

Estradiol concentrations decrease from the first to the fourth week of treatment with accumulation ratios of between approximately 0.65 and 0.88. In spite of this, the reported average Cmin values at the end of week 4 for each of the 3 formulations remain at or above 27.5 pg/ml. However, the sponsor appears to have used C_{672}, the time of the removal of patch 4, rather than the true Cmin (at least for study 6199). Although almost all of the true Cmins occur at C_{672} thus the calculated Cmins and accumulation ratios are likely very close the true values, with the true values likely to be slightly lower for Cmin and slightly greater for the fluctuation index. In spite of this the estradiol concentrations should be sufficiently high with all the formulations to provide a pharmacologic effect (see Table 14). However, for labeling purposes the sponsor will need to provide the correct values.

In contrast with the rank order in Cmax with formulation seen in the single dose study, and the evidence of a rank order with the first dose of multiple dose study B819 (see APPENDIX 4 and Table 14). This rank ordering is lost by the forth dose.

It's notable that the baseline value (immediately prior to the first dose) is nearly as high as the Cmins reported. [Baseline value is average of values from only those subjects with measurable estradiol concentrations, (n=10)] Upon investigation, it was found that a single individual had a measured baseline value of [redacted] pg/ml for treatment 1 (E2/LVG 45/15) and a baseline value of [redacted] pg/ml prior to treatment 2

(E2/LVG 45/30). All other subjects had baseline values of 12.3 pg/ml or less for both treatments. Cmin concentrations were also high after about half of the doses with both treatments for this subject. By dose 4 the Cmax and Cmin were much higher than for other subjects for treatment 1 (E2/LVG 45/15), although they were comparable to values from other subjects for treatment 2 (E2/LVG 45/30).

Excluding data from this subject, (1043), the estradiol exposures and pharmacokinetic metrics for treatment 1 (E2/LVG 45/15) are much more consistent with the values from treatment 2 (E2/LVG 45/30). Yet the concentrations are still consistent concentrations with which a pharmacologic effect would be expected, with only 3 subjects have a Cmin <20 pg/ml. Summary metrics excluding subject 1043 are also shown in Table 14.

2. Estrone

A similar pattern of decreasing exposures over time is seen with estrone, although the estrone exposures are higher with the lower levonorgestrel doses. Especially the lowest dose where the Cmin is almost double (72.5 vs. 38 pg/ml) (see Table 15).

Higher estrone exposures are again seen with subject 1043 in report 6199 for treatment 1 (E2/LVG 45/15) as compared to treatment 2 1 (E2/LVG 45/30). Subject 1043 had a single concentration above the upper limit of quantitation and an AUC >10 fold the average of all the other subjects. Excluding subject 1043 the mean values for Cmax, Cmin (i.e. C_{672}) and AUC are almost identical between the two treatments (E2/LVG 45/15 and 45/30) (see Table 15).

3. Estrone Sulfate

There appears to be a similar pattern with estrone sulfate with study B819, although as estrone sulfate concentrations were not determined in study 6199 it's impossible to deduce any patterns in estrone sulfate with levonorgestrel dose (see Table 16).

4. Levonorgestrel

For levonorgestrel there's too much variability to clearly discern any patterns. By inspection the increase in exposure appears to be less than dose proportional (see Table 17),although the sponsor's statistical analysis demonstrates proportionality (see APPENDIX 5).

In report 6199 subject 1043 has the highest exposure to levonorgestrel for both treatment 1 (E2/LVG 45/15) and treatment 2 1 (E2/LVG 45/30), with the pharmacokinetic metrics for levonorgestrel for subject 1043 much higher than the subject(s) with the next highest metrics. If data from subject 1043 was excluded levonorgestrel may appear to be more dose proportional (See Table 13).

Table 13 Levonorgestrel Metrics for Subject 1043 and the Next Highest Metrics in Report 6199

Subject	Cmax (pg/ml)		C_{672} (pg/ml)		AUC (pg/ml x hr^{-1})	
	Treatment 1	Treatment 2	Treatment 1	Treatment 2	Treatment 1	Treatment 2
1043						
1042						
1037						
1031						

5. Serum Hormone Binding Globulin (SHBG)

SHBG is much higher for subject 1043 in report 6199 than for all other subjects and may explain the unusual pharmacokinetics of estradiol, estrone and levonorgestrel in this subject.

Table 14 Summary of Multiple Dose Estradiol Pharmacokinetic Metrics (mean ± SD) Using Uncorrected Data[a]

Study / Report No. / Study No.	B819 99003				6199 304180				
Formulation	SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM		
Content E2 / LVG (mg) SA (cm^2)	4.5 / 3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22		
Nominal TDR E2 / LVG (µg/day)	45 / 40		45 / 30		45 / 30		45 / 15		
Week	1	4	1	4	1	4	1	4	4[c]
Cmax (pg/ml)	92.13 (44.206)	53.02 (11.482)	88.60 (27.700)	63.19 (22.145)		44.2 (14.38)		50.7 (28.61)	47.0 (15.3)
Cmin (pg/ml)	55.60 (24.959)	37.76 (11.438)	40.05 (11.047)	34.53 (10.582)	36.9 (16.7)	27.5 (10.07)	53.2 (68.99)	33.8 (28.71)	29.5 (10.1)
tmax (hr)	48.0 36.0 - 120	60.0 0 - 169	36.0 24.0 - 120	54.0 24.0 - 168		36.0 12.0 - 168		36.0 0.00 - 168	36.0 0.00 - 168
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)	10276.2 (4551.50)	6100.3 (1302.10)	9407.2 (2435.81)	6515.3 (1447.62)		5551 (1661.5)		6002 (1919.0)	5844 (1626.2)
Cav (pg/ml)	61.17 (27.092)	36.31 (7.751)	56.00 (14.499)	38.78 (8.617)		33.0 (9.890)		35.7 (11.42)	
FI (%)	57.55 (28.989)	44.99 (29.603)	84.62 (38.421)	66.72 (47.790)		48.9 (27.26)		47.4 (30.89)	
R[b]	N/A	0.653 (0.1670)	N/A	0.724 (0.1857)		0.876 (0.4057)		0.784 (0.3029)	
$t_{1/2}$ (hr)	N/A	3.129 (1.5452)	N/A	3.030 (0.6777)		ND		ND	ND
Baseline Value (pg/ml)						37.4 (105.1)		30.4 (71.22)	7.8 (1.5)

a Mean and (SD) reported; median (minimum, maximum) reported for tmax
b Accumulation Ratio (R) is based on AUCτ for B819 and Cmin for 6199
c Excluding subject 1043

Table 15 Summary of Multiple Dose Estrone Pharmacokinetic Metrics (mean ± SD) Using Uncorrected Data[a]

Study / Report No. / Study No.	B819 99003				6199 304180				
Formulation	SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM		
Content E2 / LVG (mg) SA (cm^2)	4.5 / 3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22		
Nominal TDR E2 / LVG (µg/day)	45 / 40		45 / 30		45 / 30		45 / 15		
Week	1	4	1	4	1	4	1	4	4[c]
Cmax (pg/ml)	58.78 (19.280)	47.33 (12.266)	58.70 (19.175)	54.97 (25.149)		44.9 (14.58)		81.6 (251.5)	43.0 (12.5)
Cmin (pg/ml)	46.83 (20.056)	38.08 (12.324)	42.44 (15.824)	40.54 (14.951)	37.3 (13.28)	33.7 (11.01)	50.3 (75.11)	72.5 (252.9)	34.5 (12.0)
tmax (hr)	60.0 (12.0, 144)	48.0 (0, 169)	48.0 (24.0, 120)	48.0 (0, 169)		48.0 0.00 - 168		48.0 0.00 - 168	48.0 0.00 – 168
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)	7649.8 (2461.72)	5935.7 (1576.20)	7149.5 (2447.91)	6226.0 (2602.84)		6050 (1890.9)		7642 (10517.8)	6080 (1825.0)
Cav (pg/ml)	45.53 (14.653)	35.33 (9.382)	42.56 (14.571)	37.06 (15.493)		36.0 (11.26)		45.5 (62.61)	
FI (%)	27.86 (18.295)	29.12 (19.389)	41.60 (27.445)	43.85 (73.224)		31.2 (25.51)		26.2 (15.33)	
R[b]	N/A	0.795 (0.1325)	N/A	0.859 (0.1334)		0.949 (0.2507)		0.964 (0.4122)	
$t_{1/2}$ (hr)	N/A	11.179 (5.0791)	N/A	16.833 (9.9842)		ND		ND	
Baseline Value (pg/ml)						32.5 (74.69)		29.0 (57.21)	

a Mean and (SD) reported; median (minimum, maximum) reported for tmax
b Accumulation Ratio (R) is based on AUCτ for B819 and Cmin for 6199
c Excluding subject 1043

Table 16 Summary of Multiple Dose Estrone Sulfate Pharmacokinetic Metrics (mean ± SD) Using Uncorrected Data[a]

Study	Report No. Study No.	B819 99003				6199 304180			
Formulation		SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM	
Content E2 / LVG (mg) SA (cm^2)		4.5 / 3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22	
Nominal TDR E2 / LVG (µg/day)		45 / 40		45 / 30		45 / 30		45 / 15	
Week		1	4	1	4	1	4	1	4
Cmax (pg/ml)		1015.5 (562.49)	673.8 (343.92)	1161.8 (1051.18)	1062.7 (1280.82)	—	ND	—	ND
Cmin (pg/ml)		689.3 (481.42)	455.2 (219.44)	797.3 (933.17)	684.3 (843.09)	—	ND	—	ND
tmax (hr)		108 (48.0, 168)	84.0 (48.0, 169)	60.0 (36.0, 144)	108 (24.0, 174)	—	ND	—	ND
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)		108954.6 (56329.06)	78136.6 (31415.55)	130295.3 (133672.75)	116077.2 (148981.82)	—	ND	—	ND
Cav (pg/ml)		648.5 (335.29)	465.1 (187.00)	775.6 (795.67)	690.9 (886.80)	—	ND	—	ND
FI (%)		52.09 (30.347)	46.75 (25.806)	60.61 (40.696)	58.19 (36.304)	—	ND	—	ND
R[b]		N/A	0.758 (0.1452)	N/A	0.821 (0.1669)	—	ND	—	ND
$t_{1/2}$ (hr)		N/A	10.978 (4.7538)	N/A	19.954 (8.8774	—	ND	—	ND

a Mean and (SD) reported; median (minimum, maximum) reported for tmax
b Accumulation Ratio (R) is based on AUCτ for B819

Table 17 Summary of Multiple Dose Levonorgestrel Pharmacokinetic Metrics (mean ± SD) Using Uncorrected Data[a]

Study / Report No. / Study No.	B819 99003				6199 304180			
Formulation	SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM	
Content E2 / LVG (mg) SA (cm^2)	4.5 / 3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22	
Nominal TDR E2 / LVG (μg/day)	45 / 40		45 / 30		45 / 30		45 / 15	
Week	1	4	1	4	1	4	1	4
Cmax (pg/ml)	490.8 (227.61)	338.7 (114.25)	332.0 (151.75)	256.9 (84.27)		314 (140.2)		194 (110.8)
Cmin (pg/ml)	230.0 (136.48)	220.31 (77.487)	154.47 (85.431)	165.47 (53.683)	203 (116.4)	216 (95.17)	226 (146.4)	153 (69.64)
tmax (hr)	60.0 (24.0, 144)	60.0 (24.0, 169)	66.0 (36.0,120)	66.0 (48.0, 120)		72.0 0.0 - 168		48.0 0.0 - 168
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)	56753.8 (24932.56)	45931.1 (15490.92)	36076.8 (15272.67)	34137.4 (11880.55)		44048 (19126.1)		27948 (16426.0)
Cav (pg/ml)	337.8 (148.41)	273.4 (92.21)	214.74 (90.909)	203.20 (70.718)		262 (113.8)		166 (97.77)
FI (%)	77.66 (33.900)	43.60 (16.774)	84.90 (50.833)	44.54 (16.644)		36 (22.03)		21 (16.34)
R[b]	N/A	0.890 (0.2675)	N/A	1.050 (0.3768)		1.29 (0.8205)		0.7 (0.3103)
$t_{1/2}$ (hr)	N/A	31.43 (6.393)	N/A	37.06 (11.123)		ND		ND

a Mean and (SD) reported; median (minimum, maximum) reported for tmax
b Accumulation Ratio (R) is based on AUCτ for B819

C. Estradiol Bioequivalence of SH P 604 FM (45/15) to SH P 604 EM (45/30)

The lowest strength combination system SH P 604 FM, with intended E2 and LVG delivery rates of 45 and 15 µg/day respectively was not studied in a prospective efficacy trial. The incidence of endometrial hyperplasia with this formulation however was examined in an endometrial protection study. Consequently, the bioequivalence of the estradiol component of this formulation must be demonstrated compared to a combination formulation that has been studied in a clinical efficacy study. This comparator formulation is SH P 604 EM with intended E2 / LVG delivery rates of 45 and 30 µg/day respectively.

As seen in Table 18 for uncorrected data and APPENDIX 6 for corrected data using the sponsor's data, these two formulations are bioequivalent with respect to estradiol. However, they are not bioequivalent with respect to estrone, and although not examined, they are also unlikely to meet bioequivalence criteria for estrone sulfate.

In spite of the lack of bioequivalence with estrone, the two formulations should be considered comparable with respect to the estradiol component. The bioequivalence criteria for metabolites, even if active, are unclear. In addition the estradiol and estrone exposure is greater with the test formulation than with the reference formulation. Consequently, control of symptoms should be adequate with the test formulation (E2/LVG 45/15). Finally, if the data from subject 1043 who is clearly unusual pharmacokinetically and physiologically is excluded, the differences in estrone metrics disappear and estradiol is likely to meet the bioequivalence criteria much more easily.

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Table 18 Statistical Analysis For Determination of Bioequivalence: Uncorrected For Baseline

Parameter	Test Mean[a] (Treatment 1)	Reference Mean[a] (Treatment 2)	Test/Reference[b]	90% Confidence Interval[c]	P-value[d] Sequence	P-value[e] Period	P-value[f] Treatment
Estradiol (E2)							
Cmax (pg/ml)	50.7	44.2	115	(98.3, 131)	0.7192	03439	0.1350
ln(Cmax)	46.3	42.0	110	(101, 121)	0 9198	0.6840	0.0809
AUC(504-672) (pg/ml x hr^{-1})	6002	5551	108	(100, 116)	0.7066	0.8374	0.0907
ln(AUC(504-672))	5724	5317	108	(101, 115)	0.6308	0.7417	0.0706
tmax (hour)	36.0	36.0	NA	NA	NA	NA	0.3133
Estrone (E1)							
Cmax (pg/ml)	81.6	44.9	182	(42.2, 321)	0 2915	0.3636	0.3307
ln(Cmax)	45.6	42.8	106	(93.6, 121)	0.2950	0.9604	0.4212
AUC(504-672) (pg/ml x hr^{-1})	7642	6050	126	(82.1, 171)	0.2607	0.4470	0.3221
ln(AUC(504-672))	6166	5787	107	(95.8, 119)	0.3652	0.9934	0.3231
tmax (hour)	48.0	48.0	NA	NA	NA	NA	0.6630

Note: Treatment 1 was a 22 cm^2 patch contaimn8 4.4 mg of 17β-estradiol and 1.39 mg levonorgestrel (SH 604 FM patch).
Treatment 2 was a 22 cm^2 patch containing 4.4 mg of 17β-estradiol and 2.75 mg levonorgestrel (SH 604 EM patch).

a - Least squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e. geometric means). For tmax, these are the median values.
b – Ratio of parameter means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
c - 90% confidence interval for ratio of parameter means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
d - P-value for difference between sequence means from ANOVA.
e - P-value for difference between period means from ANOVA.
f - P-value for difference between treatment means from ANOVA. For tmax, P-value is from Wilcoxon signed-rank test.

D. Product Performance Over Time

There's insufficient information to confirm that the products perform similarly over time.

The pivotal clinical efficacy studies used systems that ranged in age from 9 to 43 months. The pivotal pharmacokinetic studies used 22-month old systems that produced estradiol concentrations that would be expected to provide efficacy. Finally, in study 6199 the SH P 604 EM formulation was 8 months old, yet resulted in lower exposures than in study B819, where the same formulation was 22 months old. Thereby indicating that the major difference was due to the inter-subject variation and not product performance (See APPENDIX 1 and APPENDIX 4).

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VIII. CLINICAL PHARMACOLOGY

A. *Application, Adhesion & Wear*

1. Application Sites and Protocol Instructions

A summary of the patch handling instructions from the pivotal pharmacokinetics studies in section 6 is shown Table 19.

Table 19 Patch Handling Instructions in Pivotal Pharmacokinetic Studies

	Study Report Number			
	AW78	A00084	B819	6199
Application Site	Lower abdomen (between navel and groin) alternating sides	Lower abdomen (between navel and groin) alternating sides starting in lower right in period 1	All 4 Abdomen quadrants, in clockwise sequence.	All 4 Abdomen quadrants, in clockwise sequence beginning in upper left.
Wear Period	7 days	7 days	7 days	7 days
Site Preparation	Avoid using lotions, creams, ointments or any other cosmetics after last cleasing of appllication site	Avoid using lotions, creams, ointments or any other cosmetics after last cleasing of appllication site	Avoid using lotions, creams, ointments or medicated soaps at the patch appllication site 1 week prior to patch application. The patch site will be gently cleansed the morning of patch application with non-abrasive soap and water. The patch will be applied after the area has completely dried.	Avoid using lotions, creams, ointments or medicated soaps at the patch appllication site 1 week prior to patch application. The patch site will be gently cleansed the morning of patch application with non-abrasive soap and water. The patch will be applied after the area has completely dried.
Application			Press with fingers for 10 seconds.	Press with fingers for 10 seconds.
Skin			Not oily, damaged or irritated. Avoid waistline, scars, panty lines.	Not oily, damaged or irritated, or scarred. Avoid waistline and panty lines.

(Table 19 Patch Handling Instructions - Continued)

	Study Report Number			
	AW78	A00084	B819	6199
Patch Removal	Area cleansed after removal	Area cleansed after removal	Application site area cleansed with tissue or tissue wetted with cold water prn to remove residual patch matrix.	Application site area cleansed with tissue or tissue wetted with cold water prn to remove residual patch matrix.
Physical Activities	Usual activities permitted	Usual activities permitted Sauna not permitted	Subjects may not swim or participate in strenuous physical activity, which would result in sweating.	Subjects may not swim or participate in strenuous physical activity, which would result in sweating.
Washing etc.	Not mentioned	Not mentioned	Only showers allowed (no tub baths). While showering subjects were to avoid scrubbing or using soap on the patch site. Other than showering, the application site must be kept dry.	Only showers allowed (no tub baths). While showering subjects were to avoid scrubbing or using soap on the patch site. Other than showering, the application site must be kept dry.

2. Adhesion

a) Definitions

Definitions used to assess patch adherence as per the pivotal pharmacokinetic studies are shown in Table 20. (n.b. At the time this review was written the study report from the adhesion study was not available to the OCPB reviewer. This study report will be reviewed when it is available and an addendum to the review will be written.)

Table 20 Definitions Used to Determine Patch Adherence in Pivotal Pharmacokinetic Studies

Definition	Study Report			
	AW78[a]	A00084[a]	B819[b]	6199[b]
Complete Attachment	≥ 75% attachment	≥ 75% attachment	—	—
Partial Attachment	< 75% attachment	< 75% attachment	Any patch lifting without falling off.	Any patch lifting without falling off.
Complete Detachment	—	—	Patch fell off completely and a replacement made	Patch fell off completely and a replacement made
Comment	Notations were made if there were any creasing, bubble, or lifting. If there was lifting the % attached was recorded. (i.e. ≥ 75% or < 75% attachment) No taping was allowed.	Notations were made if there were any creasing, bubble, or lifting. If there was lifting the % attached was recorded (i.e. ≥ 75% or < 75% attachment) No taping was allowed.	If a patch lifts, it was pressed back on with the palm of the hand and a notation was made in the CRF. If a patch completely fell off a replacement was made and was recorded.	If a patch lifts, it was pressed back on with the palm of the hand and a notation was made in the CRF. If a patch completely fell off a replacement was made and was recorded.

a definition of complete and partial detachment as per protocol.
b definition of complete and partial detachment as per reviewer. See comments for description of what was done as per the protocol.

b) Degree of Adhesion

Summary data on the degree of adhesion observed in the pivotal pharmacokinetic studies are shown Table 21, Table 22, and Table 23. Adhesion scores were assessed at the end of the week. (n.b. At the time this review was written the study report from the adhesion study was not available to the OCPB reviewer. This study report will be reviewed when it is available and an addendum to the review will be written.)

Table 21 Patch Replacements in Pivotal PK Studies[a]

Formulation			Study Report #							
Formulation Code	E2/LVG Content (mg)	Surface Area (cm^2)	AW78		A00084		B819		6199	
			Raw Data	Percent	Raw Data	Percent	Raw Data	Percent	Raw Data	Percent
SH P 604 DM	4.5 / 3.75	30	0/23	0.0%	—	—	4/84	4.8%	—	—
SH P 604 EM	4.4 / 2.75	22	0/22	0.0%	—	—	4/84	4.8%	1/177	0.56%
SH P 604 FM	4.4 / 1.39	22	—	—	0/24	0.0%	—	—	1/177	0.56%
Cerulla/Climara		12.5	0	0.0	0/24	0.0%	—	—	—	—

a replacements per actual number of patches used

Table 22 Applications with >25% Detachment Observed in Pivotal PK Studies[a]

Formulation			Study Report #							
Formulation Code	E2/LVG Content (mg)	Surface Area (cm^2)	AW78		A00084		B819		6199	
			Raw Data	Percent	Raw Data	Percent	Raw Data	Percent	Raw Data	Percent
SH P 604 DM	4.5 / 3.75	30	4/23	17.4%	—	—	14/84	16.7%	—	—
SH P 604 EM	4.4 / 2.75	22	2/22	9.0%	—	—	6/84	7.14%	28/177	15.8%
SH P 604 FM	4.4 / 1.39	22	—	—	0/24	0.0%	—	—	22/177	12.4%
Cerulla/Climara		12.5	2/45	4.4%	0/24	0.0%	—	—	—	—

a As determined from raw data and expressed per number of applications

Table 23 Applications with < 25% Surface Area Detachment Observed in Pivotal PK Studies[a]

Formulation			Study Report #							
Formulation Code	E2/LVG Content (mg)	Surface Area (cm^2)	AW78		A00084		B819		6199	
			Raw Data	Percent	Raw Data	Percent	Raw Data	Percent	Raw Data	Percent
SH P 604 DM	4.5 / 3.75	30	0/23	0.0	—	—	—	—	—	—
SH P 604 EM	4.4 / 2.75	22	0/22	0.0	—	—	—	—	—	—
SH P 604 FM	4.4 / 1.39	22	—	—	2/24	8.3%	—	—	—	—
Cerulla/Climara		12.5	0/45	0.0	0/24	0.0%	—	—	—	—

a As determined from raw data and expressed per number of applications

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B. Tolerance

A summary of the application site reactions reported for the four pharmacokinetic studies is shown in Table 24. The first two studies, AW78 and A0084, were single dose studies with observations made and recorded by a health care professional; whereas data from the latter two studies was gleaned from subject diaries.

The discrepancy between the single dose and the multiple dose studies may either be due to lack of reporting by subjects (i.e. better reporting by the health care professionals in the single dose studies) or a decreased incidence over time.

Table 24 Incidence of Application Site Reactions in Pivotal PK Studies

STUDY REPORT #	STUDY DESIGN	Formulation			# Subjects Reporting Application Site Reactions[a]	Total # Subjects Exposed	% of Subjects with Application Site Reactions
		Code	E2/LVG Content (mg)	SA (cm^2)			
AW78	Single Dose	SH P 604 DM	4.5/3.75	30	22	23	95.6%
		SH P 604 EM	4.4/2.75	22	21	21	100%
A00084	Single Dose	SH P 604 FM	4.4/1.39	22	8	24	33.3%
B819	Multiple Dose	SH P 604 DM	4.5/3.75	30	10	20	50%
		SH P 604 EM	4.4/2.75	30	6	20	30%
6619	Multiple Dose	SH P 604 EM	4.4/2.75	30	7	22	31.8%
		SH P 604 FM	4.4/1.39	22	4	22	18.2%

a Application site reactions include irritation, redness, itching, etc.
n.b. data is from raw data supplied and values may be greater than from summary tables supplied by sponsor

C. Transdermal Delivery Rate

1. Estradiol

The sponsor's nominal transdermal delivery rate of estradiol for Climarapro™ of 45 µg/day is acceptable.

Calculation of the estradiol transdermal delivery rate (TDR) was based upon comparison with Climara® in the single dose studies. As the mean AUCs were approximately 90% of the estradiol AUCs with Climara® and Cerulla™ the assigned TDR given was 90% of the estradiol only products, 45 µg/day, (i.e. 90% of 50 µg/day).

The method used assumes a known and consistent average value for clearance and that the TDR for the estradiol only products are correct. Both assumptions cannot be verified. In addition the presence of a possible drug interaction with levonorgesterel that affects clearance, possibly beginning during the first dose makes this a troubling method with the present formulations. Consequently, the calculation of transdermal delivery rates by determining system depletion is recommended. Even though the amount of depletion is small relative to the total content, the measurements tend to be very accurate and thus this reviewer believes this is the preferred method. According to information provided by the sponsor, used and unused transdermal systems were returned in studies B819 and 6199 (see Table 25). Consequently, the sponsor was asked If these systems are still available so that system depletion may be determined from these systems.

In response, the sponsor referred to a teleconference with Dr. Angela Dorantes (OCPB) on March 25, 1996 allowing the average clearance method. However, a review for protocol 97067 and letter to the sponsor dated November 28, 1997 co-signed by Dr. Dorantes recommended use of the system depletion method. Since the studies examining TDR did not begin until January 1999 the sponsor should have used the system depletion method.

Since, it's most likely that the Climarapro™ combination product will be compared in practice to the Climara® system. Consequently, even if the TDR of the Climara™ is in error, the use of relative nominal delivery of Climarapro™ to Climara® is still appropriate.

Table 25 Systems Returned from Clinical Study Sites for Pivotal PK Studies

	Study			
	AW78	A0084	B819	6199
NUMBER OF PATCHES SUPPLIED	Not Mentioned	Not Mentioned	4 patches to be used and 4 extra patches per subject in case of falloff	4 patches to be used and 4 extra patches per subject in case of falloff
Patch Disposition	Not Mentioned	Not Mentioned	Used and Unused patches returned §5.6.3.2 and §12.1	Used and unused patches returned to 3M Pharmaceuticals (page 227 of 1809 vol 1 submitted 1/01) (§5.6.3.1 (n.b. different §# from B819) and §12.1)

2. Levonorgestrel

The nominal levonorgestrel transdermal delivery rates were not rigorously determined and are approximate. The nominal rates are 40, 30, and 15 µg/day. At this point only an additional study could unambiguously determine the transdermal delivery rates. However, as the rates are nominal and there's quite a lot of variability in nominal rates, these rates should be accepted. However, prior to accepting these delivery rates, the sponsor should provide information supporting the appropriateness of assumptions used in their calculations.

The nominal transdermal delivery rate of levonorgestrel was calculated by comparing the $AUC_{(0-\infty)}$ after a single transdermal application to the $AUC_{(0-\infty)}$ after a single 90 µg oral dose of levonorgestrel (3 x 30 µg Microlut™) when given in combination with an estradiol patch. The rate was then determined by assuming absolute bioavailabilities of 1.0 for both formulations and dividing the calculated cumulative transdermal delivery rate by 7 days. The mean values were then rounded to within 5 µg/day taking into account the content of the system (i.e. not necessarily the nearest 5 µg/day), (see.Table 26).In addition to assuming absolute bioavailabilities of 1.0, additional implicit assumptions with this method include linear kinetics and no drug interaction(s) with estradiol during the first week.

The sponsor has provided no supporting evidence regarding the appropriateness of these assumptions. In a quick search this reviewer could only find labeling for combination oral contraceptives that indicated that it is assumed that the oral bioavailability of levonorgestrel is 1.0. This appears to be based upon the fact that only a small amount of conjugated levonorgestrel is found in the feces after oral dosing. However, levonorgestrel is approximately 25% eliminated by sulfation, consequently, there may be some first pass sulfation upon oral dosing, although the extent is likely to be small.

Table 26 Single Dose Levonorgestrel Transdermal Delivery Rates

Study Report		A00084	AW78	
Formulation		SH P 604 FM vs. 3 x Microlut 30 µg	SH P 604 EM vs. 3 x Microlut 30 µg	SH P 604 DM vs. 3 x Microlut 30 µg
E2/LVG Content (mg) SA (cm^2)		4.4 / 1.39 22	4.4 / 2.75 22	4.5 / 3.75 30
n		24	22	23
$AUC_{(0\text{-}tlast)}$ ($ng/ml \times hr^{-1}$)	Patch	22.9 ± 8.86 38.7 10.1 - 45.9	42.2 ± 16.8 39.8 17.7 - 92.0	63.3 ± 28.3 44.7 21.9 - 121
	Microlut™ Tablets & E2 patch	21.0 ± 8.98 42.7 8.72 - 46.5	17.7 ± 6.36 36.0 8.47 - 33.1	20.4 ± 8.86 43.4 8.28 - 49.9
TDR (µg/day)		13.7 ± 3.74 27.3 8.18 - 24.1	32.7 ± 13.7 41.9 19.7 - 73.0	40.9 ± 18.6 45.6 22.0 - 82.8
Nominal TDR (µG/DAY)		15	30	40

D. *In Vitro – In Vivo Correlation*

An *in vitro – in vivo* correlation cannot be made, as the proposed drug release method is different than the method used for the batches utilized in human studies. Neither is there cadaveric skin permeability data.

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IX. INFORMATION REQUESTED – ADDENDA TO REVIEW TO BE WRITTEN

A. Data Requested from FDA Internal Sources

The study report for the adhesion study was not available to the OCPB reviewer, although the report was submitted to the FDA. When this report is obtained, the data will be reviewed and an addendum will be written.

B. Data Requested from Sponsor

Drug release profile data was not presented in the section 6 of the application and has been requested. This data will be reviewed when received and an addendum to the review will be written.

X. COMMENTS TO THE SPONSOR

The concentration at the end of the dosage interval is not always the same as the minimum concentration. When minimum concentration is appropriate to be reported (i.e. as for the formulation in this NDA) then the true minimum should be reported.

The calculation of transdermal delivery rate (TDR) should have been calculated based on system depletion. For estradiol the accuracy and precision of the assay should be sufficient to obtain accurate depletions in spite of the fact that the amount depleted represents a small fraction of the total amount in the patch. A review for protocol 97067 and letter to the sponsor dated November 28, 1997 co-signed by Dr. Dorantes recommended use of the system depletion method. This was the agency's last communication regarding this issue prior to beginning studies examining TDR in January 1999. Consequently, the sponsor should have used the system depletion method regardless of any prior communications.

XI. LABELING COMMENTS

Proposed deletions are marked by addition a single line ~~strikeout~~ to text to be deleted.

Proposed additions are marked by addition of a <u>double underline</u> to proposed additions.

OCPB additions and deletions are marked in red.

Whenever the draft guidance is referred to, the citation is as follows:

GUIDANCE FOR INDUSTRY
Labeling Guidance for Noncontraceptive Estrogen Drug Products —Prescribing Information for Healthcare Providers and Patient Labeling
DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1999
Labeling

Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852.

11 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

XII. SIGNATURES

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Ameeta Parekh, Ph.D. — Date

Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Meeting: Monday May 7, 2001 11:30 AM – 12:30 PM Parklawn 13B-17

Attendees: Kavanagh, Parekh, Price, Moore, Mitra, Malinowski, Hunt,

CC: NDA 21-258 (orig., 1 copy)
HFD-580 (Price, Slaughter, Moore, Mitra)
HFD-850 (Lesko)
HFD-870 (Malinowski, Hunt, Parekh, Kavanagh)
Central Document Room (Barbara Murphy)

APPENDIX 1 FORMULATIONS AND BATCHES USED IN CLINICAL STUDIES

Table 27 Formulation Batches Used in Pivotal Pharmacokinetic, Clinical Pharmacology, and Clinical Efficacy and Safety Studies

Protocol / Report Numbers	E2 / LVG Content (mg)	% of Label E2 / LVG	SA (cm^2)	E2 / LVG (µg/day)	Formulation Codes	Description	Manufacturer	Manufacturing Site	Lot Number	Batch Size (# patches)	Date of Manufacture	Date of Study	Age of Systems Used (months)	Comments
Pivotal Pharmacokinetic Studies														
ME98046 / AW78	4.5 / 3.75		30	45 / 40	SH P 604 DM	TBM	3M	Northridge, CA	PD 10055 / 971040		04 Sept 1997	Jan 99 – Jun 99	22	Pivotal SD Comparative BA Study
	4.4 / 2.75		22	45 / 30	SH P 604 EM	TBM	3M	Northridge, CA	PD 10056 / 971060		05 Sept 1997	Jan 99 – Jun 99	22	SH # P577 A -cerella 0999 C - microlut
303341 / A00084	4.4 / 1.39		22	45 / 15	SH P 604 FM	TBM	3M	Northridge, CA	PD10054 / 971038		02 Sept 1997	Oct 99 – Jan 00	22	Pivotal SD Study SH # P577 A 0999 C - Microlut
ME99003 / B819	4.5 / 3.75		30	45 / 40	SH P 604 DM	TBM	3M	Northridge, CA	981237b / PD10349 CL2336		29 Oct 1998	Apr 99 – Jun 99	8	Pivotal MD BE Study
	4.4 / 2.75		22	45 / 30	SH P 604 EM	TBM	3M	Northridge, CA	R971060 / PD10056 CL2338		05 Sept 1997	Apr 99 – Jun 99	22	
304180 / 6119	4.4/2.75		22	45 / 30	SH P 604 EM	TBM	3M	Northridge, CA	PD-99-10447 ZK5018 ZK18206		27 Oct 1998	May 00 – Jul 00	22	
	4.4/1.39		22	45 / 15	SH P 604 FM	TBM	3M	Northridge, CA	PD-99-10449 ZK5018 ZK18206		24 Oct 1998	May 00 – Jul 00	22	
Adhesion and Tolerability Studies														
3M-1304-LEVO / B573	4.4 / 2.75		22	45 / 30	SH P 604 EM	TBM						Jan 98 – Jul 98		
3M-1303-LEVO / 98185	4 4 / 2 75		22	45 / 30	SH P 604 EM	TBM						Jan 98 – Feb 98		
3M-1309-PLAC /99010					Placebo							May 98 – Jun 98		
Pivotal Clinical Efficacy and Safety Studies														
96042A /B528	4.4 / 2.75		22	45 / 30	SH P 604 EM	TBM	3M	Northridge. CA	PD10056 / 971060		05 Sept 97	Jun 98 – Oct 99	25	
	4.5 / 3.75		30	45 / 40	SH P 604 DM	TBM	3M	Northridge. CA	PD10055 / 971040 981237		04 Sept 97	Jun 98 – Oct 99	25	
96043A / B529	4.4 / 1.39		22	45 / 15	SH P 604 FM	TBM	3M	Northridge. CA	PD10054 / 971038		02 Sept 1997	Jun 98 – Mar 00		
	4.4 / 2.75		22	45 / 30	SH P 604 EM	"	3M	Northridge. CA	PD10056 / 971060		05 Sept 1997	Jun 98 – Mar 00		
	4.5 / 3.75		30	45 / 40	SH P 604 DM	"	3M	Northridge. CA	PD10055 / 971040		04 Sept 1997	Jun 98 – Mar 00		
	4.5 / 3.75		30	45 / 40	SH P 604 DM	"	3M	Northridge. CA	PD10349 / 981237b		20 Oct 1998	Jun 98 – Mar 00		
	4.4		**22**	**45**	**SH P 604 HM**		3M	**Northridge, CA**	**971083**		**07 Sept 1997**	**Jun 98 – Mar 00**		**Not TBM**
98189	4.4 / 1.39		22		SH P 604 FM									Ongoing Safety extension of 96043A
	4.4 / 2.75		22		SH P 604 EM									
	4.5 / 3.75		30		SH P 604 DM									

Table 28 Formulation Batches Used in Non-pivotal Pharmacokinetic, Clinical Pharmacology, and Ongoing Clinical Efficacy Studies

Protocol / Report Numbers	E2 / LVG Content (mg)	(ZK #)	SA (cm^2)	E2 / LVG (µg/day)	Formulation Codes	Description	Manufacturer	Manufacturing Site	Lot Number	Lot number	Batch Size (# patches)	Date of Manufacture	Date of Study	Age of Systems Used	Comments
Nonpivotal Pharmacokinetic Studies															
ME97067 / B510	4.4 / 2.75		22	45 / 30	SH P 604 EM	TBM			97-046	CL2190		Jul 15, 1997	Oct 97 – Nov 97	4.5 months	Preliminary development formulation vs. TBM formulation 4 day application
	4.4 / 2.75		22	45 / 30	*SH P 604 EN*	*NOT TBM*			96-061	CL2189		10 Aug 1996	Oct 97 – Nov 97	16 months	
ME96035 / 97031	4.4 / 2.75		22	45 / 30	SH P 604 EM	TBM			3M 96-040	Berlex CL2042		15 Apr 1996	Sep 96 – Oct 96	6.6 months	Preliminary development formulation compared to CLIMARA®
ME96015 / AM37	4.4 / 3.75		30	45 / 40	SH P 604 DM	*TBM*			3M 61011	NA		Mar 26, 1996	Apr 96 – Jul 96	4 months	3 - Preliminary development formulations made in
	4.4 / 2.75		22	45 / 30	SH P 604 EM	*TBM*			61021			Mar 27, 1996	Apr 96 – Jul 96	4 months	
	4.4 / 1.39		22	45 / 15	SH P 604 FM	*TBM*			61031			Mar 28, 1996	Apr 96 – Jul 96	4 months	
Studies															
97093 / RR AZ11 AW92	2.2		22		SH P 604 IN						Lab Scale				Why EN?
	4.4		22		SH P 604 HN										
	2.2 / 1.39		22		SH P 604 GN										
	4.4 / 2.75		22		SH P 604 EN										
97094 / RR AW91	4.4		22		SH P 604 HN						Lab Scale				1.8 cm^2 Photo Patch Test
	4.4 / 2.75		22		SH P 604 EN						Lab Scale				
97203 Report incomplete	*4.4 / 2.75*		*22*	*45 / 30*	*SH P 604 EM*	*TBM*	*3M*								***Patch cut to 11 cm^2***
	4.4 / 2.75		22	45 / 30	SH P 604 EM	*TBM*	3M								Full size Patch
Studies for Other Indications Currently Ongoing															

Table 29 Packaging Materials and Dates for Pivotal Pharmacokinetic, Clinical Pharmacology, and Clinical Efficacy and Safety Studies

Protocol / Report Numbers	E2 / LVG Content (mg)	% of Label E2/LVG	SA (cm^2)	E2 / LVG (µg/day)	Formulation Codes	Primary Packaging Materials	Manufacturer	Manufacturing Site	Manufacturing Lot Number	Date of Manufacture	Date of Packaging	Packaging Time Lag	Comments
Pivotal Pharmacokinetic Studies													
ME98046 / AW78	4.5 / 3.75		30	45 / 40	SH P 604 DM		3M	Northridge, CA	PD 10055 / 971040	04 Sept 1997			Pivotal SD Comparative BA Study
	4.4 / 2.75		22	45 / 30	SH P 604 EM		3M	Northridge, CA	PD 10056 / 971060	05 Sept 1997			SH # P577 A -cerella 0999 C - microlut
303341 / A00084	4.4 / 1.39		22	45 / 15	SH P 604 FM		3M	Northridge, CA	PD10054 / 971038	02 Sept 1997			Pivotal SD Study SH # P577 A 0999 C - microlut
ME99003 / B819	4.5 / 3.75		30	45 / 40	SH P 604 DM		3M	Northridge, CA	981237b / PD10349 CL2336	29 Oct 1998			Pivotal MD BE Study
	4.4 / 2.75		22	45 / 30	SH P 604 EM		3M	Northridge, CA	R971060 / PD10056 CL2338	05 Sept 1997			
304180 / 6119	4 4/2.75		22	45 / 30	SH P 604 EM		3M	Northridge, CA	PD-99-10447 ZK5018 ZK18206	27 Oct 1998			
	4.4/1.39		22	45 / 15	SH P 604 FM		3M	Northridge, CA	PD-99-10449 ZK5018 ZK18206	24 Oct 1998			
Adhesion and Tolerability Studies													
3M-1304-LEVO / B573	4.4 / 2.75		22	45 / 30	SH P 604 EM								
3M-1303-LEVO / 98185	4.4 / 2.75		22	45 / 30	SH P 604 EM								
3M-1309-PLAC /99010					Placebo								
Pivotal Clinical Efficacy and Safety Studies													
96042A /B528	4.4 / 2.75		22	45 / 30	SH P 604 EM		3M	Northridge, CA	PD10056 / 971060	05 Sept 97			
	4.5 / 3.75		30	45 / 40	SH P 604 DM		3M	Northridge, CA	PD10055 / 971040 981237	04 Sept 97			Manufacturing Lot number doesn't match between original NDA and 2/8/01 update (update is 981237b)
96043A / B529	4.4 / 1.39		22	45 / 15	SH P 604 FM		3M	Northridge, CA	PD10054 / 971038	02 Sept 1997			
	4.4 / 2.75		22	45 / 30	SH P 604 EM		3M	Northridge, CA	PD10056 / 971060	05 Sept 1997			
	4.5 / 3.75		30	45 / 40	SH P 604 DM		3M	Northridge, CA	PD10055 / 971040	04 Sept 1997			Manufacturing Lot number doesn't match between original NDA and 2/8/01 update (update is 971034)
	4.5 / 3.75		30	45 / 40	SH P 604 DM		3M	Northridge, CA	PD10349 / 981237b	20 Oct 1998			
	4.4		22	45	SH P 604 HM		3M	Northridge, CA	971083	07 Sept 1997			
98189	4.4 / 1.39		22	45 / 15	SH P 604 FM								Ongoing Safety extension of 96043A
	4.4 / 2.75		22	45 / 30	SH P 604 EM								
	4.5 / 3.75		30	45 / 40	SH P 604 DM								

APPENDIX 2 BIOANALYTIC ASSAY VALIDATION

Estradiol

Table 30 Summary of Estradiol Assay Validation Report

Laboratory	
Report	CA429 n.b. both estradiol and estrone reported in same assay
Date	Dated June 27, 1995 performed Oct - Dec/93
Analyst	*Not Mentioned.*
Method Description	GC/MS with liquid-liquid extraction and derivitization for both estradiol and estrone
Method Protocol	MOP CA429
Analyte	Estradiol
Internal Standards	D_4-estradiol 25 µl D_4-estrone 25 µl
Range	5 – 1000 pg/ml
Volume	1 ml
Structural Model	Linear
Error Model	1/conc
Matrix	Plasma – cleaned twice by charcoal extraction
Sample Storage Method	*Not mentioned.*
Matrix Effects	*Not determined.*
LLOQ	5 pg/ml - variability not determined with QC samples at LLOQ
Bias	≤ - 8.09%
Intra assay Precision	≤ 9.55% @ 10 pg/ml
Between assay Precision	≤ 9.13% @ 10 pg/ml
Inter assay (overall) Precision	≤ 9.31% @ 10 pg/ml
Selectivity	
Endogenous Substances	Selective – no unexpected interfering endogenous substances
Metabolites – Estriol	Relatively selective - Highest expected endogenous concentration 1 ng/ml. Selective up to 10 ng/ml.
OTC Drugs	
ACETAMINOPHEN	Selective at 25 ng/ml
Aspirin	Selective at 25 ng/ml
Caffeine	Selective at 25 ng/ml
Drugs – Rx	
Norethindrone	Selective
Stability Blood	At least 10 minutes at RT
Stability Plasma	
RT	24 hours
Refrigerated	*Not performed*
Long Term (-11 °C)	1 month (additional information suggests stable for 1 year)
Stability Freeze/Thaw	3 cycles
Stability Extracted	
RT	48 hours
Refrigerated (< 13 °C)	6 days
On Machine	*Not performed*

Table 31 Summary of Estradiol Assay Partial Validation Report – Dilution and Levonorgestrel Interference

Laboratory	
Report	CA429 Supplement 01 n.b. both estradiol and estrone reported in same assay
Date	February 2, 2000
Analyst	—
Method Description	GC/MS with liquid-liquid extraction and derivitization for both estradiol and estrone
Method Protocol	MOP CA429
Analyte	Estradiol
Matrix	**Serum – cross referenced to another partial validation (JA164), but this report was not provided.**
Dilution	2000 pg/ml can be diluted 1:10 acceptably
Bias	- 5.27%
Intra assay Precision	2.66%
Selectivity **Drugs – Rx** **Levonorgestrel**	Selective at 1000 pg/ml Levonorgestrel

Table 32 Summary of Estradiol Assay Partial Validation – Cross Validation of Plasma

Laboratory	
Report	JA164 – Determination of unconjugated estradiol and estrone in human serum samples by GC/MS, appendix III, cross validation: serum versus plasma edition 02
Date	31 January 2000
Comment	***Validation report not provided.***

Estrone

Table 33 Summary of Estrone Assay Validation Report

Laboratory	
Report	CA429 n.b. both estradiol and estrone reported in same assay
Date	Dated June 27, 1995 performed Oct - Dec/93
Analyst	*Not mentioned.*
Method Description	GC/MS with liquid-liquid extraction and derivitization for both estradiol and estrone
Method Protocol	MOP CA429
Internal Standards	D_4-estradiol 25 µl D_4-estrone 25 µl
Range	5 – 1000 pg/ml
Volume	1 ml
Structural Model	Linear
Error Model	1/conc
Matrix	Plasma – cleaned twice by charcoal extraction
Sample Storage Method	*Not mentioned.*
Matrix Effects	*Not determined.*
LLOQ	5 pg/ml
Bias	≤ -6.03%
Intra assay Precision	≤ 10.21% (at LLOQ)
Between assay Precision	≤ 13.85% (at LLOQ)
Inter assay (overall) Precision	≤ 11.65% (at LLOQ)
Selectivity	
Endogenous Substances	Selective – no unexpected interfering endogenous substances
Metabolites – Estriol	Relatively selective - Highest expected endogenous concentration 1 ng/ml (may be higher with Rx) adds 1 pg/ml to measured estrone (0.1% crossover although may be more).
Drugs - OTC	
ACETAMINOPHEN	Selective at 25 ng/ml
Aspirin	Selective at 25 ng/ml
Caffeine	Selective at 25 ng/ml
Drugs - Rx	
Norethindrone	25 ng/ml adds 20 pg/ml
Stability Blood	At least 10 minutes at RT
Stability Plasma	
RT	24 hours
Refrigerated	*Not performed*
Long Term (-11 °C)	1 month (additional information suggesting stability for 1 year)
Stability Freeze/Thaw	3 cycles
Stability Extracted	
RT	48 hours
Refrigerated (< 13 °C)	6 days
On Machine	*Not performed*

Table 34 Summary of Estrone Partial Validation – Dilution and Levonorgestrel Interference

Laboratory	
Report	CA429 Supplement 01 n.b. both estradiol and estrone reported in same assay
Date	February 2, 2000
Analyst	
Method Description	GC/MS with liquid-liquid extraction and derivitization for both estradiol and estrone
Method Protocol	MOP CA429
Analyte	Estrone
Matrix	**Serum – cross-referenced to another partial validation (JA164), but this report was not provided.**
Dilution	2000 pg/ml can be diluted 1:10 acceptably
Bias	- 1.09%
Intra assay Precision	1.27%
Selectivity **Drugs – Rx** **Levonorgestrel**	Selective at 1000 pg/ml Levonorgestrel

Table 35 Summary of Estradiol Assay Partial Validation – Cross Validation of Plasma

Laboratory	
Report	JA164 – Determination of unconjugated estradiol and estrone in human serum samples by GC/MS, appendix III, cross validation: serum versus plasma edition 02
Date	31 January 2000
Comment	***Validation report not provided.***

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Estrone Sulfate

Table 36 Summary of Estrone Sulfate Assay Validation Report

Laboratory	
Analyst	
Report	27.1 Project OCE
Date	Feb 1998
Method Description	SPE LC/MS/MS
Method Protocol	*Not reported*
Internal Standard	Estrone-2,4, 16, 16 D_4 3-Sulfate
Range	50-5000 pg/ml
Volume	0.5 ml
Structural Model	Linear LS
Error Model	$1/conc^2$
Matrix	Serum
Storage of samples	-80 °C
Matrix Effects	*Not examined*
LLOQ	Chromatogram presented for 1 source of serum. Endogenous estrone sulfate gives of peak of 12 cps, Low calibration standard of 50 pg/ml give a peak of 403 cps. Bias (5.32%) and precision (13.9%) are acceptable.
Intra & Inter assay Bias	≤ 5.32%
Intra & Inter assay Precision	≤ 13.9%
Specificity	Claimed that it was cross-checked against 6 human serum samples. Interfering peaks consistent with endogenous concentrations. Only one data set provided – see LLOQ.
Stability - Plasma **Room Temperature** **Long Term** **Freeze/Thaw**	 Stable for 24 hours *Not performed* Stable through 3 freeze/thaw cycles
Stability - Extracted **Extract** **On Machine**	 Stable for 96 hours *Not reported.*

Levonorgestrel

Table 37 Summary of Levonorgestrel Assay Validation Report

Laboratory	
Analyst	
Report	B678
Date	30 Sep 1997
Method Description	Radioimmunoassay with liquid - liquid extraction
Matrix	Serum
Method Protocol	Included within Validation Report.
Calibration Standards	3.9 – 2000 pg/ml
Analytic Range	8 – 500 pg/ml, sponsor says up to 750 pg/ml but it's pushing it. However data at 1500 pg/ml is better than 750. Pg 6 00619. In conclusion data is not good, but probably acceptable on high end.
Volume	0.1 to 0.5 ml. At 1 ml recovery is reduced from 97-98% to 92%
Structural Model	Bmax
Error Model	None
Storage of samples	-20 °C
Matrix Effects	*See parallelism and dilution.*
LLOQ	8 pg/ml gives acceptable precision and bias
Selectivity / Specificity – Endogenous	Tested against 5 lots of blank human serum
Parallelism/dilution	Only acceptable to a 1:2 dilution 1:5 dilution unacceptable
Intra assay Bias	<10% 50-500 pg/ml <15.2% 750 –1500pg/ml
Intra & Inter assay Precision	< 6.4% 50 – 75 pg/ml 15.3% 1500 pg/ml
Specificity	Some cross reactivity with levonorgestrel derivatives. However these drugs are not expected to be present in the current studies. No cross reactivity with other endogenous hormones.
Stability – Plasma **Room Temperature** **Refrigerated** **Long Term** **Freeze/Thaw**	 8 hours 1 day -20 °C for 6 months extended to 2 years 2 cycles
Stability – Extract	*Not Reported.*

APPENDIX 3 SINGLE DOSE PHARMACOKINETIC METRICS

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Estradiol

Table 38 Single Dose Uncorrected Estradiol Pharmacokinetic Metrics[a,b]

Study	AW78	AW78	A00084	AW78	AW78	A00084
Formulation	SH P 604 DM	SH P 604 EM	SH P 604 FM	Cerella 50 µg/day 12.5 cm^2	Cerella 50 µg/day 12.5 cm^2	Climara[c] 50 µg/day 12.5 cm^2
n	23	22	24	23	22	24
Cmax (pg/ml)	84.2 ± 35.8 42.6	77.0 ± 33.5 43.5	54.3±18.9 34.9	95.4±31.9 33.4	97.0±45.7 47.1	68.1±18.7 27.5
Tmax (hours)	56.1± 40.5 72.2	52.9±20.8 39.4	58.5±30.7 52.5	39.7±29.0 73.2	34.4±13.0 37.8	29.5±23.2 78.6
AUC(0-tlast) (ng/ml x hr^{-1})	9.03 ± 3.59 39.8	8.08±3.06 37.9	6.34±1.74 27.5	9.34±2.87 30.7	8.92±3.38 37.9	7.13±2.22 31.2
t1/2 (HOURS)	ND	ND	ND	ND	ND	ND
Cav (pg/ml)	53.8 ± 21.4 39.8	48.1 ± 18.2 37.9	37.7 ± 10.4 27.5	55.6 ± 17.1 30.7	53.1 ± 20.1 37.9	42.5 ± 13.2 31.2
Cmin (pg/ml)	37.4 ± 14.8 39.6	32.8 ± 12.2 37.2	27.2 ± 7.66 28.1	29.5 ± 12.6 42.5	29.2 ± 12.3 42.0	24.4 ± 9.84 40.4
FI (%)	94.0 ± 57.3 61.0 40.2 - 332	92.5 ± 59.2 63.9 36.4 - 310	70.5 ± 40.5 57.5 24.6 - 180	118 ± 36.3 30.8 66.5 - 210	126 ± 45.0 35.8 59.3 - 240	106 ± 32.6 30.7 41.2 - 191
TDR (µG/DAY)	48.1±8.84 18.4	46.7±14.8 31.7	45.7±10.0 22.0	ND	ND	ND

a Values are mean ± SD, CV and range, except
b Values are as reported by sponsor
c Nominally Climara but supplied from

Estrone

Table 39 Single Dose Uncorrected Estrone Pharmacokinetic Metrics[a,b]

Study	AW78	AW78	A00084	AW78	AW78	A00084
Formulation	SH P 604 DM	SH P 604 EM	SH P 604 FM	Cerella 50 µg/day 12.5 cm^2	Cerella 50 µg/day 12.5 cm^2	Climara[c] 50 µg/day 12.5 cm^2
n	23	22	24	23	22	24
Cmax (pg/ml)	54.9 ± 19.9 36.3	46.4 ± 18.2 39.2	43.9 ± 14.9 33.9	58.7 ± 22.7 38.6	55.3 ± 21.8 39.4	48.3 ± 13.1 27.0
Tmax (hours)	73.0 ± 36.7 50.3	82.4 ± 42.4 51.5	92.0 ± 40.0 43.5	49.6 ± 25.7 51.8	48.5 ± 23.9 49.1	54.5 ± 31.4 57.7
$AUC_{(0\text{-tlast})}$ (ng/ml x hr^{-1})	8.14 ± 2.99 36.8	7.08 ± 2.69 38.1	6.89 ± 2.52 36.3	8.13 ± 2.71 33.4	7.69 ± 2.76 35.9	7.21 ± 2.50 34.6
t1/2 (HOURS)	NR	NR	NR	NR	NR	NR
Cav (pg/ml)	48.5 ± 17.8 36.8	42.1 ± 16.0 38.1	41.0 ± 15.0 36.6	48.4 ± 16.2 33.4	45.8 ± 16.4 35.9	42.9 ± 14.9 34.6
Cmin (pg/ml)	37.5 ± 14.8 39.5	32.9 ± 11.5 34.9	32.6 ± 14.3 44.0	31.0 ± 9.84 31.8	31.6 ± 11.0 34.7	29.0 ± 12.4 42.9
FI (%)	35.1 ± 14.5 41.3 2.64 - 72.	33.3 ± 10.2 30.7 15.2 - 58.0	31.0 ± 12.9 41.5 10.8 - 58.5	55.6 ± 23.6 42.4 21.5 - 106	51.0 ± 21.7 42.5 21.8 - 90.2	49.4 ± 22.7 46.0 9.48 - 108

a Values are mean ± SD, CV and range, except
b Values are as reported by sponsor
c Nominally Climara but supplied from —

Estrone Sulfate

Table 40 Single Dose Uncorrected Estrone Sulfate Pharmacokinetic Metrics[a,b]

Study	AW78	AW78	A00084	AW78	AW78	A00084
Formulation	SH P 604 DM	SH P 604 EM	SH P 604 FM	Cerella 50 µg/day 12.5 cm^2	Cerella 50 µg/day 12.5 cm^2	Climara[c] 50 µg/day 12.5 cm^2
n	23	22	24	23	22	24
Cmax (pg/ml)	1552±886 58.2	1046±596 57.0	993±719 72.4	1609±1076 66.9	1390±696 50.0	1098±628 57.2
Tmax (hours)	83.0±33.1 40.0	75.3±33.4 44.3	97.8±40.4 41.3	55.8±24.7 44.2	56.7±18.9 33.4	63.0±34.5 54.8
AUC(0-tlast) (ng/ml x hr^{-1})	189±128 67.9	135±75.6 55.8	129±86.1 67.0	172±106 61.3	151±78.9 52.1	136±88.2 64.9
$t_{1/2}$ (hours)	NR	NR	NR	NR	NR	NR
Cav (pg/ml)	1125 ± 764 67.9	806 ± 450 55.8	765 ± 513 67.0	1026 ± 629 61.3	901 ± 469 52.1	809 ± 525 64.9
Cmin (pg/ml)	851 ± 636 74.7	613 ± 359 58.6	577 ± 389 67.3	560 ± 314 56.0	532 ± 334 62.8	506 ± 383 75.7
FI (%)	71.7 ± 42.3 58.9 15.5 - 189	52.6 ± 24.1 45.8 5.37 - 99.3	57.2 ± 20.9 36.5 5.12 - 89.6	96.5 ± 39.0 40.4 41.5 - 190	101 ± 38.0 37.8 47.4 - 166	83.2 ± 40.1 48.2 29.1 - 178

a Values are mean ± SD, CV and range, except
b Values are as reported by sponsor
c Nominally Climara but supplied from

Levonorgestrel

Table 41 Single Dose Levonorgestrel Pharmacokinetic Metrics[a,b]

Study	AW78	AW78	A00084	AW78	AW78	A00084
Formulation	SH P 604 DM	SH P 604 EM	SH P 604 FM	Microlut 30	Microlut 30	Microlut 30
n	23	22	24	23	22	24
Cmax (pg/ml)	434 ± 199 45.9	274 ± 99.8 36.4	138±51.8 37.6	1858 ± 669 36.0	1714 ± 662 38.6	2019 ± 818 40.5
Tmax (hours)	68.9 ± 25.9 37.6	77.5 ± 30.9 39.9	101±27.6 27.5	1.2 ± 0.36 30.2	1.2 ± 0.33 27.7	1.13 ± 0.27 23.6
AUC(0-tlast) (ng/ml x hr^{-1})	63.3 ± 28.3 44.7	42.2 ± 16.8 39.8	22.9±8.86 38.7	20.4 ± 8.86 43.4	17.7 ± 6.36 36.0	21.0 ± 8.98 42.7
t1/2 (HOURS)	30.5 ± 6.84 22.4	29.6 ± 6.83 23.1	28.2 ± 6.37 22.6	27.7 ± 6.73 24.3	28.0 ± 5.62 20.1	29.3 ± 7.31 24.9
Cav (pg/ml)	377 ± 168 44.7	251 ± 100 39.8	136 ± 52.7 38.7	NR	NR	NR
Cmin (pg/ml)	246 ± 112 45.6	179 ± 72.1 40.2	110 ± 41.7 38.1	NA	NA	NA
FI (%)	53.0 ± 24.9 47.0 12.7 - 101	39.4 ± 23.4 59.4 11.3 - 95.8	23.2 ± 7.79 33.6 7.64 - 38.9	NA	NA	NA
TDR (µG/DAY)	40.9± 18.6 45.6	32.7 ± 13.7 41.9	13.7±3.74 27.3	NA	NA	NA

a Values are mean ± SD, CV and range, except
b Values are as reported by sponsor
c Was this because above ULOQ?

APPENDIX 4 MULTIPLE DOSE PHARMACOKINETIC METRICS CORRECTED FOR BASELINE

Estradiol Baseline Corrected Pharmacokinetic Metrics

Table 42 Summary of Multiple Dose Estradiol Pharmacokinetic Metrics (mean ± SD) Using Baseline Corrected Data[a]

Study / Report # / Protocol #	B819 99003				6199 304180			
Formulation	SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM	
Content E2 / LVG (mg) SA (cm^2)	4.5 /3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22	
Nominal TDR E2/ LVG (µg/day)	45 / 40		45 / 30		45 / 30		45 / 15	
Week	1	4	1	4	1	4	1	4
Cmax (pg/ml)	90.02 (43.724)	50.92 (11.086)	87.28 (27.144)	61.87 (22.031)		41.7 15.73		44.3 16.50
Cmin (pg/ml)	53.50 (25.015)	35.82 (10.455)	38.73 (11.491)	33.62 (11.072)		25.7 10.34		28.1 10.33
tmax (hr)	48.0 (36.0, 120)	60.0 (0, 169)	36.0 (24.0, 120)	54.0 (24.0, 168)		36.0 (12.0, 168)		36.0 (0.0, 168)
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)	9923.0 (4473.24)	5747.4 (1372.40)	9184.0 (2457.68)	6293.7 (1545.58)		5165 1823.6		5441 1840.7
Cav (pg/ml)	59.07 (26.626)	34.21 (8.169)	54.67 (14.629)	37.46 (9.200)		30.7 10.85		32.4 10.96
FI (%)	60.15 (31.775)	48.01 (31.241)	87.25 (40.316)	68.54 (47.755)		52.3 28.37		51.6 33.04
R[b]	N/A	0.638 (0.1780)	N/A	0.716 (0.1893)	Rcmin	0.882 0.4196	Rcmin	0.761 0.3332
t1/2 (hr)	NIA	3.408 (2.2168)	N/A	2.990 (0.9916)		ND		ND

a Mean (SD) as reported by sponsor. Median (minimum, maximum) reported for tmax
b Accumulation Ratio based on AUC for report B819 and Cmin for report 6199

Estrone Baseline Corrected Pharmacokinetic Metrics

Table 43 Summary of Multiple Dose Estrone Pharmacokinetic Metrics (mean ± SD) Using Baseline Corrected Data[a]

Study / Report # / Protocol #	B819 99003				6199 304180			
Formulation	SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM	
Content E2 / LVG (mg) SA (cm^2)	4.5 / 3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22	
Nominal TDR E2 / LVG (µg/day)	45 / 40		45 / 30		45 / 30		45 / 15	
Week	1	4	1	4	1	4	1	4
Cmax (pg/ml)	37.35 (18.785)	25.91 (11.013)	38.28 (15.969)	34.55 (25.881)		24.7 12.21		55.9 197.8
Cmin (pg/ml)	25.41 (18.139)	16.979 (9.9660)	20.947 (11.8227)	20.050 (12.5942)		16.1 8.145		48.2 201.3
tmax (hr)	60.0 (12.0, 144)	48.0 (0, 169)	48.0 (24.0, 120)	48.0 (0, 169)		60.0 0.00 - 168		48.0 0.00 - 168
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)	4073.5 (2379.62)	2367.5 (1257.45)	3739.4 (1765.22)	2828.1 (2069.33)		2842 1594.4		3704 3954.4
Cav (pg/ml)	24.25 (14.164)	14.092 (7.4848)	22.258 (10.5073)	16.834 (12.3175)		16.9 9.490		22.0 23.54
FI (%)	63.63 (47.006)	114.13 (164.091)	81.19 (44.102)	97.44 (134.076)		328 1719.1		463 2693.3
R[b]	N/A	0.626 (0.2341)	N/A	0.713 (0.2517)	Rcmin	0.952 0.5273	Rcmin	0.865 1.764
$t_{1/2}$ (hr)	N/A	3.248 (2.9131)	N/A	4.810 (3.1649)				

a Mean (SD) as reported by sponsor. Median (minimum, maximum) reported for tmax
b Accumulation Ratio based on AUC for report B819 and Cmin for report 6199

Estrone Sulfate Baseline Corrected Pharmacokinetic Metrics

Table 44 Summary of Multiple Dose Estrone Sulfate Pharmacokinetic Metrics (mean ± SD) Using Baseline Corrected Data[a]

Study Report # Protocol #	B819 99003				6199 304180			
Formulation	SH 604 DM		SH 604 EM		SH 604 EM		SH 604 FM	
Content E2 / LVG (mg) SA (cm^2)	4.5 / 3.75 30		4.4 / 2.75 22		4.4 / 2.75 22		4.4 / 1.39 22	
Nominal TDR E2 / LVG (µg/day)	45 / 40		45 / 30		45 / 30		45 / 15	
Week	1	4	1	4	1	4	1	4
Cmax (pg/ml)	878.21 (542.67)	536.4 (304.93)	921.8 (762.51)	822.7 (999.33)	—	ND	—	ND
Cmin (pg/ml)	551.9 (446.23)	317.9 (193.55)	557.28 (628.018)	444.28 (553.938)	—	ND	—	ND
tmax (hr)	108 (48.0, 168)	84.0 (48.0, 169)	60.0 (36.0, 144)	108 (24.0, 174)	—	ND	—	ND
AUC(0-168 or 504-672) ($pg/ml*hr^{-1}$)	85876.6 (53993.09)	55065.2 (27574.43)	90111.6 (83786.19)	76145.9 (100401.38)	—	ND	—	ND
Cav (pg/ml)	511.2 (321.39)	327.77 (164.133)	536.4 (498.73)	453.25 (597.627)	—	ND	—	ND
FI (%)	69.37 (42.184)	72.42 (45.199)	79.37 (46.789)	92.26 (64.406)	—	ND	—	ND
R[b]	N/A	0.688 (0.1735)	N/A	0.752 (0.2512)	—	ND	—	ND
$t_{1/2}$ (hr)	N/A	8.763 (4.4629)	N/A	11.644 (10.0066)	—	ND	—	ND

a Mean (SD) as reported by sponsor. Median (minimum, maximum) reported for tmax
b Accumulation Ratio based on AUC for report B819

APPENDIX 5 LEVONORGESTREL PROPORTIONALITY

Table 45 Statistical Analysis for Determination of Proportionality of Levonorgestrel: Dose Normalized ANOVA Results[a]

Parameter	Overall P-value[b]	Treatment Group	LS Mean[c]	95% CI[d]
Cmax/dose (pg/mL/mg)	0.1110	Treatment 1	122	(105, 143)
		Treatment 2	102	(87.7, 119)
AUC(504-672)/dose (pg/ml x hr^{-1}/mg)	0.0727	Treatment 1	17558	(15062, 20469)
		Treatment 2	14400	(12353, 16787)
tmax (hour)	0.4978	Treatment 1	48.0	NA
		Treatment 2	72.0	NA

Note: Treatment 1 was a 22 cm^2 patch containing 4.4 mg of 17β-estradiol and 1.39 mg levonorgestrel (SH 604 FM patch).
Treatment 2 was a 22 cm^2 patch containing 4.4 mg of 17β-estradiol and 2.75 mg levonorgestrel (SH 604 EM patch).
a - Values as per sponsor
b - P-value from natural (ln) transformed ANOVA model testing for an overall dose effect. For tmax, P-value is from Wilcoxon signed-rank test.
c - Least-squares mean based on detransforming data from the natural log scale. For tmax, these are median values.
d - 95% confidence interval based on detransforming 95% confidence interval from the natural log scale.

Table 46 Statistical Analysis for Determination of Proportionality of Levonorgestrel: Power Model Results[a]

Parameter	Linear (slope) Estimate[b]	Linear (slope) 95% CI[c]	2-Fold Increase in Dose Estimate[d]	2-Fold Increase in Dose 95% CI[e]
Cmax (pg/ml)	0.74	(0.42, 1.06)	1.67	(1.34, 2.09)
AUC(504-672) (pg/ml x hr^{-1})	0.71	(0.39, 1.03)	1.64	(1.31, 2.04)

a - Values as per sponsor
b - Estimate of slope from power model.
c - 95% confidence interval for slope from power model. Dose proportionality requires this CI to contain 1.
d - Estimate of the given parameter for 2-fold increase in dose.
e - 95% confidence interval for a 2- fold increase in dose.

APPENDIX 6 STATISTICAL ANALYSIS FOR DETERMINATION OF BIOEQUIVALENCE: CORRECTED FOR BASELINE

Table 47 STATISTICAL ANALYSIS FOR DETERMINATION OF BIOEQUIVALENCE: CORRECTED FOR BASELINE

Parameter	Test Mean[a] (Treatment 1)	Reference Mean[a] (Treatment 2)	Test/Reference[b]	90% Confidence Interval[c]	P-value[d] Sequence	P-value[e] Period	P-value[f] Treatment
ESTRADIOL (E2)							
Cmax (pg/ml)	44.3	41.7	106	(99.5, 113)	0.5256	0.7571	0.1277
ln(Cmax)	43.0	40.3	107	(99.7, 114)	0.7693	0,9673	0.1151
$AUC_{(504-672)}$ (pg/ml x hr^{-1})	5441	5165	105	(99.5, 111)	0.3842	0.6779	0.1294
ln($AUC_{(504-672)}$)	5322	5037	106	(99.6, 112)	0.6942	0.5448	0.1219
tmax (hour)	36.0	36.0	NA	NA	NA	NA	0.1832
ESTRONE (E1)							
Cmax (pg/ml)	55.9	24.8	226	(20.5, 431)	0.2897	0.3518	0.3084
ln(Cmax)	25.6	23.9	107	(94.1, 121)	0.1408	0.2448	0.3861
$AUC_{(504-672)}$ (pg/ml x hr^{-1})	3704	2847	130	(91.7,168)	0.2094	0.4955	0.1940
ln($AUC_{(504-672)}$)	2680	2465	109	(93.9,126)	0.1986	0.7410	0.3423
tmax (hour)	48.0	60.0	NA	NA	NA	NA	0.3622

Note: Treatment 1 was a 22 cm^2 patch contaimn8 4.4 mg of 17β-estradiol and 1.39 mg levonorgestrel (SH 604 FM patch).
Treatment 2 was a 22 cm^2 patch containing 4.4 mg of 17β-estradiol and 2.75 mg levonorgestrel (SH 604 EM patch).

a - Least squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e. geometric means). For tmax, these are the median values.

b – Ratio of parameter means for untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed hack to linear scale.

c - 90% confidence interval for ratio of parameter means of untransformed and natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

d - P-value for difference between sequence means from ANOVA.

e - P-value for difference between period means from ANOVA.

f - P-value for difference between treatment means from ANOVA. For tmax, P-value is from Wilcoxon signed-rank test.

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APPENDIX 7 PROTOCOL SYNOPSES

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PROTOCOL NO.: ME98046 REPORT NO.: AW78

This was a randomized, open-label, cross-over, 2 period, 3 treatment, 4 sequence study in healthy postmenopausal female volunteers 45 – 75 yo. Subjects were caucasian or had light skin color, and a BMI of ≥ 20 and ≤ 29 kg/m^2.

The study design and number of subjects are shown in Table 48

Table 48 Treatment Sequences and Number of Subjects

Period	Sequence			
	1	2	3	4
1	Standard Treatment	Test Treatment **1**	Standard Treatment	Test Treatment **2**
2	Test Treatment **1**	Standard Treatment	Test Treatment **2**	Standard Treatment
No. of subjects planned	12	12	12	12
Completers*	11	11	10	10

* noncompleters withdrawn after period 1 due to low ferritin

There was a 2 week inter-period washout phase.

Table 49 Treatments

Treatment	Description	planned	completed
Standard Treatment	1 x Climara Patch (50 µg Estradiol /24 h) applied to the **lower abdomen** weekly x 2 weeks 3 x Microlut coated tablets (levonorgestrel 30 mg /tablet) po on day of patch application	48	45
Test Treatment 1	1 x SH P 604 DM patch (4.5 mg E2 / 3.75 mg LVG / 30 cm^2) applied to the **lower abdomen** weekly x 2 weeks	24	23
Test Treatment 2	1 x SH P 604 EM patch (4.4 mg E2 / 2.75 mg LVG / YY cm^2) applied to the **lower abdomen** weekly x 2 weeks	24	22

Source of drug products:
Asche AG Cerella
Schering AG Microlut

Blood Sampling:

Test 1 and 2 -0.5, 6, 12, 24, 36 48, 60, 72, 84, 96, 108, 120, 144, 168, 174, 180, 192, 216, 240, & 264
Std -0.5, 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 48, 60, 72, 84, 96, 108, 120, 144, 168, 174, 180, 192, & 216

Tolerability 8, 24, 36 48, 60, 72, 84, 96, 108, 120, 144, 168, 180, 192, & 216

Adhesion 8, 24, 36 48, 60, 72, 84, 96, 108, 120, 144 & 168,

Fasted in AM

Adhesion if <75% for > 24 hours subject is withdrawn

Assays
LVG – acceptable
E2 – acceptable
E1 – acceptable
E1 Sulfate – acceptable
SHBG LLOQ – 2.2 – 7.3 nMol/L
QC Precision and accuracy acceptable.

PROTOCOL NO.: 303341 **REPORT NO.: A00084**

Title:

Open-label, randomized, cross-over study to detemine the average daily delivery et estradiol (E2) and levonorgestrel (LNG) after single transdermal administrations of a patch formulation (SH P 604 FM) containing E2 and LNG (test) in comparison with a standard treatment (single transdermal administration of an E2 patch + oral administration of LNG) in 24 healthy postmenopausal women.

Subjects:

Healthy post menopausal women 45 - 75 years old, non-smokers, with FSH $\geq$ 50 IU and E2 $\leq$ 20 pg/ml. 24 women were planned for the pharmacokinetic evaluation (24 for safety analysis; 21 for the relative bioavailability of E2; and 21 for the relative bioavailability of LVG)

Treatments:

Test: single 7 day transdermal application of a patch formulation containing estradiol and levonorgestrel
SH P 604 FM [E2 / LVG (4.4 / 1.39 mg) 22 cm^2]

Reference - Single 7 day transdermal application of an estradiol patch along with a single oral administration of 3 levonorgestrel tablets (30 µg each) on day 1 at the time of patch application
CLIMARA (50 µg E2/24h; 3.8 mg E2)
MICROLUT (30 µg levonorgestrel (LVG)) oral administration of 3 coated tablets on the day of patch application

2 week inter-period wash-out phase

Pharmacokinetics:

Serum levels of estradiol (E2), levonorgestrel (LVG), estrone (E1), estrone sulfate (E1-SO4), and the sex hormone binding globulin (SHBG) were monitored.

Primary target variable: Area under the drug concentration-time curve (AUCs) of E2 and LVG or $AUC_{(0-tlast)}$

PROTOCOL NO.: B819 REPORT NO.: 99003

An Open-Label, Parallel Group Study to Determine the Pharmacokinetic Properties of 17β-Estradiol, Estrone, Estrone Sulfate and Levonorgestrel Following Repeated Weekly Application of Estradiol/Levonorgestrel 30 cm^2 or 22 cm^2 Transdermal Combination Patches for Four Consecutive Weeks in Healthy Postmenopausal Women.

Study Objectives:

Primary objective: Determination of the multiple dose pharmacokinetics of E2, EI, E1-S and LVG delivered from 30 cm^2 and 22 cm^2 estradiol/levonorgestrel combination patches after repeated weekly applications for four consecutive weeks.

Secondary objective: Assessment of the change from baseline in: sex hormone binding globulin (SHBG), cortisol binding globulin (CBG), and testosterone (T; total and free) and the protein binding of E2 and LVG.

Methodology:

This was an open label, randomized, multiple dose, parallel group study in forty healthy postmenopausal female subjects 45 to 65 years of age.

Each group of 20 subjects were assigned to a randomly ordered treatment and received a single application of one patch applied to the abdomen for seven days during each of four consecutive weeks.

Treatments:
17β-estradiol and levonorgestrel combination transdermal systems

Treatment 1 - SH P 604 DM - 30 cm^2 - Estradiol / Levonorgestrel 4.5 mg / 3.75 mg
Treatment 2 - SH P 604 EM - 22 cm^2 - Estradiol / Levonorgestrel 4.4 mg / 2.75 mg

Pharmacokinetic Sampling:

Blood samples for 17β-estradio1, estrone, estrone sulfate, and levonorgestrel were collected at:

Pre-application time (baseline for Week 1) and at specified times during the first patch wear period (0 to 168 hours during Week 1;

Prior to application of the second, third, and fourth patch;

During specified times from 0-288 h post application of the fourth patch.

Pharmacokinetics:

Pharmacokinetic parameters at weeks 1 and 4 were determined for both formulations, including: AUC(0-168), AUC (0-tlast), Cmax, tmax, Cmin, Cav, degree of fluctuation (DF), accumulation ratio (R), and t1/2 (if possible).

Pharmacodynamics:

Additionally, the study assessed the change from baseline in the following hormone levels after four weekly applications of the transdermal systems: sex hormone binding globulin (SHBG), cortisol binding globulin (CBG), and testosterone (T; total and free). In addition, the protein binding of E2 and LVG was evaluated.

Statistical Analysis:
The assessment of steady state for all analytes was performed through comparisons of Cmin values at pre-dose and weeks 1, 2, 3 and 4.

A regression analysis of Covariance (ANCOVA) model was used to statistically compare Cmin values at weeks 2, 3, and 4 and determine the existence of any week effects.

PROTOCOL NO.: 304180 **REPORT NO.: 6199**

STUDY TITLE:

An Open-Label, Two Period Crossover Study To Compare The Absorption Of 17 β-Estradiol During The Fourth Consecutive Weekly Application Of Two Patch Strengths Of An Estradiol/Levonorgestrel Transdermal Drug Delivery System In Healthy Postmenopausal Women

STUDY OBJECTIVES:

Primary: Compare the rate and extent of estradiol absorption during the fourth week of consecutive weekly patch application from two formulations (EM and FM) of a transdermal estradiol/levonorgestrel drug delivery system in postmenopausal women.

Secondary: Evaluate the proportionality of levonorgestrel between the two patch strengths

STUDY DESIGN:

This was an open label, randomized, multiple dose, two-treatment, two-period crossover study in Forty-four healthy, postmenopausal females from 45 to 70 years old.

Each 4 week treatment period consisted 4 x 7day transdermal applications.
There was a 3 week washout between periods.

Treatment Regimens:

Treatment 1: Estradiol/Levonorgestrel transdermal combination system (22 cm^2) containing 4.4 mg of 17β-estradiol and 1.39 mg levonorgestrel (FM patch).
One patch was applied to the abdomen for seven days during each of 4 consecutive weeks.

Treatment2: Estradiol/Levonorgestrel transdermal combination system (22 cm^2) containing 4.4 mg of 17 β-estradiol and 2.75 mg levonorgestrel (EM patch).
One patch was applied to the abdomen for seven days during each of 4 consecutive weeks.

Sampling:

PK Sampling Schedule: [E2, E1, and LVG] ***NOT E1-Sulfate***
Start of Week 1 (predose), start of Week 2 (168 hr), start of Week 3 (336 hr).
For the seven-day application period of Week 4, samples were obtained at:
predose, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hr post application
(equivalent to 504, 516, 528, 540, 552, 576, 600, 624, 648, and 672 hours after application of first patch).

Hormonal Sampling Schedule: Serum levels of sex hormone binding globulin (SHBG) were determined using serum samples obtained prior to the removal of each of the patches:
predose, 168, 336, 504, and 672 hours post application of the first patch.

PK ANALYSES:

E2, E1, and LVG: (Both baseline corrected and uncorrected as appropriate)
Week 4:Cmax, trnax, and AUC(504-672).
Cmin was calculated weekly.

Baseline corrected values were obtained by subtracting the respective Week 1 pre-dose value from Weeks 2, 3, and 4 serum concentration data.

STATISTICAL METHODOLOGY:

Steady State:

Steady-state of E2, EI, LVG and SHBG were evaluated from their respective baseline corrected and uncorrected Cmin values by the linear regression slope a p of 0.05 was used to test steady-state was not achieved. A second regression was also performed to test for steady-state using only three time points (336 h, 504 h, and 672 h. A paired t-test was also performed to test for steady-state using only two time points (504 h and 672 h).

Bioequivalence and other comparisons:

Analysis of variance (ANOVA) was performed and the 90% confidence intervals were generated for E2 (bioequivalence analyte) and E1 (secondary endpoint). Data for AUC(504-672) and Cmax were log transformed prior to analysis. The analysis was also performed on baseline corrected parameters. Tmax was examined using Wilcoxon's signed-rank test.

Proportionality for Levonorgestrel:

Cmax and AUC(504-672) were tested for dose proportionality using the power model. The power model assumed a linear relationship between the ln-transformed parameter and ln(dose). The ln(dose) term, a continuous variable, was used to estimate the linear relationship with the ln(parameter). If the 95% confidence intervals for the slope of Cmax and AUC(504-672) contained 1, then dose proportionality was concluded. However, if the power model was found to be inappropriate, then the results from the dose-normalized ANOVA model provided the pivotal analyses. In that case, dose-normalized Cmax and AUC(504-672) would be natural log (ln) transformed and analyzed using an ANOVA model. Dose proportionality was concluded if the overall treatment effect for ln-transformed dose normalized Cmax and AUC(504-672) from the ANOVA were not significant at the 5% level. Tmax was examined using Wilcoxon's signed-rank test.

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APPENDIX 8 PHARMACOKINETIC STUDY SUBJECT DEMOGRAPHICS SUMMARY

Table Pharmacokinetic Study Demographics[a]

Study Report	n	Race	Smoking Status	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
AW78	48	Caucasian	NS	60.5 50 - 74	162.6 [5'4"] 151 - 178	66.98 51 - 82	25.34 19.9 - 29.0
A00084	24	Caucasian	NS	59.8 ± 7.2 53 - 74	163.0 ± 4.6 153 - 168	64.3 ± 6.8 52 - 83	24.1 ± 1.9 20 - 29
B819	40	38 Caucasian 1 Black 1 Hispanic	—	56.9 ± 4.42 (7.8) 46 - 65	—	67.23±9.653 (14.4) 49.4 - 89.8	25.52
6199	44	43 Caucasian & 1 Black	—	57.5 ± 5.2 (9.1) 47.0 - 68.0	163.4 ± 6.4 (3.9) 154.9 - 180.3	71.0 ± 10.6 (14.9) 49.5 - 90.9	26.5 ± 3.1 (11.8) 19.7 - 31.2

a Mean ± SD, (CV), range

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ron Kavanagh
5/7/01 03:03:42 PM
BIOPHARMACEUTICS

Ameeta Parekh
6/1/01 03:08:29 PM
BIOPHARMACEUTICS
Note that on p. 1 of the review states 'formulation is intended to del iver – ug/day'. Dr. Kavanagh is attaching an addendum to clarify the discrepancy. Also, an addendum on adhesion and dissolution will be pro vided by Dr. Parekh.