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*APPLICATION NUMBER:*  
**203752Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**Biopharmaceutics Review Addendum**  
Office of New Drug Quality Assessment

<b>NDA</b>	203-752 (SDN-012)
<b>Applicant:</b>	Noven Pharmaceuticals, Inc.
<b>Tradename:</b>	Minivelle (estradiol) Transdermal System
<b>Stamp Dates</b>	9/17/12
<b>Established Name:</b>	17 $\beta$ -estradiol (E2)
<b>Dosage Form:</b>	Transdermal Patch
<b>Route of Administration:</b>	Topical
<b>Strength(s), and Dosing Regimen:</b>	0.1, 0.075, 0.05, 0.0375, (b) (4) mg/day; twice weekly
<b>Indication:</b>	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
<b>OND Division:</b>	Division of Reproductive and Urologic Products (DRUP)
<b>Reviewer</b>	Tapash Ghosh, Ph.D.

**SYNOPSIS**

**Submission:** This is an addendum to the original Biopharmaceutics review for NDA 203-752 for Minivelle (estradiol) Transdermal System (see *Biopharmaceutics review by Dr. Tapash Ghosh dated August 20, 2012, in DARRTS*).

The following comments were included in that original review and were discussed subsequently with the Applicant in a tele-conference held on September 11, 2012. This addendum captures the Applicant's acknowledgment and agreement on these issues as submitted officially under SDN-012 on September 17, 2012.

**1. In Vitro Drug Release Method and Acceptance Criteria**

- The following drug release method and acceptance criteria are acceptable on an interim basis.

Apparatus	Cylinder Speed	Medium	Volume	Acceptance Criteria
USP Apparatus 6	(b) (4)	Water at 32°C	(b) (4)  <b>900 ml:</b> 0.05 mg/24 hr and 0.075 mg/24 hr, 0.1 mg/24 hr	2 hr: (b) (4) 6 hr: (b) (4) <b>18 hr: TBD (report value)</b> 24 hr: (b) (4) <b>36 hr: TBD (report Value)</b>  Refer to USP <724> for L1/L2/L2 testing

- The Applicant will also collect drug release profile data for the additional 18 and 36 hours time-points for the registration batches starting at the next scheduled stability time-point and for the upcoming validation batches. The extension of the

collection period to 36 hrs will ensure that (b) (4) of drug can be consistently achieved.

- The Applicant will also investigate whether an (b) (4) will result in a higher release rate with (b) (4) of drug being released in a shorter sampling period, without losing the discriminating ability.
- The drug release data collected during the first year from approval date will be used for the setting of the final acceptance criteria.
- The collected data and a proposal for the final drug release method and acceptance criteria should be submitted to FDA within fifteen months from approval date, under a prior approval supplement (PAS) to the NDA.
- Upon review of the data provided in the PAS, the drug release methodology and acceptance criteria for Minivelle TDS will be finalized,

**Review:** In the official submission SDN-012 dated September 17, 2012, the Applicant confirmed the following commitments:

- *In the IR Response dated 31-Jul-2012 Noven agreed “to add drug release sampling timepoints at 18 and 36 hours.” “We agree to collect 18 and 36 hour data starting at the next stability timepoint and for the upcoming validation batches.” Noven further agrees to collect dissolution data including the 18 and 36 hr timepoints for 12 months. By the end of 15 months, Noven will submit the dissolution data, proposed acceptance criteria, and justification as a postapproval supplement.*
- *Noven commits to evaluating the release rate method suggestion provided by the Agency in the IR dated 13-Jul-2012. This consists of (b) (4) (b) (4) The results of this evaluation will also be included in the post approval supplement planned for submission in 15 months.*

**Reviewer’s Comment:** The above agreements are acknowledged by the reviewer and are acceptable.

**Recommendation:** The Applicant’s commitments described above will be revisited upon submission of their responses 15 months from the time of approval. Overall, from the Biopharmaceutics perspective, NDA 203-752 for (b) (4) different strengths of Minivelle (estradiol) Transdermal System is recommended for APPROVAL.

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**Tapash K. Ghosh, Ph. D.**  
Primary Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

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**Angelica Dorantes, Ph. D.**  
Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

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/s/  
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TAPASH K GHOSH  
09/18/2012

ANGELICA DORANTES  
09/18/2012

**Biopharmaceutics Review**  
Office of New Drug Quality Assessment

<b>NDA</b>	203-752 (000)
<b>Applicant:</b>	Noven Pharmaceuticals, Inc.
<b>Tradename:</b>	Minivelle (estradiol) Transdermal System
<b>Stamp Dates</b>	12/29/11; 4/27/12; 6/11/12; 7/31/12
<b>Established Name:</b>	17 $\beta$ -estradiol (E2)
<b>Dosage Form:</b>	Transdermal Patch
<b>Route of Administration:</b>	Topical
<b>Strength(s), and Dosing Regimen:</b>	0.1, 0.075, 0.05, 0.0375, (b) (4) mg/day; twice weekly
<b>Indication:</b>	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
<b>OND Division:</b>	Division of Reproductive and Urologic Products (DRUP)
<b>Reviewer</b>	Tapash Ghosh, Ph.D.

**SYNOPSIS**

**Submission:** On 12/29/2011, Noven Pharmaceuticals submitted NDA 203-752 seeking approval of Minivelle (17 $\beta$ -estradiol [E2]) Transdermal System for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause with a right of cross-reference to NDA 20-323 Vivelle (approved on 10/28/1994) and NDA 20-538 for Vivelle-Dot (approved on 7/31/1996) from Novartis. Vivelle and Vivelle-Dot are E2 transdermal systems manufactured by Noven Pharmaceuticals Inc. and marketed by Novartis. Minivelle is a revised formulation with a smaller active surface area compared to the approved products Vivelle and Vivelle-Dot.

(b) (4) dosing strengths of Minivelle are proposed to provide nominal doses of (b) (4), 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via the skin. Each corresponding system has an active surface area of (b) (4), 2.48, 3.30, 4.95, or 6.6 cm<sup>2</sup> and contains (b) (4), 0.62, 0.83, 1.24, or 1.65 mg of E2 USP, respectively.

**Review:** The Biopharmaceutics review is focused on the evaluation and acceptability of the data supporting: (1) the proposed in vitro drug release methodology and acceptance criteria, and (2) the biowaiver request for the lower strengths of Minivelle Transdermal System.

**SUMMARY OF FINDINGS AND CONCLUSIONS**

The safety and efficacy of Minivelle was bridged from Vivelle via a bioequivalence (BE) study using the highest strength of the proposed Minivelle and the approved Vivelle transdermal systems (*Study N28-004: Single-dose, 2-way crossover BE study in 100 healthy, nonsmoking postmenopausal women*).

Excerpts from Clinical Pharmacology review by Chongwoo Yu, Ph. D. is described below:

Dr. Yu's BE analysis results are summarized in Table 1 below:

**Table 1:** Reviewer's Baseline Corrected E2 BE Analysis Results (N=96)

	AUC <sub>84</sub>	AUC <sub>120</sub>	AUC <sub>inf</sub>	C <sub>max</sub>
Ratio of LSM <sup>a</sup>	86.1%	84.5%	84.5%	108.8%
90% geometric CI <sup>b</sup>	80.7-91.7%	79.2-90.3%	79.2-90.3%	102.4-115.6%

<sup>a</sup> Calculated using least-squares means according to the formula:  $e^{((b)(4)(A) - \text{Vivelle}(B))} \times 100$ .

<sup>b</sup> 90% Geometric Confidence Interval using ln-transformed data.

For baseline corrected E2, the 90% geometric confidence intervals (CI) are within the BE acceptance range (i.e., 80.00-125.00%) for AUC<sub>84</sub> and C<sub>max</sub> but not for AUC<sub>120</sub> and AUC<sub>inf</sub>. There is a shift towards slightly lower exposure from Minivelle (Test) compared to Vivelle (Reference) for AUC<sub>120</sub> and AUC<sub>inf</sub>. Considering that the patch was applied for the duration for 84 hours in this study, this reviewer finds the BE assessment based on AUC<sub>84</sub> rather than AUC<sub>120</sub> or AUC<sub>inf</sub> to be more clinically relevant as AUC<sub>120</sub> or AUC<sub>inf</sub> include time points that belong to the post-removal period.

Overall, Dr. Yu concludes that BE between Minivelle (1.65 mg E2/6.6 cm<sup>2</sup>) and Vivelle® (8.66 mg E2/29 cm<sup>2</sup>) has been established regarding C<sub>max</sub> and AUC following a single dose administration for 84 hours to the lower abdomen in postmenopausal women.

The applicant also conducted a dose proportionality study to support their biowaiver request for doses lower than 0.1 mg/day. Baseline corrected AUC<sub>84</sub> and C<sub>max</sub> increased linearly and E2 were found to be dose proportional among the 3 nominal doses of 0.025 mg/day, 0.05 mg/day, and 0.1 mg/day following a single dose of Minivelle in a three-way crossover study in postmenopausal women (see Clinical Pharmacology review).

To support the approval of the biowaiver request for the proposed (b) (4) lower strengths of Minivelle, the Applicant submitted the following information:

- (1) Establishment of BE to Vivelle at the highest strength of 0.1 mg/day;
- (2) Establishment of dose proportionality over the dose range of 0.025 - 0.1 mg/day;
- (3) Proportional composition of the formulations for the different doses of Minivelle; and
- (4) Comparable *in vitro* dissolution profiles for all the strengths of Minivelle ( $f_2 > 50$ ).

## **RECOMMENDATION:**

ONDQA-Biopharmaceutics has evaluated the information provided in NDA 203-372 for Minivelle (estradiol) Transdermal System and has the following comments:

### ***1. Biowaiver Request***

- The *in vitro* drug release profile of each one of the lower strengths of Minivelle TDS was compared vs. the drug release profile of the highest strength (6.6 cm<sup>2</sup> vs.

4.95 cm<sup>2</sup>, 6.6 cm<sup>2</sup> vs. 3.3 cm<sup>2</sup>, 6.6 cm<sup>2</sup> vs. 2.475 cm<sup>2</sup>, and 6.6 cm<sup>2</sup> vs. (b) (4).  
 The release profiles are similar in shape and met the criteria for similarity (f1 and f2 factors).

- The results from the BE study and similarity f2 test support the Applicant's request for a BA/BE waiver for the proposed lower strengths of Minivelle transdermal and the biowaiver is granted.

**2. In Vitro Drug Release Method and Acceptance Criteria**

- The following drug release method and acceptance criteria are acceptable on an interim basis.

Apparatus	Cylinder Speed	Medium	Volume	Acceptance Criteria
USP Apparatus 6	(b) (4)	Water at 32°C	(b) (4)  <b>900 ml:</b> 0.05 mg/24 hr and 0.075 mg/24 hr, 0.1 mg/24 hr	2 hr: (b) (4) 6 hr: (b) (4) <b>18 hr: TBD (report value)</b> 24 hr: (b) (4) <b>36 hr: TBD (report Value)</b>  Refer to USP <724> for L1/L2/L2 testing

- The Applicant will also collect drug release profile data for the additional 18 and 36 hours time-points for the registration batches starting at the next scheduled stability time-point and for the upcoming validation batches. The extension of the collection period to 36 hrs will ensure that (b) (4) of drug can be consistently achieved.
- The Applicant will also investigate whether an (b) (4) will result in a higher release rate with (b) (4) of drug being released in a shorter sampling period, without losing the discriminating ability.
- The drug release data collected during the first year from approval date will be used for the setting of the final acceptance criteria.
- The collected data and a proposal for the final drug release method and acceptance criteria should be submitted to FDA within fifteen months from approval date, under a prior approval supplement (PAS) to the NDA.
- Upon review of the data provided in the PAS, the drug release methodology and acceptance criteria for Minivelle TDS will be finalized,

The specific language/details for the Post Marketing Commitment (PMC) to collect and submit the additional information needs to be agreed upon with the Applicant before the action letter for this NDA is issued.

Overall, from the Biopharmaceutics perspective, NDA 203-752 for (b) (4) different strengths of Minivelle (estradiol) Transdermal System is recommended for APPROVAL.

**Tapash K. Ghosh, Ph. D.**  
**Primary Biopharmaceutics Reviewer**  
**Office of New Drug Quality Assessment**  
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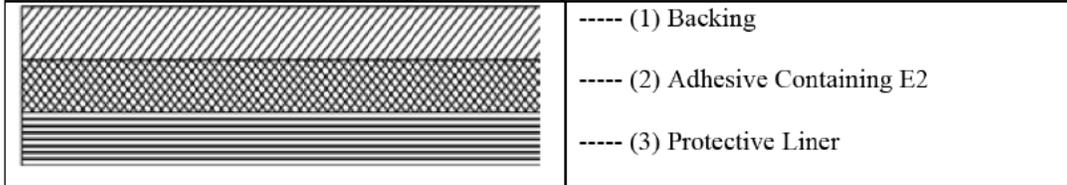
**Angelica Dorantes, Ph. D.**  
**Biopharmaceutics Team Leader**  
**Office of New Drug Quality Assessment**  
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## BIOPHARMACEUTICS ASSESSMENT

### Product Description & Formulation:

Minivelle is comprised of three layers: (1) a translucent (b) (4) film (2) an adhesive formulation containing E2, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

**Figure 1: The 3 Layers of Minidot**



**Table 1: Patch Sizes and E2 per Unit for Vivelle, Vivelle Dot, and Minivelle**

Strength	Vivelle	Vivelle-Dot	(b) (4)
<b>Active Surface Area/Patch Size</b>			
0.025 mg/day	7.25 cm <sup>2</sup>	2.5 cm <sup>2</sup>	(b) (4)
0.0375 mg/day	11.0 cm <sup>2</sup>	3.75 cm <sup>2</sup>	2.48 cm <sup>2</sup>
0.05 mg/day	14.5 cm <sup>2</sup>	5.0 cm <sup>2</sup>	3.30 cm <sup>2</sup>
0.075 mg/day	22 cm <sup>2</sup>	7.5 cm <sup>2</sup>	4.95 cm <sup>2</sup>
0.1 mg/day	29 cm <sup>2</sup>	10 cm <sup>2</sup>	6.60 cm <sup>2</sup>
<b>Estradiol Content per Unit</b>			
0.025 mg/day	2.17 mg	0.39 mg	(b) (4)
0.0375 mg/day	3.28 mg	0.585 mg	0.62 mg
0.05 mg/day	4.33 mg	0.78 mg	0.83 mg
0.075 mg/day	6.57 mg	1.17 mg	1.24 mg
0.1 mg/day	8.66 mg	1.56 mg	1.65 mg

**Table 2: Comparison of Vivelle, Vivelle-Dot and Minivelle**

(b) (4)

## **Biopharmaceutics Information:**

(b) (4) dosing strengths of Minivelle (estradiol) transdermal system are proposed to provide nominal doses of (b) (4), 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via the skin. Each corresponding system has an active surface area of (b) (4) 2.48, 3.30, 4.95, or 6.6 cm<sup>2</sup> and contains (b) (4), 0.62, 0.83, 1.24, or 1.65 mg of E2 USP, respectively.

The safety and efficacy of Minivelle is being leveraged/established via a bridging bioequivalence (BE) study between the highest strengths of the proposed Minivelle and the approved Vivelle transdermal systems (*BE study N28-004; a single-dose, 2-way crossover BE study in 100 healthy, nonsmoking postmenopausal women*). A dose proportionality study to support the biowaiver request for the doses lower than 0.1 mg/day was also conducted. Baseline corrected AUC<sub>84</sub> and C<sub>max</sub> increased linearly and E2 were found to be dose proportional among the 3 nominal doses of (b) (4) mg/day, 0.05 mg/day, and 0.1 mg/day following a single dose of Minivelle in a three-way crossover study in postmenopausal women (see Clinical Pharmacology review).

To support the approval of the (b) (4) additional lower strengths of Minivelle, a biowaiver request was submitted based on: (1) the establishment of BE to Vivelle's highest strength of 0.1 mg/day; (2) establishment of dose proportionality over the dose range of 0.025 - 0.1 mg/day; (3) the fact that different doses of Minivelle are compositionally proportional; and (4) comparable *in vitro* dissolution profiles of all strengths of Minivelle ( $f_2 > 50$ ).

***Reviewer's Comment:*** *Qualitatively Minivelle is much similar to Vivelle-Dot than Vivelle; however, as efficacy and safety information is available for the original Vivelle, the Applicant rightfully bridged the proposed Minivelle with Vivelle via a BE study.*

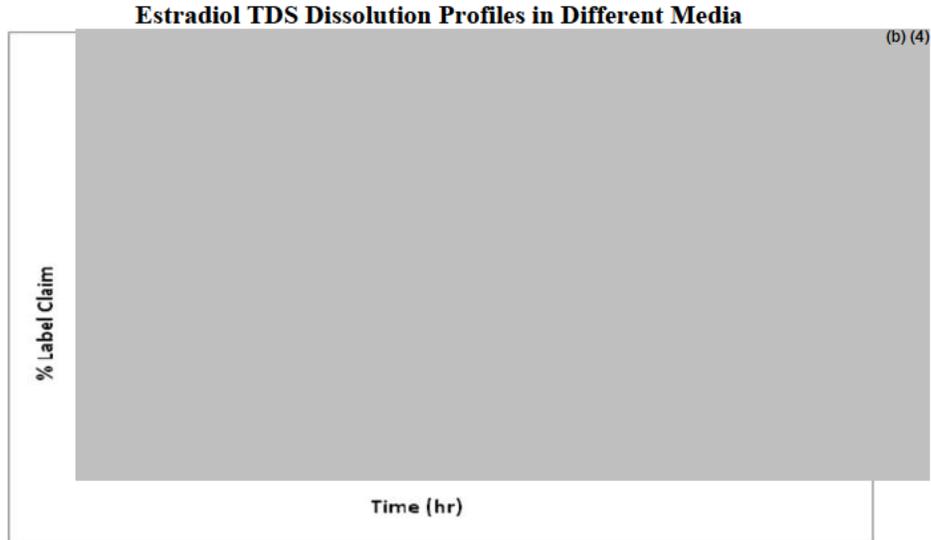
## **Proposed In Vitro Drug Release Methodology and Acceptance Criteria**

***Method Development:*** The *in vitro* drug release method for Minivelle system is similar to the method used for the Vivelle Dot (NDA 20-538) transdermal system and it employs the methodology for estradiol transdermal systems in the OGD's database.

***Apparatus:*** The drug release method for the estradiol transdermal system uses Apparatus 6, the cylinder apparatus as it has the advantage of avoiding a screen that can occlude the patch or retain bubbles and are easier to set up and start.

***Dissolution Conditions:*** Water was chosen as the dissolution medium, because it is readily available and maintains the sink condition with adequate solubility for the estradiol in the transdermal system. Buffer solutions are not necessary since the solubility of estradiol is not greatly affected by small changes in pH, as the molecule contains no strong acid or basic functionality.

In addition to water, dissolution profiles were generated for the Estradiol TDS using three other dissolution media (b) (4). Results are shown in Figure 2. Media with (b) (4)



**Speed:** Common cylinder speeds are (b) (4). The (b) (4) speed was selected to give additional resolution in the early part of the dissolution profile. 32°C is the dissolution temperature designed to be the temperature of skin.

Based on the above, the following conditions were adopted as the final release testing condition by the Applicant:

Apparatus: USP Apparatus 6  
Speed: (b) (4)  
Medium: Water at 32 ± 0.5°C  
Volume: (b) (4)  
900 mL for 0.05 mg/24hr, 0.075 mg/24hr, 0.1 mg/24hr  
Sampling Times: (b) (4) (recommended);  
Additionally a 24 hr sampling point is included.

**Drug Release Acceptance Criteria:** Using the above method, and the release profile in water, the Applicant proposed the following criteria for product release and during shelf-life testing. Drug release testing limits were established with sample times of 2, 4, 6 and 24 hours with the following acceptance criteria:

<u>Sample Time</u>	<u>%Label Claim</u>
2 hours	(b) (4)
4 hours	(b) (4)
6 hours	(b) (4)
24 hours	(b) (4)

The sample times were established to provide an early point at 2 hours to preclude too rapid drug release, two points (4 and 6 hours) in the middle of the dissolution profile, and a later point at 24 hours to ensure that the majority of the drug substance has been released. Testing results from the Bio-lots 50850, 50855, 50857, 50857 and RN059-I-P4.95 were averaged to set the mid-points of the specifications. Results from 114 patches covering time of release and through six months stability were used to set the mid points.

**Lot Numbers of Transdermal Systems Tested**

Product	Size (cm <sup>2</sup> )	Strength (mg/day)	Code number	Lot number
Estradiol TDS		(b) (4)	30016-108	50855
Estradiol TDS	2.475	0.0375	30024-08	50856
Estradiol TDS	3.3	0.05	30033-108	50857
Estradiol TDS	4.95	0.075	30049-08	RN059-1-P4.95
Estradiol TDS	6.6	0.1	30066-108	50850
Vivelle®	29.0	0.1	0129-21	44189

**Reviewer’s Comments:**

Upon review of the results, the following comments were sent to the Applicant in an IR letter dated 7/13/12.

- Based on the release data/profiles submitted earlier, it appears that (b) (4) drug release for your proposed product in water can be achieved at 36 hours using your proposed method. Therefore, it is recommend that you establish sample points and acceptance ranges at 2, 6, 18 and 36 hours for your proposed patch which is to be worn for 84 hours.
- It appears that you may be able to achieve a higher release rate of the drug by (b) (4) without loosing the discriminatory ability, which may reduce the total sampling period.

On July 31, 2012, the Applicant responded as follows:

*Noven agrees to add drug release sampling time points at 18 and 36 hours. However, at this time Noven has very limited results at these time points and is not able to set acceptance ranges based on these data. Further, the validation data currently available for the drug release method does not include the 18 and 36 hour time points, and that study also needs to be performed. We agree to collect 18 and 36 hour data starting at the next stability time point and for the upcoming validation batches. We will also evaluate the entire release profile to ensure that (b) (4) can be consistently achieved. The specification has been updated to include the new sampling times, as described below:*

Test	Acceptance Criteria	Method
Release Rate	Refer to USP <724> for individual unit acceptance criteria.	
2 hour	(b) (4)	Dissolution
6 hour	(b) (4)	
18 hour	Report Value	
24 hour	(b) (4)	
36 hour	Report Value	

Regarding the observation on (b) (4) Noven appreciates the suggestion and will take it under consideration. Any changes in (b) (4) will be submitted as a post-approval supplement.

**Reviewer's Comments:**

1. The drug release test and acceptance criteria are acceptable on an interim basis.
2. The Applicant will collect drug release profile data at 2, 6, 18, 24, and 36 hour for the registration batches starting at the next stability timepoint and for the upcoming validation batches. The extension of the collection period to 36 hrs will ensure that (b) (4) of drug can be consistently achieved.
3. The drug release data collected during the first year from approval date will be used for the setting of the final acceptance criteria.
4. The Applicant will also investigate whether an (b) (4) will result in a higher release rate with (b) (4) of drug being released in a shorter sampling period, without losing the discriminating ability.
5. The collected data and a proposal for the final drug release method and acceptance criteria should be submitted to FDA within fifteen months from approval date, under a prior approval supplement (PAS) to the NDA.
6. Upon review of the data provided in the PAS, the drug release methodology and acceptance criteria for Minivelle will be finalized,

**Biowaiver Request**

The Applicant proposed to market Minivelle in (b) (4) different dosage strengths and requested a biowaiver for the lower dosage strengths of (b) (4) 0.0375 mg/day, 0.05 mg/day, and 0.075 mg/day with the following justifications per 21 CFR §314.90:

- The patches for the lower strengths have the same formulations as the highest strength used in the BE study. All of them are from the same sheet of the formulation and the only difference is the size (surface area) of the patches.
- Establishment of BE between Minivelle and Vivelte at the highest strength of 0.1 mg/day.
- Establishment of dose proportionality over the dose range of 0.025-0.1 mg/day.
- *In vitro* dissolution profiles for all strengths of Minivelle are comparable ( $f_2 > 50$ )

**Comparative Dissolution in Water Medium:** Comparative dissolution profile testing was performed for the proposed highest strength of the Minivelle transdermal system vs. the highest Vivelle Transdermal System. To support the biowaiver request, each one of the proposed lower strengths of Estradiol TDS was compared vs. the highest strength (tested in the BE study). The results are described below:

Figure 1: Vivelle 29.0 sq. cm TDS vs. Estradiol 6.6 sq. cm TDS

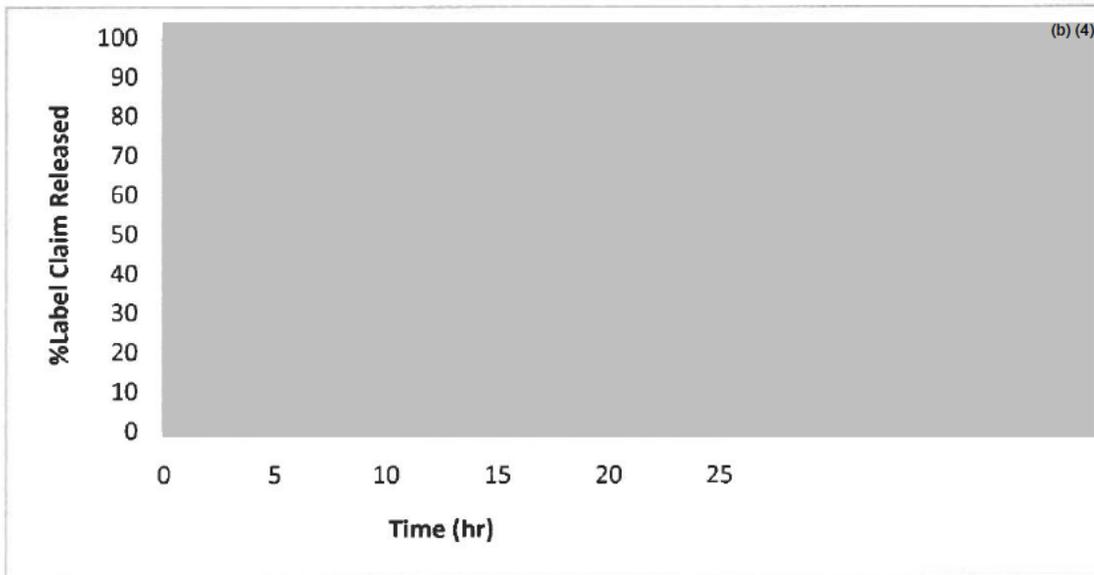


Table 2: Comparison of Vivelle 29.0sq. cm TDS and Estradiol 6.6 sq. cm TDS

Time (hr)	Average %Label Claim (Vivelle 29.0 cm2 TDS)	Average %Label Claim (Estradiol 6.6 cm2 TDS )	Difference Factor f1	Similarity Factor f2
1	(b) (4)		92	34
2				
4				
6				
8				
10				
12				
24				

Figure 2: Estradiol 6.6 sq. cm TDS vs. Estradiol 4.95 sq. cm TDS

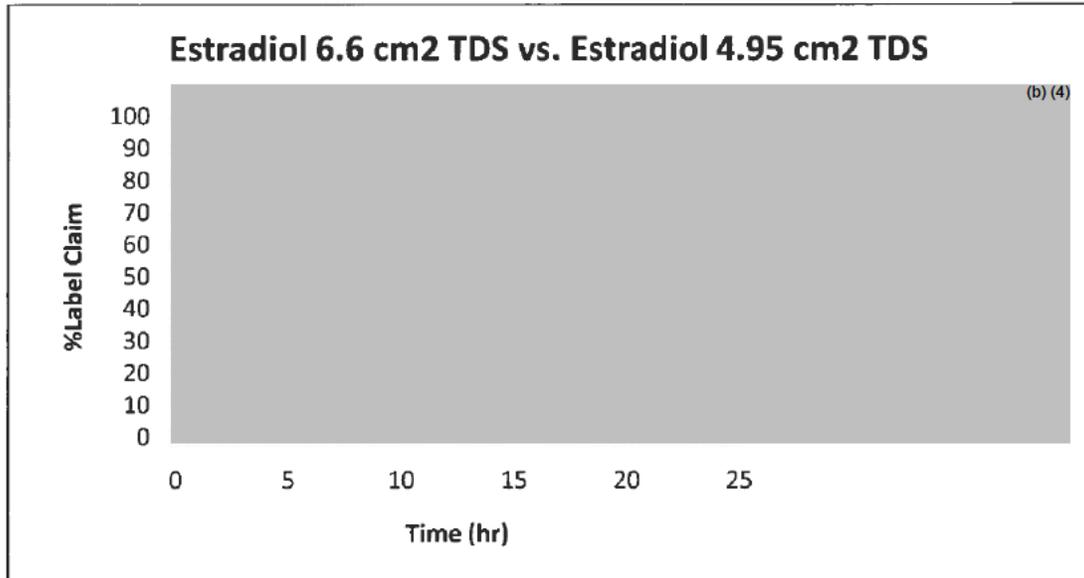


Table 3: Comparison of Estradiol 6.6 sq. cm TDS and Estradiol 4.95sq. cm TDS

Time (hr)	Average %Label Claim (Estradiol 6.6 cm2 TDS)	Average %Label Claim (Estradiol 4.95 cm2 TDS)	Difference Factor f1	Similarity Factor f2
1	(b) (4)		3	89
2				
4				
6				
8				
10				
12				
24				

Figure 3: Estradiol 6.6 sq. cm TDS vs. Estradiol 3.3 sq. cm TDS

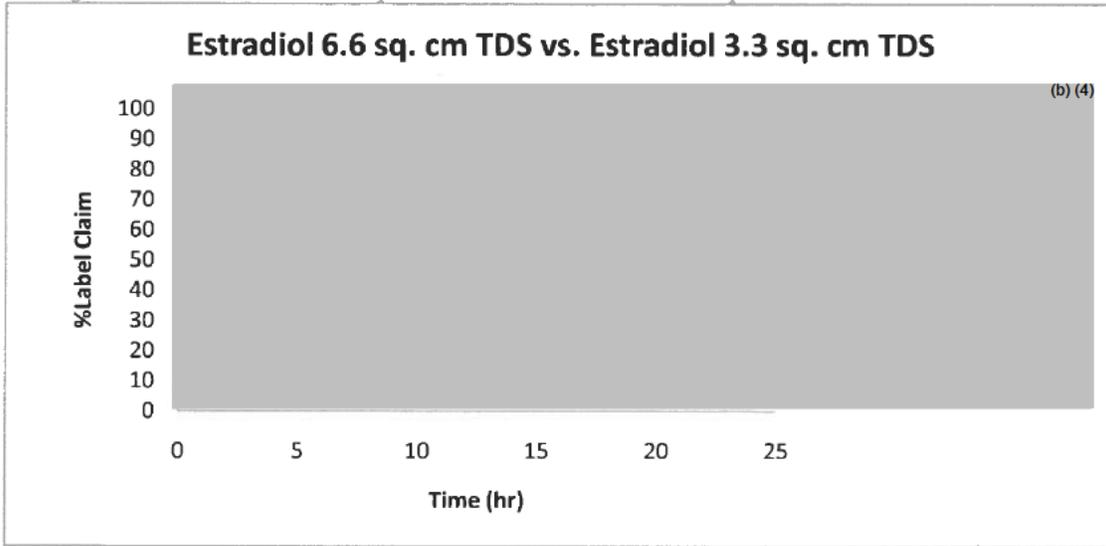


Table 4: Comparison of Estradiol 6.6 sq. cm TDS and Estradiol 3.3 sq. cm TDS

Time (hr)	Average %Label Claim (Estradiol 6.6 cm2 TDS)	Average %Label Claim (Estradiol 3.3 cm2 TDS)	Difference Factor f1	Similarity Factor f2
1	(b)(4)			
2				
4				
6				
8			1	94
10				
12				
24				

Figure 4: Estradiol 6.6 sq. cm TDS vs. Estradiol 2.475 sq. cm TDS

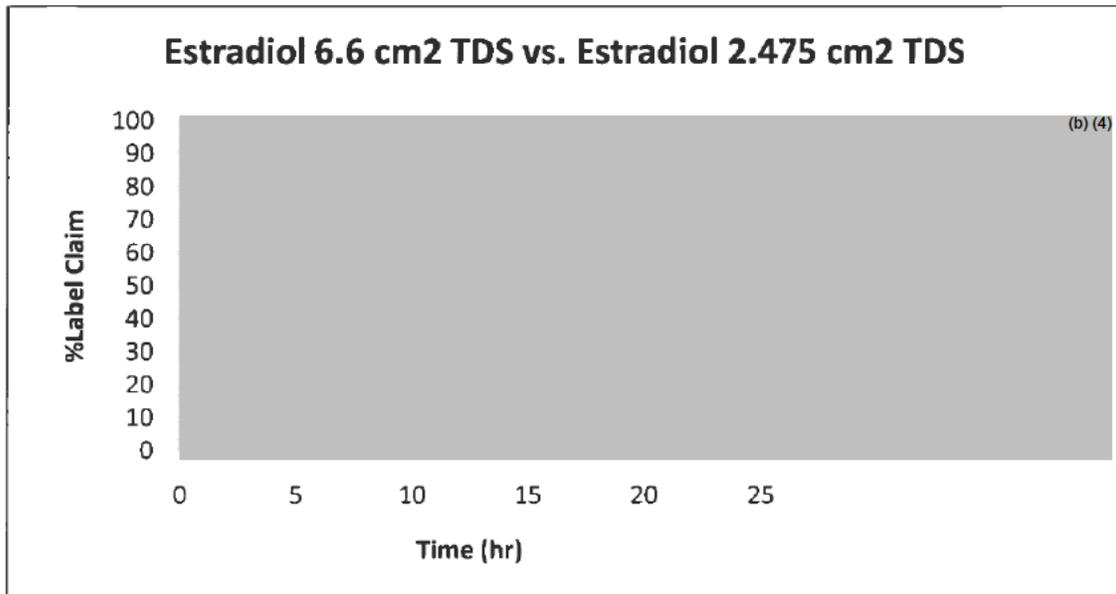


Table 5: Comparison of Estradiol 6.6 sq. cm TDS and Estradiol 2.475 sq. cm TDS

Time (hr)	Average %Label Claim (Estradiol 6.6 cm2 TDS)	Average %Label Claim (Estradiol 2.475 cm2 TDS)	Difference Factor f1	Similarity Factor f2
1	(b) (4)		5	83
2				
4				
6				
8				
10				
12				
24				

**Reviewer's Comments:**

- 1. The in vitro drug release profile of each one of the lower strengths of Minivelle (estradiol) TDS was compared vs. the release profile of the highest strength (6.6 cm<sup>2</sup> vs. 4.95 cm<sup>2</sup>, 6.6 cm<sup>2</sup> vs. 3.3 cm<sup>2</sup>, 6.6 cm<sup>2</sup> vs. 2.475 cm<sup>2</sup>, and 6.6 cm<sup>2</sup> vs. (b) (4) (redacted). The release profiles are similar in shape and met the criteria for similarity (f1 and f2 factors).*
- 2. The results from the BE study and similarity f2 test support the Applicant's request for a BA/BE waiver for the proposed lower strengths of Minivelle transdermal and the biowaiver is granted.*
- 3. Upon review of the in vitro drug release data to be submitted within 15 months from the NDA's action date for this proposed product, the in vitro drug release methodology and the acceptance criteria will be finalized.*

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/s/  
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TAPASH K GHOSH  
08/20/2012

ANGELICA DORANTES  
08/20/2012



## 1 Executive Summary

The Sponsor submitted a 505(b)(1) new drug application (NDA) to seek approval of MINIVELLE (17 $\beta$ -estradiol [E2] transdermal patch) for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause with a right of cross-reference to NDA 020323 Vivelle (approved on October 28, 1994) and NDA 020538 Vivelle-Dot (approved on July 31, 1996) from Novartis. Vivelle and Vivelle-Dot are E2 transdermal patches manufactured by Noven Pharmaceuticals Inc. and marketed by Novartis. (b) (4)

MINIVELLE contains E2 in a multi-polymeric adhesive. It is designed to release the active component, E2, continuously upon application to intact skin. The remaining components of the system are pharmacologically inactive. (b) (4) dosage strengths of MINIVELLE are available to provide nominal delivery rates of (b) (4), 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via the skin. Each corresponding system has an active surface area of (b) (4) 2.48, 3.30, 4.95, or 6.6 cm<sup>2</sup> and contains (b) (4), 0.62, 0.83, 1.24, or 1.65 mg of E2 USP, respectively.

The recommended starting dose of MINIVELLE is 0.0375 mg/day. The adhesive side of MINIVELLE should be placed on a clean, dry skin area of the abdomen (i.e., below the umbilicus) or buttocks twice weekly. The sites of application must be rotated (i.e., left vs. right; abdomen vs. buttocks), with an interval of at least 1 week allowed between applications to a particular site. Dosage adjustment should be evaluated periodically (e.g., 3-6 month intervals) and guided by the clinical response (i.e., the frequency and severity of VMS symptoms). Therapy should last for the shortest duration consistent with the treatment goals.

Vivelle and Vivelle-Dot are available in five dosage strengths (b) (4) to provide nominal delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via skin but their active surface areas are larger. Vivelle-Dot which has a smaller active surface area compared to Vivelle, was approved based on the establishment of bioequivalence (BE) to Vivelle. Vivelle and Vivelle-Dot should be applied to the abdomen (i.e., below the umbilicus) or buttocks and should be replaced twice weekly.

In this current NDA, the Sponsor submitted 4 Clinical Pharmacology studies including a pivotal BE study (Study N28-004) and a dose-proportionality study (Study N28-005) that used the to-be-marketed (TBM) formulation. The safety and efficacy of MINIVELLE is supported via bridging to the findings of Vivelle by demonstrating BE. In addition, skin adhesion was evaluated in the pivotal BE (Study N28-004) and dose-proportionality (Study N28-005) studies. Out of the 4 studies submitted, Study N28-004 and Study N28-005 were reviewed. The other 2 studies were not reviewed as they were not relevant to the TBM product.

While there are (b) (4) different dosage strengths of MINIVELLE developed, the BE study was conducted with only the highest strength (i.e., 0.1 mg/day) and a dose proportionality study was conducted to support the biowaiver request for dosage strengths lower than 0.1 mg/day. A biowaiver request was submitted for the (b) (4) lower dosage strengths (i.e., (b) (4), 0.0375, 0.05, and 0.075 mg/day) based on: (1) the establishment of BE to Vivelle at the highest strength of 0.1 mg/day; (2) the establishment of dose proportionality over the dose range of 0.025-0.1 mg/day; (3) the fact that different dosage strengths of MINIVELLE are compositionally proportional; and (4) the comparable *in vitro* dissolution profiles of all strengths of MINIVELLE ( $f_2 > 50$ ).

For the pivotal BE study (Study N28-004), a formal consult to the Office of Scientific

Investigations (OSI) was made for clinical and bioanalytical study site inspections.

### 1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 203752 submitted on December 29, 2011 and April 27, 2012. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

### 1.2 Post-marketing Requirements or Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

#### BE Assessment:

BE between MINIVELLE (1.65 mg E2/6.6 cm<sup>2</sup>) and Vivelle (8.66 mg E2/29 cm<sup>2</sup>) at the highest strength (i.e., nominal delivery of 0.1 mg/day) was established following a single dose administration to the lower abdomen in a 2-way crossover study (Study N28-004) in 100 healthy, nonsmoking postmenopausal women.

**Table 1:** Baseline Corrected E2 BE Results (N=96)

	AUC <sub>84</sub>	AUC <sub>120</sub>	AUC <sub>inf</sub>	C <sub>max</sub>
Ratio of LSM <sup>a</sup> x 100	86.1%	84.5%	84.5%	108.8%
90% geometric CI <sup>b</sup>	80.7-91.7%	79.2-90.3%	79.2-90.3%	102.4-115.6%

<sup>a</sup> Calculated using least-squares means (LSM) according to the formula:  $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$

<sup>b</sup> 90% Geometric Confidence Interval (CI) using ln-transformed data

For baseline corrected E2, the 90% geometric confidence intervals (CI) were within the BE acceptance range (i.e., 80.00-125.00%) for AUC<sub>84</sub> and C<sub>max</sub> but not for AUC<sub>120</sub> and AUC<sub>inf</sub> (Table 1). There is a shift towards slightly lower exposure from MINIVELLE (Test) compared to Vivelle (Reference) for AUC<sub>120</sub> and AUC<sub>inf</sub>. Considering that the patch was applied for the duration for 84 hours in this study, the BE assessment was based on the AUC<sub>84</sub> and C<sub>max</sub> rather than AUC<sub>120</sub> or AUC<sub>inf</sub>.

#### Adhesion

In the BE study and dose proportionality study consisting of 208 observations for MINIVELLE, 98% of the observations (203 out of 208 observations) had an adhesion score of 0 (i.e., ≥ 90% adhered to the skin) over the 84 hour wear period.

#### Dose Proportionality

Based on the baseline corrected E2 AUC<sub>84</sub> and C<sub>max</sub>, dose proportionality was established from 0.025 mg/day to 0.1 mg/day.

#### Distribution, Metabolism, and Excretion

No new E2 distribution, metabolism, and excretion studies were conducted with MINIVELLE. Distribution, metabolism, and excretion of E2 are expected to be the same as those from Vivelle. The Sponsor is proposing to use the information regarding E2 distribution, metabolism, and excretion from Vivelle for labeling.

#### Drug-Drug Interactions (DDI):

No new DDI studies were conducted with MINIVELLE. The Sponsor is proposing to use the information used regarding DDI from Vivelle for labeling.

**Use in Specific Populations:**

- Pediatric use: No pediatric studies were conducted with MINIVELLE. The Sponsor's pediatric waiver request is pending from the Pediatric Review Committee's (PeRC) approval. This is scheduled to be discussed on September 19, 2012.
- Geriatric use: No geriatric studies were conducted. The results of the Women's health Initiative (WHI) study indicate a higher risk of older postmenopausal women (i.e., age 65 to 79 years) developing probable dementia after receiving daily conjugated estrogen. However, it is unknown whether this finding would apply to younger postmenopausal women taking MINIVELLE.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairment. MINIVELLE is contraindicated for known liver impairment or disease. No additional safety concerns are expected for patients with renal impairment.

**Bioanalytical Methods:**

Acceptance criteria and method performance for E2 concentration measurements were in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable.

Serum samples were analyzed for E2 using validated bioanalytical methods. Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were used in the pivotal BE study (Study N28-004) and the dose proportionality study (Study N28-005). Incurred sample reanalysis (ISR) was conducted on approximately 10% of the study samples in both studies. Approximately 96% and 97% of the ISR results met the acceptance criteria of being within  $\pm 20\%$  of the original reported concentration value for at least 67% of the ISR samples from Studies N28-004 and N28-005, respectively.

An OSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study (Study N28-004) was requested on February 13, 2012. There were no significant objectionable issues identified and the Form FDA 483 was not issued. Details of the OSI inspection findings can be found in Drs. Jyoti B. Patel and Gopa Biswas' OSI consult review (dated July 1, 2012 in DARRTS; see Appendix Section 4.2 of this review).

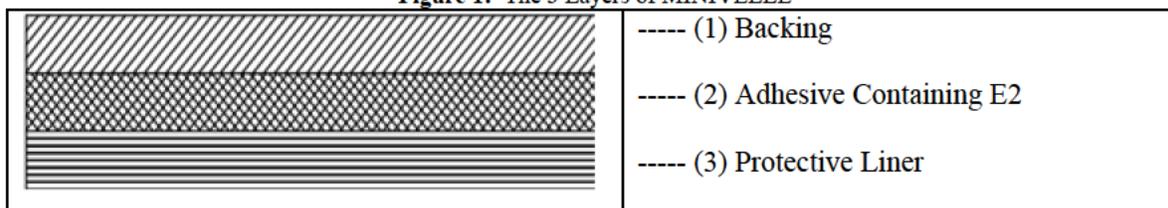
## 2 Question Based Review

### 2.1 General Attributes

#### 2.1.1 What is MINIVELLE and what is its active pharmacological ingredient?

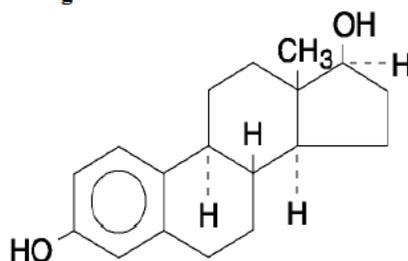
MINIVELLE contains E2 in a multi-polymeric adhesive. It is designed to release E2 continuously upon application to intact skin. (b) (4) dosage strengths of MINIVELLE are available to provide nominal delivery rates of (b) (4) 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via the skin. Each corresponding system has an active surface area of (b) (4) 2.48, 3.30, 4.95, or 6.6 cm<sup>2</sup> and contains (b) (4) 0.62, 0.83, 1.24, or 1.65 mg of E2 USP, respectively. MINIVELLE is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent (b) (4) film (2) an adhesive formulation containing E2, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.

Figure 1: The 3 Layers of MINIVELLE



The active component of MINIVELLE is E2. Identical E2 USP, a white, crystalline powder, chemically described as *estra-1,3,5(10)-triene-3,17 $\beta$ -diol* is used for all different strengths of MINIVELLE. The structural formula is shown in Figure 2. The remaining components of MINIVELLE are pharmacologically inactive.

Figure 2: Structural Formula of E2



The molecular formula of E2 is C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>. The molecular weight is 272.39.

#### 2.1.2 What are the Sponsor's justifications of submitting their biowaiver request?

As indicated in Table 2, the Sponsor proposes to market MINIVELLE in (b) (4) different strengths and is requesting a biowaiver for the lower strengths of (b) (4) 0.0375 mg/day, 0.05 mg/day, and 0.075 mg/day with the following justifications per 21 CFR §314.90:

- BE establishment of MINIVELLE to Vivelle at the highest strength of 0.1 mg/day
- Establishment of dose proportionality over the dose range of 0.025-0.1 mg/day
- Different doses of MINIVELLE are compositionally proportional
- *In vitro* dissolution profiles of all strengths of MINIVELLE are comparable ( $f_2 > 50$ )

**Table 2: Patch Sizes and E2 per Unit for Vivelle and MINIVELLE**

Strength	Vivelle	MINIVELLE
0.1 mg/day	8.66 mg/29 cm <sup>2</sup>	1.65 mg/6.6 cm <sup>2</sup>
0.075 mg/day	6.57 mg/22 cm <sup>2</sup>	1.24 mg/4.95 cm <sup>2</sup>
0.05 mg/day	4.33 mg/14.5 cm <sup>2</sup>	0.83 mg/3.3 cm <sup>2</sup>
0.0375 mg/day	3.28 mg/11 cm <sup>2</sup>	0.62 mg/2.48 cm <sup>2</sup>
0.025 mg/day	2.17 mg/7.25 cm <sup>2</sup>	(b) (4)

The Office of New Drug Quality Assessment (ONDQA) review team will review and determine the acceptability of the Sponsor's biowaiver request.

### 2.1.3 What is the regulatory history of the product?

In general, the Sponsor has complied with the Division's guidance throughout their drug development. Reference is made to the September 11, 2007 pre-IND meeting minutes (dated October 5, 2007 in DARRTS) and the advice/information request letters dated July 16, 2010 and March 18, 2011 in DARRTS for further details of the Division's recommendations to the Sponsor.

## 2.2 General Clinical Pharmacology

### 2.2.1 What is the relevant Clinical Pharmacology information submitted in this NDA?

This NDA contains the following:

- Draft product label in physician labeling rule (PLR) format
- Information on the composition of drug products used in the clinical studies
- Full clinical trial reports of the 4 Clinical Pharmacology studies
- Biowaiver request
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies

The Clinical Pharmacology studies submitted to this NDA are summarized in the Table 3 below:

**Table 3: Summary of Clinical Pharmacology Studies**

Study	Objective	Population	Dosing Regimen	Design
N28-004 TBM formulation	Pivotal BE	100 healthy, nonsmoking, postmenopausal women (40-65 yrs)	Treatment A: MINIVELLE 1.65 mg/6.6 cm <sup>2</sup> Treatment B: Vivelle 8.66 mg/29 cm <sup>2</sup> Both treatments for 84 hrs	Open label, single dose, two treatment, two-way crossover study
N28-005 TBM formulation	Dose proportionality	36 healthy, nonsmoking, postmenopausal women (40-65 yrs)	Treatment A: MINIVELLE 1.65 mg/6.6 cm <sup>2</sup> Treatment B: MINIVELLE 0.83 mg/3.3 cm <sup>2</sup> Treatment C: MINIVELLE 0.41 mg/1.65 cm <sup>2</sup> All treatments for 84 hrs	Open label, single dose, three treatment, three-way crossover study
N28-001 Non-TBM formulation	Relative BA	25 healthy, nonsmoking, postmenopausal women (40-60 yrs)	Treatment A: (b) (4) Treatment B: (b) (4) Treatment C: (b) (4) All treatments for 84 hrs	Open label, single dose, three treatment, three-way crossover study
N28-003 Non-TBM formulation	Relative BA	18 healthy, nonsmoking, postmenopausal women (40-60 yrs)	Treatment A: (b) (4) Treatment B: (b) (4) Treatment C: (b) (4) All treatments for 84 hrs	Open label, single dose, three treatment, three-way crossover study

### 2.2.2 What is the mechanism of action?

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in

a dynamic equilibrium of metabolic interconversions, E2 is the principal intracellular human estrogen and is substantially more potent than its metabolites, E1 and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of E2 daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to E1 in the peripheral tissues. Thus, E1 and the sulfate conjugated form, estrone sulfate (E1S), are the most abundant circulating estrogens in postmenopausal women.

### **2.2.3 What are the currently available treatment options for the treatment of VMS?**

A number of products are currently approved for VMS, but all are hormonal, either estrogen-alone (used only in women without a uterus) or estrogen + progestin products. Most approved VMS products demonstrate a statistically significant and clinically meaningful reduction in the frequency of hot flashes by Week 4 of treatment, with the treatment effect maintained through at least 12 weeks of use (the duration of most clinical trials). The DRUP has generally considered that a reduction of at least 2 hot flashes per day better than placebo constitutes a clinically meaningful treatment effect.

Labeled contraindications to hormonal therapy (HT) include breast cancer, arterial or venous thrombotic or thromboembolic disease, and liver impairment. The labels also contain warnings about cardiovascular disorders (e.g., stroke, coronary heart disease, and venous thromboembolism), cancer, probable dementia, and gallbladder disease.

Since the publication of safety data on HT from the WHI study in 2002, the Agency has encouraged the use of “the lowest dose and for the shortest duration consistent with treatment goals and risks for the individual woman.” A variety of lower dose products have been approved since WHI was published. The efficacy of the lower dose products is generally less than that of higher dose products, but, as most HT products have a range of dose options, women can start at the lowest dose and titrate up as needed to manage their symptoms. In addition, HT products (aside from some of the lower-dose products) are typically also approved for vulvar and vaginal atrophy (VVA), another bothersome symptom of menopause. The Sponsor is not seeking this indication for MINIVELLE.

Currently available VMS/VVA treatments include the following estrogen alone or estrogen + progestin products:

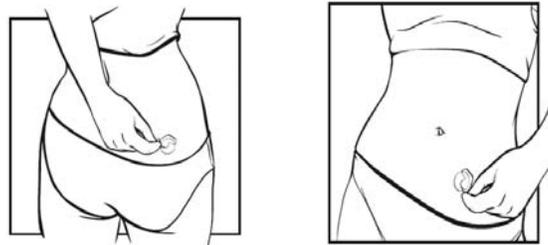
- Oral tablets: Premarin (conjugated estrogens); Estrace (E2), Femtrace (estradiol acetate), Prempro/Premphase (conjugated estrogens plus medroxyprogesterone acetate), Prefest (E2 plus norgestimate), Activella (E2 plus norethindrone acetate)
- Transdermal patches: Alora (E2), Climara (E2), Estraderm (E2) Vivelle (E2), Vivelle-Dot (E2), Climara-Pro (E2 plus levonorgestrel)
- Vaginal ring: Femring (estradiol acetate).

### **2.2.4 What are the administration instructions and dosing regimen?**

In general, use of estrogen alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Vivelle is approved for: (1) treatment of moderate to severe VMS associated with the menopause; (2) treatment of moderate to severe symptoms of VVA associated with the menopause; (3) treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; and (4) prevention of postmenopausal osteoporosis. However, the lowest

effective dose of Vivelle has not been determined for any indications that Vivelle is approved for. For treatment of moderate to severe VMS associated with menopause, start therapy with MINIVELLE 0.0375 mg/day applied to a clean, dry area of skin of the abdomen (i.e., below the umbilicus) or buttocks twice weekly (every 3-4 days). Users are to determine the 2 days they will change their patch (e.g., Mondays and Thursdays).

**Figure 3:** Application sites of MINIVELLE



MINIVELLE should not be applied to the breasts. The sites of application must be rotated (i.e., left vs. right side; abdomen vs. buttocks), with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The patch should be applied immediately after opening the pouch and removing the protective liner. The patch should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact with the skin, especially around the edges. In the event that a patch should fall off, the same patch may be reapplied. If the same patch cannot be reapplied, a new patch should be applied to another location. If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. In either case, the original treatment schedule should be continued. The interruption of treatment in women taking MINIVELLE might increase the likelihood of breakthrough bleeding, spotting, and recurrence of symptoms.

Dosage adjustment should be guided by the clinical response (i.e., the frequency and severity of VMS symptoms) that should be evaluated periodically (e.g., 3-6 month intervals).

### **2.2.5 Is BE between MINIVELLE and Vivelle established adequately?**

Yes. BE between MINIVELLE (1.65 mg E2/6.6 cm<sup>2</sup>) and Vivelle (8.66 mg E2/29 cm<sup>2</sup>) at the highest strength (i.e., nominal delivery of 0.1 mg/day) was established following a single dose administration to the lower abdomen in an open-label, single-center, 2-way crossover study (Study N28-004) in 100 healthy, nonsmoking postmenopausal women (40-65 yrs) under fed state (i.e., after a standardized breakfast).

In each of the 2 treatment periods, subjects received one of the following study medications according to the randomization schedule at approximately 8 a.m. ( $\pm$  10 minutes) on Day 1 and Day 22 of the study:

- Treatment A (Test): One MINIVELLE patch (1.65 mg E2/6.6 cm<sup>2</sup>) applied for 84 hours
- Treatment B (Reference): One Vivelle patch (8.66 mg E2/29 cm<sup>2</sup>) applied for 84 hours

Subjects were allowed to shower during the period of patch application but immersion bathing was not permitted. Subjects were prohibited from using any soap, body lotion, oil, or cream on or around the patch application site. Once the system was applied and for up to 72 hours after removal, the application site was not rubbed. There was a washout period of approximately 17.5

days between treatment periods (i.e., between the removal of the prior patch at 84 hours post-dose on Day 4 and the application of the next patch on Day 22).

Blood samples were collected for a 24 hour period before patch application for E2 and E1 baseline characterization and for 120 hours post-dose in each period for PK characterization.

All 100 subjects enrolled were randomized and 99 subjects received both treatments. The following 2 subjects that did not complete one of the two treatments were excluded from the BE analysis:

- Subject 004-01-029: The patch was detached from the subject's skin and was not present at 24 hour post-dose of Treatment A
- Subject 004-01-048: Withdrew consent prior to the second treatment period (i.e., Treatment B)

In addition, Subjects 004-01-015 and 004-01-063 were excluded from the BE analysis due to the high E2 baseline concentrations ( $> 20$  pg/mL).

Blood samples were analyzed for E2, unconjugated E1, and total E1. PK analysis was performed for all 3 analytes. E2 data were analyzed with and without baseline correction.

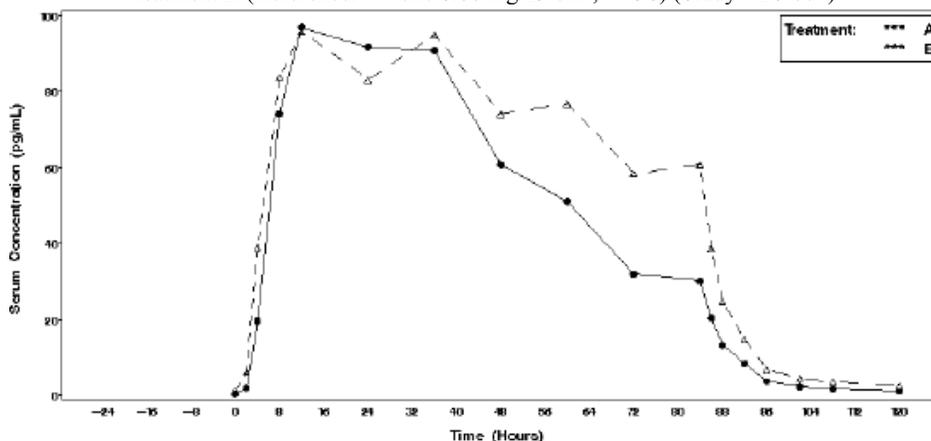
As endogenous E2 exists in the body and the study objective was to compare the exposure of E2 by the contribution of the drug products, baseline corrected E2 PK parameters were selected as the primary parameters for BE analysis. This review is focused on PK characterization and BE assessment based on E2 exposure.

E2 Baseline Correction: The Sponsor employed a time-matched baseline correction based on a 24 hour baseline PK measurement. The mean baseline concentration values for E2 at each different time points before initiating the patch therapy ranged between 3.9 and 5.5 pg/mL (individual baseline concentration range: 1.02-18.9 pg/mL). Published literature suggests that endogenous E2 concentration in postmenopausal women is within the range of 5-25 pg/mL (DeCherney and Nathan, 2003). Baseline E2 concentration values obtained from this study were found to be lower than what was reported in literature.

Twelve (12) E2 baseline values were below the lower limit of quantitation (LLOQ) of 1 pg/mL. All but 2 baseline values were  $< 20$  pg/mL. The 2 concentration values that were  $> 20$  pg/mL were obtained in Treatment Period 2 before drug administration for Subjects 004-01-015 ( $C_0 = 34.9$  pg/mL) and 004-01-063 ( $C_0 = 89.3$  pg/mL). Due to the E2 baseline concentrations  $> 20$  pg/mL, data from these 2 subjects were excluded from the BE assessment.

BE Assessment: The mean average concentration-time profiles for baseline-corrected E2 are presented in Figure 4 below. It should be noted that the patch was removed at 84 hours post-dose.

**Figure 4:** Mean Baseline-corrected E2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (Test: MINIVELLE 1.65 mg/6.6 cm<sup>2</sup>; N=99) and Treatment B (Reference: Vivelle 8.66 mg/29 cm<sup>2</sup>; N=98) (Study N28-004)



The Sponsor’s baseline corrected and uncorrected BE analysis results are summarized in Table 4 below.

**Table 4:** Sponsor’s Baseline Corrected and Uncorrected E2 BE Analysis Results (Study N28-004; N=97)

	AUC <sub>84</sub>	AUC <sub>120</sub>	AUC <sub>inf</sub>	C <sub>max</sub>
Baseline Corrected				
Ratio of LSM <sup>a</sup> x 100	86.4%	84.9%	84.2%	109%
90% geometric CI <sup>b</sup>	81.0-92.2%	79.5-90.6%	78.9-89.8%	103-116%
Baseline uncorrected				
Ratio of LSM <sup>a</sup> x 100	87.0%	85.8%	NR <sup>c</sup>	109%
90% geometric CI <sup>b</sup>	81.9-92.5%	80.8-91.1%	NR <sup>c</sup>	103-115%

<sup>a</sup> Calculated using LMS according to the formula:  $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$

<sup>b</sup> 90% Geometric CI using ln-transformed data

<sup>c</sup> Not reported

The Sponsor’s BE analysis results were confirmed to be valid based on this reviewer’s own BE analysis. All analyses of variances (ANOVA) were performed with the SAS (Version 9.2 for Windows) general linear models (GLM) procedure. Based on pair-wise comparisons of the ln-transformed of AUC<sub>84</sub>, AUC<sub>120</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> data, the ratios of the LSM, calculated according to the formula “ $e^{(X-Y)} \times 100$ ”, as well as the 90% geometric CIs for ln-transformed AUC<sub>84</sub>, AUC<sub>120</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> were determined. This reviewer’s BE analysis results are summarized in Table 5 below:

**Table 5:** Reviewer’s Baseline Corrected E2 BE Analysis Results (Study N28-004; N=96)

	AUC <sub>84</sub>	AUC <sub>120</sub>	AUC <sub>inf</sub>	C <sub>max</sub>
Ratio of LSM <sup>a</sup> x 100	86.1%	84.5%	84.5%	108.8%
90% geometric CI <sup>b</sup>	80.7-91.7%	79.2-90.3%	79.2-90.3%	102.4-115.6%

<sup>a</sup> Calculated using least-squares means according to the formula:  $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$

<sup>b</sup> 90% Geometric Confidence Interval using ln-transformed data

For baseline corrected E2, the 90% geometric CIs were within the BE acceptance range (i.e., 80.00-125.00%) for AUC<sub>84</sub> and C<sub>max</sub> but not for AUC<sub>120</sub> and AUC<sub>inf</sub>. There is a shift towards slightly lower exposure from MINIVELLE (Test) compared to Vivelle (Reference).

Considering that the patch was applied for the duration for 84 hours in this study, the BE assessment was based on AUC<sub>84</sub> rather than AUC<sub>120</sub> or AUC<sub>inf</sub>.

BE assessments of lower strengths were not conducted as the Sponsor submitted a biowaiver request based on: (1) BE establishment of MINIVELLE to Vivelle at the highest strength of 0.1 mg/day; (2) establishment of dose proportionality over the dose range of 0.025-0.1 mg/day; (3) the fact that different doses of MINIVELLE are compositionally proportional; and (4) the comparable *in vitro* dissolution profiles of all strengths of MINIVELLE ( $f_2 > 50$ ).

Details of the pivotal BE study can be found in Appendix Section 4.1.1 of this review.

### **2.2.6 Is the dose proportionality established for E2 from MINIVELLE?**

Yes. Based on the baseline corrected E2 AUC<sub>84</sub> and C<sub>max</sub>, dose proportionality of E2 was established from 0.025 mg/day to 0.1 mg/day following a single dose of MINIVELLE in a three-way crossover study in postmenopausal women.

Sponsor conducted a dose proportionality study to support their biowaiver request for the dosage strengths below 0.1 mg/day. This study was a Phase 1, open-label, single-center, randomized, single-dose, three-way crossover study in 36 healthy, non-smoking postmenopausal women (aged 40 to 65 years).

Each subject received a single dose of each of the following 3 treatments:

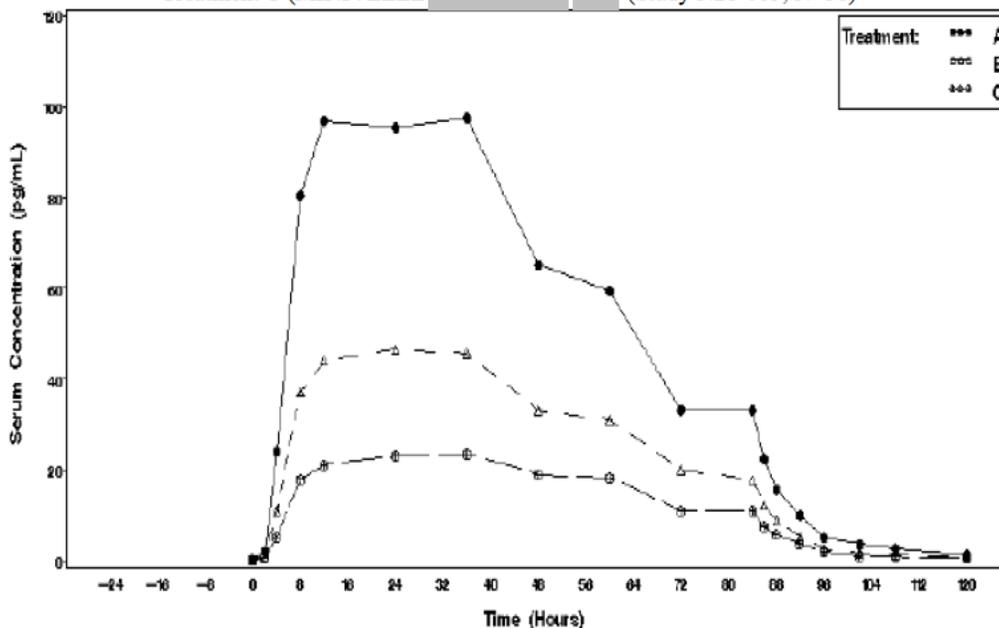
- Treatment A: one 1.65 mg/6.6 cm<sup>2</sup> MINIVELLE patch (0.1 mg/day)
- Treatment B: one 0.827 mg/3.3 cm<sup>2</sup> MINIVELLE patch (0.05 mg/day)
- Treatment C: one [REDACTED] (b) (4) MINIVELLE patch (0.025 mg/day)

Each patch was worn for 84 hours. There was a washout period of approximately 17.5 days between treatment periods (i.e., between the removal of the prior patch at 84 hours post-dose on Days 4 and 25 and the application of the next patch on Days 22 and 43).

Blood samples were collected for a 24 hour period before patch application for baseline characterization and for 120 hours post-dose in each period for PK characterization.

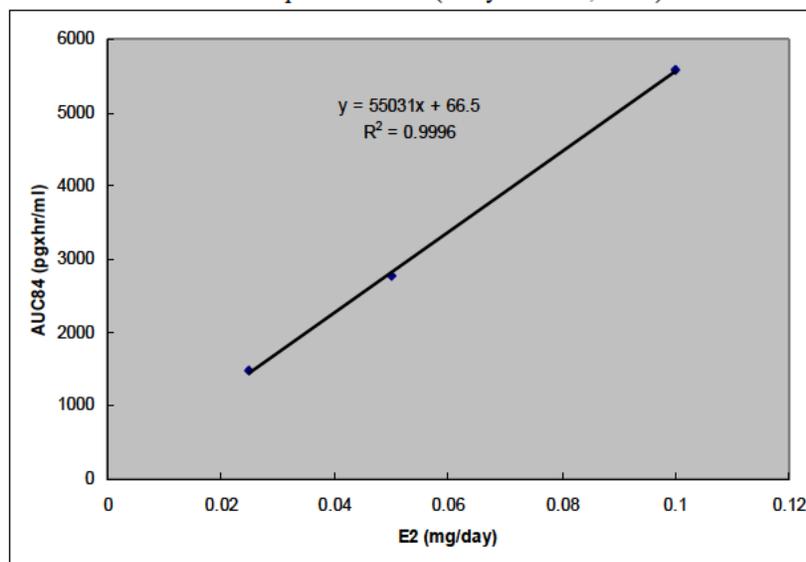
Figure 5 illustrates the mean serum baseline corrected E2 concentrations of MINIVELLE at 3 different strengths (0.025, 0.05, and 0.1 mg/day).

**Figure 5:** Mean Baseline-corrected E2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (MINIVELLE 1.65 mg/6.6 cm<sup>2</sup>), Treatment B (MINIVELLE 0.827 mg/3.3 cm<sup>2</sup>), and Treatment C (MINIVELLE [REDACTED]<sup>(b) (4)</sup>) (Study N28-005; N=36)

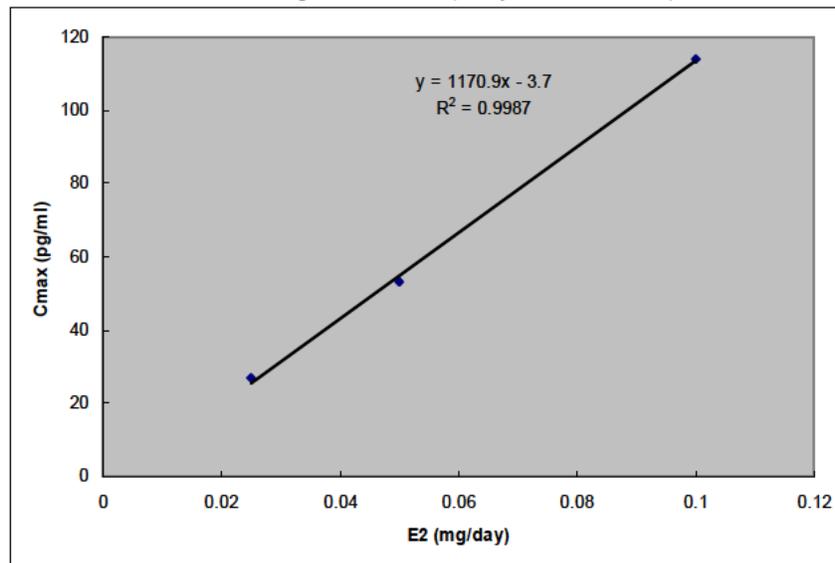


As shown in Figures 6 and 7,  $AUC_{84}$  and  $C_{max}$  increased linearly and E2 were found to be dose proportional from 0.025 mg/day to 0.1 mg/day following a single dose of MINIVELLE.

**Figure 6:** Relationship between E2 Dose and Mean  $AUC_{84}$  Following a Single Dose of MINIVELLE in Postmenopausal Women (Study N28-005; N=36)



**Figure 7:** Relationship between E2 Dose and Mean C<sub>max</sub> Following a Single Dose of MINIVELLE in Postmenopausal Women (Study N28-005; N=36)



## 2.3 Intrinsic Factors

### 2.3.1 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

The Sponsor's pediatric waiver request is pending for the PeRC approval and it is scheduled to be discussed on September 19, 2012.

As outlined in product labeling for various E2 products, estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Otherwise, there is no therapeutic use for E2 in the neonate, infant, or child. No pediatric studies were conducted with MINIVELLE.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to this application, the Sponsor believes that they would be exempt from this requirement.

### 2.3.2 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct studies with MINIVELLE in renal and/or hepatic impaired patients. MINIVELLE is contraindicated for known liver impairment or disease. No additional safety concerns are expected for patients with renal impairment.

## 2.4 Extrinsic Factors

### 2.4.1 Did the Sponsor conduct any DDI studies?

No DDI studies were conducted with MINIVELLE. The Sponsor is proposing to use the following information used for Vivelle for labeling: *In vitro* and *in vivo* studies have shown that oral estrogens are metabolized partially by CYP3A4. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's wort (*hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

These effects have not been studied with transdermal estrogen therapy. Both Vivelle and Vivelle-Dot have the same information on their product labels.

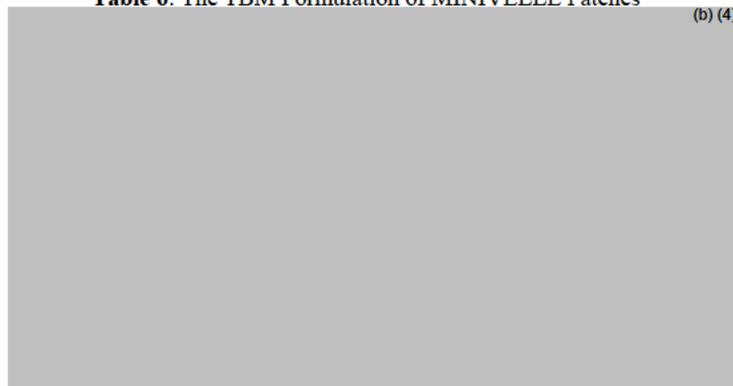
## 2.5 General Biopharmaceutics

### 2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?

As shown in Table 2, the Sponsor proposes to market MINIVELLE in <sup>(b)</sup><sub>(4)</sub> different strengths that are designed to provide same nominal E2 doses as Vivelle and Vivelle-Dot, but from a smaller active surface area. Patches of different strengths of MINIVELLE are from the same sheet of formulation with different active surface areas. The composition of the drug product is summarized in the Table 6 below:

Table 6: The TBM Formulation of MINIVELLE Patches

(b) (4)



Studies N28-004 and N28-005 were conducted with the TBM formulation.

### 2.5.2 Is the skin adhesion profile of the patches acceptable?

Yes. Based on combined data for MINIVELLE from the BE study (Study N28-004) and the dose proportionality study (Study N28-005) consisting of 208 observations, approximately 98% of the observations (203 out of 208 observations) from various dosage strengths of MINIVELLE treatments had an adhesion score of 0 and 65% of the 208 observations were made from the dosage strength of 0.1 mg/day MINIVELLE. Approximately 97% of the observations from the dosage strength of 0.1 mg/day MINIVELLE had an adhesion score of 0 (132 out of 136

observations).

During the period of MINIVELLE wear, the adhesion of MINIVELLE was evaluated at 2, 4, 8, and 12 hours post-dose and then every 12 hours until MINIVELLE was removed at 84 hours post-dose. In the BE study, 97 out of 100 subjects treated with MINIVELLE had an adhesion score of 0 at 84 hours post-dose (97 out of 100 observations). In the dose proportionality study, 34 out of 36 subjects had an adhesion score of 0 at 84 hours post-dose in all 3 MINIVELLE treatment periods (106 out of 108 observations).

In the BE study, there were 2 subjects whose adhesion scores were  $\geq 2$  (i.e.,  $\geq 50\%$  and  $< 75\%$  adhered) and 2 subjects who had adhesion scores of 1 (i.e., adhesion of  $\geq 75\%$  to  $< 90\%$ ) in addition to a subject whose patch became detached during the 24 hour post-dose time point. In the dose proportionality study, there were 2 subjects with an adhesion score of 1.

## 2.6 Bioanalytical Methods

### 2.6.1 Did the Sponsor use validated bioanalytical methods to generate data in the clinical studies?

Yes. Bioanalytical method validation and study reports were submitted for all studies that were reviewed. Acceptance criteria and method performance for E2 concentration measurement was in compliance with the Agency's *Bioanalytical Method Validation Guidance* and the bioanalytical methods were found to be acceptable.

Serum samples were analyzed for E2 by validated bioanalytical methods. Studies N28-004 and N28-005 employed a validated LC-MS/MS method. ISR was conducted on approximately 10% of the study samples in both studies. Approximately 96% and 97% of the ISR results met the acceptance criteria of being within  $\pm 20\%$  of the original reported concentration value for at least 67% of the ISR samples from Studies N28-004 and N28-005, respectively.

An OSI consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study (Study N28-004) was requested on February 13, 2012. There were no significant objectionable issues identified and the Form FDA 483 was not issued. Details of the OSI inspection findings can be found in Drs. Jyoti B. Patel and Gopa Biswas' OSI consult review (dated July 1, 2012 in DARRTS; see Section 4.2 of this review).

The bioanalytical methods are summarized in Table 7.

**Table 7:** Summary of Bioanalytical Methods

Study Number	Study Title	Biological Matrix	Analyte	Method	Dynamic Range
N28-004	Single Dose BE Study	Serum	E2	LC-MS/MS	1-100 pg/mL
N28-005	Dose proportionality study	Serum	E2	LC-MS/MS	1-100 pg/mL

### 3 Detailed Labeling Recommendations

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted in this NDA. ~~Strikes~~ are used for deletion and double underline is used for addition for the OCP's preliminary response to the Sponsor's proposal. Please note that Sections illustrated below does not necessarily reflect the entire corresponding Section of the product label.

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

**Reviewer's Comment:** *This reviewer recommends the following:*

- *Clarification of application sites (i.e., abdomen below the umbilicus or buttocks) to be consistent with the Phase 3 studies conducted under NDA 020323 for Vivelle.*
- *The inclusion of the pivotal BE study (Study N28-004) description and results.*
- *Replacement of PK data following application of Vivelle with PK data obtained using MINIVELLE (Study N028-005). Correction of mean half-life values under the Excretion subsection was made using data obtained in Studies N28-004 and N28-005.*
- *Addition of the adhesion data to Section 12.3.*

## 4 Appendices

### 4.1 Individual Study Reviews

#### 4.1.1 BE Study: Study N28-004

**Title:** A Phase 1, Single Center, Single Dose, Open-label, Randomized, Crossover study to Determine BE of MINIVELLE versus Vivelle in Healthy Postmenopausal Women

**Objectives:**

- Primary: To demonstrate BE between the highest strength (i.e., nominal delivery rates of 0.1 mg/day) of MINIVELLE and Vivelle
- Secondary: To assess wear characteristics, safety, and tolerability of the patches.

**Clinical Study Center:** Elite Research Institute, Miami, FL

**Clinical Study Period:** February 2, 2011 - May 5, 2011

**Bioanalytical Study Center:** (b) (4)

**Bioanalysis Period:** May 4, 2011 - June 17, 2011

**Study Design:**

This was an open-label, single-center, single-dose, 2-way crossover study with 2 treatments and administration in healthy, nonsmoking postmenopausal women (40-65 yrs). Eligible subjects reported to the clinic on Day -1 and Day 21 in the evening at approximately 7:00 p.m. and subjects were housed during each treatment period. Baseline measurements were taken on Day 0 of the study. There was a washout period of approximately 17.5 days between treatment periods (i.e., between the removal of the prior patch at 84 hours post-dose on Day 4 and the application of the next patch on Day 22).

**Treatments and Study Drug Administration:**

In each of the 2 treatment periods, subjects received one of the following study medications according to the randomization schedule at approximately 8 a.m. ( $\pm 10$  minutes) on Day 1 and Day 22 of the study:

- Treatment A (Test): One MINIVELLE patch (1.65 mg E2/6.6 cm<sup>2</sup>) applied for 84 hours
- Treatment B (Reference): One Vivelle patch (8.66 mg E2/29 cm<sup>2</sup>) applied for 84 hours

Study medication in each treatment period was administered under fed state (i.e., after a standardized breakfast). The application area was required to be clean, dry, non-oily, and not irritated. No shaving was allowed. One (1) hour prior to application, the skin region was cleaned carefully with lukewarm water and patted dry with a clean soft towel. Patches were applied to the left or right side of the lower abdomen according to randomization code, avoiding the waistline, as clothing could interfere with adherence of the patch. Prior to patch application, site personnel confirmed that the skin was clean (freshly washed), dry, cool, free of any powder/oil/lotion, and free of cuts and/or irritation (rashes or other skin problems). The entire patch was pressed firmly into place with the palm of the hand over the patch for approximately 30 seconds, assuring that the entire patch was in contact with the skin.

Subjects were allowed to shower during the period of patch application but immersion bathing was not permitted. Subjects were prohibited from using any soap, body lotion, oil, or cream on or

around the patch application site. Once the system was applied and for up to 72 hours after removal, the application site was not rubbed.

**Inclusion Criteria:**

- Healthy postmenopausal, non-smoking women of any race between ages of 40 and 65 years at screening.
- Body Mass Index (BMI)  $\geq 18.5$  and  $< 29.9$  kg/m<sup>2</sup>.
- Subjects who had a screening serum E2 concentration of  $\leq 20$  pg/mL.

**Exclusion Criteria:**

- Premenopausal, perimenopausal, pregnant, or lactating women.
- Findings that indicated with any suspicion of breast malignancy.
- Subjects with tobacco use, obesity, undiagnosed abnormal genital bleeding or a history of significant risk factors for endometrial cancer.
- Subjects with a history of venous thromboembolism, pulmonary embolism, stroke, endometrial cancer, breast cancer, cholestatic jaundice, hypertension, serious heart problems, heart failure, myocardial infarction, ventricular arrhythmia, exertional chest pain, insulin dependent diabetes, hypercholesterolemia, hypertriglyceridemia, systemic lupus erythematosus, impaired liver function, or impaired renal function.
- Subjects with a medical history of significant dermatologic diseases, conditions, or cancer to alter skin appearance or physiologic response.
- Subjects who had existing medical conditions which might interfere with absorption, distribution, metabolism, or excretion of study medication.
- Any clinically significant abnormal laboratory test results found during medical screening.
- Positive test for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening.
- ECG abnormalities (clinically significant) or vital sign abnormalities (systolic blood pressure lower than 90 or over 150 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 45 or over 90 bpm) at screening.
- Subjects who had used any of the following hormone replacement therapies within the specified time prior to the screening visit:
  - Vaginal hormonal products (e.g., rings, creams, or gels) for at least 1 week
  - Transdermal estrogen alone or estrogen/progestin containing products for at least 4 weeks.
  - Oral estrogen and/or intrauterine progestin therapy for at least 8 weeks.
  - Progestin implants and estrogen alone injectable drug therapy for at least 3 months
  - Estrogen pellet therapy or progestin injectable drug therapy for at least 6 months
  - Percutaneous estrogen lotions/gels for at least 4 weeks.
- Use of an investigational drug or participation in an investigational study within 30 days prior to treatment administration.
- Subjects who had used any prescription medications within 14 days of the screening visit.
- Subjects who had used any over-the-counter (OTC) preparations including herbal or nutritional supplements and multivitamins within 10 days prior to screening.
- Subjects who had consumed foods or beverages containing caffeine/xanthine or alcohol within 72 hours prior to receiving the first study treatment.

**Disposition of Subjects:**

One hundred (100) postmenopausal women were enrolled and randomized to the study. All 100 completed Treatment Period 1 and 99 out of 100 subjects (99%) completed Treatment Period 2.

One subject (Subject 01-048) withdrew consent after completing the first treatment period due to a mild first degree sunburn. This subject had been randomized to treatment sequence AB. Thus, 100 subjects received Treatment A (MINIVELLE) and 99 subjects received Treatment B (Vivelle). Refer to the *Protocol Deviations and Exclusion from PK and BE Analysis Section* below for the detail information on subjects excluded from the PK and BE analyses.

The mean age of the 97 subjects that the Sponsor included in the Sponsor's BE analysis was 54.2 (range: 40-65 years) with a mean BMI of 25.7 kg/m<sup>2</sup> (range: 19.7-29.9 kg/m<sup>2</sup>). There were 90 Caucasians (92.8%) and 7 Black or African Americans.

**Concomitant Medication:**

Subjects were prohibited from taking prescription medications or OTC products including multivitamin, herbal, or nutritional supplements.

**PK Characterization:**

Blood samples for baseline and PK characterization were took at 24, 22, 20, 18, 16, 12, 10, 8, 4, and 0.5 hours before drug application, and 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 90, 92, 96, 102, 108, and 120 hours post-dose in each treatment period.

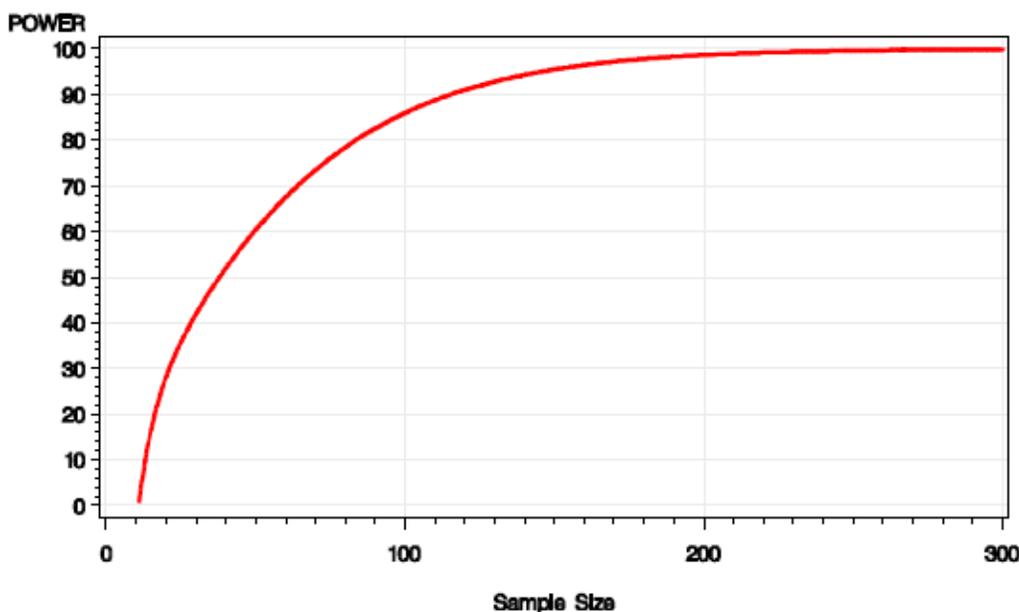
The following PK parameters were calculated for baseline uncorrected E2, baseline corrected E2, unconjugated E1, and total E1:

- $C_{max}$ : the maximum serum concentration observed
- $AUC_{84}$ : the area under the serum concentration-time profile; calculated from time 0 to 84 hour (wear time)
- $AUC_{last}$ : the area under the serum concentration-time profile; calculated from time 0 to the last measurable concentration by the linear trapezoidal rule (120 hours post-dose)
- $AUC_{inf}$ : the area under the serum concentration-time profile extrapolated to infinity
- $T_{max}$ : the time of the maximum observed concentration
- $k_{el}$ : elimination rate constant (slope of the log concentration vs. time curve between 84 and 120 hours)
- $t_{1/2}$ : elimination half-life ( $\ln 2/k_{el}$ )

**Sample Size Determination:**

SAS 9.2 was used for the sample size calculation which was designed to provide sufficient statistical power for the selected primary endpoints (AUC and  $C_{max}$ ). Per Sponsor, the sample size calculation was based on the assumption of BE between the Test (Treatment A: MINIVELLE; 1.65 mg/6.6 cm<sup>2</sup>) and Reference (Treatment B: Vivelle; 8.66 mg/29.0 cm<sup>2</sup>) products with a ratio of geometric means equal to 0.90 (AUC) and 1.12 ( $C_{max}$ ). A BE limit of 80-125% and a level of significance ( $\alpha$ ) of 5% were also used in this calculation. Sample size estimations are presented in Figure A-1-1.

**Figure A-1-1: Sample Size and Statistical Power Calculation (Ratio 1.12; BE Limit 80-125%)  
Equivalence Tests for Two Means In 2x2 Crossover Design using Ratio**



In an equivalence test of means using two one-sided tests at a 0.05% significance level on data from a two-period cross-over design, a total sample size of 84 achieved 80.2% power when the true ratio of means was 1.12, the coefficient of variation was 0.52 on the original, unlogged scale, and the equivalence limits of the mean ratio were 80% to 125%. Assuming a dropout rate of ~20%; the total sample size used was 100 subjects.

**Statistical Analysis for BE Assessment:**

ANOVA was performed on the natural log-transformed  $AUC_{last}$ ,  $AUC_{inf}$ , and  $C_{max}$  for E2. The statistical analysis of the BE data included the construction of 90% CIs for Test/Reference ratios of LSM derived from logarithmic-transformed metrics of exposure for baseline uncorrected E2  $C_{max}$ ,  $AUC_{84}$ , and  $AUC_{last}$  and for baseline-corrected E2  $C_{max}$ ,  $AUC_{84}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ .

**Nominal Delivery Rate Analysis:**

The amount of drug released during the hours of application of the patch was determined by measuring the amount of drug remaining in the patch after removal and subtracting that amount from the amount measured in the control patches. The average control value for each treatment was used as the control potency to determine the individual nominal amount of drug released.

$$\text{Individual nominal amount of drug released} = \text{Average control} - \text{Individual residual}$$

The mean residual E2 amount (i.e., drug released) was used to derive the nominal delivery rate.

Used patches were collected and stored frozen until they were shipped to the Sponsor at the completion of the study for determination of residual E2 content.

**Skin Adhesion and Skin Irritation Assessment:**

During the period of patch wear, the skin adhesion of the patches was evaluated at 2, 4, 8, and 12 hours and then every 12 hours until patch removal at 84 hours post-dose. All evaluations were completed within  $\pm 10$  minutes of the scheduled time. Findings were recorded as an estimate of

the percentage of the system surface in contact with the skin, according to the scale provided in Table A-1-1.

Table A-1-1: Skin Adhesion Scale

Score	Definitions
0	≥ 90% adhered (essentially no lift off the skin)
1	≥75% < 90% adhered (some edges only lifting off the skin)
2	≥50% < 75% adhered (less than half of the system lifting off the skin)
3	0% to < 50% adhered but not detached (more half of the system lifting off the skin without falling off)
4	0% adhered - System detached (ETS completely off the skin)

Prior to patch application (0 hour), immediately prior to removal (84 hours following application), immediately after removal, and at 1, 12, 24, and 36 hours post removal (85, 96, 108, and 120 hours following application), the application site was observed for the presence or absence of skin irritation. All evaluations were completed within ±10 minutes of the scheduled time. Findings were graded and recorded according to scales provided below (based on Agency's *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*; December 1999):

- 0 = no evidence of irritation;
- 1 = minimal erythema, barely perceptible;
- 2 = definite erythema, readily visible; minimal edema or minimal papular response;
- 3 = erythema and papules;
- 4 = definite edema;
- 5 = erythema, edema and papules;
- 6 = vesicular eruption;
- 7 = strong reaction spreading beyond application site.

**Reviewer's Comment:** *The skin irritation assessment data were not reviewed as the Clinical review team will review the data. Please refer to Dr. Phil Price's clinical review for details.*

**Safety Assessments:**

- Adverse events (AE): AEs considered to be treatment-emergent were summarized and reported.
- Laboratory measurements: All clinical laboratory measurements were listed. Clinical laboratory results were also presented by time point and treatment. Changes from baseline and shift tablets (based on laboratory normal ranges) were presented.
- Vital signs: All vital sign measurements were listed. Vital sign measurements were also presented by time point and treatment. Changes from baseline were also summarized descriptively.
- ECG: QTc interval measurements were summarized as continuous variables and presented by time point and treatment. Changes from baseline and outlier assessments were also presented.

**Bioanalytical Method:**

Blood samples were collected at times specified by the protocol and the obtained serum samples were analyzed for E2, unconjugated E1, and total E1 concentrations. As E2 was the primary analyte for BE assessment, only the bioanalytical method for E2 analysis was reviewed.

Bioanalyses for E2 was performed at (b) (4) between May 4, 2011 and June 17, 2011. Four thousand four hundred eighty four (4,484) human serum samples and 47 duplicates

were received frozen from Elite Research Institute, Miami, FL between April 21, 2011 and June 14, 2011. The samples were stored at -20°C or below until analysis. All samples were analyzed within the demonstrated long-term storage stability (1,952 days for E2) in unstripped human serum at -20 °C or below.

Freeze/thaw stability was evaluated by analyzing low- and high-level quality controls (QC) subjected to 3 freeze/thaw cycles. Samples were thawed at room temperature. No apparent abnormalities associated with up to 3 freeze/thaw cycles were observed.

A LC-MS/MS method was developed and validated with the dynamic range of 1-100 pg/mL.

Because E2 is an endogenous steroid, measurable levels are expected to be present in the blood from all human donors. The study was conducted using calibration standards and QC pools prepared in a “blank” surrogate matrix that contained negligible levels of these analytes, as per the validated method. The surrogate matrix was modified human serum, containing tripotassium EDTA, which had been stripped with activated charcoal to remove small organic molecules and then fortified with ascorbic acid. Additional QC concentrations were prepared in unstripped human serum fortified with ascorbic acid. Long-term storage stability of E2 in stripped and unstripped human serum treated with 5.0 mM ascorbic acid has been demonstrated for 390 days at -20 °C.

A 500 µL sample aliquot is fortified with 25 µL of internal standard (IS) working solution. Analytes are isolated through liquid-liquid extraction (LLE) with 5.0 mL of 10:90 ethyl acetate/hexane (v/v). The solvent is evaporated under a stream of nitrogen at 40-50°C and the remaining residue is derivatized. The derivatized analytes are extracted into 3.0 mL of 10:90 ethyl acetate/hexane, the solvent is evaporated, and the remaining residue is reconstituted with 150 µL of acetonitrile and 200 µL of water. The final extract is analyzed via LC-MS/MS.

Each calibration curve was calculated using a linear (1/concentration weighted) least-squares regression algorithm. Precision and accuracy were evaluated by replicate analyses of surrogate matrix QC pools (QCs 1, 3, and 5) prepared at three concentrations spanning the calibration range. Additional QCs were prepared in human serum (QCs 2 and 4).

Mean inter-assay accuracy of back-calculated concentrations in calibrators ranged between 99.0% and 101.2% and precision was 3.4-9.2%. QC samples for E2 (range: 2.0-75.0 pg/mL) had an accuracy of 100.0-104.0 % and a precision of 5.0-11.5%.

ISR was performed on 466 out of 4,483 samples (approximately 10.4%; 4-5 samples per subject for all 100 enrolled subjects) for E2. Four hundred forty six (446) out of 466 (95.7%) ISR results met the acceptance criteria of being within ±20% of the original reported concentration value for at least 67% of the ISR samples.

**Reviewer’s Comment:** *Acceptance criteria and assay performance for E2 bioanalysis were in compliance with the Agency’s Bioanalytical Method Validation Guidance and the bioanalytical method was found to be acceptable.*

#### **Nominal Delivery Rate Analysis Results**

The extent of exposure was determined by measuring the amount of residual E2 remaining in the patches and estimating the nominal delivery rate of E2. The nominal delivery rate analysis is summarized in Table A-1-2 below.

**Table A-1-2: Nominal Delivery Rate Analysis Summary**

Product	Loaded E2 (mg/unit)	Mean Control E2 (mg/unit)	Mean Residual E2 (mg/unit)	Mean Released Drug (mg/unit) <sup>(b) (4)</sup>
MINIVELLE	1.65			
Vivelle	8.66			

In summary, the nominal delivery rates from MINIVELLE and Vivelle in this study were determined to be <sup>(b) (4)</sup> mg/day and <sup>(b) (4)</sup> mg/day, respectively, while they are labeled as 0.1 mg/day.

### Protocol Deviations and Exclusion from BE Analysis

During the study, most of the deviations reported were related to various inclusion/exclusion criteria. These included:

- four (4) subjects (004-01-027, 004-01-028, 004-01-029, and 004-01-045) who had follicle-stimulating hormone (FSH) levels less than 40 mIU/mL;
- twenty-seven (27) subjects with hematocrit values slightly below 40%
- three (3) subjects (004-01-006, 004-01-047, and 004-01-077) who slightly exceeded the study defined maximum 239 g/dL for cholesterol

None of these were considered to be significant enough to be excluded from the study enrollment or data analysis by the Investigator.

All 100 subjects enrolled were randomized and 99 subjects received both treatments. The following two subjects did not complete one of the two treatments and were excluded from the BE analysis:

- Subject 004-01-029: The patch was detached from the subject's skin and was not present at 24 hours post-dose of Treatment A
- Subject 004-01-048: withdrew consent prior to Treatment B administration, second treatment period

In addition, Subjects 004-01-015 and 004-01-063 were also excluded from the BE analysis due to the E2 baseline concentrations higher than 20 pg/mL.

### PK Results:

Serum samples obtained were analyzed for E2, unconjugated E1, and total E1 and PK analysis was performed for all 3 analytes. E2 data were analyzed with and without baseline correction.

As endogenous E2 exists in the body and the study objective is to compare the exposure of E2 by the contribution of the drug products, baseline corrected E2 PK parameters were selected as the primary parameters for BE analysis. This review is focused on PK characterization and BE assessment based on E2 exposure.

### E2 Baseline Correction

For E2 baseline correction, pre-dose E2 concentration values at respective time points were subtracted from appropriate E2 concentrations after dosing, as follows:  $C_{0(\text{first period})} - (C_{-24} + C_{0(\text{first period})})/2$ ,  $C_{0(\text{second period})} - (C_{-24} + C_{0(\text{first period})})/2$ ,  $C_2 - C_{-22}$ ,  $C_4 - C_{-20}$ ,  $C_8 - C_{-16}$ ,  $C_{12} - C_{-12}$ ,  $C_{24} - (C_{-24} + C_{0(\text{first period})})/2$ ,  $C_{36} - C_{-12}$ ,  $C_{48} - (C_{-24} + C_{0(\text{first period})})/2$ ,  $C_{60} - C_{-12}$ ,  $C_{72} - (C_{-24} + C_{0(\text{first period})})/2$ ,  $C_{84} - C_{-12}$ ,  $C_{86} - C_{-10}$ ,  $C_{88} - C_{-8}$ ,  $C_{92} - C_{-4}$ ,  $C_{96} - (C_{-24} + C_{0(\text{first period})})/2$ ,  $C_{102} - C_{-18}$ ,  $C_{108} - C_{-12}$ , and  $C_{120} - (C_{-24} + C_{0(\text{first period})})/2$ .

**Reviewer's Comment:** *The Sponsor employed a time-matched baseline correction based on a 24 hour baseline PK measurement. The mean baseline concentration values for E2 at each different*

time points before initiating the patch therapy ranged between 3.9 and 5.5 pg/mL (individual baseline concentration range: 1.02-18.9 pg/mL). Published literature suggests that endogenous E2 concentration in postmenopausal women is within the range of 5-25 pg/mL (DeCherney and Nathan, 2003). Baseline E2 concentration values obtained from this study were found to be lower than what was reported in literature.

Twelve (12) E2 baseline values were below the lower limit of quantitation (LLOQ) of 1 pg/mL. All but 2 baseline values were < 20 pg/mL. The 2 concentration values that were > 20 pg/mL were obtained in Treatment Period 2 before drug administration for Subjects 004-01-015 ( $C_0 = 34.9$  pg/mL) and 004-01-063 ( $C_0 = 89.3$  pg/mL). Due to the E2 baseline concentrations > 20 pg/mL, data from these 2 subjects were excluded from the BE assessment.

### Baseline Corrected PK Parameters

The individual PK parameters obtained for baseline-corrected E2 by non-compartmental analysis. Baseline corrected E2 PK parameters for each treatment are shown in Table A-1-3.

**Table A-1-3:** Mean (SD) Serum PK Parameters of Baseline Corrected E2 Following a Single Dose of either MINIVELLE or Vivelle

Parameter	Treatment A: MINIVELLE (N=99 <sup>b</sup> )	Treatment B: Vivelle (N=98 <sup>c</sup> )
AUC <sub>84</sub> (pg·hr/mL)	5231 (2103)	6151 (2777)
AUC <sub>120</sub> (pg·hr/mL)	5431 (2153)	6505 (2887)
AUC <sub>inf</sub> (pg·hr/mL)	5461 (2160)	6522 (2891)
C <sub>max</sub> (pg/mL)	118 (52.1)	108 (48.7)
T <sub>max</sub> (hr) <sup>a</sup>	24.0 (8.0-84.0)	24.0 (8.0-60.0)
t <sub>1/2</sub> (hr)	6.15 (2.66)	5.88 (1.82)

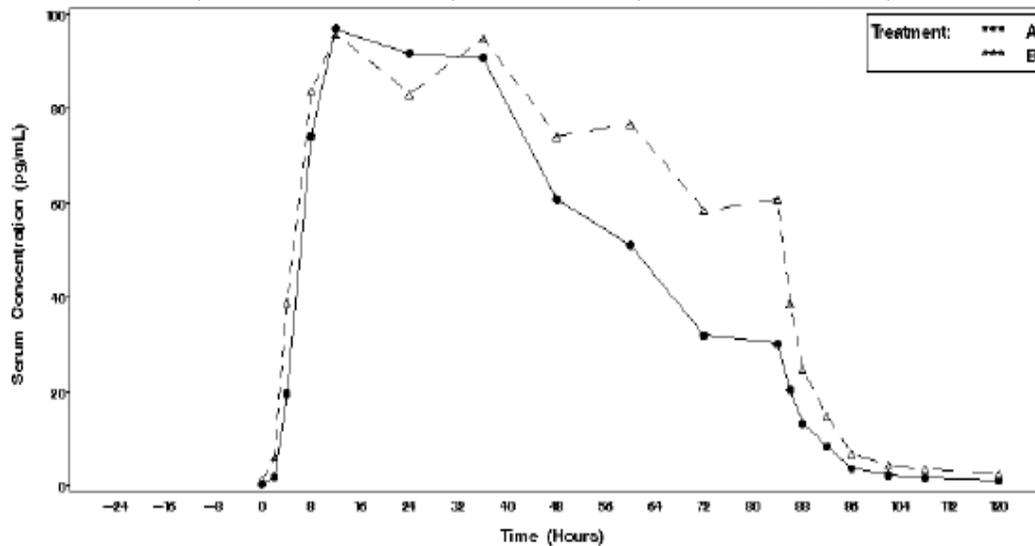
<sup>a</sup> Median (minimum-maximum)

<sup>b</sup> Excluded subjects: 004-01-029

<sup>c</sup> Excluded subjects: 004-01-048 and 004-01-063

The obtained mean concentration-time profiles for baseline-corrected E2 are presented in Figure A-1-2 below. It should be noted that the patch was removed at 84 hours post-dose.

**Figure A-1-2:** Mean Baseline-corrected E2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (Test: MINIVELLE; N=99) and Treatment B (Reference: Vivelle; N=98)



**Baseline Uncorrected PK Parameters**

The individual PK parameters obtained for baseline uncorrected E2 by non-compartmental analysis. Baseline uncorrected E2 PK parameters for each treatment are shown in Table A-1-4.

**Table A-1-4:** Mean (SD) Serum PK Parameters of Baseline Uncorrected E2 Following a Single Dose of MINIVELLE or Vivelle

Parameter	Treatment A: MINIVELLE (N=99 <sup>b</sup> )	Treatment B: Vivelle (N=98 <sup>c</sup> )
AUC <sub>84</sub> (pg·hr/mL)	5584 (2098)	6498 (2732)
AUC <sub>120</sub> (pg·hr/mL)	5939 (2156)	7007 (2830)
C <sub>max</sub> (pg/mL)	122 (51.8)	112 (48.1)
T <sub>max</sub> (hr) <sup>a</sup>	24.0 (8.0-84.0)	24.0 (8.0-60.0)

<sup>a</sup> Median (minimum-maximum)

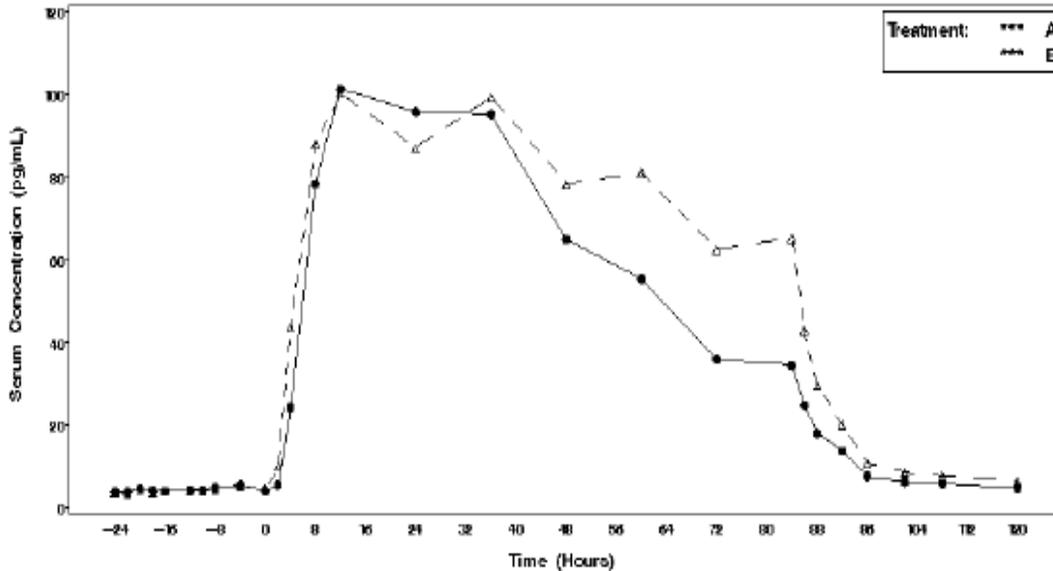
<sup>b</sup> Excluded subjects: 004-01-029

<sup>c</sup> Excluded subjects: 004-01-048 and 004-01-063

**Reviewer Comment:** *The obtained half-life and AUC<sub>inf</sub> values were not reported by the Sponsor.*

The obtained mean concentration-time profiles for baseline uncorrected E2 are presented in Figure A-1-3 below.

**Figure A-1-3:** Mean Baseline Uncorrected E2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (Test: MINIVELLE; N=99) and Treatment B (Reference: Vivelle; n=98)



**BE Assessment:**

The Sponsor’s baseline corrected and uncorrected BE analysis results are summarized in Table A-1-5 below.

**Table A-1-5: Sponsor's Baseline Corrected and Uncorrected E2 BE Analysis Results (N=97)**

	AUC <sub>84</sub>	AUC <sub>120</sub>	AUC <sub>inf</sub>	C <sub>max</sub>
Baseline Corrected				
Ratio of LSM <sup>a</sup> x 100	86.4%	84.9%	84.2%	109%
90% geometric CI <sup>b</sup>	81.0-92.2%	79.5-90.6%	78.9-89.8%	103-116%
Baseline uncorrected				
Ratio of LSM <sup>a</sup> x 100	87.0%	85.8%	NR <sup>c</sup>	109%
90% geometric CI <sup>b</sup>	81.9-92.5%	80.8-91.1%	NR <sup>c</sup>	103-115%

<sup>a</sup> Calculated using least-squares means according to the formula:  $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$

<sup>b</sup> 90% Geometric Confidence Interval using ln-transformed data

<sup>c</sup> Not reported

**Reviewer's Comment:** *The Sponsor's BE analysis results were confirmed to be valid based on this reviewer's own BE analysis. All ANOVAs were performed with the SAS (version 9.2 for Windows) GLM procedure. Based on pair-wise comparisons of the ln-transformed of AUC<sub>84</sub>, AUC<sub>120</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> data, the ratios of the LSM, calculated according to the formula " $e^{(X-Y)} \times 100$ ", as well as the 90% geometric CIs for ln-transformed AUC<sub>84</sub>, AUC<sub>120</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> were determined. This reviewer's BE analysis results are summarized in Table A-1-6 below:*

**Table A-1-6: Reviewer's Baseline Corrected E2 BE Analysis Results (N=96)**

	AUC <sub>84</sub>	AUC <sub>120</sub>	AUC <sub>inf</sub>	C <sub>max</sub>
Ratio of LSM <sup>a</sup> x 100	86.1%	84.5%	84.5%	108.8%
90% geometric CI <sup>b</sup>	80.7-91.7%	79.2-90.3%	79.2-90.3%	102.4-115.6%

<sup>a</sup> Calculated using least-squares means according to the formula:  $e^{(\text{MINIVELLE (A)} - \text{Vivelle (B)})} \times 100$

<sup>b</sup> 90% Geometric Confidence Interval using ln-transformed data

*For baseline corrected E2, the 90% geometric CIs are within the BE acceptance range (i.e., 80.00-125.00%) for AUC<sub>84</sub> and C<sub>max</sub> but not for AUC<sub>120</sub> and AUC<sub>inf</sub>. There is a shift towards slightly lower exposure from MINIVELLE (Test) compared to Vivelle (Reference).*

*Considering that the patch was applied for the duration for 84 hours in this study, the BE assessment was based on AUC<sub>84</sub> rather than AUC<sub>120</sub> or AUC<sub>inf</sub>.*

*This reviewer concludes that BE between MINIVELLE (1.65 mg E2/6.6 cm<sup>2</sup>) and Vivelle<sup>®</sup> (8.66 mg E2/29 cm<sup>2</sup>) at the strength of 0.1 mg/day has been established following a single dose administration for 84 hours to the lower abdomen in postmenopausal women.*

BE assessments of lower strengths were not conducted as the Sponsor submitted a biowaiver request based on: (1) BE establishment of MINIVELLE to Vivelle at the highest strength of 0.1 mg/day; (2) establishment of dose proportionality over the dose range of 0.025-0.1 mg/day; (3) the fact that different doses of MINIVELLE are compositionally proportional; and (4) the comparable *in vitro* dissolution profiles of all strengths of MINIVELLE ( $f_2 > 50$ ).

#### **Skin Adhesion:**

Following both Treatment A (MINIVELLE) and Treatment B (Vivelle), 97% (97 out of 100 observations) and 98% (8 out of 100 observations) of subjects had adhesion scores of 0 (i.e.,  $\geq 90\%$  adhered) at the 84 hour post-dose time point, respectively. There was 1 Treatment A subject (Subject 004-04-029) whose patch became detached during the 24 hour post-dose time point and there were 2 Treatment A subjects whose adhesion scores were  $\geq 2$  (i.e.,  $\geq 50\%$  and  $< 75\%$  adhered). In Treatment B, there were no patch detachments and there were 2 subjects who had adhesion scores of 1 (i.e., adhesion of  $\geq 75\%$  to  $< 90\%$ ). The adhesion profile from Treatments A and B were comparable.

**Safety Results:**

No deaths or serious adverse events (SAE) were reported during this study. One subject presented 2 significant AEs "Musculoskeletal pain" and "Haematoma infection." The health of this subject was not at risk during the study.

A total of 208 treatment emergent AEs (TEAE) were recorded by 80 subjects during the study: The most commonly reported TEAEs were related to study drug application site, with "Application site erythema" and "Application site pruritus" being reported by 63.4% (n=58) and 12.9% (n=12), respectively.

**Reviewer's Comment:** *The safety data were not reviewed by this reviewer as the Clinical review team will review the data. It appears that the Test (MINIVELLE) and Reference (Vivelle) treatments had similar safety profiles. Please refer to Dr. Phil Price's clinical review for details.*

**Conclusion:**

This reviewer concludes that BE between MINIVELLE (1.65 mg E2/6.6 cm<sup>2</sup>) and Vivelle (8.66 mg E2/29 cm<sup>2</sup>) at the highest strength (i.e., nominal delivery of 0.1 mg/day) was established following a single dose administration to the lower abdomen for 84 hours in an open-label, single-center, 2-way crossover study (Study N28-004) in 100 healthy, nonsmoking postmenopausal women (40-65 yrs) under fed state (i.e., after a standardized breakfast).

#### 4.1.2 Dose Proportionality Study: Study N28-005

**Title:** A Single-Center, Single-Dose, Open-Label, Randomized, Three-Period, Three-way Crossover Study to Evaluate Dose Proportionality in PK of E2 Following MINIVELLE Application in Healthy Postmenopausal Women

**Objectives:**

- Primary: To assess the dose proportionality of the MINIVELLE in healthy postmenopausal women to support the biowaiver request for the doses below 0.1 mg/day.
- Secondary: To assess safety, tolerability, and characteristics of the patches

**Clinical Study Center:** Cetero Research, Miami Gardens, FL

**Clinical Study Period:** March 20, 2011 - June 3, 2011

**Bioanalytical Study Center:** (b) (4)

**Bioanalysis Period:** June 13, 2011 - July 8, 2011

**Study Design:**

This was a Phase 1, open-label, single-center, randomized, single-dose, three-way crossover study in 36 healthy, non-smoking postmenopausal women (aged 40 to 65 years). Subjects were housed during Treatment Period 1 from approximately 36 hours prior to dosing through the 120 hour post-dose assessment. During Treatment Periods 2 and 3 subjects were housed from approximately 12 hours prior to dosing through the 120 hour post-dose assessments.

Each subject received a single dose of each of the 3 treatments. Each MINIVELLE patch was worn for 84 hours. There was a washout period of approximately 17.5 days between treatment periods (i.e., between the removal of the prior patch at 84 hours post-dose on Days 4 and 25 and the application of the next patch on Days 22 and 43). Eligible subjects reported to the clinical research unit (CRU) on Day -1, Day 21, and Day 42 in the evening at approximately 7:00 p.m. and were housed in the CRU until their release following completion of the 120 hour blood collection (Day 6, Day 27, and Day 48).

Blood samples for baseline correction were collected on Day 0, and then serial collections were made during subsequent treatment periods: Period 1 (Days 1-6), Period 2 (Days 22-27), and Period 3 (Days 43-48).

**Treatments and Study Drug Administration:**

The three treatments included in this study were:

- **Treatment A** (Test 1): one 84-hour application of the 1.65 mg/6.6 cm<sup>2</sup> MINIVELLE patch
- **Treatment B** (Test 2): one 84-hour application of the 0.827 mg/3.3 cm<sup>2</sup> MINIVELLE patch
- **Treatment C** (Test 3): one 84-hour application of the (b) (4) MINIVELLE patch

Study medication in each treatment period was administered under fed state (i.e., after a standardized breakfast). The application area was required to be clean, dry, non-oily, and not irritated. No shaving was allowed. One (1) hour prior to application, the skin region was cleaned carefully with lukewarm water and patted dry with a clean soft towel. Patches were applied to the

left or right side of the lower abdomen according to randomization code, avoiding the waistline, as clothing could interfere with adherence of the patch.

**Inclusion Criteria:**

- Healthy postmenopausal, non-smoking women of any race between ages of 40 and 65 years at screening.
- BMI  $\geq 18.5$  and  $< 29.9$  kg/m<sup>2</sup>.
- Subjects who had a screening serum E2 concentration of  $\leq 20$  pg/mL.

**Exclusion Criteria:**

- Premenopausal, perimenopausal, pregnant, or lactating women.
- Findings that indicated with any suspicion of breast malignancy.
- Subjects with tobacco use, obesity, undiagnosed abnormal genital bleeding or a history of significant risk factors for endometrial cancer.
- Subjects with a history of venous thromboembolism, pulmonary embolism, stroke, endometrial cancer, breast cancer, cholestatic jaundice, hypertension, serious heart problems, heart failure, myocardial infarction, ventricular arrhythmia, exertional chest pain, insulin dependent diabetes, hypercholesterolemia, hypertriglyceridemia, systemic lupus erythematosus, impaired liver function, or impaired renal function.
- Subjects with a medical history of significant dermatologic diseases, conditions, or cancer to alter skin appearance or physiologic response.
- Subjects who had existing medical conditions which might interfere with absorption, distribution, metabolism, or excretion of study medication.
- Any clinically significant abnormal laboratory test results found during medical screening.
- Positive test for hepatitis B, hepatitis C, or HIV at screening.
- ECG abnormalities (clinically significant) or vital sign abnormalities (systolic blood pressure lower than 90 or over 150 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 45 or over 90 bpm) at screening.
- Subjects who had used any of the following hormone replacement therapies within the specified time prior to the screening visit:
  - Vaginal hormonal products (e.g., rings, creams, or gels) for at least 1 week
  - Transdermal estrogen alone or estrogen/progestin containing products for at least 4 weeks.
  - Oral estrogen and/or intrauterine progestin therapy for at least 8 weeks.
  - Progestin implants and estrogen alone injectable drug therapy for at least 3 months
  - Estrogen pellet therapy or progestin injectable drug therapy for at least 6 months
  - Percutaneous estrogen lotions/gels for at least 4 weeks.
- Use of an investigational drug or participation in an investigational study within 30 days prior to treatment administration.
- Subjects who had used any prescription medications within 14 days of the screening visit.
- Subjects who had used any OTC preparations including herbal or nutritional supplements and multivitamins within 10 days prior to screening.
- Subjects who had consumed foods or beverages containing caffeine/xanthine or alcohol within 72 hours prior to receiving the first study treatment.

**Sample Size Determination:**

The sample size for this dose proportionality study was chosen by the Sponsor based on a type I error ( $\alpha=0.05$ ) and a type II error (power=80%). The intra-subject CV was determined to be 30% (maximum for  $C_{max}$  and AUC from unspecified previous study. For the given doses, the proposed

sample size was 31 subjects. Assuming the drop-out rate to be ~16%, the total sample size was determined to be N=36.

**Disposition of Subjects:**

Thirty six (36) post-menopausal women were enrolled, randomized, and received all 3 treatments. The mean age of the 36 subjects was 55.0 (range: 49-65 years) with a mean BMI of 27.5 kg/m<sup>2</sup> (range: 21.9-29.9 kg/m<sup>2</sup>). All 36 females were Caucasians.

**Concomitant Medication:**

Subjects were prohibited from taking or using prescription medications or OTC products including multivitamin, herbal, or nutritional supplements.

**PK Characterization:**

Blood samples for baseline and PK characterization were taken at 24, 22, 20, 18, 16, 12, 10, 8, 4 hours and 10 minutes before drug application, and 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 92, 96, 102, 108, and 120 hours post-dose in each period.

The following PK parameters were calculated for baseline uncorrected E2, baseline corrected E2, unconjugated E1, and total E1:

- C<sub>max</sub>: the maximum serum concentration observed
- AUC<sub>84</sub>: the area under the serum concentration-time profile; calculated from time 0 to 84 hour (wear time)
- AUC<sub>last</sub>: the area under the serum concentration-time profile; calculated from time 0 to the last measurable concentration by the linear trapezoidal rule (120 hours post-dose)
- AUC<sub>inf</sub>: the area under the serum concentration-time profile extrapolated to infinity
- T<sub>max</sub>: the time of the maximum observed concentration
- k<sub>el</sub>: elimination rate constant (slope of the log concentration vs. time curve between 84 and 120 hours)
- t<sub>1/2</sub>: elimination half-life (ln 2/k<sub>el</sub>)

**Nominal Delivery Rate Analysis:**

The amount of drug released during the hours of application of the patch was determined by measuring the amount of drug remaining in the patch after removal and subtracting that amount from the amount measured in the control patches. The average control value for each treatment was used as the control potency to determine the individual nominal amount of drug released.

Individual nominal amount of drug released = Average control - Individual residual

The mean residual E2 amount (i.e., drug released) was used to derive the nominal delivery rate.

Used patches were collected and stored frozen until they were shipped to the Sponsor at the completion of the study for determination of residual E2 content.

**Skin Adhesion and Skin Irritation Assessment:**

During each treatment period, the skin adhesion of the patches was evaluated at 2, 4, 8, and 12 hours after application and then every 12 hours thereafter until patch removal at 84 hours post-dose. All evaluations were completed within ±5 minutes of the scheduled time. Findings were recorded as an estimate of the percentage of the system surface in contact with the skin, according to the scale provided in Table A-2-1.

Table A-2-1: Skin Adhesion Scale

Score	Definitions
0	≥ 90% adhered (essentially no lift off the skin)
1	≥75% < 90% adhered (some edges only lifting off the skin)
2	≥50% < 75% adhered (less than half of the system lifting off the skin)
3	0% to < 50% adhered but not detached (more half of the system lifting off the skin without falling off)
4	0% adhered - System detached (ETS completely off the skin)

Prior to patch application (0 hour), immediately prior to removal (84 hours following application), immediately after removal and at 1, 12, and 24 hours post removal (85, 96, and 108 hours following application), the application site was observed for the presence or absence of skin irritation. All evaluations were completed within ±10 minutes of the scheduled time. Findings were graded and recorded according to scales provided below (based on Agency's *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*; December 1999):

- 0 = no evidence of irritation;
- 1 = minimal erythema, barely perceptible;
- 2 = definite erythema, readily visible; minimal edema or minimal popular response;
- 3 = erythema and papules;
- 4 = definite edema;
- 5 = erythema, edema and papules;
- 6 = vesicular eruption;
- 7 = strong reaction spreading beyond application site.

**Reviewer's Comment:** *The skin irritation assessment data were not reviewed as the Clinical review team will review the data. Please refer to Dr. Phil Price's clinical review for details.*

**Safety Assessments:**

- AE: AEs considered to be treatment-emergent were summarized and reported.
- Laboratory measurements: All clinical laboratory measurements were listed. Clinical laboratory results were also presented by time point and treatment. Changes from baseline and shift tablets (based on laboratory normal ranges) were presented.
- Vital signs: All vital sign measurements were listed. Vital sign measurements were also presented by time point and treatment. Changes from baseline were also summarized descriptively.
- ECG: QTc interval measurements were summarized as continuous variables and presented by time point and treatment. Changes from baseline and outlier assessments were also presented.

**Bioanalytical Method:**

Blood samples were collected at times specified by the protocol and the obtained serum samples were analyzed for E2, unconjugated E1, and total E1 concentrations. As E2 was the primary analyte for BE assessment, only the bioanalytical method for E2 was reviewed.

Bioanalyses for E2 was performed at (b) (4) between June 13, 2011 and July 8, 2011. Two thousand two hundred sixty eight (2,268) human serum samples were received frozen from Cetero Research, Miami, FL on June 1, 2011. The samples were stored at -20°C or below until analysis. All samples were analyzed within the demonstrated long-term storage stability (1,952 days for E2) in unstripped human serum at -20 °C or below.

Freeze/thaw stability was evaluated by analyzing low- and high-level QCs subjected to 3 freeze/thaw cycles. Samples were thawed at room temperature. No apparent abnormalities associated with up to three freeze/thaw cycles were observed.

A LC-MS/MS method was developed and validated with the dynamic range of 1-100 pg/mL.

Because E2 is an endogenous steroid, measurable levels are expected to be present in the blood from all human donors. The study was conducted using calibration standards and QC pools prepared in a “blank” surrogate matrix that contained negligible levels of these analytes, as per the validated method. The surrogate matrix was modified human serum, containing tripotassium EDTA, which had been stripped with activated charcoal to remove small organic molecules and then fortified with ascorbic acid. Additional QC concentrations were prepared in unstripped human serum fortified with ascorbic acid. Long-term storage stability of E2 in stripped and unstripped human serum treated with 5.0 mM ascorbic acid has been demonstrated for 390 days at -20 °C.

A 500 µL sample aliquot is fortified with 25 µL of IS working solution. Analytes are isolated through LLE with 5.0 mL of 10:90 ethyl acetate/hexane (v/v). The solvent is evaporated under a stream of nitrogen at 40-50°C and the remaining residue is derivatized. The derivatized analytes are extracted into 3.0 mL of 10:90 ethyl acetate/hexane, the solvent is evaporated, and the remaining residue is reconstituted with 150 µL of acetonitrile and 200 µL of water. The final extract is analyzed via LC-MS/MS.

Each calibration curve was calculated using a linear (1/concentration weighted) least-squares regression algorithm. Precision and accuracy were evaluated by replicate analyses of surrogate matrix QC pools (QCs 1, 3, and 5) prepared at three concentrations spanning the calibration range. Additional QCs were prepared in human serum (QCs 2 and 4).

Mean inter-assay accuracy of back-calculated concentrations in calibrators ranged between 98.5% and 102.1% and precision was 3.1-8.1%. QC samples for E2 (range: 2.0-75.0 pg/mL) had an accuracy of 99.7-103.0 % and a precision of 4.3-11.4%.

ISR was performed on 227 out of 2,268 samples (approximately 10.0%; 5-8 samples per subject for all 36 enrolled subjects) for E2. Two hundred twenty (220) out of 227 (96.9%) ISR results met the acceptance criteria of being within  $\pm 20\%$  of the original reported concentration value for at least 67% of the ISR samples.

**Reviewer’s Comment:** *Acceptance criteria and assay performance for E2 bioanalysis were in compliance with the Agency’s Bioanalytical Method Validation Guidance and the bioanalytical method was found to be acceptable.*

#### **Nominal Delivery Rate Analysis Results**

The extent of exposure was determined by measuring the amount of residual E2 remaining in the patches and estimating the nominal delivery rate of E2. The nominal delivery rate analysis is summarized in Table A-2-2 below.

**Table A-2-2: Nominal Delivery Rate Analysis Summary**

MINIVELLE Strength	Loaded E2 (mg/unit)	Mean Control E2 (mg/unit)	Mean Residual E2 (mg/unit)	Mean Released Drug (mg/unit) <sup>(b) (4)</sup>
1.65 mg/6.6 cm <sup>2</sup>	1.65			
0.83 mg/3.3 cm <sup>2</sup>	0.83			
0.41 mg/1.65 cm <sup>2</sup>	0.41			

The mean absolute amounts released were proportional to dose and the percentages released (range: <sup>(b) (4)</sup>) were very similar across the 3 treatments. The nominal delivery rates from different doses of MINIVELLE in this study were determined to be <sup>(b) (4)</sup> mg/day, respectively, while they are labeled as 0.1, 0.05, and <sup>(b) (4)</sup> mg/day, respectively.

**PK Results:**

Serum samples obtained were analyzed for E2, unconjugated E1, and total E1 and PK analysis was performed for all 3 analytes. E2 data were analyzed with and without baseline correction. The Sponsor did not use PK parameters of baseline uncorrected E2 for dose proportionality assessment.

**Reviewer Comment:** *Baseline corrected E2 was the primary analyte for dose proportionality assessment. However, it should be noted that baseline uncorrected E2 PK parameters were traditionally employed for labeling for the treatment of VMS in postmenopausal women.*

E2 Baseline Correction

Ten (10) E2 baseline values were below the LLOQ of 1 pg/mL and all baseline values were below 20 pg/mL. For E2 baseline correction, pre-dose E2 concentration values at respective time points were subtracted from appropriate E2 concentrations after dosing, as follows:  $C_{0 \text{ (first period)}} - (C_{-24} + C_{0 \text{ (first period)}})/2$ ,  $C_{0 \text{ (second period)}} - (C_{-24} + C_{0 \text{ (first period)}})/2$ ,  $C_2 - C_{-22}$ ,  $C_4 - C_{-20}$ ,  $C_8 - C_{-16}$ ,  $C_{12} - C_{-12}$ ,  $C_{24} - (C_{-24} + C_{0 \text{ (first period)}})/2$ ,  $C_{36} - C_{-12}$ ,  $C_{48} - (C_{-24} + C_{0 \text{ (first period)}})/2$ ,  $C_{60} - C_{-12}$ ,  $C_{72} - (C_{-24} + C_{0 \text{ (first period)}})/2$ ,  $C_{84} - C_{-12}$ ,  $C_{86} - C_{-10}$ ,  $C_{88} - C_{-8}$ ,  $C_{92} - C_{-4}$ ,  $C_{96} - (C_{-24} + C_{0 \text{ (first period)}})/2$ ,  $C_{102} - C_{-18}$ ,  $C_{108} - C_{-12}$ , and  $C_{120} - (C_{-24} + C_{0 \text{ (first period)}})/2$ .

**Reviewer Comment:** *The Sponsor employed a time-matched baseline correction based on a 24-hr baseline PK measurement. As there were two pre-dose baseline time points (i.e.,  $C_{-24}$  and  $C_{0 \text{ (first period)}}$ ) available, the Sponsor subtracted the average of these two for baseline corrections of  $C_0$ ,  $C_{24}$ ,  $C_{48}$ ,  $C_{72}$ ,  $C_{96}$ , and  $C_{120}$ .*

*The mean baseline concentration values for E2 at each different time point before initiating the patch therapy ranged between 3.2-4.3 pg/mL (individual baseline concentration range: 1.10-10.4 pg/mL). Published literature suggests that endogenous E2 concentration in postmenopausal women is within the range of 5-25 pg/mL (DeCherney and Nathan, 2003). Baseline E2 concentration values obtained from this study were found to be lower than what was reported in literature.*

Baseline Corrected PK Parameters

Baseline corrected E2 PK parameters for each treatment are shown in Table A-2-3.

**Table A-2-3: Mean (SD) Serum PK Parameters of Baseline Corrected E2 Following a Single Dose of MINIVELLE or Vivelle**

Parameter	MINIVELLE 0.1 mg/day 1.65 mg/6.6 cm <sup>2</sup> (N=36)	MINIVELLE 0.05 mg/.day 0.83 mg/3.3 cm <sup>2</sup> (N=36)	MINIVELLE 0.025 mg/day (b) (4) (N=36)
AUC <sub>84</sub> (pg·hr/mL)	5586 (1855)	2769 (960)	1475 (574)
AUC <sub>120</sub> (pg·hr/mL)	5836 (1932)	2905 (1003)	1565 (605)
AUC <sub>inf</sub> (pg·hr/mL)	5855 (1935)	2937 (1014) <sup>a</sup>	1603 (605) <sup>b</sup>
C <sub>max</sub> (pg/mL)	114 (39.0)	53.0 (17.3)	26.8 (10.8)
T <sub>max</sub> (hr) <sup>c</sup>	24.0 (8.0-60.0)	24.0 (8.0-60.0)	36.0 (8.0-84.0)
t <sub>1/2</sub> (hr)	7.90 (2.57)	7.74 (3.76) <sup>a</sup>	6.77 (3.06) <sup>b</sup>

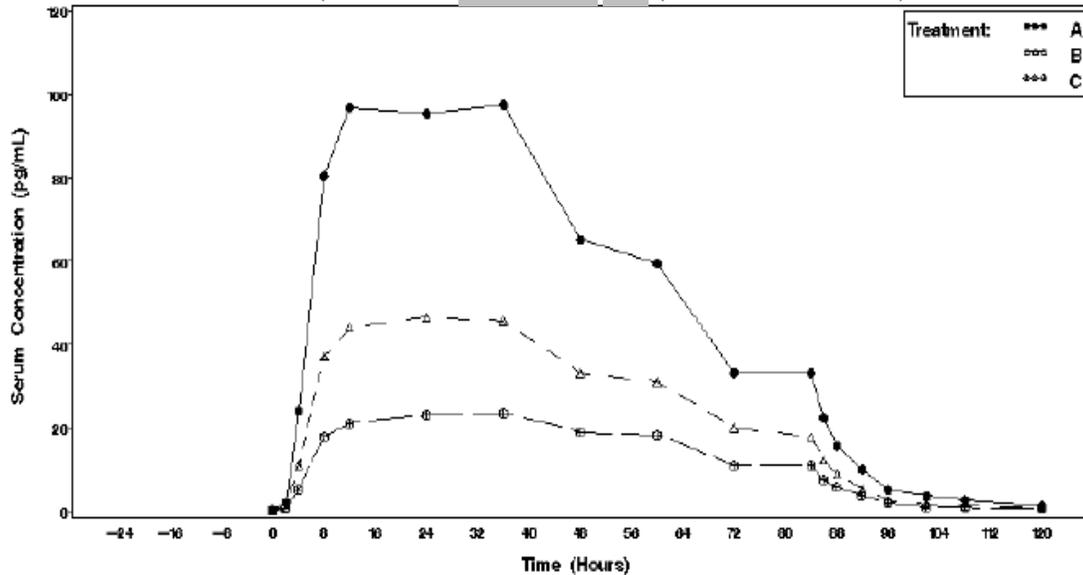
<sup>a</sup> N=35 (Subject 005-001-034 is missing AUC<sub>inf</sub> due to r<sup>2</sup><sub>adjusted</sub> < 0.6)

<sup>b</sup> N=34 (Subjects 005-001-027 and 005-001-034 are missing AUC<sub>inf</sub> due to r<sup>2</sup><sub>adjusted</sub> < 0.6)

<sup>c</sup> Median (minimum-maximum)

The obtained mean concentration-time profiles for baseline corrected E2 are presented in Figure A-2-1 below.

**Figure A-2-1: Mean Baseline Corrected E2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (MINIVELLE 1.65 mg/6.6 cm<sup>2</sup>), Treatment B (MINIVELLE 0.827 mg/3.3 cm<sup>2</sup>), and Treatment C (MINIVELLE (b) (4) (N=36 for each treatment))**



Baseline Uncorrected PK Parameters

Baseline uncorrected E2 PK parameters for each treatment are shown in Table A-2-4.

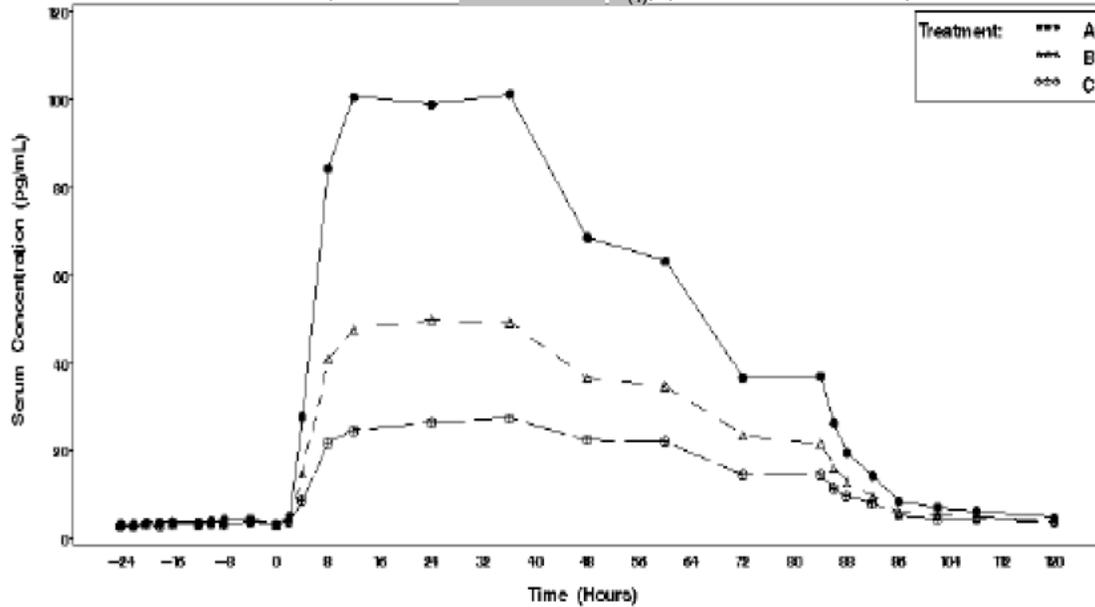
**Table A-2-4: Mean (SD) Serum PK Parameters of Baseline Uncorrected E2 Following a Single Dose of MINIVELLE or Vivelle**

Parameter	MINIVELLE 0.1 mg/day 1.65 mg/6.6 cm <sup>2</sup> (N=36)	MINIVELLE 0.05 mg/.day 0.83 mg/3.3 cm <sup>2</sup> (N=36)	MINIVELLE 0.025 mg/day (b) (4) (N=36)
AUC <sub>84</sub> (pg·hr/mL)	5875 (1857)	3057 (980)	1763 (600)
AUC <sub>120</sub> (pg·hr/mL)	6252 (1938)	3320 (1038)	1979 (648)
C <sub>max</sub> (pg/mL)	117 (39.3)	56.6 (17.6)	30.3 (11.1)
T <sub>max</sub> (hr) <sup>a</sup>	24.0 (8-60)	24.0 (8-60)	36.0 (8-84)

<sup>a</sup> Median (minimum-maximum)

The obtained mean concentration-time profiles for baseline uncorrected E2 are presented in Figure A-2-2 below.

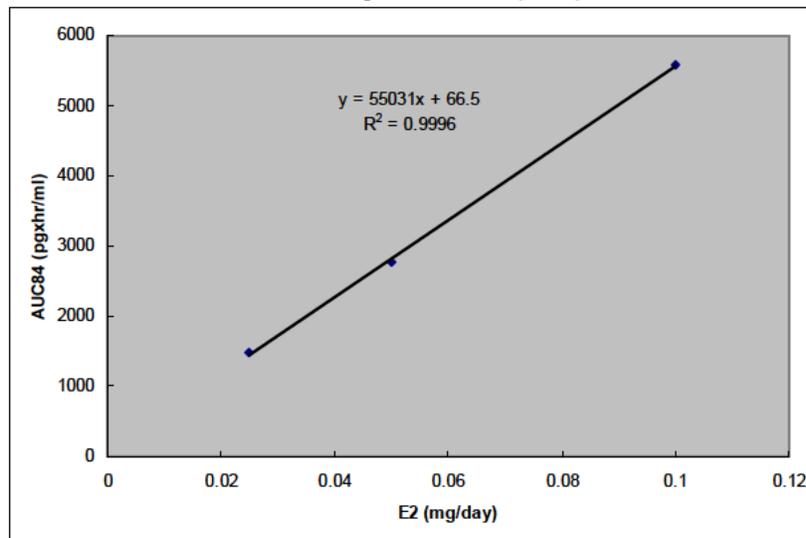
**Figure A-2-2: Mean Baseline Uncorrected E2 Serum Concentration-Time Profiles Following a Single Dose of Treatment A (MINIVELLE 1.65 mg/6.6 cm<sup>2</sup>), Treatment B (MINIVELLE 0.827 mg/3.3 cm<sup>2</sup>), and Treatment C (MINIVELLE 0.413 mg/1.65 cm<sup>2</sup>) (N=36 for each treatment)**



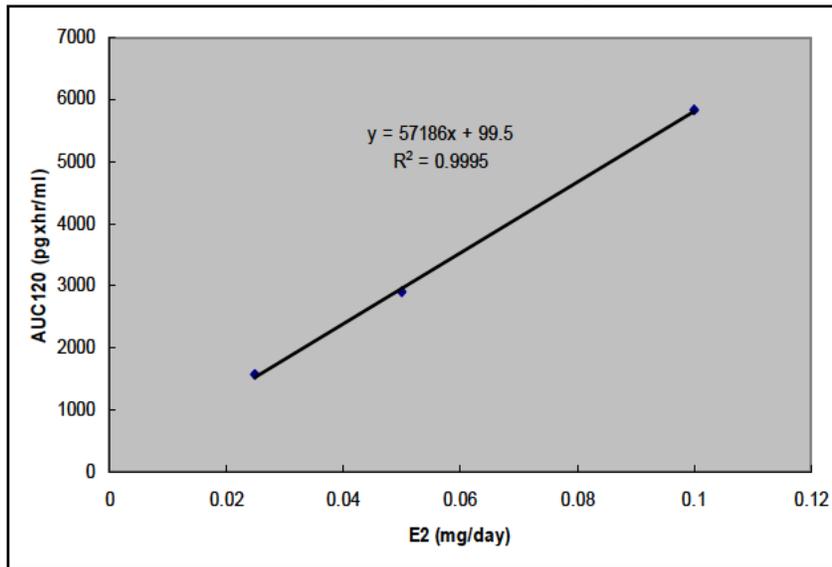
**Dose Proportionality Assessment:**

As shown in Figures A-2-3, A-2-4, A-2-5, and A-2-6, AUC and C<sub>max</sub> increased linearly and E2 were found to be dose proportional among the 3 different strengths of 0.025 mg/day, 0.05 mg/day, and 0.1 mg/day following a single dose of MINIVELLE in postmenopausal women.

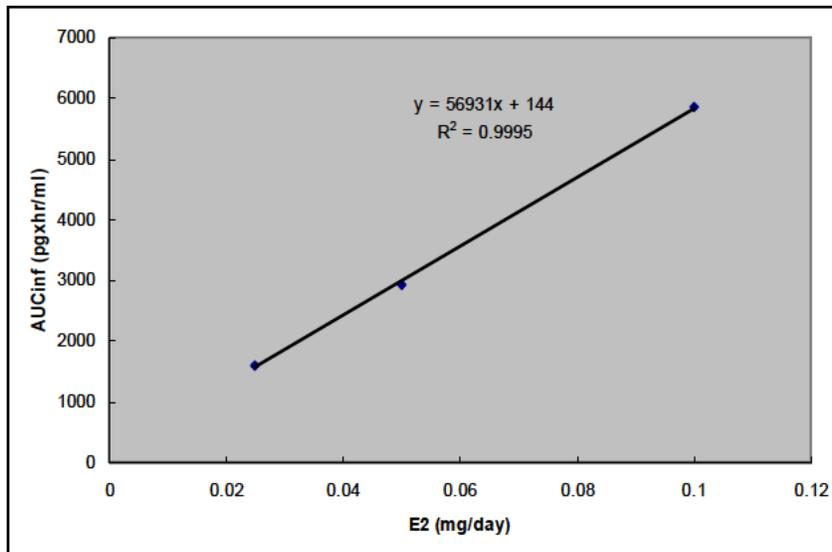
**Figure A-2-3: Relationship between E2 Dose and Mean AUC<sub>84</sub> Following a Single Dose of MINIVELLE in Postmenopausal Women (N=36)**



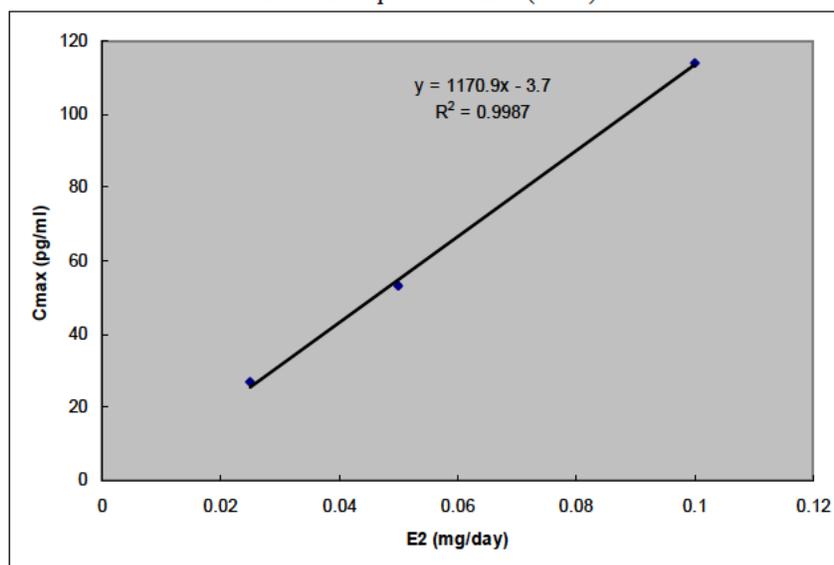
**Figure A-2-4:** Relationship between E2 Dose and Mean AUC<sub>120</sub> Following a Single Dose of MINIVELLE in Postmenopausal Women (N=36)



**Figure A-2-5:** Relationship between E2 Dose and Mean AUC<sub>inf</sub> Following a Single Dose of MINIVELLE in Postmenopausal Women (N=36)



**Figure A-2-6:** Relationship between E2 Dose and Mean  $C_{max}$  Following a Single Dose of MINIVELLE in Postmenopausal Women (N=36)



**Skin Adhesion:**

Thirty four (34) out of 36 subjects had an adhesion score of 0 (i.e.,  $\geq 90\%$  adhered) at 84 hours post-dose in all 3 MINIVELLE treatment periods (106 out of 108 observations).

There was 1 subject each in Treatments A and B with an adhesion score of 1 (i.e., adhesion of  $\geq 75\%$  to  $< 90\%$ ). There were no subjects whose patch became completely detached.

**Safety Results:**

Per Sponsor, 11 subjects (31%) experienced a total of 19 TEAEs during Treatment A (MINIVELLE 1.65 mg/6.6 cm<sup>2</sup>), as compared to 11 subjects (31%) experiencing a total of 14 TEAEs during Treatment B (MINIVELLE 0.827 mg/3.3 cm<sup>2</sup>) and 10 subjects (28%) experiencing a total of 25 TEAEs during Treatment C (MINIVELLE [REDACTED] (b) (4)). All TEAEs were mild in intensity and most were deemed possibly related to treatment.

No deaths or other SAEs occurred during the study and no subjects were withdrawn from the study due to an AE.

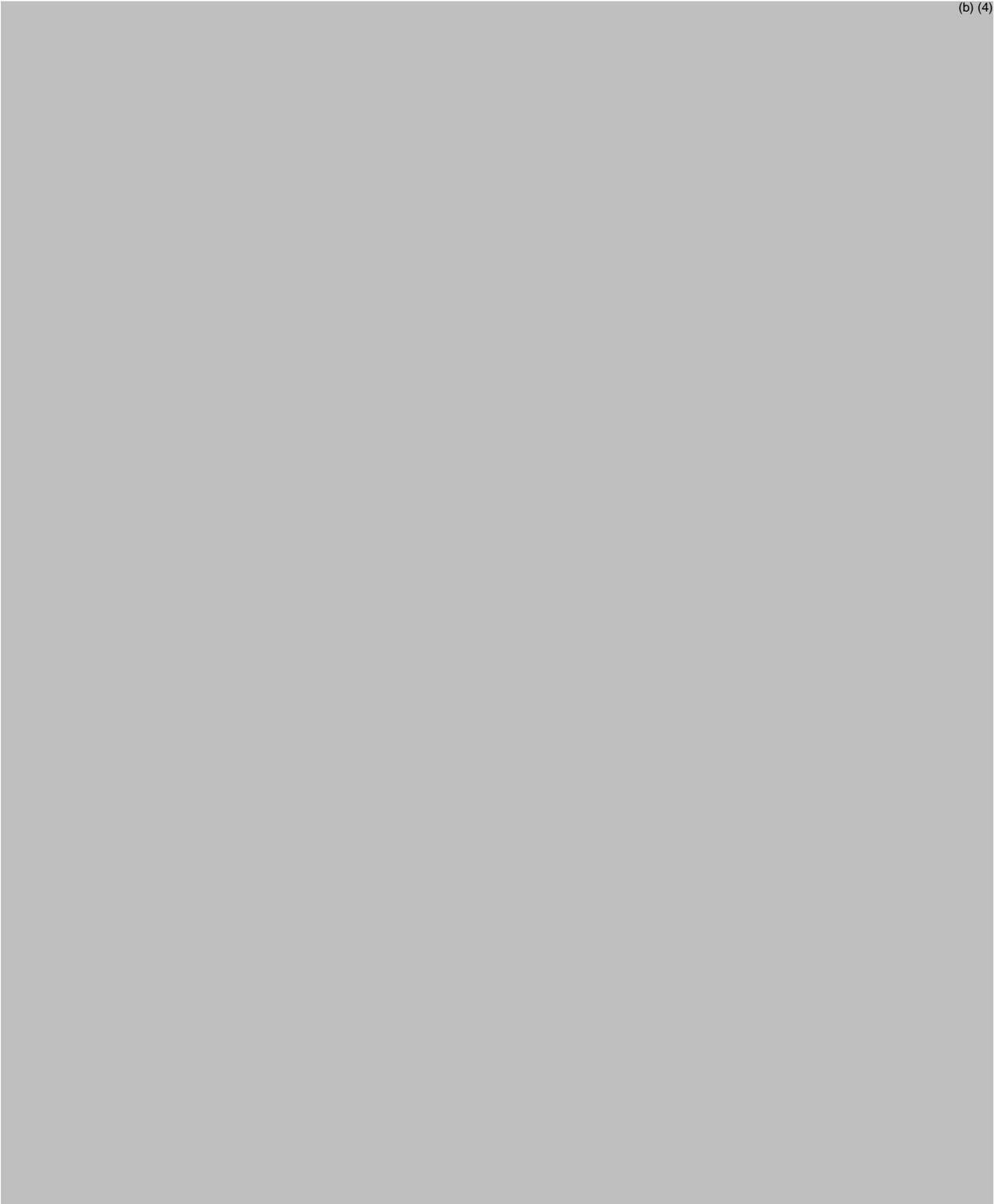
**Reviewer's Comment:** *The safety data was not reviewed by this reviewer. It appears that all 3 treatments had similar safety profiles. Please refer to Dr. Phil Price's clinical review for details.*

**Conclusion:**

Based on the baseline corrected E2 AUC<sub>84</sub> and  $C_{max}$ , dose proportionality of E2 was established from 0.025 mg/day to 0.1 mg/day following a single dose of MINIVELLE in a three-way crossover study in postmenopausal women.

## 4.2 Office of Scientific Investigations Consult Report

(b) (4)



2 Pages Have Been Withheld As A Duplicate Copy Of The "Office of Scientific Investigations Consult Report" dated June 26, 2012 Which Is Located In The Other Reviews Section Of This NDA Approval Package.

7 Pages Have Been Withheld As A Duplicate Copy Of The "Clinical Pharmacology Filing Memo" dated February 14, 2012 which Is Located at the end of this Section Of This NDA Approval Package

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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.**  
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/s/  
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CHONGWOO YU  
08/15/2012

MYONG JIN KIM  
08/16/2012

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence (BE) data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			A 0.1 mg/day single dose BE study using (b)(4) (test) and Vivelle® (reference)
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refers to distribution, metabolism, and excretion information publically available (i.e., Vivelle® label)
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			BE approach to a reference product (i.e., Vivelle®)
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	BE approach to a reference product (i.e., Vivelle®)
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	BE approach to a reference product (i.e., Vivelle®)
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	BE approach to a reference product (i.e., Vivelle®)

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	BE approach to a reference product (i.e., Vivelle <sup>®</sup> )
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	BE approach to a reference product (i.e., Vivelle <sup>®</sup> )
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?** \_\_\_Yes\_\_\_

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

*None.*

*Chongwoo Yu*

*2/8/2012*

\_\_\_\_\_  
Reviewing Clinical Pharmacologist

\_\_\_\_\_  
Date

*Hyunjin Kim*

*2/8/2012*

\_\_\_\_\_  
Acting Team Leader

\_\_\_\_\_  
Date

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Filing Memo

### Clinical Pharmacology Review

**NDA:** 203752  
**Compound:** (b) (4)<sup>TM</sup> (17 $\beta$ -estradiol [E2] transdermal system [ETS]): nominal delivery of 0.1 mg/day, 0.075 mg/day, 0.05 mg/day, 0.0375 mg/day, (b) (4)<sup>TM</sup>  
**Sponsor:** Noven Pharmaceuticals, Inc.  
**Date:** 2/8/2012  
**Reviewer:** Chongwoo Yu, Ph.D.

#### Introduction:

Noven Pharmaceuticals Inc. submitted New Drug Application (NDA) 203752 for (b) (4)<sup>TM</sup> in accord with Section 505 (b)(1) on December 29, 2011 to seek an approval for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause with a right of cross-reference to NDA 020323 Vivelle<sup>®</sup> (approved on October 28, 1994) and NDA 020538 Vivelle-Dot<sup>®</sup> (approved on July 31, 1996) from Novartis. Vivelle<sup>®</sup> and Vivelle-Dot<sup>®</sup> are ETSS manufactured by Noven Pharmaceuticals Inc. and marketed by Novartis Pharmaceuticals Corporation. (b) (4)<sup>TM</sup>

The recommended starting dose of (b) (4)<sup>TM</sup> is 0.0375 mg/day applied to skin twice weekly. (b) (4)<sup>TM</sup> dosage strengths of (b) (4)<sup>TM</sup> have been developed to provide nominal *in vivo* delivery rates (b) (4)<sup>TM</sup> 0.0375, 0.05, 0.075, or 0.1 mg of E2 per day via skin. The adhesive side of (b) (4)<sup>TM</sup> should be placed on a clean, dry area of the trunk of the body (including the abdomen or buttocks). The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site.

#### Regulatory History

Clinical Pharmacology related comments conveyed to the Sponsor during their drug development include the following. Please note that (b) (4)<sup>TM</sup> is a different formulation from (b) (4)<sup>TM</sup> but the same comments apply to (b) (4)<sup>TM</sup>:

#### Pre-IND Meeting (September 11, 2007)

- A pivotal single dose, two-way crossover *in vivo* bioequivalence (BE) study comparing the highest strength of Vivelle<sup>®</sup> (not Vivelle-Dot<sup>®</sup>) and (b) (4)<sup>TM</sup> will provide support for approval of (b) (4)<sup>TM</sup>
- Conduct separate studies to assess for BE (between Vivelle<sup>®</sup> and (b) (4)<sup>TM</sup>) and dose proportionality of (b) (4)<sup>TM</sup>
- You need to provide appropriate data on patch adhesion and irritability
- Consideration of the 0.075, 0.05, 0.0375 and (b) (4)<sup>TM</sup> mg/day dosage strengths will be based on the determination that:
  - All the lower strengths are proportionally similar in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an *in vivo* BE study;
  - *In vitro* dissolution profiles of all strengths of (b) (4)<sup>TM</sup> are comparable ( $f_2 > 50$ ).
  - Pharmacokinetics of (b) (4)<sup>TM</sup> are dose proportional over the dose range of 0.025 to 0.1 mg/day.The BE requirement for lower strengths would be waived based on the assessments above.
- Assess the baseline (24 hr baseline) serum levels of estradiol and its metabolites
- BE calculation should be based on both, baseline corrected and uncorrected relevant PK parameters.

#### Advice/Information Request Letter (July 16, 2010)

- Because estradiol is known to be a CYP3A4 substrate, co-administration of CYP3A4 inducers and inhibitors that can affect estradiol concentration should be prohibited during the study.
- The application site for the proposed study is the lower abdomen. The proposed application site(s) and dosing regimen for the to-be-marketed product are unclear. Clarify the proposed application site(s) and dosing regimen for your product.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

- Your proposal to report only the percentage of subjects to which the product adhered completely over a single application period is insufficient. We recommend a standardized adhesion scale to address patch wearability. The following is an example of a standardized adhesion scale:
  - 0: > 90% adhered (no lift)
  - 1: ≤ 75% adhered but ≤ 90% (some edges showing lift)
  - 2: ≤ 50% adhered but < 75% (< half of system lifts off)
  - 3: < 50% adhered (≥ half of system lifts off, but undetached)
  - 4: patch completely detached
- You should evaluate the effect of chronic use of (b) (4) ETS on skin irritation and sensitization. We refer you to the September 11, 2007, Pre-IND meeting minutes.

**Advice/Information Request Letter (March 18, 2011)**

- Measurements of E2 and estrone (E1) are sufficient to comply with the FDA requirements.
- As communicated at the September 11, 2007 pre-IND meeting, we recommend conducting separate studies of BE (between Vivelle® and (b) (4) and dose proportionality of (b) (4). The effect of chronic use of (b) (4) on skin irritation and sensitization should be evaluated. We refer you to the September 11, 2007 pre-IND meeting minutes and our advice letter dated July 16, 2010. If evaluation of irritation and sensitization from the BE and dose proportionality studies reveal concerning results, a formal skin irritation and sensitization study may be requested. Your protocols should include a specific rating scale to assess skin irritation.
- We continue to recommend that you conduct a dose proportionality study as discussed at the September 11, 2007, pre-IND meeting.

Reference is made to the September 11, 2007 Pre-IND meeting minutes dated October 5, 2007 in DARRTS and the advice/information request letter dated July 16, 2010 and March 18, 2011 in DARRTS, respectively, for further details of the Division's recommendations to the Sponsor.

It should be noted that Vivelle-Dot® was approved on the basis of the following:

- Establishment of BE to Vivelle® at the highest dose of 0.1 mg/day
- Establishment of dose proportionality over the dose range of 0.025-0.1 mg/day
- Different doses of Vivelle-Dot® are compositionally proportional
- In vitro dissolution profiles of all strengths of Vivelle-Dot® are comparable ( $f_2 > 50$ )

**Clinical Pharmacology Studies in this NDA**

This application contains full reports of the following two studies that used the final to-be-marketed (TBM) formulation:

Best Available Copy

**Table 1: Summary of Clinical Pharmacology Studies using the TBM Formulation**

Study Phase Protocol Number	Study Objective	Study Design	Study Population	Dosing Regimen/Routes	No. of Patients Planned /No. of Patients Enrolled	PK Methodology
<b>Primary Studies</b>						
Phase 1 N28-004	Primary: To demonstrate bioequivalence of (b) (4) versus Vivelle.  Secondary: • To assess wear characteristics of the transdermal systems. • To assess safety and tolerability of the transdermal systems.	Open-label, single-center, single-dose, two-way crossover study with two treatments and two treatment periods, separated by a minimum 21-day washout period between treatment administrations.	Healthy, nonsmoking, postmenopausal women, 40 to 65 years of age.	Treatment A (Test): One (b) (4) (1.65 mg/0.6 cm <sup>2</sup> ) applied for 84 hours.  Treatment B (Reference): One Vivelle (8.66 mg/29 cm <sup>2</sup> ) applied for 84 hours.	100/100	On Day 0, nine baseline blood samples were collected at -24, -22, -20, -18, -16, -12, -10, -8, and -4 hours. Subjects received their assigned treatment on Day 1 and Day 22. During each treatment period, subjects underwent serial blood sample collection. Samples were collected 30 minutes pre-dose and at 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 92, 96, 102, 108, and 120 hours after treatment administration in each treatment period (18 samples/treatment).  PK parameters (C <sub>max</sub> , AUC <sub>0-∞</sub> , AUC <sub>0-24</sub> , AUC <sub>0-48</sub> , t <sub>max</sub> , K <sub>el</sub> , half-life) were determined for baseline corrected estradiol and baseline uncorrected estradiol, unconjugated estrone, and total estrone concentrations by noncompartmental methods using Phoenix WinNonlin.  The assessment of bioequivalence included the construction of 90% CI for Test/Reference ratios for baseline uncorrected estradiol C <sub>max</sub> , AUC <sub>0-4</sub> , and AUC <sub>0-24</sub> and for baseline corrected estradiol C <sub>max</sub> , AUC <sub>0-4</sub> , AUC <sub>0-24</sub> , and AUC <sub>0-∞</sub> .

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Phase 1 N28-005	<p>Primary: To assess the dose proportionality of (b) (4) in healthy postmenopausal women.</p> <p>Secondary:</p> <ul style="list-style-type: none"> <li>To assess wear characteristics of the transdermal systems.</li> <li>To assess safety and tolerability of the transdermal systems.</li> </ul>	Randomized, single-center, open-label, single-dose, three-way crossover study with three treatments and three treatment periods with a minimum 21-day washout period between treatment administration.	Healthy, nonsmoking, postmenopausal women, 40 to 65 years of age.	<p>Treatment A: One (b) (4) 1.65 mg/6.6 cm<sup>2</sup> applied for 84 hours.</p> <p>Treatment B: One 0.827 mg/3.3 cm<sup>2</sup> (b) (4) applied for 84 hours.</p> <p>Treatment C: One (b) (4)</p>	36/36	<p>On Day 0, nine baseline blood samples were collected at -24, -22, -20, -18, -16, -12, -10, -8, and -4 hours. Subjects received their assigned treatment on Day 1, Day 22, and Day 43. During each treatment period, subjects underwent serial blood sample collection. Samples were collected 30 minutes pre-dose and at 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 92, 96, 102, 108, and 120 hours after treatment administration in each treatment period (18 samples/treatment).</p> <p>PK parameters (<math>C_{max}</math>, <math>AUC_{0-84}</math>, <math>AUC_{inf}</math>, <math>AUC_{inf}</math>, <math>t_{max}</math>, <math>K_{el}</math>, half-life) were determined for baseline corrected estradiol and baseline uncorrected estradiol, unconjugated estrone, and total estrone concentrations by noncompartmental methods using Phoenix WinNonlin.</p> <p>The Mixed-Effects Power Model applied to <math>C_{max}</math>, <math>AUC_{0-84}</math>, <math>AUC_{inf}</math>, and <math>AUC_{inf}</math> of baseline corrected estradiol was used to assess PK dose proportionality. It measured the degree of nonproportionality and associated CIs and critical regions (0.84, 1.16).</p>
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Full reports of the following studies that used previous formulations were also submitted as supportive information:

**Table 2: Summary of Clinical Pharmacology Studies using Previous Formulations**

Study Phase Protocol Number	Study Objective	Study Design	Study Population	Dosing Regimen/Routes	No. of Patients Planned /No. of Patients Enrolled	PK Methodology
N28-001	<p>Primary:</p> <ul style="list-style-type: none"> <li>To determine the relative bioavailability of 2 (b) (4) formulations to Vivelle</li> <li>To determine the wear characteristics these transdermal systems</li> </ul>	Randomized, single center, open label, single center, 3 way cross-over with 7 day wash out period in between	Healthy, nonsmoking, postmenopausal women, 40 to 60 years of age.	<p>Treatment A: (b) (4) (b) (4) ETS applied for 84 hours</p> <p>Treatment B: (b) (4) (b) (4) ETS applied for 84 hours</p> <p>Treatment C: (b) (4) (b) (4) applied for 84 hours.</p>	26/25	<p>The time points for blood sample collections in this study were: pre-dose (30 min prior), 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 92, 96, 102, 108, and 120 hours after treatment administration in each treatment period (18 samples/treatment).</p> <p>Serum estradiol and estrone concentrations were assayed.</p> <p>The assessment of bioequivalence included the construction of 90% confidence intervals (CI) for Test/Reference ratios</p>
N28-003	<p>Primary:</p> <ul style="list-style-type: none"> <li>To assess the BE 2 (b) (4) formulations</li> <li>To assess the wear characteristics of the 2 (b) (4) formulations</li> <li>To assess the safety and tolerability of the 2 (b) (4) formulations</li> </ul>	Randomized, open-label, single-center, single-dose, 3-period crossover study with at least a 7 day wash out period in between	Healthy, nonsmoking postmenopausal women 40 to 60 years of age	<p>Treatment A: (b) (4) (b) (4) ETS applied for 84 hours</p> <p>Treatment B: (b) (4) (b) (4) ETS applied for 84 hours</p> <p>Treatment C: (b) (4) (b) (4) applied for 84 hrs.</p>	18/18	<p>Blood samples for estradiol and estrone analysis were collected prior to dosing and at 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 86, 88, 92, 96, 102, 108, and 120 hours following application in each treatment period.</p>

N=Number of subjects in the sample;  $C_{max}$  maximum observed serum concentration,  $AUC_{inf}$ : area under the serum concentration curve from time 0 to last measurable concentration,  $AUC_{inf}$ : area under the serum concentration curve extrapolated to infinity,  $AUC_{0-84}$ : area under the serum concentration curve from time 0 to 84 hours (patch wear period),  $T_{max}$ : time to maximum concentration,  $K_{el}$ : elimination constant, CI: confidence interval, ETS: Estradiol transdermal system, BE=bioequivalence.

### Drug Product Formulation:

(b) (4)™ is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: 1) a flexible backing film; 2) an adhesive formulation containing E2, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP and dipropylene glycol; and 3) a polyester release liner that is attached to the adhesive surface and must be removed before the patch can be used. The active component of the system is E2. The remaining components of the system are pharmacologically inactive.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Figure 1: The 3 Layers of (b) (4)™



As shown in Table 3, the Sponsor proposes to market (b) (4)™ in (b) (4) different dosage strengths that have been designed to deliver the same therapeutic concentrations of E2 as Vivelle® and Vivelle-Dot® but from a smaller active surface area.

Table 3: Dosage Forms of Vivelle®, Vivelle Dot®, and (b) (4)™

Strength	Vivelle	Vivelle-Dot	(b) (4)
Active Surface Area/Patch Size			
0.025 mg/day	7.25 cm <sup>2</sup>	2.5 cm <sup>2</sup>	(b) (4)
0.0375 mg/day	11.0 cm <sup>2</sup>	3.75 cm <sup>2</sup>	2.48 cm <sup>2</sup>
0.05 mg/day	14.5 cm <sup>2</sup>	5.0 cm <sup>2</sup>	3.30 cm <sup>2</sup>
0.075 mg/day	22 cm <sup>2</sup>	7.5 cm <sup>2</sup>	4.95 cm <sup>2</sup>
0.1 mg/day	29 cm <sup>2</sup>	10 cm <sup>2</sup>	6.60 cm <sup>2</sup>
Estradiol Content per Unit			
0.025 mg/day	2.17 mg	0.39 mg	(b) (4)
0.0375 mg/day	3.28 mg	0.585 mg	0.62 mg
0.05 mg/day	4.33 mg	0.78 mg	0.83 mg
0.075 mg/day	6.57 mg	1.17 mg	1.24 mg
0.1 mg/day	8.66 mg	1.56 mg	1.65 mg

The composition of the drug product is summarized in the Table 4 below:

Table 4: The TBM Formulation (b) (4)™ Patches used in Study N28-004

(b) (4)

**Absorption, Distribution, Metabolism, and Excretion (ADME)**

Only single dose studies assessing BE or dose proportionality were conducted using (b) (4)™. The Sponsor is proposing to use the publically available information of Vivelle® for their product.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Drug-Drug Interactions:

No DDI studies were conducted with (b) (4)™.

## Specific Populations:

- Pediatric use: No pediatric studies were conducted
- Geriatric use: No geriatric studies were conducted
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments. Contraindicated for known liver impairment of disease
- Contraindicated for known or suspected pregnancy

## Biowaiver Request:

As indicated in Table 3, the Sponsor proposes to market (b) (4)™ in (b) (4) different dosage strengths and is requesting a biowaiver for the lower dosage strengths of (b) (4) mg/day, 0.0375 mg/day, 0.05 mg/day, and 0.075 mg/day with the following justifications per 21 CFR §314.90:

- Establishment of BE to Vivelle® at the highest dose of 0.1 mg/day
- Establishment of dose proportionality over the dose range of 0.025-0.1 mg/day
- Different doses of (b) (4)™ are compositionally proportional: Per Sponsor, the patches are different strengths of the same formulation and are from the same sheet of formulation. The only difference is the surface area of the patches.
- *In vitro* dissolution profiles of all strengths of (b) (4)™ are comparable: Per Sponsor,  $f_1$  and  $f_2$  factors were within the Agency's guideline

The office of new drug quality assessment (ONDQA) review team will review and determine the acceptability of the Sponsor's biowaiver request.

## Bioanalytical Method validation:

Serum samples were analyzed for E2, unconjugated E1, and total E1 by validated bioanalytical methods. Studies N28-004 and N28-005 employed a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Incurred sample reanalysis (ISR) was conducted on approximately 10% of the study samples in both studies. An Office of Scientific Investigation (OSI) consult requesting inspections of the clinical and bioanalytical sites of the pivotal BE study (Study N28-004) was requested and signed off in DARRTS by Dr. Dennis Bashaw on February 13, 2012..

## Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 203752 is fileable.

## Comments for the Sponsor:

None

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	203752	Brand Name	(b) (4)™	
OCP Division	DCP3	Generic Name	17β-estradiol (E2)	
Medical Division	DRUP	Drug Class	Steroid hormone	
OCP Reviewer	Chongwoo Yu, Ph.D	Indication(s)	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause	
Acting OCP Team Leader	Hyunjin Kim, Pharm. D.	Dosage Form	Film, extended release (b) (4) 0.0375, 0.05, 0.075, and 0.1 mg/day	
Secondary Reviewer	Myong Jin Kim, Pharm. D.	Dosing Regimen	Starting dose at 0.0375 mg/day, twice weekly	
Date of Submission	December 29, 2011	Route of Administration	Transdermal	
Estimated Due Date of OCP Review	August 29, 2012	Sponsor	Noven Pharmaceuticals, Inc.	
PDUFA Due Date	October 29, 2012	Priority Classification	Standard	
Division Due Date	October 8, 2012			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:	X	2		N28-001, N28-003
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	1		N28-005
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 1:				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
PK:				
PD:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design, single / multi dose:	X	1		N28-004
replicate design, single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
Irritation and sensitization	X			N28-004, N28-005
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Immunogenicity profile</b>				
<b>Thorough QT study</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>				
		4		
<b>Other comments</b>				
	<b>Comments</b>			
<b>QBR questions (key issues to be considered)</b>	<ol style="list-style-type: none"> <li>1. Establishment of BE between (b) (4)™ and Vivelle® at 0.1 mg/day</li> <li>2. Establishment of dose proportionality over the dose range of 0.025-0.1 mg/day</li> <li>3. Are different doses of (b) (4)™ compositionally proportional? (ONDQA will review)</li> <li>4. Are <i>in vitro</i> dissolution profiles of all strengths of (b) (4)™ are comparable (F2 &gt; 50)? (ONDQA will review)</li> <li>5. OSI inspection on clinical and bioanalytical sites for the pivotal BE study</li> <li>6. Acceptability of bioanalytical assay validation and performance</li> </ol>			
<b>Other comments or information not included above</b>	<ul style="list-style-type: none"> <li>• A formal OSI consult on clinical and bioanalytical study sites was requested and signed off in DARRTS by Dr. Dennis Bashaw on February 13, 2012..</li> </ul>			

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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.**  
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/s/  
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CHONGWOO YU  
02/14/2012

HYUNJIN KIM  
02/14/2012