

# FDA Advisory Committee Review of ORTHO EVRA® Contraceptive Patch

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Janssen Research & Development, LLC  
December 9, 2011

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## Overview

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Joanne Waldstreicher, MD  
Chief Medical Officer,  
Janssen Research & Development, LLC

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## Need for Contraceptive Options

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- Unintended pregnancy a significant problem
  - ~50% of pregnancies are unintended
    - Neonatal morbidity/mortality is significantly higher in this subgroup than in planned pregnancies
    - 42% of unintended pregnancies are terminated

3

## Institute of Medicine Position: 2011<sup>1</sup>

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- Women need multiple safe and effective contraceptive options
- Contraceptive needs vary with medical, lifestyle, social and cultural factors
- Contraceptive needs may change over time
- Women need to be adequately informed about each option

<sup>1</sup>IOM (Institute of Medicine). 2011. *Clinical Preventive Services for Women: Closing the Gaps*.

4

## Hormonal Contraceptive Class

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- Benefits
  - High efficacy
  - Female-controlled
  - Prompt contraceptive reversibility
  - Allows for spontaneity
- Well-known VTE risks
  - VTE rates ~3-9/10,000 woman-years<sup>1</sup>
    - Lower than in pregnancy and post-partum
  - Described in class labeling for all hormonal contraceptive products
  - Product-specific risks in labeling

<sup>1</sup> CDER, FDA. Background Document for Dec 9, 2011 Joint Advisory Committee Meeting: Ortho Evra. Nov 14, 2011.

5

## Need for Contraceptive Options

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- OCs account for 92% of all combined hormonal contraceptive prescriptions
- Many women acknowledge difficulty adhering to a daily OC regimen
  - In one study, 30%-51% of OC users missed at least 3 pills in each cycle<sup>1</sup>
- Lack of adherence to daily OC regimens creates a need for alternatives

<sup>1</sup> Potter L, et al Measuring Compliance among Oral contraceptive Users. Family Planning Perspective. 1996;28:154-158

6

## Development of a Transdermal Contraceptive System

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- 1963: Company's first oral contraceptive: ORTHO NOVUM®
- 1980s: Explored the development of a non-oral hormonal contraceptive
  - Physician and patient surveys ranked the transdermal patch ahead of buccal, implant, injectable, nasal spray, vaginal ring
- ORTHO EVRA®: the first and only transdermal contraceptive system available in the U.S

7

## ORTHO EVRA Overview

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- Square, flexible, extended-release matrix patch system
- Contains norelgestromin (NGMN) and ethinyl estradiol (EE) for use in a weekly dosing schedule
- Approved by the FDA for the prevention of pregnancy in November 2001
  - Clinical development program
    - >3,300 women treated with OE
    - >22,000 cycles of use
  - 5.5 million woman-years of use since launch



8

## Early Post-marketing Surveillance

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- Product launched: April 2002
- 2003: Higher-than-expected number of spontaneous reports of adverse events, including:
  - Myocardial infarction (MI)
  - Ischemic stroke
- 2003: Began enhanced surveillance
- Epidemiology studies proposed to FDA

9

## Epidemiology Studies

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- Protocol developed in collaboration with FDA and:
  - Boston Collaborative Drug Surveillance Program (BCDSP)
  - i3 (Ingenix)
- Primary endpoint: MI + Ischemic Stroke
- Secondary endpoint: VTE (pulmonary embolism, deep vein thrombosis)

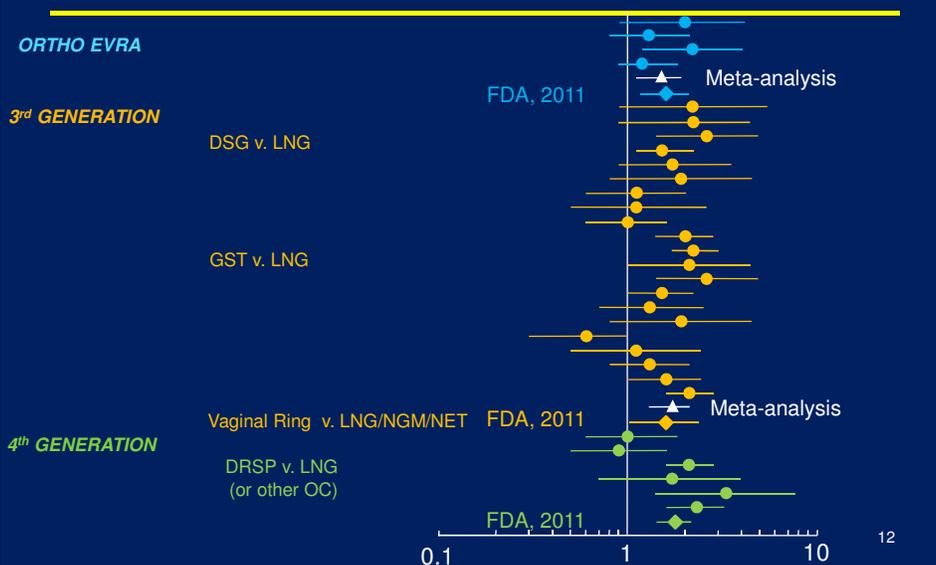
10

## Epidemiology Studies

- Primary endpoint: MI + Ischemic Stroke
  - No difference between ORTHO EVRA and NGM-containing OCs in either study
- Secondary endpoint: VTE
  - BCDSP study:
    - Odds ratio: 0.9 (initial cohort)
    - Odds ratio: 1.2 (final)
  - i3 study:
    - Odds ratio: 2.4 (initial cohort)
    - Odds ratio: 2.2 (final)
  - BCDSP conducted 2 additional epidemiology studies
    - Utilizing 2 separate health claims databases
    - Levonorgestrel-containing OC comparators

11

## VTE Risk Compared to Second Generation OCs



12

# ORTHO EVRA

## Indications and Usage

Renal and Hepatic Impairment  
 No formal studies were conducted with ORTHO EVRA<sup>®</sup> to evaluate the

ORTHO EVRA<sup>®</sup> is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

The pharmacokinetic profile for the ORTHO EVRA<sup>®</sup> transdermal patch is different from that of an oral contraceptive. Healthcare professionals should balance the higher estrogen exposure and the possible increased risk of venous thromboembolism with ORTHO EVRA<sup>®</sup> against the chance of pregnancy if a contraceptive pill is not taken daily.

Weight  
 The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA<sup>®</sup> patch compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel or norgestimate was assessed in four U.S. case-control studies using electronic healthcare claims data. The odds ratios ranged from 1.2 to 2.2; one of the studies found a statistically significant increased risk of VTE for current users of ORTHO EVRA<sup>®</sup>.

Healthcare professionals who consider ORTHO EVRA<sup>®</sup> for women at or above 198 lbs. should discuss the patient's individual needs in choosing the most appropriate contraceptive option.

13

# ORTHO EVRA Labeling

## Boxed Warning: Risk of VTE

ORTHO EVRA<sup>®</sup>  
 (norelgestromin / ethinyl estradiol  
 TRANSDERMAL SYSTEM)

WARNING: INCREASED RISK OF VENOUS THROMBOEMBOLISM (VTE) ASSOCIATED WITH SMOKING, OBESITY, AND PHARMACOKINETIC

### Risk of Venous Thromboembolism

The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA<sup>®</sup> patch compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel or norgestimate was assessed in four U.S. case-control studies using electronic healthcare claims data. The odds ratios ranged from 1.2 to 2.2; one of the studies found a statistically significant increased risk of VTE for current users of ORTHO EVRA<sup>®</sup>.

Reference ID: 2922394

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14

## Differences in Patients Prescribed the Patch vs. the Pill

Planned Parenthood study<sup>1</sup>: Prior history of pregnancy

<b>PRE-STUDY PREGNANCIES</b>	<b>ORTHO EVRA</b>	<b>OCs</b>
<b>Prior</b> Term Deliveries	39%	7%
>1 Term Delivery	16%	3%
<b>Prior</b> Abortions	59%	10%
>1 Abortion	26%	1%

<sup>1</sup>Bakhr A, Stanwood N. Performance of contraceptive patch compared with oral contraceptive pill in a high-risk population. *Obstet Gynecol* 2006; 108:378-386

15

## Agenda

### Overview

**Joanne Waldstreicher, MD**  
Chief Medical Officer  
*Janssen Research & Development, LLC*

### Clinical Development & Post-marketing Surveillance

**Diane Harrison, MD, MPH, FACOG**  
Global Medical Safety Physician  
*Janssen Research & Development, LLC*

### Epidemiology

**Noel Weiss, MD, DrPH**  
Professor of Epidemiology  
*School of Public Health, University of Washington*

### Benefit/Risk Assessment

**Anita Nelson, MD, FACOG**  
Professor of Obstetrics and Gynecology  
*David Geffen School of Medicine, UCLA*

### Concluding Remarks

**Joanne Waldstreicher, MD**  
Chief Medical Officer  
*Janssen Research & Development, LLC*

16

## Additional External Consultants

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- Philip C. Comp, MD, PhD  
Professor of Medicine, Hematology  
University of Oklahoma, Health Sciences Center
- Maida Taylor, MD, MPH, FACOG  
Clinical Professor, Department of Obstetrics,  
Gynecology and Reproductive Science,  
University of California, San Francisco
- Alan C. Fisher, DrPH  
Biostatistician  
Independent Consultant

17

## ORTHO EVRA Clinical Development Program

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Diane Harrison, MD, MPH, FACOG  
Global Medical Safety Physician  
Janssen Research & Development, LLC

18

## Topics to Be Discussed

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- Overview of Development Program
- Clinical Pharmacology
- Clinical Efficacy
- Clinical Safety
- Post-marketing Safety Surveillance

19

## Clinical Development Program Overview

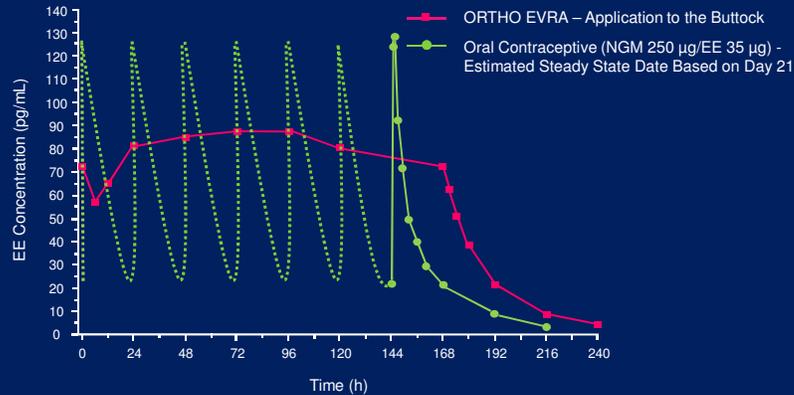
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Type of Study	# of Studies
<b>Phase 1 Pharmacokinetic and Bioavailability</b> Single dose, multiple dose, bioavailability, extremes of wear (heat, humidity, exercise), site of application, drug interaction, adhesion, skin sensitivity	12
<b>Dermal Safety</b>	4
<b>Phase 2 Dose-Ranging</b>	1
<b>Specialized</b> Such as endometrial safety and effects on metabolism and coagulation parameters	4
<b>Phase 3 Efficacy &amp; Safety</b>	3
<b>Total Development Program</b>	<b>24</b>

20

## Clinical Pharmacology

- The transdermal contraceptive patch was a first-in-class product
- Estimates of drug exposure from a 35 µg EE/250 µg NGM OC were used as a starting point to select potentially efficacious hormone exposures



This graph represents data from 2 studies overlaid to provide perspective on the relative profiles 21

## Phase 2 Dose-Ranging Study

- Randomized multi-center 4-arm study
  - ORTHO-CYCLEN (35 µg EE/250 µg NGM, n= 153)
  - 20 cm<sup>2</sup> patch (0.75 mg EE/6.0 mg NGMN, n= 157)
  - 15 cm<sup>2</sup> patch (0.56 mg EE/4.5 mg NGMN, n= 150)
  - 10 cm<sup>2</sup> patch (0.38 mg EE/3.0 mg NGMN, n= 150)
- Endpoints
  - Ovulation rate (<10% in cycles 1 and 3)
  - Breakthrough bleeding/spotting (<15% in cycle 3)
- Result
  - Only the 20 cm<sup>2</sup> patch met both endpoints

22

## Descriptive PK Study: PHI-017

(Two 20 $\mu$ g EE OCs, One Triphasic\* OC and ORTHO EVRA)

- Objective: illustration of concentration-time profiles of oral and transdermal delivery systems
- Not designed as a pivotal trial
- PK results for ORTHO EVRA were consistent with previous studies
- Issue with OC comparison due to comparator doses and AUCs for all 3 OCs ~50% lower than in product labeling

\*Triphasil : 30/40/30  $\mu$ g EE, 50/75/125  $\mu$ g LNG

23

## Comparative PK Study: NED-1 ORTHO EVRA vs. OC

- AUC and  $C_{avg/ss}$ : 60% higher for ORTHO EVRA
- $C_{max}$ : 25% higher for OC
- Higher variability (%CV) for ORTHO EVRA

### Inter-Subject Variability (%CV)

	OC	ORTHO EVRA
$C_{max}$	28%	32%
$AUC_{24}$	27%	33%
$C_{avg/ss}$	27%	33%

24

## Clinical Efficacy Evaluation

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25

### PHASE 3 TRIALS

## Efficacy Results

N = 3,330

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Global, non-comparative study

- 73 sites
- Pearl Index: ORTHO EVRA = **0.71**

North American randomized, controlled study

- 45 sites in US and Canada
- Pearl Index: ORTHO EVRA = **1.24**; Triphasil = **2.18**

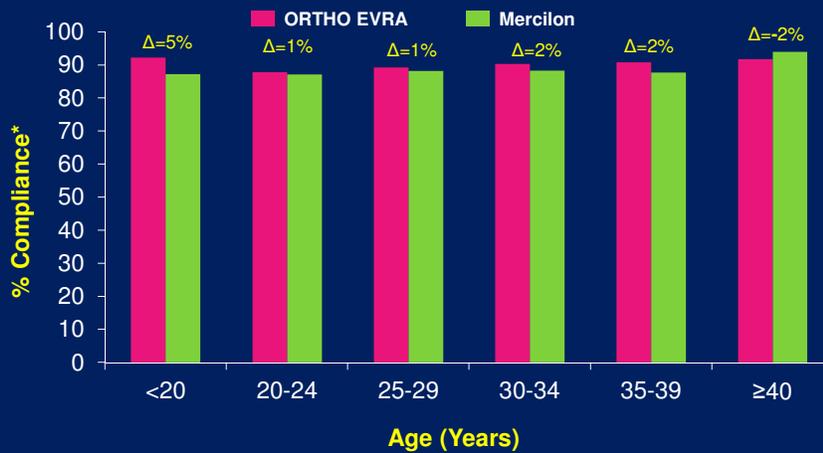
European/South African randomized, controlled study

- 65 sites
- Pearl Index: ORTHO EVRA = **0.88**; Mercilon = **0.56**

Triphasil : 30/40/30 µg EE; 50/75/125 µg LNG  
Mercilon : 20 µg EE; 150 µg DSG (not available in US)

26

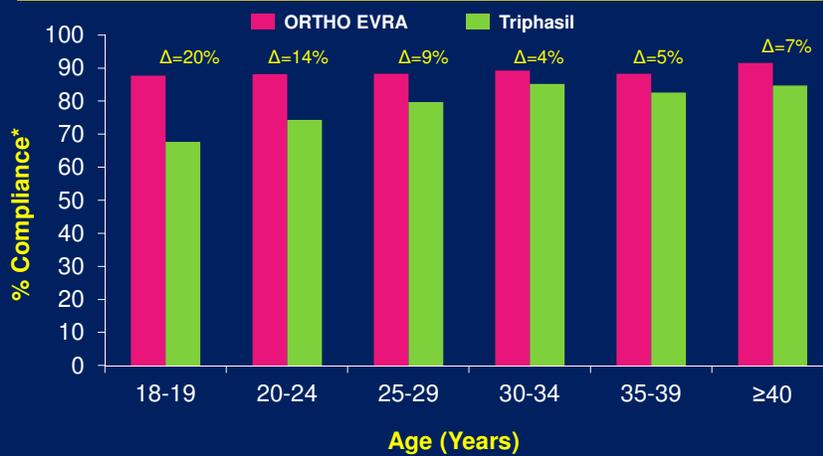
## Compliance by Age Group European/South African Comparative Study



\* Compliance is defined as 21 consecutive days of contraceptive use followed by a 7 day 'hormone-free' period

27

## Compliance by Age Group North American Comparative Study



Compliance is defined as 21 consecutive days of contraceptive use followed by a 7 day 'hormone-free' period

Archer et al. Fertil Steril. 2002 Feb;77(2 Suppl 2):S27-31

28

## Clinical Safety Evaluation

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29

PHASE 3 TRIALS

### Most Common Adverse Events ORTHO EVRA vs. Triphasil

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EVENT	ORTHO EVRA (N = 812)	Triphasil (N = 605)
	Overall	Overall
Headache	22%	22%
Application Site Reaction	20%	n/a
Nausea	20%	18%
Breast Symptoms	19%	6%
Dysmenorrhea	13%	10%
Abdominal Pain	8%	8%

30

## PHASE 3 TRIALS

## Most Common Adverse Events

### ORTHO EVRA vs. Mercilon

EVENT	ORTHO EVRA (N = 846)	Mercilon (N = 643)
	Overall	Overall
Breast Symptoms	25%	6%
Headache	20%	24%
Application Site Reaction	14%	n/a
Nausea	12%	6%
Abdominal Pain	11%	11%
Dysmenorrhea	5%	4%

31

## PHASE 3 TRIALS

## Most Common Adverse Events

### ORTHO EVRA (Single-Arm Study)

EVENT	ORTHO EVRA (N = 1,672)
	Overall
Breast Symptoms	22%
Headache	21%
Application Site Reaction	18%
Nausea	17%
Dysmenorrhea	11%
Abdominal Pain	9%

32

## PHASE 3 TRIALS

## Serious Adverse Events Reported in at Least 2 Subjects

<b>EVENT</b>	<b>ORTHO EVRA</b> N = 3,330	<b>Triphasil</b> N = 605	<b>Mercilon</b> N = 643
Abdominal Pain	0.24% (8)	0.17% (1)	0.30% (2)
Injury	0.18% (6)	0.50% (3)	0
Pneumonia	0.06% (2)	0	0.30% (2)
Pyelonephritis	0.06% (2)	0.33% (2)	0
Abnormal Pap	0.09% (3)	0	0
Cholecystitis	0.06% (2)	0.17% (1)	0
Meningitis	0.06% (2)	0	0
Pulmonary Embolism	0.06% (2)	0	0
<b>TOTAL SUBJECTS w/ SAEs</b>	<b>1.5% (50)</b>	<b>1.8% (11)</b>	<b>2.0% (13)</b>

33

## Pulmonary Embolus Cases Phase 3 Trials

- 30 year-old female with no known risk factors:
  - Developed cough after 8 months of treatment
  - V/Q scan → pulmonary embolus
  - Leg Doppler studies negative
  - Coagulation and autoimmune studies normal
  - Anti-coagulation treatment and resolution
- 34 year-old female with risk factors:
  - Obese (BMI: 32.6 kg/m<sup>2</sup>)
  - Extensive plastic surgery 2.5 months after starting ORTHO EVRA (Bilateral breast augmentation, liposuction, abdominoplasty)
  - Patch removed 1 day before surgery and discontinued
  - Pulmonary embolus diagnosed ~3 weeks post-op
  - Treated and lost to follow-up

34

## Clinical Trial Conclusions

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- Highly efficacious contraceptive
- High rates of compliance across age groups
- Breast symptoms and sometimes nausea more frequent among ORTHO EVRA users
- 2 non-fatal pulmonary emboli in ORTHO EVRA users

35

## Post-marketing Safety Surveillance

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36

## Janssen Safety Surveillance

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- AE reports are received from multiple sources
  - Including patients, healthcare professionals, medical literature, litigation, and regulatory authorities (e.g. FDA)
- Regularly-scheduled reviews of post-marketing safety data are conducted
  - Real-time review of reports of serious adverse events
  - Aggregate reviews from Company safety database
  - Evaluation of product quality reports
  - Data mining of regulatory databases (e.g., FDA AERS)

37

## Findings from Surveillance

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- 2003: Higher number of adverse event reports for ORTHO EVRA compared to the Company's OCs
  - Serious adverse events (e.g. MI, stroke, VTE)
  - Non-serious adverse events (e.g. abdominal pain)

38

## Thrombotic Adverse Events

### Spontaneous Reports Apr. 2002 – Feb. 2004

- Reports of VTE, arterial thrombotic events (i.e., MI, stroke) from April 2002 to February 2004 were reviewed and compared to company OCs
- The numbers of events per 100,000 woman-years (reporting rates) were higher for ORTHO EVRA than the OC comparators
- The number of these events divided by the cumulative events of all serious adverse events for the product (fractional reporting ratios) were similar across the products

<sup>a</sup> Spontaneous reports per cumulative exposure (per 100,000 woman-years)

39

## Stimulated Reporting

- Adverse event reporting is said to be “stimulated” when there is an increase in the number of reports caused by factors unrelated to the true event frequency, such as
  - Recent product approval
  - Media coverage
  - Litigation
  - Direct-to-consumer marketing
  - Release of new safety information
- A challenge in post-marketing safety surveillance is determining whether higher-than-expected report frequency is related to the product or to stimulated reporting

40

## Summary of Post-marketing Surveillance

- Initial signal for thromboembolic events identified in 2003
- Interpretation confounded by stimulated reporting
- Enhanced surveillance implemented
- Results of comparative analyses did not provide consistent answers
- Plan:
  - Continue enhanced surveillance
  - Design and implement epidemiologic studies to evaluate relative risk compared to oral contraceptives

41

## Agenda

Overview	<b>Joanne Waldstreicher, MD</b> Chief Medical Officer <i>Janssen Research &amp; Development, LLC</i>
Clinical Development & Post-Marketing Surveillance	<b>Diane Harrison, MD, MPH, FACOG</b> Global Medical Safety Physician <i>Janssen Research &amp; Development, LLC</i>
<b>Epidemiology</b>	<b>Noel Weiss, MD, DrPH</b> Professor of Epidemiology <i>School of Public Health, University of Washington</i>
<b>Benefit/Risk Assessment</b>	<b>Anita Nelson, MD, FACOG</b> Professor of Obstetrics and Gynecology <i>David Geffen School of Medicine, UCLA</i>
<b>Concluding Remarks</b>	<b>Joanne Waldstreicher, MD</b> Chief Medical Officer <i>Janssen Research &amp; Development, LLC</i>

42

## ORTHO EVRA Epidemiology

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Noel S. Weiss, MD DrPH  
Professor of Epidemiology  
School of Public Health, University of Washington

43

## Disclosures

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- Dr. Weiss has consulted for Janssen Research & Development, LLC on epidemiology related to the safety of ORTHO EVRA

44

## Why Epidemiologic Studies?

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- Clinical trials program too small to estimate rates of uncommon events
- Post-marketing surveillance (of spontaneous adverse event reports) for hypothesis generation – needs confirmatory studies
- Prospective study (stroke + MI + PE) would require many years and a very large sample size
- Long history of using claims databases to study health effects of OCs

45

## Choice of Comparators

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- 2 studies used norgestimate (NGM) containing OCs as comparator for ORTHO EVRA
  - Because Norelgestromin (NGMN) is primary active metabolite of NGM, this comparison focused on delivery method
- 2 studies used levonorgestrel (LNG) containing OCs as the comparator for ORTHO EVRA
  - Levonorgestrel (LNG) deemed “gold standard” for safety by European health authority (lowest VTE risk)
- In another study, BCDSP showed similar VTE risks between NGM-containing OCs and LNG-containing OCs
  - Thus, in terms of progestins, results should be comparable across all studies

46

## Post-marketing Epidemiologic Studies

- Similar designs:
  - Case-control studies nested in the cohort of women 15 – 44 years old exposed to the study medications
  - All subjects had to be members of the health plan for 4 – 6 months prior to the index date (date of case's event)
  - Reported odds ratio (OR) or incidence rate ratio (IRR) for ORTHO EVRA relative to the comparator
  - ORs were to be adjusted for covariates that changed the primary effect estimate by  $\geq 10\%$ , but none were identified

47

## i3 Study Overview

### ORTHO EVRA and NGM-Containing OCs

- Ingenix Research Data Mart April 2002 – December 2006
- Enrollment of 14 million people during the study period
  - 600,000 women exposed to ORTHO EVRA or NGM-containing OCs
- Outcomes – incident cases (as confirmed by chart review) of:
  - Myocardial infarction or Ischemic stroke (combined) – Primary
  - Myocardial infarction
  - Ischemic stroke
  - Venous thromboembolism (VTE)
- Comparators: NGM-containing OCs with 35  $\mu\text{g}$  EE
- Controls matched to cases on birth year, index date, and drug use pattern (new users, switchers, other)

48

## i3 Study Overview Results

### ORTHO EVRA and NGM-Containing OCs

<b>Idiopathic Events</b>	<b>Cases (ORTHO EVRA)</b>	<b>Cases (NGM OC)</b>	<b>OR (95% CI)</b>
Myocardial Infarction + Ischemic Stroke	7	23	1.2 (0.4 – 3.4)
Myocardial Infarction	5	10	1.6 (0.2 – 6.5)
Ischemic Stroke	2	13	0.8 (0.2 – 4.5)
VTE	30	45	2.2 (1.2 – 4.0)

<b>All Events</b>	<b>Cases (ORTHO EVRA)</b>	<b>Cases (NGM OC)</b>	<b>OR (95% CI)</b>
Myocardial Infarction + Ischemic Stroke	7	26	0.9 (0.3 – 2.5)
Myocardial Infarction	5	11	1.2 (0.3 – 4.7)
Ischemic Stroke	2	15	0.6 (0.1 – 3.2)
VTE	39	63	2.0 (1.2 – 3.3)

49

## BCDSP Study Overview

### ORTHO EVRA and NGM-Containing OCs

- PharMetrics Database April 2002 – October 2007
- 83,000 woman-years of ORTHO EVRA exposure
- 141,000 woman-years of NGM-containing OC exposure
- Study limited to new users
- Outcomes - incident idiopathic cases of:
  - Myocardial infarction or Ischemic stroke (combined) – primary outcome
  - Myocardial infarction
  - Ischemic stroke
  - VTE
- Comparators: NGM-containing OCs with 35 µg EE
- Controls matched to cases on birth year and index date

50

## i3 Validation of BCDSP Case Identification Algorithm

- Following chart validation, applied BCDSP algorithm to same i3 dataset
- Positive predictive value of algorithm was 91%

51

## BCDSP Study Results ORTHO EVRA and NGM-Containing OCs

Event*	Cases (ORTHO EVRA)	Cases (NGM OC)	Crude IRR (95% CI)
Myocardial Infarction + Ischemic Stroke	9	17	0.8 (0.3 – 1.9)
Myocardial Infarction	1	7	0.2 (0.004 – 1.7)
Ischemic Stroke	8	10	1.2 (0.4 – 3.4)

\* These estimates are for April 2002 – March 2005.

Event	Cases (ORTHO EVRA)	Cases (NGM OC)	OR (95% CI)
VTE	70	92	1.2 (0.9 – 1.8)

52

## BCDSP Study Overview

### ORTHO EVRA and LNG-Containing OCs

- Women aged 15- 44 current new users of either ORTHO EVRA or OCs with levonorgestrel (LNG) and 30 µg EE
- **PharMetrics Database**
  - April 1, 2002 - March 31, 2006
  - 186,148 women exposed to either of the study medications
    - LNG-containing OCs: 42,153 woman-years
    - ORTHO EVRA : 53,755 woman-years
  - 46 VTE cases and 207 controls

53

## BCDSP Study Results

### ORTHO EVRA and LNG-Containing OCs

	Cases (ORTHO EVRA)	Cases (LNG OC)	IRR (95% CI)
<b>Arterial events</b>			
Myocardial Infarction	1	3	0.2 (0.03 – 1.6)
Ischemic Stroke	5	7	0.5 (0.2 – 1.5)
	Cases (ORTHO EVRA)	Cases (LNG OC)	OR (95% CI)
VTE	30	16	2.0 (0.9 – 4.1)

54

## BCDSP Study Overview

### ORTHO EVRA and LNG-Containing OCs

- Women aged 15-44 current new users of either ORTHO EVRA or OCs with levonorgestrel (LNG) and 30 µg EE
- **MarketScan Database**
  - April 1, 2002 – December 31, 2007
    - LNG-containing OCs: 251,001 woman-years
    - ORTHO EVRA: 186,473 woman-years
  - 100 VTE cases and 394 controls

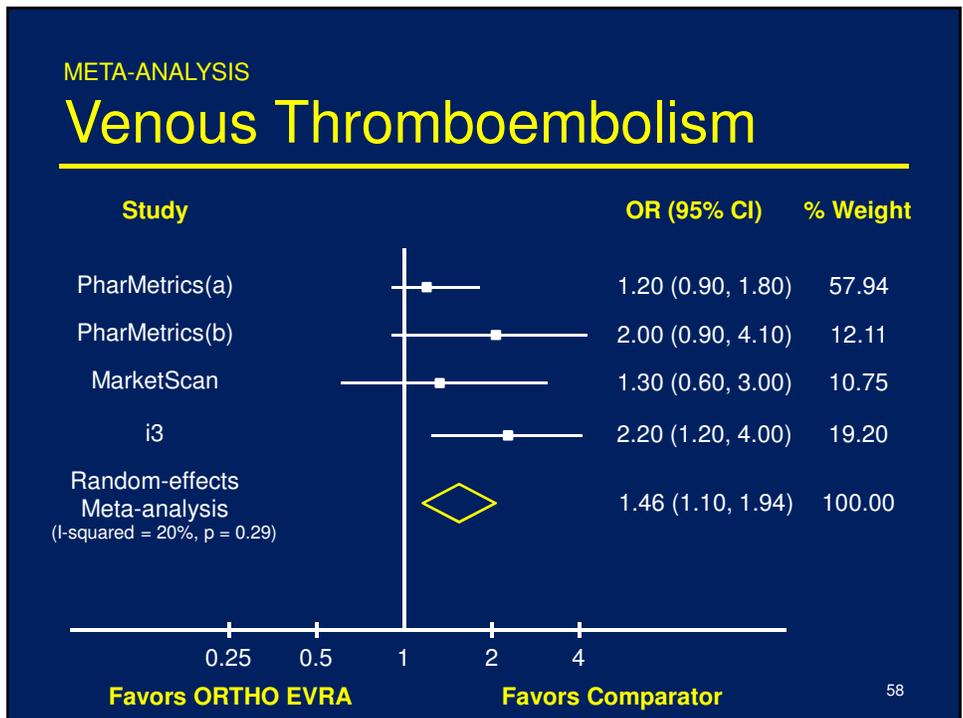
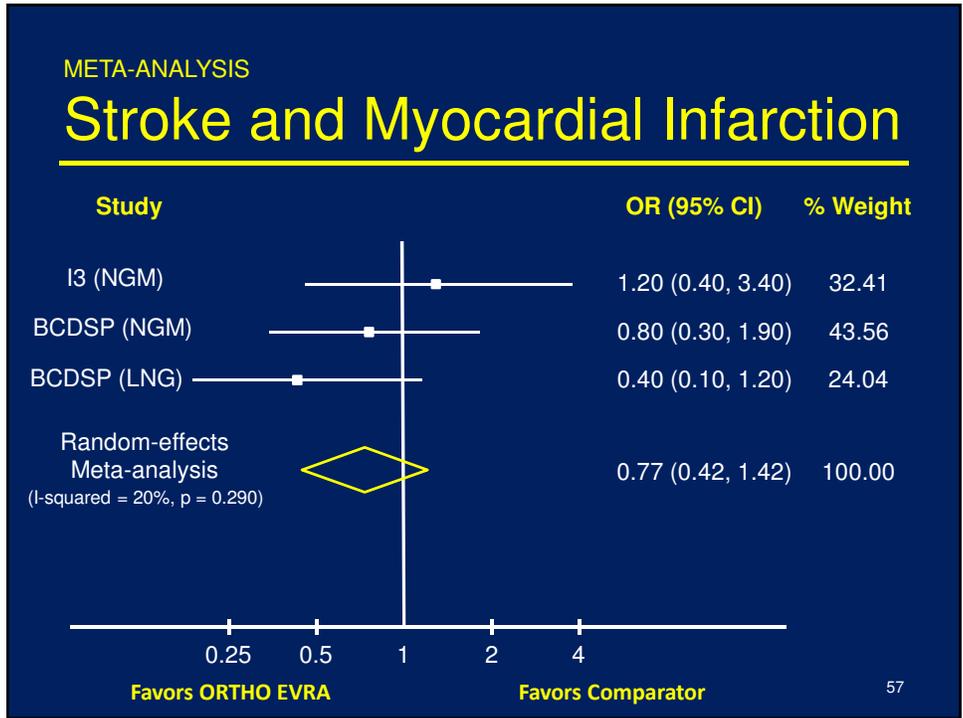
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## BCDSP Study Results

### ORTHO EVRA and LNG-Containing OCs

	Cases (ORTHO EVRA)	Cases (LNG OC)	OR (95% CI)
VTE All Ages	48	52	1.3 (0.8 – 2.1)

56



## FDA-Sponsored Study (CHCs and the Risk of CVD Endpoints): Overview

- Endpoints: VTE, MI, ischemic stroke
  - Hospitalized cases (all MI, all ischemic stroke, and some VTE): Confirmed from hospital records
  - Outpatient cases (VTE): Chart confirmation for those from Kaiser Northern CA, with 89% positive predictive value
- Comparators
  - Mixed oral contraceptives (30% with 20 µg EE)
  - Levonorgestrel with 30 µg EE

59

## Relative Hazard of ATE and VTE

ORTHO EVRA vs. combined oral contraceptive comparators

	ATE	VTE
All Users	1.31 (0.63, 2.74)	1.55 (1.17, 2.07)
New Users	1.07 (0.36, 3.23)	1.35 (0.90, 2.02)

ORTHO EVRA vs. 30 µg EE – LNG oral contraceptive

	ATE	VTE
All Users	1.14 (0.52, 24.8)	1.34 (0.97, 1.83)
New Users	0.9 (0.28, 2.91)	1.19 (0.75, 1.87)

FDA-sponsored study, 2011

60

## FDA-Sponsored Study VTE Results by Duration of Use

- Hazard ratio (adjusted) ORTHO EVRA vs. Comparator OCs
  - Use for < 3 months 1.58 (0.91, 2.77)
  - Use for 3-6 months 0.89 (0.33, 2.41)
  - Use for 7-12 months 0.39 (0.09, 1.72)
  - Use for >12 months 3.05 (1.23, 7.53)

61

## Long-term Use in FDA Study

- Is there reason to believe that the increased risk of VTE is particularly high among women who have used ORTHO EVRA for more than a year?

62

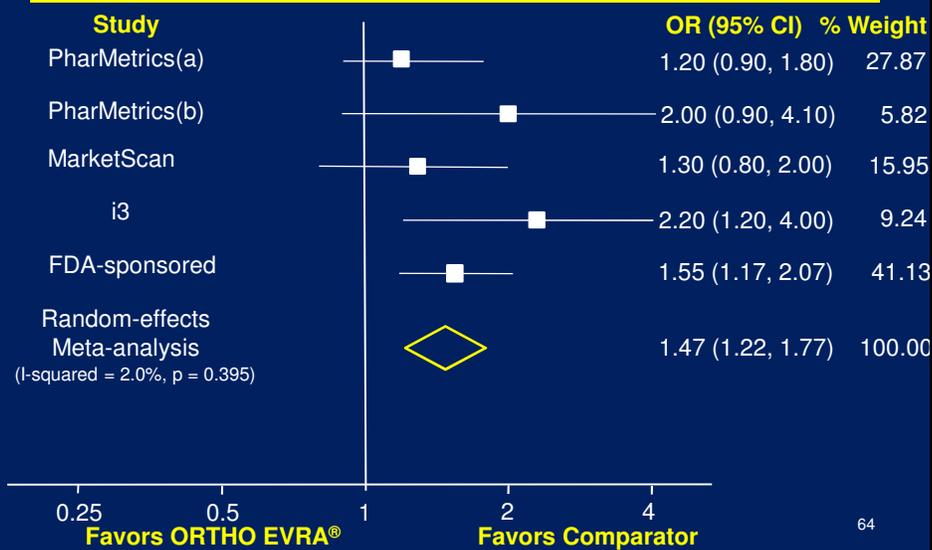
## Long-term Use: Interpretation

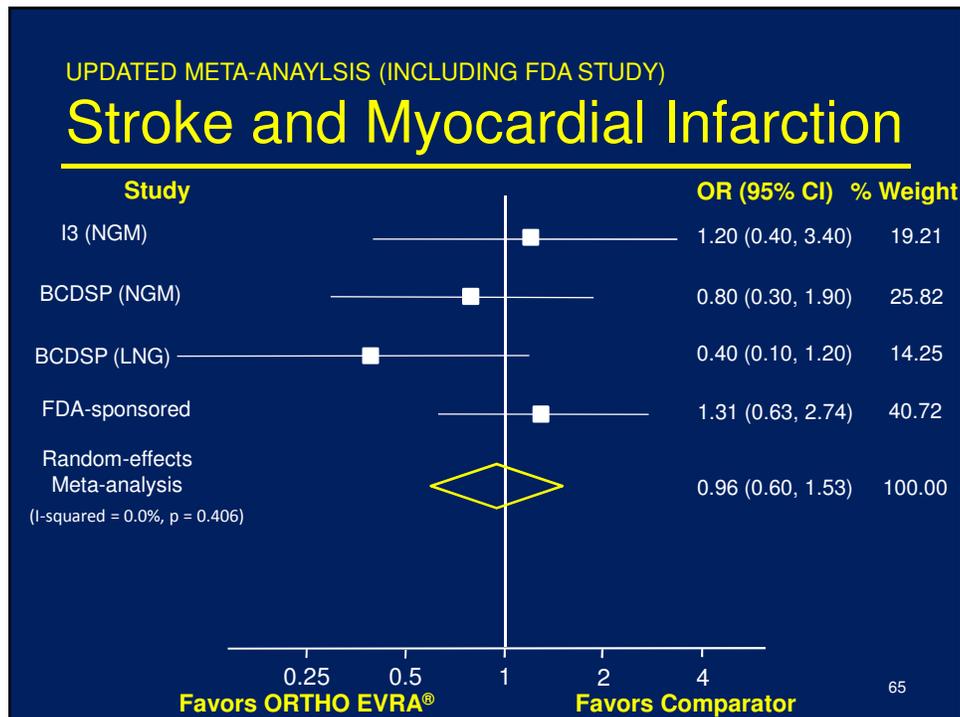
- Many subgroups were examined in the FDA-sponsored study, affecting the interpretation of statistically “significant” results in any one subgroup
- No hint of an increased risk was present in women who used ORTHO EVRA for 3-12 months
- The association between the use of other hormonal contraception and VTE has been assessed many times, and appears not to be duration-dependent
- The i3 study did not observe an influence of duration of use on the association between use of ORTHO EVRA and VTE

63

UPDATED META-ANALYSIS (INCLUDING FDA STUDY)

## Venous Thromboembolism





## Limitations of Claims Database Studies

- Medical claims databases did not identify deaths that occurred outside the context of the medical care system
- Several potentially important confounders were not captured or were not adequately captured (e.g., smoking, obesity, professional sampling)
  - Bias could go in either direction

## Absolute Rate of VTE

- VTE rate among women using NGM-containing OCs:  
~ 6/10,000 woman-years
- Assuming OR = 1.5, VTE rate among women using  
ORTHO EVRA is 9/10,000 woman-years
- Excess events: 3 per 10,000 woman-years
- This would require 3,333 women using OE for a year to  
give an extra event, assuming the increased VTE rate  
with ORTHO EVRA is causal

Assumptions for computational purposes only

67

## Agenda

Overview	<b>Joanne Waldstreicher, MD</b> Chief Medical Officer <i>Janssen Research &amp; Development, LLC</i>
Clinical Development & Post-Marketing Surveillance	<b>Diane Harrison, MD, MPH, FACOG</b> Global Medical Safety Physician <i>Janssen Research &amp; Development, LLC</i>
Epidemiology	<b>Noel Weiss, MD, DrPH</b> Professor of Epidemiology <i>School of Public Health, University of Washington</i>
<b>Benefit/Risk Assessment</b>	<b>Anita Nelson, MD, FACOG</b> Professor of Obstetrics and Gynecology <i>David Geffen School of Medicine, UCLA</i>
<b>Concluding Remarks</b>	<b>Joanne Waldstreicher, MD</b> Chief Medical Officer <i>Janssen Research &amp; Development, LLC</i>

68

## Benefits and Risks of the ORTHO EVRA Transdermal Contraceptive System: The Importance of Choice

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Anita L. Nelson, MD, FACOG  
Professor, Department of OB-GYN  
David Geffen School of Medicine at UCLA

69

## Importance of Family Planning

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- CDC recognized family planning as one of the 10 greatest public health initiatives of the 20<sup>th</sup> century<sup>1</sup>
- Contraception contributes significantly to all 8 of the Millennium Development Goals<sup>2</sup>
- Expanded use of contraception has been credited with saving over 1 million lives worldwide, 1990-2005<sup>3</sup>

<sup>1</sup>MMWR *Morb Mortal Wkly Rep.* 1999(12):241-3; <sup>2</sup>Cates W. *Contraception.* 2010;(16):460-1;  
<sup>3</sup>Stover J, Ross J. *Matern Child Health J.* 2010;(5):687-95

70

## Importance of Contraceptive Choice

- Selection of a birth control method is complex
  - No “universal best option” for birth control
- Best option is the safest, most effective method that the couple will use correctly and consistently
- Women are more apt to correctly use methods that they want to use
- Choice is more important in contraception than in any other area of medicine
- More at stake than just the patient’s health
  - Social, economic and environmental impacts
- IOM endorsement of options<sup>1</sup>

<sup>1</sup>IOM (Institute of Medicine). 2011. *Clinical Preventive Services for Women: Closing the Gaps*.

71

## Contraceptive Options

Contraceptive Method	Dosing Frequency	First Year Failure Rates in Typical Use
Implant	3 years	0.05%
Intrauterine devices	5-10 years	<1.0%
Injections	3 months	6.0%
Oral contraceptives	Daily	9.0%
ORTHO EVRA patch	Weekly	9.0%
Vaginal ring	Monthly	9.0%
Male condoms	With each act	18.0%
Fertility awareness	With each act	24.0%
No Method	- - -	85.0%

Trussel J et al. *Contraceptive Technology*. 2011: 791

72

## Individualizing Contraceptive Choice

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- No contraception is as hazardous as pregnancy
- Medical eligibility simplified by CDC MEC<sup>1</sup>
  - Evidence-based recommendations
  - Endorsed by ACOG<sup>2</sup>
- US MEC recommendations for women with VTE risk are the same for pills and the patch
- Practice challenge
  - To determine which of the eligible methods will be used most effectively by the patient

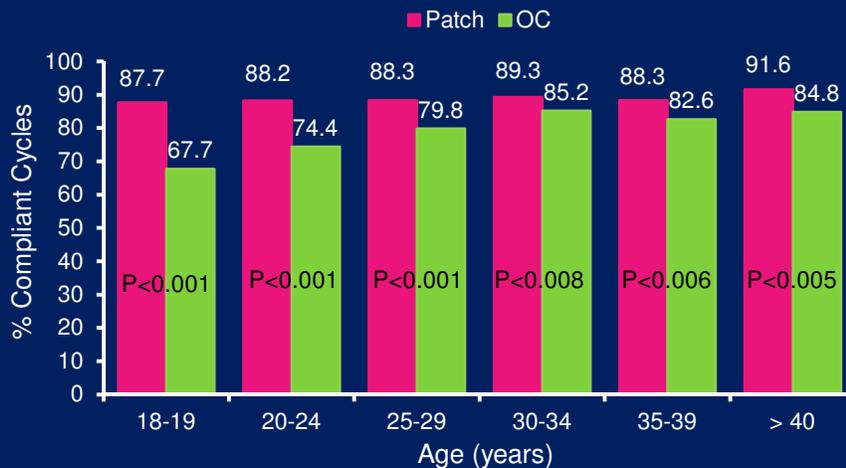
<sup>1</sup>CDC US Medical Eligibility Criteria for Contraceptive Use: MMWR 2010;59(No.RR-4)  
<sup>2</sup>ACOG Committee Opinion 506; September 2011

## Transdermal Patch Properties

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- Unique dosing schedule
  - Once-a-week application for convenience
- Unique transdermal system
  - Facilitates verifiability
  - Enables women who can't take pills for medical reasons to use combined hormonal contraception
- Safe and effective method for women who choose transdermal contraception

## Contraceptive Patch vs. Pills: Successful Utilization by Age Group



Archer D, et al. *Contraception*. 2004;69(3):189-95

75

## Patch vs. Pills: Development Clinical Trials

- No difference in efficacy seen in clinical trials
  - Subjects had to be willing to be randomized to use patch or pill
- Discontinuation rates higher among patch users
  - Patch was new
- Estrogen-related side effect differences resolve early. Related to complex factors
  - Not a surrogate for high serum estrogen levels
  - Not predictive of longer-term health impacts

76

## Real World Utilization

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- Difficult to take daily medication for any asymptomatic condition
- In the third cycle of COCs, >50% of women missed 3 or more pills<sup>1</sup>
  - Inconsistent use contributes to 1 million pregnancies each year in US pill users
- Inconsistent use → spotting → stopping pills
  - Median time to pregnancy: 2.5-3 cycles<sup>2</sup>
  - Mean time to new effective method: 5 months<sup>3</sup>

<sup>1</sup>Potter L et al. *Fam Plann Perspect.* 1996;28(4):154-8

<sup>2</sup>Mansour D et al. *Contraception.* 2011;85(5):465-77

<sup>3</sup>Frost JJ et al. *Perspect Sex Reprod Health.* 2007;39(1):48-55

## Identifying Patch Candidates

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- Consider the woman's medical eligibility
- Offer top tier options (Implants and IUDs)
- If desires combined hormonal method, ask
  - “Do you think you will be able to take a pill at the same time each day?”
- If she is concerned about her ability to do so, we offer transdermal or vaginal methods
- Virtually all patch users have used other methods
  - 70% have used other hormonal methods

## Real Life Satisfaction Assessments

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- 2004 National Health and Wellness Survey
  - Patch satisfaction was at least as high as with pills<sup>1</sup>
- International studies of women who used a transdermal contraceptive patch consistently reported higher satisfaction among patch users, especially among women who switched from pills<sup>2,3</sup>

<sup>1</sup>Wan GJ et al. *Contraception*. 2007;(4):281-4

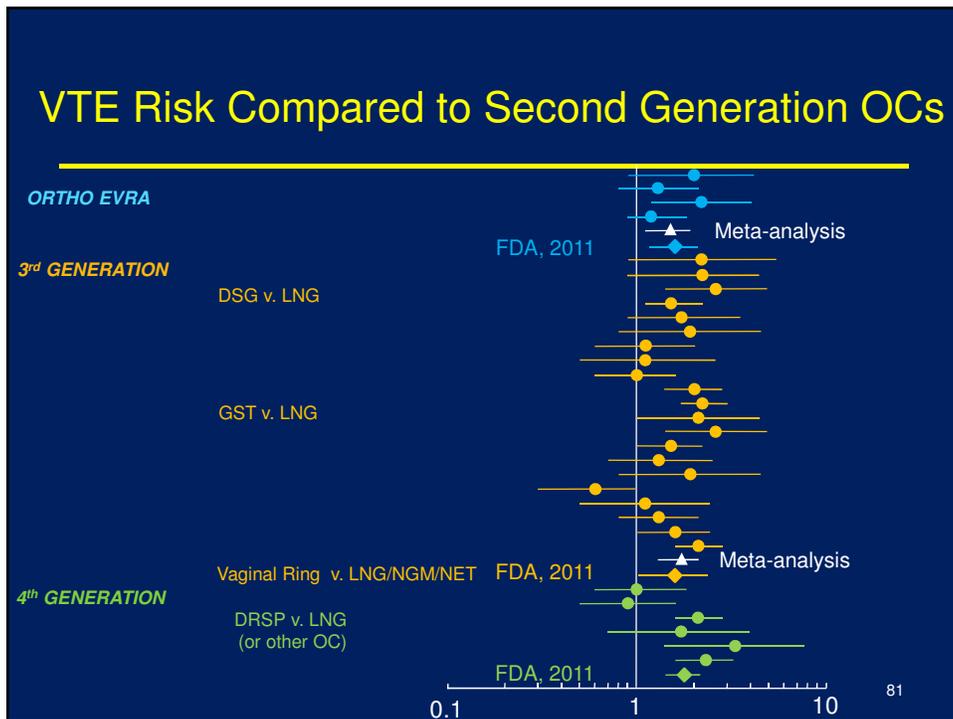
<sup>2</sup>Crosignani PG et al. *Gynecol Endocrinol*. 2011;(10):849-56

<sup>3</sup>Weisberg F et al. *J Obstet Gynaecol Can*. 2005;(4):350-9

## Patch Benefits Many Women

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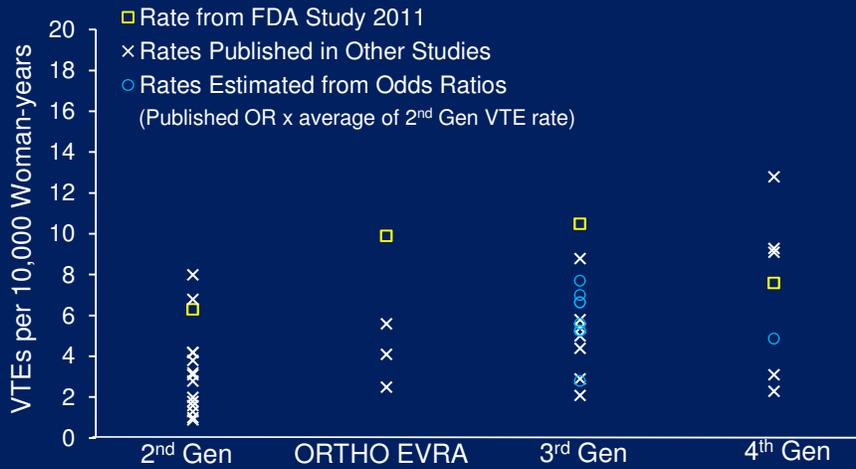
- Patch meets needs of women who want to use hormonal contraception and who...
  - Benefit from its convenient once-weekly dosing
    - Are challenged by daily pill use
    - Have “failed” pills in the past
  - Appreciate verifiability of patch
- Neither more motivation nor education is likely to transform these women into successful pill users
  - Contraceptive failure exposes women to significant health risks



## Describing Risks to Patients

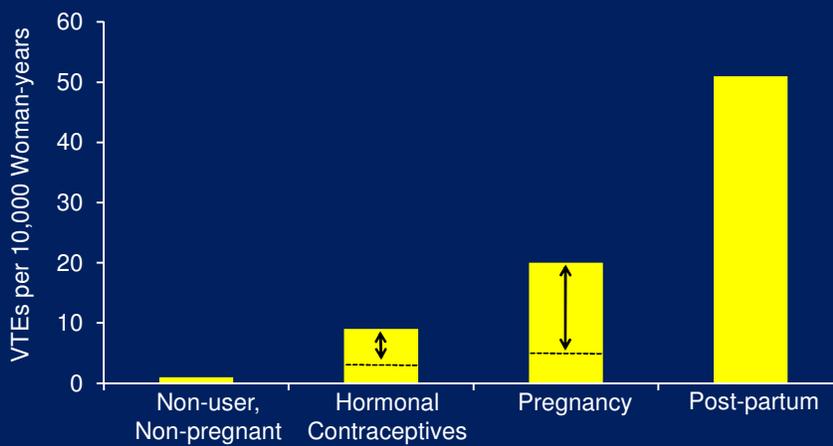
- Risk communication is critical to informed decision-making
- Absolute risks are the statistics both patients and the public need to know
  - What is the actual risk that they will experience a blood clot both...
    - With the method they are considering and
    - With the alternatives they face with non-use

## Absolute VTE Rates Among CHC Users Unadjusted Rates from Studies Published Jan 1995 – Nov 2011



83

## Absolute VTE Rates



ACOG Practice Bulletin 123, September 2011  
 Heit et al, Ann Intern Med. 2005;143:697-706

84

## Why Contrast Patch Risks to Pregnancy Risk?

- Claim: “She can always use another method”
- Not borne out by facts
  - Women who discontinue pills often do not adopt any other method or they turn to less effective methods<sup>1</sup>
  - 2002 NSFP: after pill discontinuation<sup>2</sup>
    - 63.1% used other method within 1 month
    - 21.7% got pregnant
  - Average gap to effective method – 5 months<sup>3</sup>

<sup>1</sup>Rosenberg MJ et al. *Am J Obstet Gynecol.* 1998;17(3 Pt1):577-8

<sup>2</sup>Vaughan B et al. *Contraception.* 2008;78(4):271-84

<sup>3</sup>Frost JJ et al. *Perspect Sex Reprod Health.* 2007;39(1):48-55

85

## Putting Risks into Context in the United States

- Pregnancy with unprotected intercourse
  - 85% in 12 months
- Maternal mortality: 14.5:100,000 live births<sup>1</sup>
- Another 34,000 experience “near misses”<sup>2</sup>
- 13% of pregnant women hospitalized for complications at least once<sup>3</sup>
- Annual mortality rate: healthy, non-smoking women age 15-34 due to OCs
  - Less than 1 woman in 1 million<sup>4</sup>

<sup>1</sup>WHO Trends in Maternal Mortality 2008 WHO Press Geneva 2010

<sup>2</sup>Kuklina EV et al. *Obstet Gynecol.* 2009;13(2pt1):293-9293

<sup>3</sup>Bacak SJ et al. *Am J Obstet Gynecol.* 2005;192:592-597

<sup>4</sup>Trussell J et al. *Contraception.* 2006;(5):437-9

86

## Current Understanding of Risks

- Women significantly over-estimate health risks of hormonal contraception
  - 76% of women surveyed rated pills as more hazardous to women's health than pregnancy<sup>1</sup>
- Women significantly under-estimate the health risks of pregnancy
  - 30% surveyed did not know that pregnancy increases risks of blood clots<sup>1</sup>

<sup>1</sup>Nelson AL, Rezvan A. *Contraception* 2012, in press

## Interpretation of Findings

- Unfavorable news about contraceptive safety may inflate women's existing anxiety
  - Especially if not put into context of alternative risks
- May well increase unintended pregnancies and abortions
- Pattern seen in UK and Norway following "pill scare" with third generation formulations
  - Unintended pregnancy and abortion rates increased for several years<sup>1</sup>
  - No decline in VTE rates seen<sup>2</sup>

<sup>1</sup>Szarewski A et al. *Hum Reprod Update*. 1999;(6):627-32

<sup>2</sup>Farmer RD et al. *BMJ*. 2000;(7259):477-9

## Closing Comments

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- Planning and preparing for pregnancy optimizes pregnancy outcomes
  - Unintended pregnancies pose significant health hazards to both the woman and to her fetus
  - Pregnancies that are not planned and prepared for also have adverse social and environmental impacts
- Contraception enables women to prepare for pregnancy

89

## Closing Comments

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- All contraception has risks
- Health risks associated with hormonal contraception are substantially less than the health risks of pregnancy
- ORTHO EVRA has a risk profile comparable to many other hormonal contraceptives
- Contraceptive success requires a comprehensive array of options
  - Need to maintain and expand couples' options

90

## Closing Comments

- ORTHO EVRA is a unique birth control method that meets the needs of specific women
  - Convenience and ease of use
  - Verifiability
- Selection of a method that best prevents pregnancy is most effectively made by each woman working with her health care provider
- How we discuss risks with patients and with the public can have both profound impacts and unintended consequences

91

## Agenda

Overview	<b>Joanne Waldstreicher, MD</b> Chief Medical Officer <i>Janssen Research &amp; Development, LLC</i>
Clinical Development & Post-Marketing Surveillance	<b>Diane Harrison, MD, MPH, FACOG</b> Global Medical Safety Physician <i>Janssen Research &amp; Development, LLC</i>
Epidemiology	<b>Noel Weiss, MD, DrPH</b> Professor of Epidemiology <i>School of Public Health, University of Washington</i>
Benefit/Risk Assessment	<b>Anita Nelson, MD, FACOG</b> Professor of Obstetrics and Gynecology <i>David Geffen School of Medicine, UCLA</i>
<b>Concluding Remarks</b>	<b>Joanne Waldstreicher, MD</b> Chief Medical Officer <i>Janssen Research &amp; Development, LLC</i>

92

## Concluding Remarks

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Joanne Waldstreicher, MD  
Chief Medical Officer,  
Janssen Research & Development, LLC

93

## Concluding Remarks

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- ORTHO EVRA VTE risk in meta-analysis and FDA-commissioned study:
  - Nearly identical (Odds Ratios: 1.5 vs. 1.55)
  - Higher than LNG- and NGM-containing OCs
  - In the range of other combined hormonal contraceptives

94

# ORTHO EVRA

## Indications and Usage

Renal and Hepatic Impairment  
 No formal studies were conducted with ORTHO EVRA<sup>®</sup> to evaluate the

ORTHO EVRA<sup>®</sup> is indicated for the prevention of pregnancy in women who elect to use a transdermal patch as a method of contraception.

The pharmacokinetic profile for the ORTHO EVRA<sup>®</sup> transdermal patch is different from that of an oral contraceptive. Healthcare professionals should balance the higher estrogen exposure and the possible increased risk of venous thromboembolism with ORTHO EVRA<sup>®</sup> against the chance of pregnancy if a contraceptive pill is not taken daily.

Weight  
 The greater proportion of pregnancies among women at or above 198 lbs. was statistically significant and suggests that ORTHO EVRA<sup>®</sup> may be less effective in these women.  
 Healthcare professionals who consider ORTHO EVRA<sup>®</sup> for women at or above 198 lbs. should discuss the patient's individual needs in choosing the most appropriate contraceptive option.

# ORTHO EVRA Labeling

## Boxed Warning: Risk of VTE

ORTHO EVRA<sup>®</sup>  
 (norelgestromin / ethinyl estradiol  
 TRANSDERMAL SYSTEM)  
**WARNING: RISK OF VENOUS THROMBOEMBOLISM AND PHARMACOKINETIC**

### Risk of Venous Thromboembolism

The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA<sup>®</sup> patch compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel or norgestimate was assessed in four U.S. case-control studies using electronic healthcare claims data. The odds ratios ranged from 1.2 to 2.2; one of the studies found a statistically significant increased risk of VTE for current users of ORTHO EVRA<sup>®</sup>.

# Current Product Labeling

Epidemiologic Study	Comparator Product	Odds Ratio (95% CI)
i3 Ingenix NGM Study in Ingenix Research Datamart	NGM/35 µg EE	2.2 (1.2-4.0) *
BCDSP NGM Study in Pharmetrics Database	NGM/35 µg EE	1.2 (0.9-1.8)
BCDSP LNG Study in Pharmetrics Database	LNG/30 µg EE	2.0 (0.9-4.1)
BCDSP LNG Study in MarketScan Database	LNG/30 µg EE	1.3 (0.8-2.0)

\* Increase in risk of VTE is statistically significant

97

# Detailed Patient Labeling – Other Considerations

- Hepatitis or yellowing of the whites of your eyes or pregnancy or during previous use of hormone ORTHO EVRA®, NORGESTIMATE®, or the birth control
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy
- Severe high blood pressure
- Diabetes with complications of the kidneys, eyes, or
- Headaches with neurological symptoms
- Use of oral contraceptives (birth control pills)
- Disease of heart valves with complications
- Need for a prolonged period of bed rest following an
- An allergic reaction to any of the components of OR

Tell your healthcare professional if you have ever had healthcare professional can recommend a non-hormonal

**OTHER CONSIDERATIONS BEFORE USING OR**  
Hormones from ORTHO EVRA® get into the blood by the body differently than hormones from birth exposed to about 60% more estrogen if you use OR a typical birth control pill containing 35 micrograms increased estrogen may increase the risk of side effects.

The risk of venous thromboembolic events (blood clot may be increased with ORTHO EVRA® use compared Studies examined the risk of these serious blood clot ORTHO EVRA® or birth control pills containing (levonorgestrel or norgestimate) and 30-35 micrograms studies ranged from an approximate doubling of risk increase in risk in women using ORTHO EVRA® use control pills.

You should discuss this possible increased risk with before using ORTHO EVRA®. Call your healthcare professional of the adverse side effects listed under "WARNING SIGNALS" using ORTHO EVRA®. (See below.)

Also talk to your healthcare professional about using OR

## OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA®

Hormones from ORTHO EVRA® get into the blood stream and are processed by the body differently than hormones from birth control pills. You will be exposed to about 60% more estrogen if you use ORTHO EVRA® than if you use a typical birth control pill containing 35 micrograms of estrogen. In general, increased estrogen may increase the risk of side effects.

The risk of venous thromboembolic events (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA® use compared with use of birth control pills. Studies examined the risk of these serious blood clots in women who used either ORTHO EVRA® or birth control pills containing one of two progestins (levonorgestrel or norgestimate) and 30-35 micrograms of estrogen. Results of these studies ranged from an approximate doubling of risk of serious blood clots to no increase in risk in women using ORTHO EVRA® compared to women using birth control pills.

You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA®. Call your healthcare professional immediately if any of the adverse side effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA®. (See below.)

Reference ID: 2379249

98

## Detailed Patient Labeling – Risk of Blood Clots

- you smoke
- you are recovering from the birth of a baby

The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA<sup>®</sup> compared with that of oral contraceptives containing norgestimate and 35 micrograms of estrogen (see the earlier section).

### 1. Risk of Developing Blood Clots

Blood clots and blockage of blood vessels that can cause death or serious disability are some of the most serious side effects of using hormonal contraceptives, including the ORTHO EVRA<sup>®</sup> contraceptive patch. In particular, a clot in the legs can cause thrombophlebitis, and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision. The risk of venous thromboembolic disease (blood clots in the legs and/or the lungs) may be increased with ORTHO EVRA<sup>®</sup> compared with that of oral contraceptives containing norgestimate and 35 micrograms of estrogen (see the earlier section OTHER CONSIDERATIONS BEFORE USING ORTHO EVRA<sup>®</sup>). You should discuss this possible increased risk with your healthcare professional before using ORTHO EVRA<sup>®</sup>. Call your healthcare professional immediately should any of the adverse effects listed under "WARNING SIGNALS" occur while you are using ORTHO EVRA<sup>®</sup>.

the ORTHO EVRA<sup>®</sup> contraceptive patch. In particular, a clot in the legs can cause thrombophlebitis, and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

Pain, loss of vision, or any eye pain with ORTHO EVRA<sup>®</sup> contraceptive patch use may indicate an increased risk of developing liver cancer. However, liver cancer is rare.

Reference ID: 2079249

32

Reference ID: 2079249

33

99

## Detailed Patient Labeling – Warning Signals Including...

- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or tightness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)

### WARNING SIGNALS

If any of these adverse effects occur while you are using ORTHO EVRA<sup>®</sup>, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or tightness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)

3. Vaginal Bleeding  
Irregular vaginal bleeding or spotting may occur while you are using ORTHO EVRA<sup>®</sup>. Irregular bleeding may vary from light staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding may occur during the first few months of contraceptive patch use but may also occur after you have been using the contraceptive patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using your contraceptive patches on schedule. If the bleeding occurs in more than a few cycles or lasts for more than a few days, talk to your healthcare professional.

Reference ID: 2079249

36

100

## Concluding Remarks

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- A wide array of safe and effective contraceptive options is needed
- Choose method best suited for the individual woman
  - Based on medical history, non-medical needs and product attributes
- ORTHO EVRA:
  - Is a unique contraceptive option (transdermal, weekly dosing schedule)
  - Contains a unique Indication, Warnings and Precautions
  - Is for women who elect to use a transdermal patch

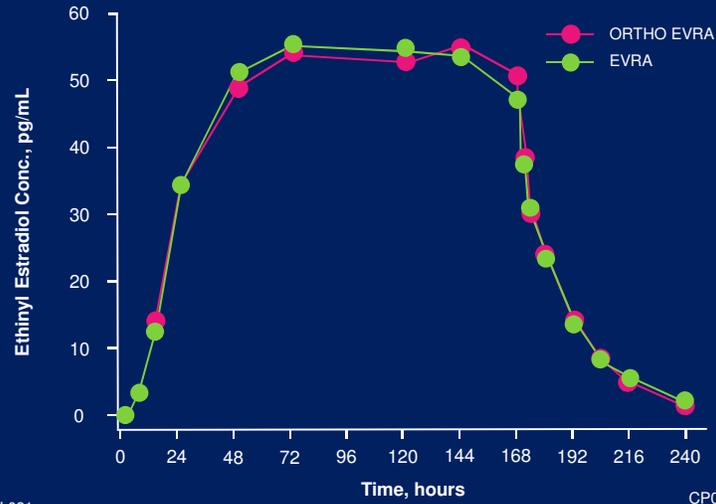
101

## Back-up Slides

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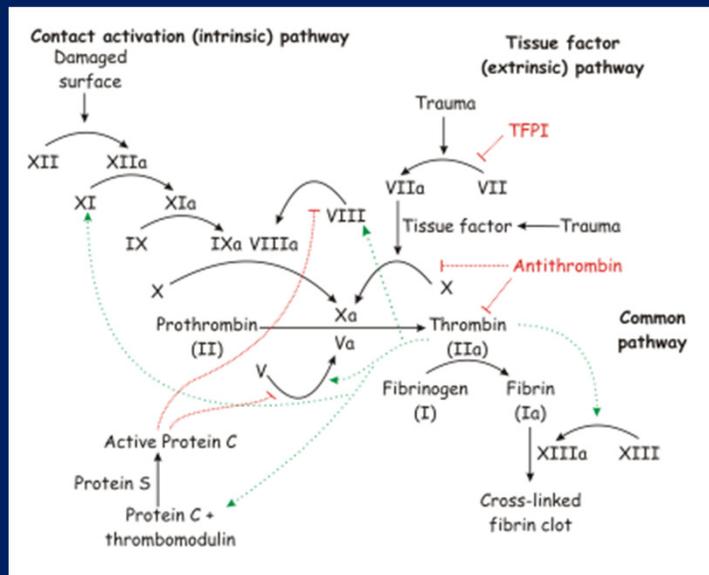
102

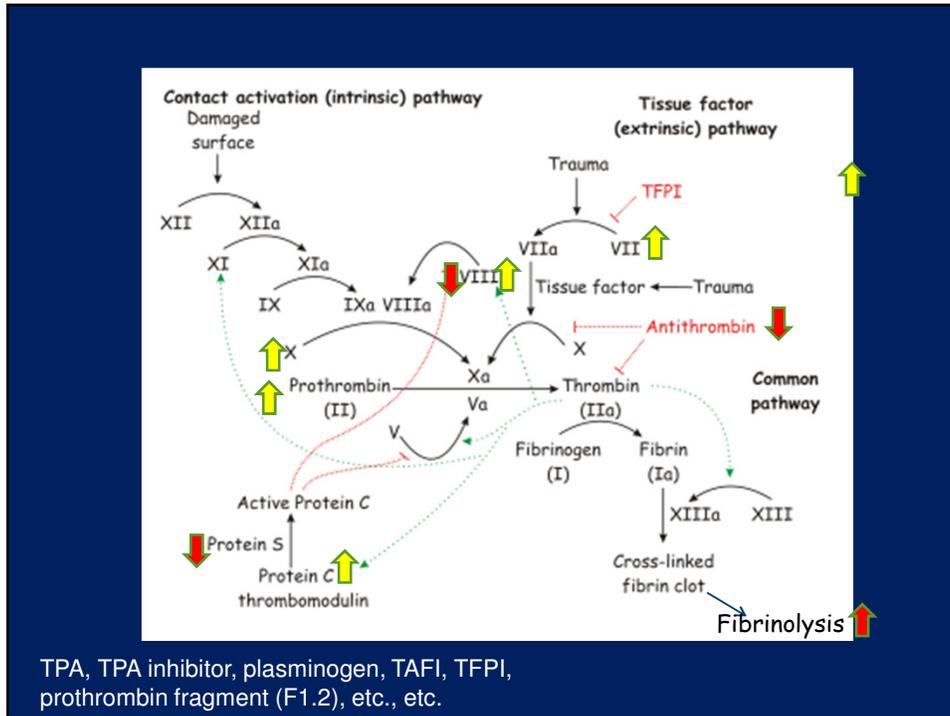
## EE Concentrations are Comparable for ORTHO EVRA & EVRA



Study PHI-021

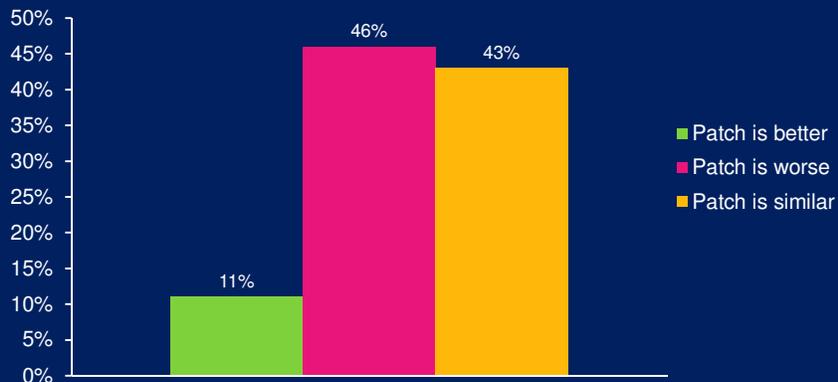
CP015 - 103





## Prescribers' Perception of VTE with ORTHO EVRA Compared to OCs

How Patch Compares to Pills: Risk of VTEs (n=127)



SRVY - 106

## Survey Results: Patients

- Primary reason for selecting the patch varied across patients; convenience features were the primary drivers for patch use for a majority of patients

<b>Reason Patch was Selected</b>	<b>% of Patients (n=200)</b>
Don't have to remember to take a pill every day	27%
Convenience/once a week dosing	11%
Don't have to swallow pills	8%
Don't have to take a pill at the same time every day	7%
<b>Total</b>	<b>53%</b>

- "Newer" patch patients (<2 years) were more motivated by opportunity to avoid having to swallow pills
- Not having to remember to take a daily pill was the most frequent reason for patch selection among patients who have tried other contraceptive methods (34%)

SRVY - 107