SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	RWJ10553 (EVRA®)

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Status: Approved

Date: 19 October 2018

Prepared by: Janssen Research & Development, LLC

Protocol No.: RWJ10553CON4001

Title of Study: A Randomized, Double-blind, 2-Way Crossover, Bioequivalence and Adhesion Study of a Transdermal Contraceptive Patch Manufactured With Newly Sourced Adhesive Components and Currently Marketed EVRA® in Healthy Adult Women

EudraCT NUMBER: 2017-002186-22

NCT No.: NCT03274297

Clinical Registry No.: CR108360

Principal Investigator: Freya Rasschaert, MD

Study Center: The study was conducted at a single center in Belgium - Clinical Pharmacology Unit, Janssen R&D, [redacted] Belgium

Publication (Reference): None

Study Period: 28 September 2017 to 07 May 2018

Phase of Development: 4

Objectives:

Primary Objectives

The primary objectives were:

- To determine the bioequivalence of the hormones (ie, norelgestromin [NGMN] and ethinyl estradiol [EE]) from the transdermal contraceptive patch using the newly sourced adhesive component, as compared to the currently marketed EVRA patch.
- To evaluate the adhesion of the transdermal contraceptive patch using the newly sourced adhesive component, as compared to the currently marketed EVRA patch.

Secondary Objectives

The secondary objectives were:

- To evaluate the irritation potential of the transdermal contraceptive patch using the newly sourced adhesive component, as compared to the currently marketed EVRA patch.
- To assess the safety and tolerability of the transdermal contraceptive patch using the newly sourced adhesive component and the currently marketed EVRA patch.

Hypotheses

- The transdermal contraceptive patch using the newly sourced adhesive component (test contraceptive patch) is bioequivalent to the currently marketed EVRA patch (reference contraceptive patch) based on steady-state concentrations (C_{ss}) and area under the plasma concentration-time curves (AUCs; AUC from time 0 [patch application] to time 168 hours postdose [AUC_{168h}] and AUC from time 0 [patch application] to infinite time [AUC_{∞}]) for NGMN and EE.
- The ratios of the mean cumulative adhesion percentage values of the test to reference contraceptive patch will be greater than or equal to 90%.

Methodology: This was a randomized, double-blind, single-center, 2-way crossover, bioequivalence and adhesion study of a single 7-day application of a transdermal contraceptive patch using a newly sourced adhesive component (test contraceptive patch) and the currently marketed EVRA patch (reference contraceptive patch).

Subjects received both of the following treatments:

- **Treatment A**: Single 7-day application of the currently marketed EVRA patch (reference)
- **Treatment B**: Single 7-day application of the transdermal contraceptive patch using the newly sourced adhesive component high molecular weight polyisobutylene (HMW PIB) (test)

The study consisted of a screening phase (within 28 days before patch application on Day 1 of Treatment Period 1), a double-blind treatment phase of 11 days for each period with 7-day single-application of the test or reference patch, and a 21-day washout between treatment periods. Subjects entered the study site on the afternoon of Day –1 of each treatment period and remained there until after collection of the 240-hour pharmacokinetic (PK) samples on Day 11 (Treatment Period 1) or completion of the end-of-study assessments, following the collection of 240-hour PK sample on Day 11 (Treatment Period 2).

On the morning of Day 1 of each treatment period, 1 patch (either test or reference on left or right buttock, as determined by the randomization schedule) was applied to the buttock of each subject by designated study-site personnel. Residue formation was assessed on the release liner once it had been removed from the patch (prior to patch application). PK blood samples were collected at pre-dose (0), and at 24, 48, 72, 96, 120, 144, 168, 168.5, 171, 174, 180, 192, 216, and 240 hours after patch application for measurement of plasma concentrations of NGMN and EE.

Adhesion assessments were performed within 5 minutes after patch application on Day 1 (baseline), and every 24 hours after patch application up to patch removal at 168 hours (Day 8). Residue formation was assessed on the transdermal patch once the patch had been removed from the skin on Day 8. Subsequent adhesion assessments were performed at the indicated times ±20 minutes. Concurrent with adhesion assessments, a qualitative evaluation of cold flow was also made. The skin site to which a transdermal patch was applied was monitored for skin site reactions (including erythema, edema, pustules, papules, and itching) at screening, prior to patch application, and at 0.5 and 24 hours after patch removal.

To document adhesion and irritation, digital photographs of the patch application site were taken at predose (0) and at 24, 48, 72, 96, 120, 144, 168, 168.5, 192 hours respectively. The digital images taken for adhesion documentation involved taking 3 pictures at each time point; 1 top view and 2 lateral views to ensure that the entire patch application site was visible.

Safety and tolerability were assessed throughout the study from signing of the informed consent form (ICF) onwards until the subject's last study-related activity. End-of-study assessments were performed after collection of the 240-hour PK sample on Day 11 of Treatment Period 2, or upon early withdrawal.

Number of Subjects (planned and analyzed): Sixty-eight healthy adult female subjects were planned to be enrolled to ensure that at least 57 subjects completed both periods. However, due to higher than expected dropouts/withdrawals in early cohorts, 2 additional subjects were enrolled to ensure that at study completion, usable data would be available for at least 57 subjects. In total, 70 subjects were enrolled and 63 (90%) subjects completed both periods.

Diagnosis and Main Criteria for Inclusion: Healthy women, aged 18 to 45 years, with body mass index (BMI) between 18 and 30 kg/m² and body weight no more than 100 kg were enrolled in this study. Subjects signed an ICF prior to first study procedure.

Test and Reference Product, Dose and Mode of Administration, Batch No.:

Test Patch (Treatment B): A single 20 cm^2 transdermal contraceptive patch containing 6 mg NGMN and 600 µg EE, manufactured with the adhesive component Oppanol N100, applied to the buttock for 7 days.

Lohmann LTS Batch/Lot number: 7094547, Manufacturing Date: 6 July 2017, Expiry Date: Not Applicable.

Reference Patch (Treatment A): currently marketed EVRA patch, ie, a 20 cm^2 transdermal contraceptive system containing 6 mg NGMN and 600 µg EE, manufactured with the adhesive component Oppanol B100, applied to the buttock.

Lohmann LTS Batch/Lot number: 7112187A, Janssen Pharmaceutica Batch/Lot number: HFZSH_1, Manufacturing Date: 20 June 2017, Expiry Date: June 2019.

Duration of Treatment: The duration of participation in the study for an individual subject was approximately 2 months (28-day screening, 2 treatment periods of 11 days each and an inter-period washout period of 21 days) from screening to end-of-study.

Criteria for Evaluation:

P**harmacokinetics**: Plasma concentration-time data for NGMN and EE were analyzed using non-compartmental analysis with actual application and sampling times to estimate the following PK parameters: maximum observed plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), steady-state concentration (C_{ss}), area under the curve from time 0 to a specified time point (AUC_{168h}, AUC_{240h}), and AUC from time 0 to infinity (AUC_{∞}).

Patch Adhesion

Patch adhesion was assessed using the European Medicines Agency (EMA) 0-5 scoring system.

In addition, at each time point when adhesion assessments were performed, a qualitative evaluation of cold flow, such as the formation of a dark ring around the transdermal patch during use, patch movement or displacement, and wrinkling was also made.

Skin Reaction

The application skin site was monitored for skin site reactions using a 3- point scale for extent of erythema, papules/pustules and edema; and a 4-point scale for assessment of severity of itching and erythema.

If skin discoloration other than erythema occurred at the application site, the color was also noted. The size, shape, color, and location relative to the patch of any skin discoloration (other than erythema) were detailed. The severity of skin adverse events (AEs) reflected the maximum severity that occurred.

Safety: Safety and tolerability were evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, 12-lead electrocardiogram (ECG) measurements, vital signs measurements, and physical examination results from signing of the ICF onwards until the subject's last study-related activity.

Statistical Methods:

Sample Size:

Based on an estimated intrasubject coefficient of variation (CV) of less than 25% for AUC_{240h} and C_{ss} of NGMN and EE from previous studies, a sample size of 57 completers was sufficient to conclude bioequivalence for each analyte (EE and NGMN) of test product compared with the reference product, with 97.5% power for each analyte and overall power of 90%, when the test and reference treatment means differ by 5%. Approximately 68 healthy female subjects were to be enrolled in the study to ensure that at least 57 subjects completed both assigned treatments with a patch adhesion score of 0 or 1. This sample size was considered adequate for assessment of adhesion, with greater than 80% power.

Assuming an intrasubject CV of 20% for a sample size of 57 subjects, the probability that the lower limit of the 2-sided 90% confidence intervals (CIs) for the ratio of means of cumulative adhesion percentages for the test and reference product to be ≥90%, was estimated to be higher than 80%.

Pharmacokinetic Analysis: Plasma concentration time data for all subjects that received at least 1 patch application, and had at least 1 PK sample, were included in the PK analysis set. PK analysis was performed using WinNonlin version 8.0. For each treatment, descriptive statistics (arithmetic mean, standard deviation [SD], %CV, geometric mean, median, minimum, and maximum) were calculated for the NGMN and EE plasma concentrations at each sampling time and for all PK parameters of NGMN and EE.

For evaluation of bioequivalence, only subjects who completed both periods and had an adhesion score of 0 (completely on) or 1 (edges lifting) were included. Log-transformed AUCs (AUC_{168h} and AUC_{∞}) and C_{ss} of NMGN and EE were compared using a mixed-effect analysis of variance model that included treatment, treatment period, and treatment sequence as fixed effects, and subject as a random effect.

Using the estimated least squares (LS) means and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale between test (Treatment B) and reference (Treatment A) were reported. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean PK parameters of the test to reference product. Test and reference patches were considered bioequivalent if the 90% CIs of the ratios for AUC_{168h}, AUC_{∞}, and C_{ss} fall within the 80.0% and 125.0% limits.

Adhesion Analysis: All subjects who were randomized, received at least 1 patch application and had at least 1 adhesion assessment were included in the adhesion analysis.

The analysis was performed on log transformed cumulative adhesion percentages. A mixed effects model that included treatment, treatment period, and treatment sequence as fixed effects, and subject as a random effect, were used to estimate the LS means and intrasubject variance.

Using these estimated LS means and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale between test (Treatment B) and reference (Treatment A) were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean values for adhesion percentage of the test to reference product. The mixed effects model was implemented using SAS Proc Mixed procedure.

Qualitative evaluation of patch adhesion was listed. This included:

- Residue formation on release liner prior to patch application and on transdermal patch upon removal.
- Cold flow, such as the formation of a dark ring around the transdermal patch during use, patch movement or displacement, and wrinkling; concurrently with adhesion assessments.

Irritation Analysis: The number and percentage of subjects with specific application site reactions were summarized for each treatment. Data listings for application site reactions were generated.

Safety Analysis: All subjects who were randomized, received at least partial patch application (adhesion percentage ≥ 0 at baseline) of the transdermal system were included in the safety analysis. Baseline for all laboratory evaluations, 12-lead ECGs, and vital signs measurements was defined as the last evaluation done before the first patch application. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results, 12 lead ECGs, and vital signs measurements from the screening phase through study completion, including the washout interval.

RESULTS:

STUDY POPULATION:

Overall, 70 female subjects were enrolled and randomized for the study and 63 subjects completed both treatment periods. In the study, 69 subjects received the reference patch (Treatment A) and 67 subjects received the test patch (Treatment B).

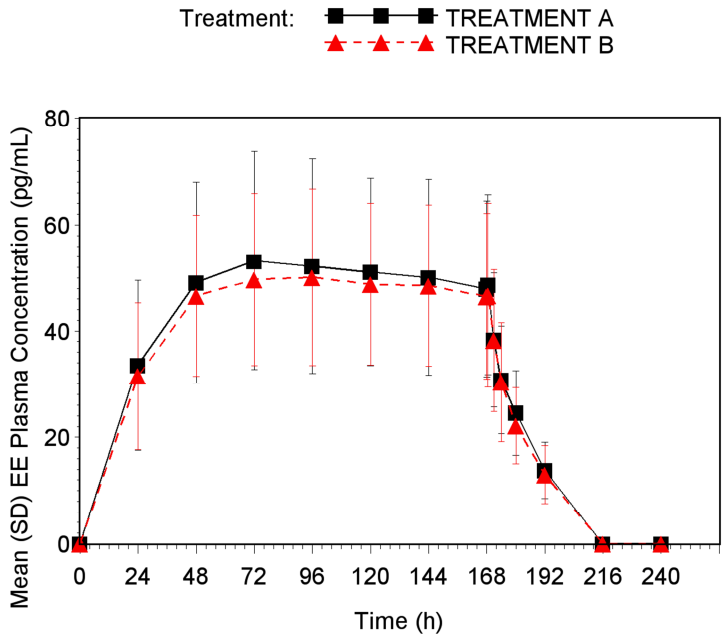
Of the 70 subjects, 62 (88.6%) were white, 3 (4.3%) were Black/African American, 3 (4.3%) were Asian subjects, 1 (1.4%) subject was American Indian/ Alaska Native and 1 (1.4%) subject was reported to be of multiple races. The mean (SD) age was 31.5 (7.87) years, mean (SD) body weight was 66.1 (8.578) kg, and mean (SD) BMI was 24.0 (2.858) kg/m^2.

Three subjects discontinued from the study due to treatment-emergent adverse events (TEAEs): 2 subjects reported influenza like illness and 1 subject reported eczema. Two subjects were withdrawn by the sponsor due to patch detachment, one subject was withdrawn by the sponsor due to protocol violation (patch was detached and reapplied by the subject without any notification to the investigator), and another subject withdrew consent (personal reasons).

PHARMACOKINETIC RESULTS:

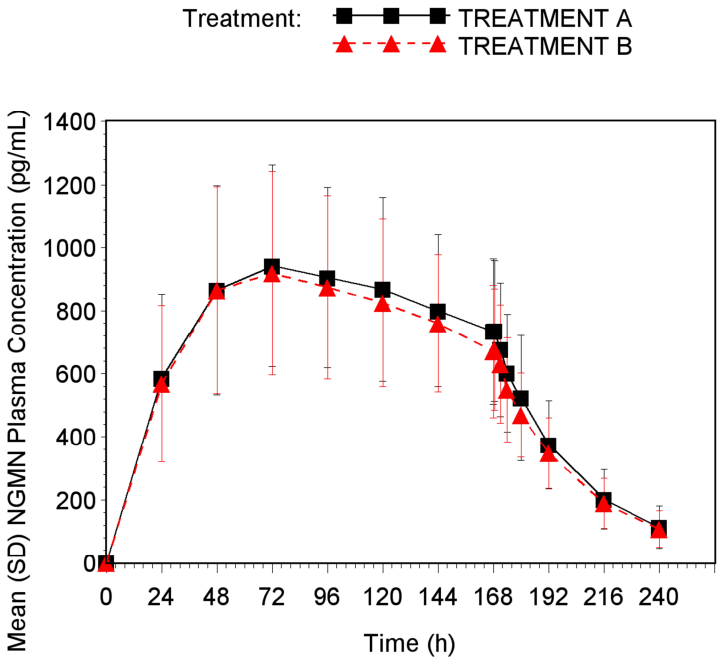
A total of 70 subjects had at least 1 patch application and at least 1 PK sample. There were 62 subjects in both reference (Treatment A) and test (Treatment B) groups who had a patch adhesion score of 0 or 1 at the end of the treatment period and whose PK profiles allowed accurate calculation of the PK parameters. Only 57 of those subjects had an evaluable PK profile and an adhesion score of 0 or 1 in both periods; others completed only 1 of the 2 periods. The mean plasma concentration time profiles of EE and NGMN after a single 7-day application of the test patch (Treatment B) were comparable to the reference patch (Treatment A).

Mean (SD) EE Plasma Concentrations Versus Time Profiles (Linear Scale)



Treatment A (Reference): Single application of the currently marketed EVRA patch
Treatment B (Test): Single application of the transdermal contraceptive patch using the newly sourced adhesive component HMW PIB

Mean (SD) NGMN Plasma Concentrations Versus Time Profiles (Linear Scale)



Treatment A (Reference): Single application of the currently marketed EVRA patch
Treatment B (Test): Single application of the transdermal contraceptive patch using the newly sourced adhesive component HMW PIB

A total of 57 subjects, with adhesion score of 0 or 1, and PK data from both treatment periods, were included in statistical analysis for bioequivalence. The test patch (Treatment B) was comparable to the reference patch (Treatment A) as the 90% CIs of the geometric mean ratios for C_{ss}, AUC_{168h} and AUC_{∞} fell within the bioequivalence range of 80.0% and 125.0%, for both EE and NGMN.

Summary of the Statistical Analysis of the PK Parameters After Single Application of EVRA Reference Patch (Treatment A) and the Test Patch (Treatment B)
PK Analysis set (Study RWJ10553CON4001)

PK Parameter	Geometric Means: Treatment A (Reference)	Geometric Means: Treatment B (Test)	Geometric Mean Ratio (%)	Lower Limit 90% CI (%)	Upper Limit 90% CI (%)	CV (%)
			EE			
N	57[a]	57[a]				
C_{ss} (pg/mL)	46.2	45.8	99.27	94.90	103.84	14.34
AUC_{168h} (pg.h/mL)	6848	6757	98.66	94.16	103.39	14.89
AUC_{∞} (pg.h/mL) [a]	7810	7701	98.61	93.91	103.53	14.74
			NGMN			
N	57	57				
C_{ss} (pg/mL)	805	781	96.98	92.52	101.65	14.99
AUC_{168h} (pg.h/mL)	120232	117085	97.38	92.72	102.28	15.64
AUC_{∞} (pg.h/mL)	148254	143136	96.55	92.21	101.09	14.63

a: n=52 for AUC_{∞}
Analysis done on log-transformed data and results were back-transformed using anti-logarithm
Treatment A (Reference): Single application of the currently marketed EVRA patch
Treatment B (Test): Single application of the transdermal contraceptive patch using the newly sourced adhesive component HMW PIB

PATCH ADHESION

Comparisons of test (Treatment B) and reference (Treatment A) patches were based on estimated cumulative adherence percentage of adhesion scores.

Based on mean and median cumulative adhesion percentages, there were no discernable differences between the site of patch application (left buttock, right buttock) within each treatment (Treatment A, Treatment B), therefore pooled data from the 2 sites of application for the test (Treatment B) and reference (Treatment A) patches were used in the analysis.

Cumulative Adhesion Percentages by Patch Application Location
Adhesion Analysis Set (Study RWJ10553CON4001)

	Cumulative Adhesion Percentage				
	N	Mean (SD)	Median	Range	90% CI
Analysis Set: Adhesion	70				
Treatment					
Treatment A (Reference, Left)	35	752.7 (115.85)	777.0	(100; 800)	719.54 - 785.77
Treatment A (Reference, Right)	34	769.6 (28.19)	777.5	(658; 795)	761.44 - 777.80
Treatment B (Test, Left)	33	752.9 (119.69)	780.0	(100; 799)	717.58 - 788.17
Treatment B (Test, Right)	33	776.5 (20.22)	778.0	(709; 800)	770.49 - 782.42

Key: SD=Standard Deviation; CI=Confidence Interval
Treatment A (Reference): Single application of the currently marketed EVRA patch.
Treatment B (Test): Single application of the transdermal delivery system (TDS) contraceptive patch using the newly sourced adhesive component HMW PIB.

The point-estimates of the ratio of the mean value for cumulative adhesion percentages, and 90% CIs for the ratios demonstrated similarity of adhesion between test (Treatment B) and reference (Treatment A) patches.

Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals Adhesion Percentage

Adhesion Analysis Set (Study RWJ10553CON4001)

		N		Geometric Means					
Parameter	Comparisons	Test	Reference	Test (Treatment B)	Reference (Treatment A)	Ratio (%)	Lower Limit 90 % CI (%)	Upper Limit 90 % CI (%)	Intra-Subject CV (%)
Cumulative Adhesion Percentages (%)	Test vs Reference	66	68	749.5	747.4	100.3	93.22	107.88	25.70

Treatment A (Reference): Single application of the currently marketed EVRA patch.
Treatment B (Test): Single application of the transdermal delivery system (TDS) contraceptive patch using the newly sourced adhesive component HMW PIB.
CV= Coefficient of Variation
Notes: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.
All dropout subjects, the last adhesion percentage assessment were imputed for the subsequent scheduled time-points adhesion assessments.
All missing adhesion assessments at scheduled time points were imputed from the value from the last scheduled time point, non-missing assessment.
Subject [redacted] is excluded from the analysis due to major protocol deviation.

For both treatments A and B, most of the subjects exhibited 90-100% patch adhesion until patch removal on Day 8.

The incidence of appearance of a dark ring around the transdermal patch, movement or displacement of the patch, and wrinkling of the patch was similar between the 2 treatments.

SKIN REACTION: The extent of edema, papules/pustules and erythema were similar for both treatments. Overall, the test patch (Treatment B) had similar irritation profile as the reference patch (Treatment A).

The severity of itching was scored as a zero (none) for greater than 86% of subjects in both treatments. Only 1 subject in reference (Treatment A) group reported a severity of 2 (moderate) on Day 8. No subjects reported a score of 3 (severe) on any day. The severity of erythema was scored as a zero (none) or 1 (noticeable redness) for most of the subjects, with only 1 subject reporting a severity of 2 (well-defined redness) on both Days 8 and 9 in the reference (Treatment A) group and 1 subject reporting a severity of 2 on Day 8 in the test (Treatment B) group. No subjects reported a severity of 3 (beet redness) on any day.

The irritation potential of the transdermal contraceptive patch using the newly sourced adhesive component was low and appeared to have a similar profile as the reference, currently marketed EVRA patch.

SAFETY RESULTS

Overall, 65 (92.9%) of 70 subjects reported at least 1 TEAE during the treatment phase. In Treatment A, 55 (79.7%) of 69 subjects, and in Treatment B, 57 (86.4%) of 66 subjects, reported at least 1 TEAE. Headache was the most common TEAE reported, followed by acne, application site pruritus, abdominal pain and breast tenderness (Table below). Most of the TEAEs in both treatment groups were of mild severity with a few TEAEs being of moderate severity. None of the TEAEs were severe.

Number of Subjects With Treatment-Emergent Adverse Events in >10% Subjects in any Group by Preferred Term
Safety Analysis Set (Study RWJ10553CON4001)

	Treatment A (reference)	Treatment B (test)
Headache	18 [26.1%]	20 [30.3%]
Acne	15 [21.7%]	14 [21.2%]
Application site pruritis	8 [11.6%]	7 [10.6%]
Abdominal pain	7 [10.1%]	9 [13.6%]
Breast tenderness	9 [13.0%]	6 [9.1%]

Treatment A (Reference): Single application of the currently marketed EVRA patch.
Treatment B (Test): Single application of the TDS contraceptive patch using the newly sourced adhesive component HMW PIB.
Note: Subjects are counted only once within each Preferred term, and once within each SOC, regardless of the number of times they actually experienced the event.
Percentages are calculated with corresponding count of number of subjects in the respective treatment group as denominator.
Adverse events are coded using Medical Dictionary for Regulatory Activities Version 20.1

Four of the enrolled subjects showed mild persistent TEAEs of eczema, facial acne, back pain and facial dry skin at end of study/early withdrawal and 3 subjects discontinued the study drug due to TEAEs of moderate influenza like symptoms/illness, ear pain and mild eczema which were assessed as either doubtfully related or not related to the study drug by the investigator.

Based on analysis of the safety data the test EVRA contraceptive patch (Treatment B) has similar safety profile to the currently marketed reference EVRA contraceptive patch (Treatment A). All TEAEs were mild/moderate in severity and are aligned with the established TEAE profile of the product (no unexpected TEAE). No subject discontinued due to treatment-related AE. There were no serious adverse events (SAE) or deaths reported.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- The test patch (Treatment B) using the newly sourced adhesive component HMW PIB was bioequivalent to the currently marketed EVRA patch (Treatment A, reference) for both active moieties of EE and NGMN.
- The adhesion of the test patch using the newly sourced adhesive component was similar to that of the currently marketed EVRA reference patch.
- Both patches had a low irritation potential. The irritation potential of the test patch using the newly sourced adhesive component was similar to that of the currently marketed EVRA reference patch.
- A single 7-day application of the test contraceptive patch using the newly sourced adhesive component was safe and well tolerated. Neither the test nor the currently marketed EVRA patch elicited any clinically relevant safety signals.

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