European Review for Medical and Pharmacological Sciences 2020; 24: 5668-5675

Elution from intact and broken vaginal contraceptive rings: an *in vitro* study

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Abstract. – OBJECTIVE: The *in vitro* elution of the active substances etonogestrel (ETO) and ethinylestradiol (EE) of Ornibel® (a vaginal delivery system) was determined after a deliberate breakage of the vaginal contraceptive ring and compared to the standard elution and hormone release of intact rings under the same experimental conditions.

MATERIALS AND METHODS: Ornibel® intact and broken vaginal rings were placed in a dissolution buffer and subject to a repetitive sampling of ETO and EE following a standardized *in vitro* elution (IVE) procedure for 21 days. The hormone dissolution profile was determined by HPLC using a fully validated analytical method. In a second study, rings were broken after day seven, and their elution profiles were compared to that of intact rings. For all utilized batches, the stability conditions established were 24 months at 5°C. Furthermore, no special storage conditions are needed.

RESULTS: The instantaneous elution on day 1 of ETO and EE for intact rings were 119±8 µg/day and 15±1 µg/day, respectively (mean ± SD), which was non-significantly different to the immediate release of ETO and EE for broken rings (118±4 µg/day and 14±1 µg/day). The average elution profile for days 2-20 were 132±5 µg/day and 18±1 µg/day (ETO/EE, intact rings) and 132±4 µg/day and 19±1 µg/day (ETO/EE, broken rings) respectively. On day 21, the elution of ETO and EE was numerically similar 111±5 (±4) µg/day and 18±1 µg/day) for both intact and broken rings. The IVE results from intact rings and vaginal rings deliberately cut on day seven similarly did not differ in their release of ETO and EE.

CONCLUSIONS: Our study concludes that the hormonal release of ETO and EE from Ornibel® are similar for intact and broken vaginal rings under standardized *in vitro* conditions.

Key Words:
Contraceptive vaginal ring, Breakage, *In vitro* elution.

Introduction

The contraceptive vaginal ring is a well-established device for hormonal contraception[1,2]. It has several advantages compared to oral contraception, as the released hormones avoid the passage of the intestinal tract as well as the hepatic first-pass effect[3]. When compared to oral contraceptives, vaginal rings containing ethinylestradiol (EE) leads to a lower level of systemic hormonal exposure, which provides a more uniform release resulting in fewer side effects due to EE. Vaginal rings claim to increase patient compliance with a similar contraceptive efficacy than oral contraception[4,5]. Hence, contraceptive rings represent a contraceptive method, which is increasingly appreciated[6].

Nuvaring®, a vaginal delivering system (VDS) releasing 120 µg etonogestrel (ETO) and 15 µg ethinylestradiol (EE) per day, has been commercialized since its approval in 2001[7,8]. This ring consists of a core of magnesium stearate and 28% ethylene vinyl acetate (EVA) and an outer membrane containing 9% EVA[9]. In 2017, Ornibel® was approved as a second-generation vaginal contraceptive ring, proven to be bioequivalent to Nuvaring®, but differing in its polymer composition. The core of Ornibel® consists of polyurethane, which serves as a reservoir for the active compounds EE and ETO. The external membrane of Ornibel® contains 28% EVA and controls the release of the hormones. Within the polyurethane core, the hormones are dissolved below their saturation limit. This leads to a more gradual hormone release on the first day of application as compared to other vaginal rings[10-12]. Furthermore, no special storage conditions are needed[13].

Vaginal contraceptive rings occasionally break upon their application either when inserting the ring in the vagina or during use[9,13]. This frequently raises the question if the clinical efficacy is maintained as an alteration in the hormonal release of EE and ETO (or both) can occur. The present study investigates the hormonal release of EE and ETO from the Ornibel® vaginal ring in a standardized *in vitro* elution (IVE) test system[14]. The IVE test

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system used in this study is the same that was used for the regulatory procedures for the market authorization of Ornibel®. This former test described in previous publications[10] is based on an *in vitro in vivo* correlation (IVIVC) model of category A as defined by the FDA[15-17], allowing to perform extrapolations about the hormone release from the rings from *in vitro* to *in vivo*.

Ring break is a described adverse event[13] listened in the summary of product characteristic of Ornibel® with a possible rate of ≥ 1/1.000 till < 1/100. Nevertheless, no data are till now available regarding the hormonal elution of both active substances after ring break. The aim of the present study is therefore to obtain first *in vitro* data of the amount of the hormonal elution in broken rings compared to intact rings to reaffirm the safety of this pharmaceutical delivery system.

Materials and Methods

The standardized test procedure is designed to measure the elution of ETO and EE for 21 days, while the ring is incubated in a defined buffer system at defined temperature mimicking vaginal conditions. High-performance liquid chromatography (HPLC) determines the quantity of ETO and EE released into the medium for designated time points using a fully validated analytical method. The IVIVC model specifies certain acceptance limits for the hormone release within the test system. Hence this *in vitro* test complies with the criteria that are considered to meet the standard regulatory approved specifications of Ornibel®.

In one study, the *in vitro* elution of ETO and EE was analyzed over 21 days for vaginal rings that were broken at the beginning of the test and compared to intact rings incubated in parallel.

Since breakage may occur while the ring is in use, a second study was performed where Ornibel® rings were broken after seven days of incubation in dissolution buffer. The IVE elution profile was compared to that of intact rings from the same batches incubated in parallel for a total of 21 days. No *in vivo* test was performed since IVIVC model was established.

Test Material

For all experiments, vaginal contraceptive rings (Ornibel®; etonogestrel/ethinylestradiol 11.00/3.47 mg, Exeltis Healthcare SA, Spain) were taken from routine batches. Rings (12 in a total for part 1 of the study (six were broken, and six were intact) from the same batch were used, and six (three broken and three intact of 2 different batches) were used for part 2 of the survey.

In vitro Elution (IVE) of Etonogestrel (ETO) and Ethinylestradiol (EE)

The IVE procedure is a standardized experimental approach, that has been described and approved in the assessment report of Ornibel®[14]. It is the method to measure the daily release for both active pharmaceutical ingredients, and the label of the product is based on this regular release. For IVE, contraceptive rings were weighed into individual flasks containing 500 ml dissolution medium (25 mM acetate buffer pH 4.2 with 0.05% of the surfactant Kolliphor HS15) and incubated at 37°C and 60 rpm for 21 days. For the measurements of the elution of ETO and EE from the rings, aliquots from each flask were taken daily and subjected to high-performance liquid chromatography (HPLC) analysis. The remaining medium was discarded, and 250 ml of fresh dissolution medium was added into each vial.

In the first study IVE was performed as described for 21 days, and samples for HPLC were taken daily. For the second study the analysed rings were subjected to *in vitro* elution as described, and on day 7, one ring of each batch was broken deliberately. IVE was continued until day 21. Samples were taken on days 2, 4, 7, 10, 14, 17, and 21.

High-Performance Liquid Chromatography (HPLC) Analysis

For HPLC, a chromatographic system with ultraviolet/fluorescence detector (UV/FLD) detectors was used utilizing the column "Zorbax XDB C8 Eclipse 4.6×150 mm 5 µm". HPLC conditions were as follows. Flow: 1.0 mL/min; column temperature: 30°C; injection temperature: 10°C; injection volume: 100 µl; mobile phase: acetonitrile: water [60:40; v/v]; runtime: 5 min (but was adjusted if necessary). ETO was detected with the UV detector at 240 nm, while for EE, fluorescence detection was used (excitation at l_{exc} = 285 nm and emission at l_{em} = 310 nm). The analytical method for the quantification of ETO and EE has been fully validated according to ICH guidelines.

Data Analysis

The amount of active substance (ETO and EE) in the dissolution medium was calculated by comparing the peak areas of the active substanc-

es in the sample medium to corresponding peak areas of standard solutions in the HPLC profiles according to the following equation: API [µg/day] = $A_m/A_{std} \times P_{std} \times D_m/_{Dstd} \times F/day \times 1000$ with:

- A_m: peak area corresponding to the active substance in the sample solution
- A_{std}: mean of peak areas of an active substance in the standard solution
- P_{Std}: weight of active substance standard in the standard solution [mg]
- D_m: dilution of the sample solution [ml]
- D_{std}: dilution of active substance standards in the standard solution [ml]
- F: purity of active substance standard [amount per once]
- Day: day since the last sample

Mean values between replicates and corresponding standard deviations were calculated. For the described IVE procedure, acceptance limits for API elution have been defined in the assessment report of Ornibel®. They are given for day 1, days 2-20 (data pooled, and mean value between the days are used) and for day 21. Experimentally obtained data were compared to these criteria to evaluate the elution behavior of the rings.

To identify potential differences between batches, % Δ was calculated as follows: % D = (C – R)/R × 100, with C representing the mean of IVE daily release of the product in a study [broken rings; µg/day] and R representing the mean of IVE daily release in reference product [intact rings; mg/day].

For the demonstration of equivalence, the percentage difference of daily release between samples must be less than 20%, as defined in the assessment report of Ornibel®.

Statistical Analysis

Analysis and results are expressed as mean ± SD. Non-parametric pair-wise comparison was performed to test for differences. Results with a significance level of $p < 0.05$ were considered as statistically significant.

Results

Elution of Etonogestrel (ETO) and Ethinylestradiol (EE) from Intact and Broken Vaginal Rings

The elution of ETO and EE from broken Ornibel® contraceptive rings was analyzed to evaluate whether ring breakage alters hormonal release and availability in quantity and over time. For that, each six broken and six intact Ornibel® vaginal rings were subjected to an IVE experiment for 21 days. The amount of ETO and EE (mean ± SD) released by the rings was determined daily by HPLC analysis, and mean values between the replicates were identified (Table I). On the first day, 119±8 µg and 118±4 µg ETO were eluted from intact and broken rings, respectively. Between day 2 and 20, 132±5/±4 µg ETO was eluted on average from both broken and intact rings. On day 21, in both cases, 111±5/±4 µg ETO was released. Similar comparable results were obtained for the second active component EE (Table I). The *in vitro* elution for EE was 15±1 µg/day (intact) and 14±1 µg/day (broken) on day 1. On days 2-22 the average elution of EE was 18 ±1 µg/day (entire) and 19 ±1 µg/day (broken), whereas the release of EE on day 21 was similar for both broken and intact rings (18 ±1 µg/day).

Further, to meet the specifications of Ornibel®, certain acceptance limits for ETO and EE elution must be fulfilled for the IVE test system (Table I). To fulfill the acceptance limits, less than 250 µg

Table I. Average in vitro elution from intact and broken – breakage on day 1.

	Time course in days	Intact vaginal ring [µg/day]	Broken vaginal ring [µg/day]	Acceptance elution limit [µg/day]
Etonogestrel	Day 1	119 ± 8 [SD]	118 ± 4 [SD]	≤ 250
	Day 2-21	132 ± 5 [SD]	132 ± 4 [SD]	116-142
	Day 21	111 ± 5 [SD]	111 ± 4 [SD]	≥ 80
Ethinylestradiol	Day 1	15 ± 1 [SD]	14 ± 1 [SD]	≤ 30
	Day 2-21	18 ± 1 [SD]	19 ± 1 [SD]	16-20
	Day 21	18 ± 1 [SD]	18 ± 1 [SD]	≥ 10

In vitro elution of the active compounds from intact and broken vaginal contraceptive rings compared to the acceptance limits. Mean values of each 6 replicates are given. Data from day 2-20 are averaged. IVE = *in vitro* elution

ETO must be eluted on day one. Between 116 and 142 µg ETO should be eluted between days 2-20, and more than 80 µg ETO must be detected in dissolution buffer on day 21. These acceptance limits were met throughout the whole experiment (Table I). Additionally, also, the elution of EE reached the acceptance limits of the Ornibel® specification as detailed in Table I. As both experiments (broken and non-broken) are within the specifications, they can be considered as equivalent ($p < 0.05$).

The IVE elution profile by time is shown in Figure 1, which displays the average elution of ETO and EE from broken and intact rings for each day as well as the standard deviation between the replicates. The graph shows the ETO/EE elution from Ornibel® vaginal rings with slightly enhanced hormone availability on day 1, followed by a more stable hormone release during the days 2-20. The ETO/EE hormonal release was similar for both broken and intact rings, thus displaying a similarity in bioavailability. The analogy was further demonstrated by calculating the percentage difference between the mean values of broken and intact rings. On each day, the difference between the eluted active compounds was less than 10 % (Table II). The average difference was 1.8% for ETO and 2.4% for EE over the whole 21 days, thus being in accordance with the specifications of Ornibel® ($p < 0.05$).

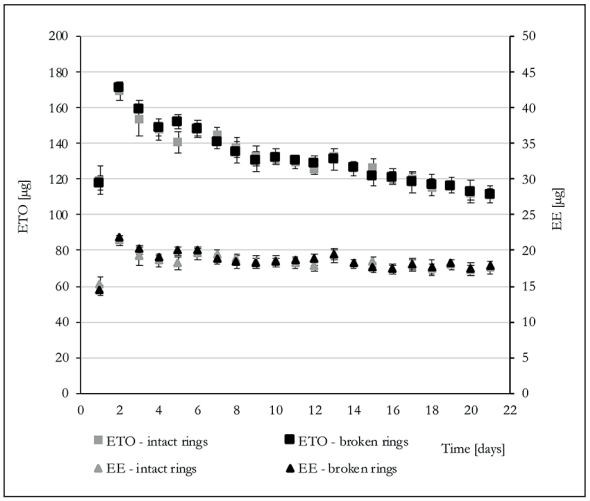

Figure 1. IVE of ETO (*squares*) and EE (*triangles*) from 6 intact and 6 broken rings from a similar batch by time. Mean values of the elution of active substance from intact rings (*gray symbols*) and broken rings (*black symbols*) are shown. Standard deviation between the samples is depicted with error bars. Different ordinates for ETO (*left ordinate*) and EE (*right ordinate*) are applied.

Table II. *In vitro* elution (=IVE) of etonogestrel (=ETO) and ethinylestradiol (=EE) from intact and broken vaginal rings.

	Mean values				Standard deviation					
	Intact		Broken		Intact		Broken		% Δ	
Day	ETO	EE	ETO	EE	ETO	EE	ETO	EE	ETO	EE
1	119.30	15.3	117.80	14.4	7.87	1.03	3.74	0.68	1.30	6.1
2	169.20	21.4	170.90	21.7	5.19	0.72	2.34	0.36	1.03	1.3
3	153.30	19.2	158.90	20.1	8.82	1.25	5.40	0.67	3.65	4.9
4	147.60	18.5	149.00	18.9	6.13	0.87	4.44	0.66	0.95	2.2
5	140.70	18.2	152.00	19.9	6.06	0.88	3.89	0.52	7.98	9.5
6	148.40	19.5	147.60	19.9	4.71	0.74	3.49	0.57	0.50	2.2
7	144.40	19.3	140.50	18.8	5.02	0.75	3.45	0.67	2.60	2.3
8	137.80	18.7	134.80	18.4	5.58	0.88	6.00	0.88	2.20	1.5
9	132.90	18.4	130.10	18.2	5.46	0.86	5.72	0.76	2.10	1.2
10	132.80	18.5	132.10	18.4	4.43	0.74	2.72	0.4	0.50	0.8
11	129.60	18.2	130.20	18.5	3.58	0.62	3.07	0.51	0.47	1.7
12	125.60	17.7	128.30	18.7	3.14	0.51	4.98	0.76	2.11	5.8
13	132.90	19.3	130.80	19.3	3.91	0.7	5.93	0.94	1.50	0
14	127.10	18.2	126.10	18.1	2.98	0.59	3.85	0.64	0.80	0.1
15	126.50	18.4	121.20	17.6	4.77	0.78	4.69	0.76	4.20	4.6
16	121.60	17.4	120.70	17.4	3.89	0.64	3.59	0.58	0.70	0.1
17	120.00	18	118.50	18	3.81	0.65	5.82	0.92	1.30	0.3
18	115.30	17.4	116.70	17.6	4.61	0.78	5.94	1.01	1.22	1.4
19	116.90	18	115.70	18.2	4.19	0.63	3.24	0.56	1	1.4
20	112.00	17.2	113.00	17.4	3.60	0.72	6.40	0.93	0.87	1
21	111.30	17.6	110.90	17.8	4.61	0.82	3.93	0.74	0.40	1.3

Mean values (*left part*), their corresponding standard deviations (*right part*) and the percentage difference between intact and broken rings as calculated from the mean values (*last column*) are shown.

Table III. IVE of ETO and EE from vaginal rings of three different batches. Rings were broken on day 7 or were left intact.

	Time course in days	Intact vaginal ring [µg/day]	Broken vaginal ring [µg/day]	Acceptance elution limit [µg/day]
IVE				
Etonogestrel	Day 2-21	137 ± 2	132 ± 1	116-142
	Day 21	116 ± 2	110 ± 2	≥ 80
IVE				
Ethinylestradiol	Day 2-21	18 ± 0	17 ± 0	16-20
	Day 21	17 ± 0	16 ± 0	≤ 10

Mean values between the batches (*left part*), their corresponding standard deviations (*right part*) and percentage difference between intact and broken rings as calculated from the mean values (*last column*) are shown.

The Behavior of Rings Broken After Seven Days of Incubation

Since the breakage of rings may occur after several days of use, a second study was performed in order to simulate these conditions.

The IVE standard procedure was performed with contraceptive rings that were intentionally broken on day seven and compared to intact rings. In this study, the differences in elution of ETO and EE between the replicates were low, as depicted by the standard deviation between them (Table III and Figure 2). The mean values of the elution data of the replicates over time are presented in Figure 2. For both broken and intact vaginal rings, the elution profiles of ETO and EE were as expected with an elution behavior similar between broken and intact rings (Figure 2). The calculated percentage difference between elution from broken and intact rings was less than 10% throughout the whole experiment (Table III). Hence, the acceptance limits were met for both ETO and EE, irrespectively of whether the rings were broken or intact (Table IV). Thus, the results may also be considered equivalent to those of the first experimental setup (breakage on day 1) ($p < 0.05$).

Discussion

For vaginal contraceptive rings like Nuvaring® and Ornibel®, a small number of ring breakages are reported with a frequency of less than 1%[9,13]. While the use of contraception with vaginal rings becomes increasingly important[15], there is growing interest in exploring the relevance of ruptures and device breakage. For Ornibel®, the inner core consisting of polyurethane serves as a reservoir for etonogestrel (ETO) and ethinylestradiol (EE), while the outer layer, composed of 28% evathane is essential for regulating the release of both ETO and EE[10]. When a ring breaks while it is applied by women, small parts of the cross-sectional region of the core may become exposed to the environment, which adequately questions whether an undesirable dose dumping may occur. To address this question, we applied an *in vitro* test system widely used for the development and evaluation of vaginal rings[18,19]. This *in vitro* elution (IVE) procedure is part of an *in vivo/in vitro* correlation (IVIVC) model of category A, as defined by the FDA[16]. IVIVC models of category A are highly informative, show less than 5% prediction errors, and can potentially even be used for

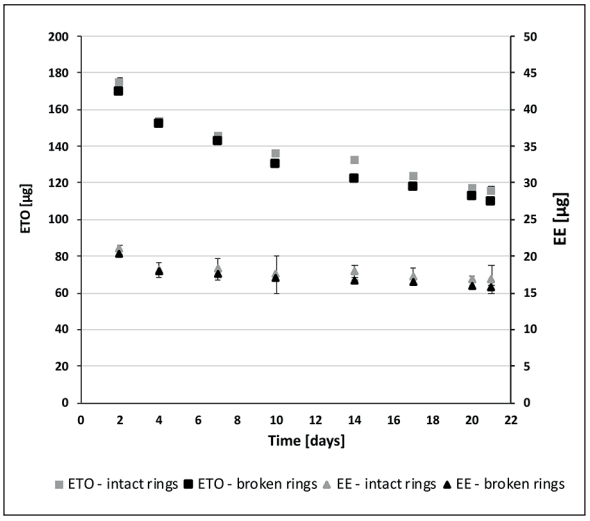

Figure 2. IVE of ETO (*squares*) and EE (*triangles*) from rings of three different batches by time. Rings from the batches were broken on day 7 (*black symbols*) or left intact (*gray symbols*) for the entire 21 days of the study. Mean values of the elution of active substance from broken (*black symbols*) or intact (*gray symbols*) rings and the standard deviations between the samples are shown.

Table IV. *In vitro* elution of the active compounds from intact vaginal rings and rings broken on day 7 compared to the acceptance limits of Ornibel®.

	Mean values				Standard deviation					
	Intact vaginal ring		Broken vaginal ring		Intact vaginal ring		Broken vaginal ring		% Δ	
Day	ETO	EE	ETO	EE	ETO	EE	ETO	EE	ETO	EE
2	174.9	21.1	169.4	20.3	2.4	0.4	0.5	0.2	-3.1	-3.4
4	153.3	18.1	151.9	18.0	0.5	0.1	1.0	0.1	-0.9	-0.9
7	145.2	18.2	142.5	17.5	1.5	0.2	1.4	0.2	-1.9	-4.0
10	135.9	17.5	130.2	17.0	1.4	0.2	2.5	0.3	-4.2	-3.0
14	132.2	18.0	122.3	16.7	1.3	0.1	0.9	0.1	-7.5	-7.1
17	123.7	17.3	117.9	16.5	1.3	0.2	1.1	0.4	-4.7	-4.1
20	116.8	16.8	112.5	16.0	2.2	0.5	0.4	0.1	-3.7	-5.0
21	115.8	16.8	109.5	15.7	2.1	0.4	1.9	0.3	-5.5	-7.0

Mean values of each 3 replicates are given. Data from day 2-20 was pooled. IVE = *in vitro* elution.

bioequivalence studies[17]. For the present model, a linear point-to-point relationship between drug release *in vitro* and *in vivo* is described in the application report of Ornibel®[14]. The model may thus be used to predict the $_{Cmax}$ (maximum observed plasma concentration) and the AUC (cumulative area under the plasma concentration curve) *in vivo* from data obtained *in vitro*. During the development of Ornibel®, the system was proven suitable to discriminate between factors like ring composition and membrane thickness[14].

In the present study, the elution of ETO and EE from broken rings was examined using the standardized IVE test system. There is a small peak release on the first day (also named burst effect), which should not exceed 250 µg for ETO and 30 µg for EE, in order to meet the specifications of Ornibel®. This immediate release has been described *in vivo* when the plasma concentration of ETO and EE is determined on day one of ring insertion[10]. This was also observed in our current *in vitro* study (Figure 1), where the release of both ETO and EE remained within the given limits for both intact and broken rings (Table I). During the entire time-course of the *in vitro* elution, broken rings showed a similar elution profile as intact vaginal rings. The elution of ETO and EE differed less than 10% between broken test rings and their intact counterparts (Tables II, III and IV) and consequently, elution can be considered equal between broken and non-broken rings[14].

Elution of ETO and EE *in vitro* was not influenced by a breakage of Ornibel® vaginal rings, irrespectively of being broken on day one or after seven days of pre-incubation. When broken, the core of Ornibel® is exposed without being covered by the outer membrane. The outer layer of Ornibel® is necessary for release control, and vaginal rings without the outer layer may elute ETO and EE more rapidly. Our experiments demonstrate that the exposed surface area is neglectable at a simple ring breakage providing a similar hormone elution of ETO and EE between broken and intact rings over 21 days. This constant release of vaginal rings is the great advantage of this contraceptive method[20]. Van den Heuvel et al[4] described that for women who used vaginal rings for contraception the exposure to EE was on average 3.4 times lower than for those who used the transdermal patch and approximately twice as low as those who used a COC and that the differences were statistically significant. As no changes in the elution profile could be detected the overall efficacy, safety, and patient acceptability of vaginal contraceptive rings as described by Weisberg et al[2,11,21] and Wieder et al[22] will remain even in the case of broken rings.

Since the IVE test system allows some extrapolations to the situation *in vivo*, a rupture of a vaginal ring will not influence the hormonal availability in the vagina. It may be concluded that the pharmacokinetic behavior of the released ETO and EE would, therefore, be the same for broken rings as described for intact rings during bioequivalence experiments[10]. Consequently, blood plasma levels of ETO and EE would be comparable to those described for

Ornibel®[10], and contraceptive efficacy would not be impaired by a ruptured ring. Further studies are needed to address whether this also applies to vaginal rings manufactured under different specifications.

Conclusions

Comparative *in-vitro* hormonal elution profiles show that both broken and intact vaginal rings release ETO and EE at a similar rate. All values of the released ETO and EE over time were within a ± 10% required margin, hence, demonstrating equivalence for both broken and intact vaginal rings in their release of hormones for this vaginal delivery system.

Conflict of Interest

Pedro Antonio Regidor and Anna Müller are employees of Exeltis Healthcare. Sonia Matilla and Carlos Díez are employees of Laboratorios Leon Farma S.A., Leon, Spain (Chemo-Insud Pharma).

Funding

This trial was funded by Insud Pharma.

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