

## No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA)

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### ABSTRACT

**Objective:** To estimate the incidence and recurrence of breast cancer (BC) in patients with vulvovaginal atrophy (VVA) treated with ospemifene and matched untreated VVA patients using real-world data.

**Study design:** Retrospective matched cohort study.

**Main Outcome Measures:** VVA patients were identified from the 2011–2018 US MarketScan® insurance claims database. For incidence, ospemifene-treated VVA patients without evidence of BC prior to index treatment were matched to two untreated VVA controls similarly without history of BC on age, index VVA year, geographic region, Charlson Comorbidity categories, and follow-up time. BC after the index treatment was identified by BC diagnosis codes, mastectomy, chemotherapy, or radiation procedure. Incidence rate, rate ratio (RR) and their 95 % confidence intervals (CI) were calculated. The process was repeated to estimate BC recurrence in patients with a history of BC in 1:1, 1:2 and 1:3 matches.

**Results:** 1728 ospemifene users and 3456 untreated patients met the inclusion and matching criteria for assessing incidence. The average number of days for which ospemifene was supplied was 314 (standard deviation [SD] = 340). Average follow-up time from index treatment was 937 days (SD = 392) for treated patients and 915 days (SD = 396) for controls. BC incidence rates per 1000 person-years was 2.03 (95 % CI: 1.06 – 3.91) for treated patients and 3.53 (95 % CI: 2.49 – 4.99) for controls (RR = 0.58, 95 % CI: 0.28 – 1.21). No difference in recurrence was observed between ospemifene-treated and matched untreated patients. Ten (32.3 %) treated vs. 25 (40.3 %) controls in the 1:2 matched analysis had a recurrence.

**Conclusion:** No differences were observed in the BC incidence and recurrence rates in ospemifene users compared with matched controls.

### 1. Introduction

Vulvovaginal atrophy (or VVA), part of the genitourinary syndrome of menopause (GSM), is a condition that develops in an estrogen-deficient setting that affects peri- and post-menopausal women causing several distressing urogenital symptoms including dryness, reduced lubrication, itching, burning, irritable bladder symptoms and painful intercourse [1,2]. An estimated 50 % of postmenopausal women will

experience symptoms of VVA [1], greatly impacting their quality of life [1,3]. Treatment for VVA consist of over the counter lubricants, moisturizers or vaginal prescription estrogen therapies, and prescription dehydroepiandrosterone (DHEA) [3–5], however their use is reported in less than half of the VVA patients [3]. A patient preference survey found that of those reporting use of treatments, only a quarter of patients reported use of vaginal estrogen therapies, citing long-term safety concerns including breast cancer (BC) [3].

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Physicians hesitate to prescribe vaginal estrogen therapies in BC survivors with VVA due to a fear of increased cancer recurrence and possible interferences with tamoxifen [6]. As such, estrogen therapy was only prescribed by 21 % of physicians in one study [6]. Even when prescribed, this survey found 43 % of women refuse to take it, with another 36.5 % asking for reassurance prior to use. Despite its perceived efficacy over non-hormonal treatments, vaginal estrogen therapy is mostly a second-line treatment after moisturizers and lubricants; even with an absence of documented benefit of moisturizers and lubricants for the cellular and pH changes needed to reconstitute normal physiology [7]. A recently published meta-analysis in *The Lancet* 2019 found that across 128,435 cases with invasive BC and 366,965 patients without BC, there was significant excess risk of BC associated with > 1 year of oral or transdermal estrogen and estrogen-progestogen hormone therapy use [8]. Therefore, VVA may pose a serious problem for BC survivors, as there is no clear safe and effective treatment option.

Ospemifene (OSPHENA®, SENSHIO) is a selective estrogen-receptor modulator (SERM) approved by the FDA in 2013 for the treatment of moderate to severe dyspareunia, a symptom of VVA, due to menopause [9]. Ospemifene is also approved in Europe for the treatment of moderate to severe symptomatic VVA in postmenopausal women who are not candidates for local vaginal estrogen therapy [10]. Ospemifene evolved from a tamoxifen metabolite and is a weak antiestrogen on the breast tissue. Though the clinical trial program did not specifically study ospemifene (60 mg) in women with BC [9], clinical studies since its approval have indicated no increased risk for BC or breast-related safety concerns among patients receiving ospemifene [11–16]. This study aimed to assess the risk of BC incidence or recurrence and expand the evidence base of ospemifene safety regarding BC [9].

## 2. Methods

### 2.1. Study objectives

The overall study objective was to estimate the incidence of BC in ospemifene users in a real-world setting. This study assessed the incidence rate of BC among postmenopausal women with VVA without a history of BC treated with ospemifene to matched patients without any VVA-related treatments. A secondary analysis explored recurrence of BC among postmenopausal women with VVA with history of BC after ospemifene treatment compared with an untreated, matched cohort.

### 2.2. Study design and data source

This retrospective, observational study was conducted using the 2011–2018 IBM® MarketScan® Commercial and Medicare supplemental database, one of the largest collections of individual-level, de-identified, healthcare claims data from employers, health plans, hospitals and Medicare and Medicaid programs in the US [17]. The database includes inpatient and outpatient episode diagnoses (both ICD-9-CM and ICD-10-CM), procedures (CPT and HCPCS) and prescription records (retail and mail-order). Available prescription data include the National Drug Code (NDC), J-codes and the dispensed quantity supply [17].

### 2.3. Study populations

#### 2.3.1. Incidence of breast cancer

The primary analysis calculated the BC incidence in VVA patients treated with ospemifene versus untreated matched controls. The study included women with a diagnosis of VVA, defined as > 45 years old and a diagnosis of postmenopausal atrophic vaginitis (ICD-9 code 627.3, ICD-10 code N95.2) or > 55 years and a diagnosis of atrophy of vulva (ICD-9 code 624.1, ICD-10 code N90.5) or dyspareunia (ICD-9 code 625.0, ICD-10 code N94.1). Women with BC or a history of BC were excluded from the study. BC was defined as 1) two BC diagnoses in outpatient settings in non-consecutive days within 90-day period, 2)

mastectomy, 3) BC diagnosis with chemotherapy procedure, or 4) BC diagnosis with radiation procedures. History of BC was assessed using ICD-9/10 codes V10.3, Z853. The ospemifene cohort were patients treated with ospemifene and no other VVA-related treatment after the first diagnosis of VVA. Untreated controls were VVA women without any prescribed VVA-related treatment. Data for over-the-counter treatments for VVA were not available from this data source and were therefore not considered.

Matching methodology ensured treated cases and controls had similar baseline characteristics and comorbid conditions. Each ospemifene-treated patient was randomly matched to two controls in a two-step process. Step 1 matched each treated woman with any number of controls on age at index VVA date, year of index VVA, US region, and follow-up month from index VVA to last record. The index treatment date was copied from the treated to the matched controls as pseudo-index treatment date. Only patients and suitable matches with 1)  $\geq 1$  year of pharmacy and medical enrollment prior to index VVA date and 2)  $\geq 1$  year after the index treatment date, and 3) without evidence of BC (defined above) before treatment date were included for the next match step.

Step 2 randomly matched with two untreated controls on age at index VVA date, Charlson Comorbidity Index (CCI) categories at index VVA date [18], year of index VVA, US region, and follow up month from index VVA to the last record.

While the matching process matched on VVA index date, incidence analyses were based on treatment index dates. Incident BC cases after treatment index date for both cases and controls were defined using the BC definition stated above. Follow-up times ended at either cancer onset date or last record in the database, whichever occurred first.

#### 2.3.2. Recurrence of breast cancer

A secondary analysis assessed BC recurrence in VVA patients in BC remission. The study population was female with a diagnosis of VVA and evidence of BC in remission, defined as a diagnosis of confirmed BC or dispensing of  $\geq 6$  months of aromatase inhibitor (AI) 180 days prior to initiating ospemifene for patients receiving ospemifene. An ospemifene-treated group and an untreated-group were created using two steps. Step 1 selected all available cases and controls based on the above patient identification criteria. Controls were assigned pseudo-index dates based on their VVA index date plus the additional day gap between confirmed BC diagnosis or use of last AI to first ospemifene treatment in the treated patients. Among the 58 treated patients, there were 54 different day gap periods; therefore, each control patient had 54 potential pseudo-index dates. Only cases and controls with  $\geq 1$  year of pharmacy and medical enrollment prior to and after treatment- or pseudo-index dates and no evidence of receiving chemotherapy or other BC treatments within 180 days of the index treatment date or pseudo-index date were kept for the next matching process. Step 2 randomly selected matched controls in 1:1, 1:2, and 1:3 ratios on age, index treatment year, region and CCI score at index treatment date. The order of the 54 pseudo-index dates followed a random variable from a uniform distribution for the matching process. Controls did not have a single, definite pseudo-index date until matching was complete. In the analysis, the index date for cases was the date of first ospemifene treatment, the pseudo-index date for control was their VVA index date + the day gaps from matched case patient. The recurrence rate was assessed after index date for both cases and controls.

Though combination of tamoxifen and another AI combination has been found to be ineffective in clinical trials [19], the study explored its use in breast cancer recurrence cohort.

### 2.4. Statistical analyses

Descriptive statistics were used to summarize the demographic characteristics of the incidence cohorts. Continuous variables were described with mean, median, and standard deviation (SD). Categorical

variables were described with frequency and percentage. The BC incidence rate was calculated using total incident cases divided by total follow-up time from index treatment date until first observed BC event or the end of follow-up for each cohort. The rate ratio was calculated as the incidence rate in treated cohort over control cohort. The corresponding 95 % confidence intervals (CI) for BC in each cohort were calculated using Poisson regression with log link function without adjusting covariates. Time to BC onset was estimated using Kaplan-Meier (KM) analyses. The difference in survival probabilities between treated and untreated cohorts were assessed using long-rank tests. A life-table with 6-month intervals was constructed for the incident BC cases. A chi-squared test was used to test the association between BC recurrence and treatment because of the small sample size.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

### 3. Results

#### 3.1. Incidence of breast cancer

1,602,233 patients with  $\geq 1$  claim for VVA were identified in the MarketScan® database between 1 January 2011 and 31 December 2018. From these patients, 3157 patients met our ospemifene-treated case definition and 157,269 patients met our untreated control definition. After the first step matching, 3057 cases and 32,244 controls met the previously described criteria. After the second matching which required each case to have exactly 2 matched controls on CCI and no history of BC prior to treatment index date, a total of 1728 cases and 3456 controls were included for further analysis.

Included patients had a mean age of 57.8 (SD: 4.0). No statistically significant differences across demographic variables were observed. Average days ospemifene supplied was 313.7 days (SD = 340.3). The median follow-up time from index VVA to end of the follow-up was 969 days (31.8 months) (IQR: 659.5–1326.5 days) for cases and 970 days (31.9 months or 136.7 Weeks) (IQR: 656.0–1323.0) for controls ( $p = 0.91$ ). The median follow-up days from treatment index to the end of the follow-up differed by 22 days between cases and controls; cases had a median 884 days (IQR: 597.0–1204.5) compared to a median 906 days (IQR: 616.5–1244.0) for controls ( $p = 0.05$ ). This difference is likely clinically insignificant, and an artifact powered by a large sample size.

There was no statistically significant difference between incidence of BC among ospemifene-treated cases and the untreated controls; 9 cases (0.52 %) and 32 controls (0.93 %) had a BC diagnosis on or after ospemifene treatment index date ( $p = 0.121$ ). BC incidence rate was 2.03 per 1000 person-years (PY) (95 % CI: 1.06–3.91) in ospemifene-treated patients and 3.53 per 1000 PY (95 % CI: 2.49–4.99) in control group. The incidence rate ratio of 0.58 (95 % CI: 0.28–1.21) indicates a lower incidence of BC among ospemifene-treated patients, although not statistically significant (Table 1). A similar trend (2.83 per 1000 PY in the treated group vs. 3.51 in the control group) was observed after the

first matching step of cases to controls.

The KM curves of BC incidence further demonstrated lower incidence in ospemifene-treated patients, although not statistically significant (log-rank  $p = 0.137$ ); note the KM median was not reached (Fig. 1). For ospemifene-treated patients, the BC-free rate at 60 months was 99.2 % compared to 98.4 % in untreated patients. KM curves were similar when cases were matched to many controls. With the given sample size in each cohort and median follow-up time, the study had a 70 % of power to detect  $\geq 2$  hazard ratio between ospemifene and controls, a threshold commonly used to assess the safety of new products, and an 81.7 % power to detect  $\geq 2.2$  hazard ratio, both at 5% significance level.

A life-table at six-month post-treatment follow-up intervals demonstrated no increased incidence in BC between the two groups during the follow-up period (Table 2 a and b). Only three of the nine patients were diagnosed with BC while receiving ospemifene treatment, whereas more frequent diagnoses of BC occurred in the untreated group over time, including 21 diagnoses in the first 18 months of follow-up (Table 2a).

#### 3.2. Recurrence of breast cancer

After the first matching step, 58 patients with VVA treated with ospemifene had a history of BC and 14,657 patients with untreated VVA had a history of BC. 17 of 58 (29 %) ospemifene treated patients and 10,937 of 14,657 (75 %) controls had BC recurrence. After 1:1 matching at the second matching step, 46 of 58 ospemifene patients had 1 matched control and there was no observed increase in risk of BC recurrence in patients treated with ospemifene. Additional analyses were conducted with cases further matched 1:2 (each case must have 2 matched controls) and 1:3 with controls; each analysis demonstrated no increased risk in BC recurrence (Table 3). Of note, in the 1:1 matched cohort, only one treated patient and one control patient received treatment with tamoxifen and another AI combination therapy, thereby limiting any risk bias associated with AI and tamoxifen combinations.

### 4. Discussion

This study investigated the incidence and recurrence of BC among patients with VVA treated with ospemifene using MarketScan® database from 2011 to 2018. The use of ospemifene in women with BC was not studied in its clinical development program and is currently advised against in women with known or suspected BC or with a history of BC [9]. In Europe, ospemifene can be prescribed to cancer survivors, if they have completed their active/adjuvant treatment [10]. Preclinical/animal model studies showed ospemifene had no effect on normal breast tissue and subsequent analyses using clinical data have demonstrated no increased risk in BC-related outcomes [12,13,15,20,21]. Therefore, the safety of ospemifene use in women with BC, BC survivors or women at risk for BC is of interest to both physicians and patients.

Since its 2013 approval, clinical studies have reported results in

**Table 1**

Incidence rate of breast cancer per 1000 patients per follow-up year and treatment year.

Crude Analysis	Treated group (N = 1728)	Untreated Group (N = 3456)	Rate Ratio
<i>Assessment per follow-up year</i>			
Total number of patients with breast cancer diagnosis any time on or after treatment index date (%)	9 (0.52)	32 (0.93)	
Total number of treatment years between index date and follow-up end date	4428	9074	
Incidence rate of breast cancer per 1000 patients per follow-up year (95 % CI)	2.03 (1.06–3.91)	3.53 (2.49–4.99)	0.58 (0.28–1.21)
<i>Assessment per treatment year</i>			
Total number of patients with breast cancer diagnosis any time while on treatment (only use first continuous treatment - 90-day gap)	3	–	
Total number of treatment years between treatment start and treatment end	1420	–	
Incidence rate of breast cancer per 1000 patients per treatment year (95 % CI)	2.11 (0.44–6.18)		

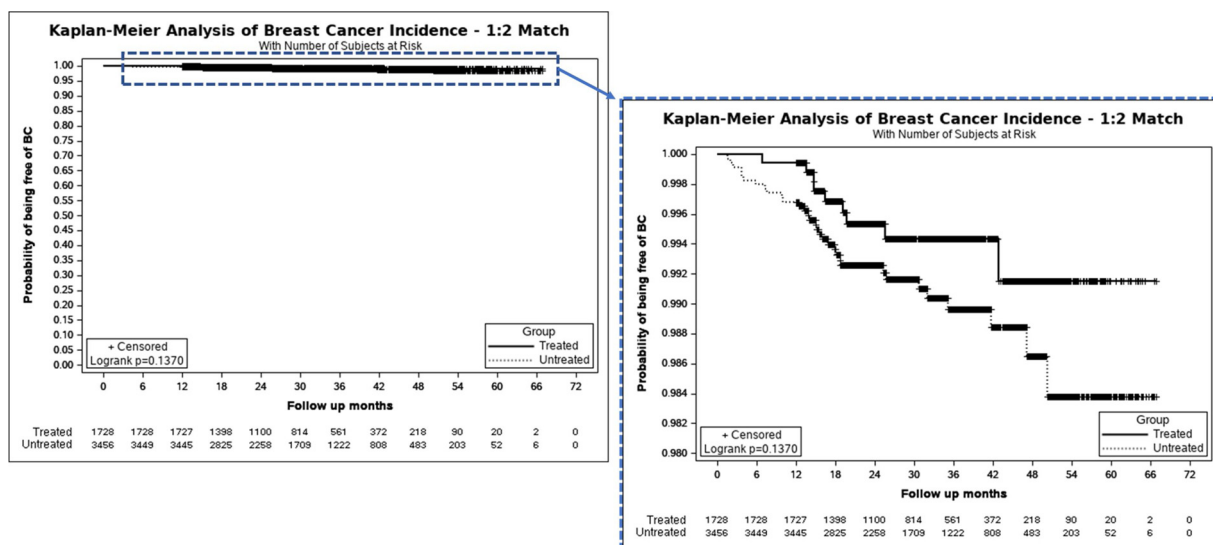


Fig. 1. Kaplan-Meier analysis of breast cancer incidence (1:2 matching). Fig. 1A shows the Kaplan-Meier curve with the probability of breast cancer free on a 0–1.00 scale. Fig. 1B is a zoomed-in view of the Kaplan-Meier curves with a probability of breast cancer free scale of 0.980–1.00.

support of ospemifene use in women with BC or suspected history [11–16]. Most recently, a 2019 meta-analysis of randomized trials on VVA treatment found that the incidence of BC was not significantly different between patients receiving ospemifene and those receiving placebo [11]. The longest of the studies included, a 52-week follow-up investigation (after a 12-week treatment period) of the long-term safety of ospemifene in the treatment of hysterectomized patients with VVA, mean age 59.4, found that in 301 subjects there were no instances of BC [12]. A study in postmenopausal women, mean ages 57.7–58.4, with a uterus similarly found no instances of BC after 52 weeks of ospemifene treatment [13]. In both these studies, the patients were approximately the same age as women in our study.

To the authors’ knowledge, this is the first study to utilize a large, national database to assess the relation between BC incidence, recurrence and ospemifene treatment. With median follow-up data of over 126 weeks and 1728 cases, this study found that there was a no significant difference in incidence of BC in patients with VVA treated with ospemifene versus matched untreated patients. Additionally, there was no increased recurrence of BC in patients in remission treated with ospemifene versus untreated. This may be a result of ospemifene’s antiestrogen effect in the breast tissue.

4.1. Limitations

While administrative claims databases’ ability to facilitate real-world safety and efficacy research is unquestioned, these databases do present certain limitations. Assessing ospemifene treatment utilization as prescribed is a limitation with claims data. MarketScan® provides a record of drug dispensing claims; however, it does not provide adherence information, as such, patients prescribed ospemifene may not have used it as prescribed, potentially biasing safety results here.

Certain BC risk or prognostic factors [e.g. age at menarche and menopause, parity, family history, prior use of SERMS or AI in a preventative manner, BC stage at diagnosis (applies only to recurrence analysis) and breast atypia] were not available in this data source. As such, it was not possible to match patients or balance the cohorts based on these factors. Further, rationales for recorded interventions were not available. It was difficult to ascertain whether mastectomy, used in this study as a proxy for BC diagnosis, was done prophylactically, as a contralateral prophylactic mastectomy (CPM). However, rates of CPM are significantly lower than unilateral mastectomies and would likely represent a small proportion of our case population [22]. Furthermore,

prophylactic procedures would be billed using specific procedure codes for CPM, which were not included in our definition of mastectomy. Claims databases are subject to possible coding errors, coding for the purpose of rule-out rather than actual disease, and under-coding, without the possibility of verifying reported diagnoses. Generally, this type of non-directional misclassification error should bias to the null and therefore make our results more conservative.

The two-year time horizon may confer additional limitations. Studies have shown that BC recurrence in estrogen receptor-positive (ER+) BC may have late recurrence [23–25]. However, it is rare that recurrence curves would cross over time and therefore it would be unexpected to see drastically different results over longer follow-ups. Nonetheless, additional studies are warranted to verify that the trends remain consistent over longer periods.

From an analytical perspective, the case-control matched approach had limitations. This method aims to mitigate observable risk factors and confounding variables that may impact risk of BC incidence and recurrence; given the strict matching criteria, where cases were matched with two controls, the full sample of patients was not fully utilized.

4.2. Conclusions

Ospemifene-treated VVA patients did not have a higher incidence of breast cancer or breast cancer recurrence than postmenopausal women with VVA without any prescribed VVA-related treatment. This analysis further supports the findings of prior evidence reporting no increased risk for breast cancer-related safety concerns among patients receiving ospemifene [14–18,20]. Additional efforts should be made to educate both physicians and patients of the safety of ospemifene as a treatment option for postmenopausal women with VVA who have had or may be at risk for breast cancer.

Contributors

Bin Cai conceptualized the study and contributed to the data analysis, data interpretation, and review and editing of the manuscript.

James Simon contributed to data interpretation, and review and editing of the manuscript.

Paola Villa contributed to data interpretation, and review and editing of the manuscript.

Nicoletta Biglia contributed to data interpretation, and review and

**Table 2**

Life table estimate of the risk of breast cancer over 6-month post-treatment follow-up intervals, (a) censoring patients discontinuing treatment and those lost to follow and (b) only censoring patients lost to follow-up.

(a)						
Group	Interval		Number of patients at the beginning of interval	Number of breast cancer diagnoses	Number of patients censored during the interval	Cumulative probability of cancer free
	Follow-up month begins	Follow-up month ends				
Ospemifene-treated group	0	6 months	1728	0	724	1.0000
	6 months	12 months	1004	1	216	1.0000
	12 months	18 months	787	1	229	0.9989
	18 months	24 months	557	1	158	0.9974
	24 months	30 months	398	0	139	0.9953
	30 months	36 months	259	0	98	0.9953
	36 months	42 months	161	0	62	0.9953
	42 months	48 months	99	0	46	0.9953
	48 months	54 months	53	0	31	0.9953
	54 months	60 months	22	0	18	0.9953
	60 months	66 months	4	0	4	0.9953
	66 months	.	0	0	0	0.9953
	Untreated group	0	6 months	3456	7	0
6 months		12 months	3449	4	0	0.9980
12 months		18 months	3445	10	610	0.9968
18 months		24 months	2825	3	564	0.9936
24 months		30 months	2258	2	547	0.9925
30 months		36 months	1709	3	484	0.9915
36 months		42 months	1222	1	413	0.9894
42 months		48 months	808	1	324	0.9885
48 months		54 months	483	1	279	0.9869
54 months		60 months	203	0	151	0.9841
60 months		66 months	52	0	46	0.9841
66 months		72 months	6	0	6	0.9841
72 months		.	0	0	0	0.9841

(b)						
Group	Interval		Number of patients at the beginning of interval	Number of breast cancer diagnoses	Number of patients censored during the interval	Cumulative probability of cancer free
	Follow-up month begins	Follow-up month ends				
Ospemifene-treated group	0	6 months	1728	0	0	1.0000
	6 months	12 months	1728	1	0	1.0000
	12 months	18 months	1727	4	325	0.9994
	18 months	24 months	1398	2	296	0.9969
	24 months	30 months	1100	1	285	0.9953
	30 months	36 months	814	0	253	0.9942
	36 months	42 months	561	0	189	0.9942
	42 months	48 months	372	1	153	0.9942
	48 months	54 months	218	0	128	0.9909
	54 months	60 months	90	0	70	0.9909
	60 months	66 months	20	0	18	0.9909
	66 months	72 months	2	0	2	0.9909
	72 months	.	0	0	0	0.9909
Untreated group	0	6 months	3456	7	0	1.0000
	6 months	12 months	3449	4	0	0.9980
	12 months	18 months	3445	10	610	0.9968
	18 months	24 months	2825	3	564	0.9936
	24 months	30 months	2258	2	547	0.9925
	30 months	36 months	1709	3	484	0.9915
	36 months	42 months	1222	1	413	0.9894
	42 months	48 months	808	1	324	0.9885
	48 months	54 months	483	1	279	0.9869
	54 months	60 months	203	0	151	0.9841
	60 months	66 months	52	0	46	0.9841
	66 months	72 months	6	0	6	0.9841
	72 months	.	0	0	0	0.9841

Note: The assessment period was between the first claim date of ospemifene and the last claim date after accounting for days of supply. Continuous treatment duration was not considered.

editing of the manuscript.

Nicholas Panay contributed to data interpretation, and review and editing of the manuscript.

Stora Djumaeva contributed to data interpretation, and review and editing of the manuscript.

Martire Particco contributed to data interpretation, and review and editing of the manuscript.

Hemanth Kanakamedala contributed to the study conception and design, data analysis and review and editing of the manuscript.

Corrado Altomare contributed to data interpretation, and review

**Table 3**

: Recurrence of breast cancer in patients with VVA treated with ospemifene compared to untreated patients.

Matching (N cases, N controls)	Patients with Breast Cancer Diagnosis After Treatment Index Date		p-value <sup>1</sup>
	Ospemifene-Treated Group (N, %)	Untreated Group (N, %)	
1:1 (46, 46)	14 (30.43 %)	21 (45.65 %)	0.1328
1:2 (31, 62)	10 (32.26 %)	25 (40.32 %)	0.4492
1:3 (20, 60)	7 (35.00 %)	24 (40.00 %)	0.6910

<sup>1</sup> Chi-squared test was used to test for the association between breast cancer occurrence and treatment.

and editing of the manuscript.

All authors approved the manuscript for submission.

### Conflict of interest

Bin Cai is an employee of Shionogi, sponsor of the manuscript.

James Simon did not receive financial support for this work. However, he had previously served as a consultant for Shionogi.

Paola Villa did not receive financial support from Shionogi for this work and declares there is no conflict of interest.

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Stora Djumaeva is an employee of Shionogi, sponsor of the manuscript.

Martire Particco is an employee of Shionogi, sponsor of the manuscript.

Hemant Kanakamedala is an employee of the vendor contracted by Shionogi for analytical support.

Corrado Altomare is an employee of Shionogi, sponsor of the manuscript.

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Shionogi, Inc. (Florham Park, NJ) paid Genesis Research, LLC (Hoboken, NJ) to license US MarketScan® Commercial and Medicare Supplemental insurance claims database, conduct the analyses, and prepare the manuscript.

### Ethical approval

This study was conducted using an anonymous, publicly available secondary dataset that meets the US HIPPA requirement. Ethics approval and consent to participate were not applicable.

### Provenance and peer review

This article was not commissioned and was externally peer reviewed.

### Research data (data sharing and collaboration)

There are no linked research data sets for this paper. The license to use the third-party database is not transferable, as per the license contract. However, other researchers can obtain a license to access the same database from the data owner.

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