

Estimated impact of fezolinetant versus placebo on work productivity and indirect costs among women experiencing vasomotor symptoms associated with menopause

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Abstract

Objectives: This study evaluated the impact of fezolinetant versus placebo on work productivity and indirect costs among women with moderate to severe vasomotor symptoms (VMS) associated with menopause in seven countries.

Methods: This post hoc analysis used Work Productivity and Activity Impairment (WPAI) questionnaire data from the SKYLIGHT 1 (NCT04003155), SKYLIGHT 2 (NCT04003142), and DAYLIGHT (NCT05033886) trials to compare absenteeism, presenteeism, and productivity loss among fezolinetant-treated versus placebo-treated women with moderate to severe VMS (population 1) and among these women for whom hormone therapy (HT) was unsuitable (population 2). Missed work time was calculated as the product of patient-reported work productivity loss and country-specific work hours and employment rates extracted from publicly available, country-specific sources. Annualized indirect costs were estimated based on missed work time and country-specific estimated salaries.

Results: Over 1 year, fezolinetant improved work productivity versus placebo. In population 1, increases ranged from 2.8 (Brazil) to 4.2 (United States) weekly work hours per woman with fezolinetant versus placebo. Fezolinetant resulted in estimated annualized cost savings per woman versus placebo in population 1 of 7,791 USD (United States), 7,295 CAD (Canada), 3,878 GBP (United Kingdom), 8,953 AUD

(Australia), 6,193 EUR (Germany), 3,901 EUR (France), and 2,754 BRL (Brazil). Overall work productivity loss improved with fezolinetant versus placebo (population 1: -12.4% [$P < 0.0001$]; population 2: -10.2% [$P < 0.0001$]).

Conclusions: Fezolinetant demonstrated improvements in work productivity and reduced estimated indirect costs versus placebo for women with moderate to severe VMS, including HT-unsuitable women who often face limited treatment options, maintained through 52 weeks.

Key Words: Absenteeism, Change of life, Economics, Hot flashes, Presenteeism.

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Menopause, the permanent cessation of menstrual periods, typically occurs between the ages of 40 and 60 years, with a median age of onset around 49–51 years.^{1–3} Menopause is characterized by a wide range of symptoms caused by hormone fluctuations and other physiological changes, with the most common being vasomotor symptoms (VMS; ie, hot flashes and night sweats).^{1,4,5} Affecting up to 80% of women during men-

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Inclusive language: In our report, we use gender-specific language, as reflected in the referenced publications and protocols. However, we recognize that some individuals who experience vasomotor symptoms associated with menopause may identify differently from the gender and pronouns used here.

Details for how researchers may request access to anonymized participant-level data, trial-level data and protocols from Astellas-sponsored clinical trials can be found at <https://www.clinicaltrials.astellas.com/transparency/>.

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opause, VMS contribute to sleep disturbances, anxiety, mood changes, fatigue, and cognitive impairment, all of which impact quality of life and work productivity.^{1,2,4,6-8}

Although a variety of treatments exist for VMS associated with menopause, there are major concerns about the long-term safety of their use.⁷ Hormone therapy (HT) is the mainstay of menopause treatment, yet it is contraindicated in some women due to concerns of increased risk of breast and endometrial cancer, cardiovascular disease, and venous thromboembolism.^{4,7,9-11} Moreover, many eligible women choose to forgo HT due to personal preferences or perceived risks, reinforcing the need for effective non-HT alternatives.^{12,13} Non-HT options are not often recommended due to limited efficacy or serious adverse events.^{4,7}

Fezolinetant, an oral, nonhormone, selective neurokinin-3 receptor antagonist, is a novel treatment option for moderate to severe VMS associated with menopause.^{9,14-16} The efficacy and safety of fezolinetant, compared with placebo, in reducing moderate to severe VMS in women have been demonstrated in several phase 3 randomized, placebo-controlled trials, including SKYLIGHT 1 (NCT04003155)¹⁴ and SKYLIGHT 2 (NCT04003142),¹⁵ which enrolled women with VMS, and DAYLIGHT (NCT05033886), which enrolled women with VMS for whom HT was unsuitable.^{9,16} Including this HT-unsuitable population in the study was important because it represents a key unmet need and an area of particular clinical and economic interest. Based on the results of SKYLIGHT 1 and 2, fezolinetant was approved in many regions, including North America, Europe, Asia, and Australia, to treat moderate to severe VMS associated with menopause at a dose of 45 mg once daily.¹⁷⁻²²

This study evaluated the effect of fezolinetant compared with placebo on work productivity and

estimated indirect costs among women with moderate to severe VMS in the United States, Canada, the United Kingdom, Germany, France, Australia, and Brazil. This analysis used patient-reported data collected from the Work Productivity and Activity Impairment (WPAI) questionnaire in three fezolinetant clinical trials specific to VMS (WPAI-VMS) outcomes along with country-specific national statistics regarding employment rates, work hours, and wage data to estimate missed work hours and annualized indirect costs associated with VMS.

METHODS

Study design and data sources

This post hoc analysis was conducted using patient-reported data collected from the WPAI-VMS in three fezolinetant clinical trials (SKYLIGHT 1, SKYLIGHT 2, and DAYLIGHT) combined with data on work hours, employment rates, and wages extracted from publicly available, country-specific sources (Fig. 1).

The six-item WPAI-VMS collects patient-reported VMS-related absenteeism, presenteeism, overall productivity loss, and activity impairment over the preceding 7 days²³; note that the activity impairment item reflects general daily activities and was not included in the work productivity loss calculation. For this analysis, WPAI items were adapted by specifying that all questions referred explicitly to VMS, consistent with previous adaptations of the WPAI instrument. WPAI-VMS outcomes are expressed as percentages, with higher percentages denoting worse outcomes.

In the SKYLIGHT 1 and SKYLIGHT 2 trials, WPAI-VMS data were collected at weeks 0 (baseline), 4, and 12 for women treated with fezolinetant or placebo and at weeks 24 and 52 for women treated with fezolinetant; although women in the placebo arm were switched to the fezolinetant arm after the 12-week

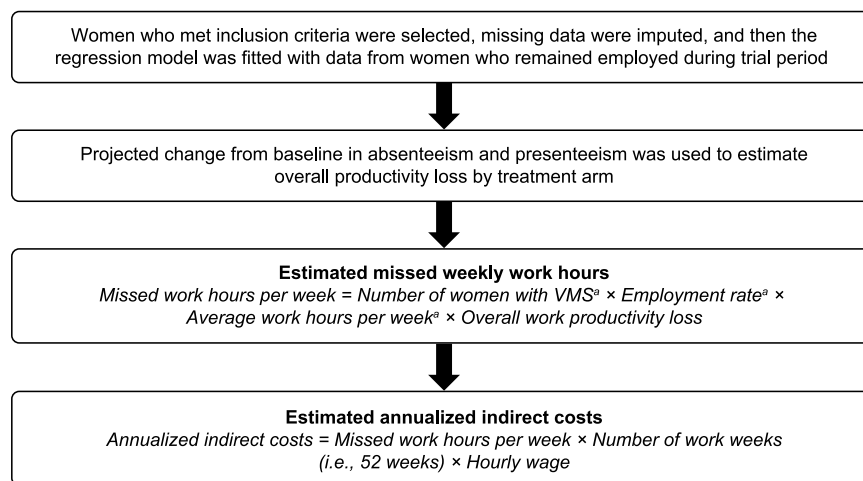


FIG. 1. Overview of the study analysis with equations for estimated missed weekly work hours and annualized indirect costs. ^aCountry-specific input. VMS, vasomotor symptoms.

placebo-controlled period, this analysis included only women who were randomized to fezolinetant at baseline and excluded those who were switched from the placebo arm. In the DAYLIGHT trial, WPAI-VMS data were collected at weeks 0, 4, 12, 16, and 24 for women treated with fezolinetant or placebo. Missing WPAI-VMS values were imputed using the last observation carried forward (LOCF) method up to week 52 for both fezolinetant and placebo, except when the last available observation was at baseline, in which case linear interpolation was applied between baseline and the first postbaseline value (Supplemental Digital Content 1, <http://links.lww.com/MENO/B487> study design schematic).

Publicly available, country-specific sources were resourced for employment rate, work hours, and wage data for women in an age group close to the trial population range (40–65 y) in each of the seven countries included in the analysis. These national sources included the US Bureau of Labor Statistics, Statistics Canada, the Office for National Statistics (United Kingdom), the Federal Statistics Office of Germany, the National Institute of Statistics and Economic Studies (France), the Australian Bureau of Statistics, and the Brazilian Institute of Geography and Statistics, as well as the Organization for Economic Co-operation and Development (OECD), which is an intergovernmental organization comprising 38 member countries.²⁴ These data were then applied to the WPAI-VMS outcomes directly reported by patients to generate country-specific indirect cost estimates and missed work hours.

Study population

Two study populations were included based on the criteria listed below. Population 1 included employed women from the SKYLIGHT 1 and 2 trials with moderate to severe VMS associated with menopause who received either fezolinetant 45 mg or placebo at randomization and had a baseline WPAI-VMS assessment. Population 2 included employed women from the SKYLIGHT 1 and 2 and DAYLIGHT trials with moderate to severe VMS associated with menopause who received fezolinetant 45 mg or placebo at randomization, were HT-unsuitable, and had a baseline WPAI-VMS assessment. Women who met the inclusion criteria were further classified into one of two groups based on their employment status during the trial follow-up period: (1) those who were employed at any point during follow-up (ie, had ≥ 1 postbaseline WPAI-VMS score) or (2) those who were unemployed through the entire follow-up period (ie, no postbaseline WPAI-VMS score). LOCF methods were applied only to data from the first group, as this analysis required ≥ 1 postbaseline WPAI-VMS score. This classification bolstered estimations of missed work hours and indirect costs.

Statistical analysis

All analyses were performed separately for the two study populations. Baseline demographic and clinical characteristics were analyzed descriptively, with pairwise

comparisons between treatment arms conducted using Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. Nonparametric tests were selected because WPAI-VMS outcomes are typically skewed and not normally distributed, consistent with prior literature.²⁵ Scoring formulas for WPAI-VMS domains followed standard published methods.²³ Weekly work hours were calculated as the weighted average of hours worked by full-time and part-time employees.

The WPAI is a questionnaire that collects raw data (eg, hours missed due to health problems, hours worked) reported by individual patients at different time points. These data were analyzed to estimate absenteeism and presenteeism over specific periods (baseline or follow-up) within a defined population (the pooled cohort of fezolinetant- and placebo-treated women or by treatment arm). Among all women who were employed at baseline, regardless of employment status at trial follow-up, pretreatment absenteeism and presenteeism rates were estimated by a pooled cohort of fezolinetant- and placebo-treated women, and overall work productivity loss was calculated using formula (1).

$$\begin{aligned} &\text{Overall work productivity loss} \\ &= \left[\frac{\text{Absenteeism}}{100} + \left(\frac{\text{Presenteeism}}{100} \right) \right. \\ &\quad \left. \times \left(1 - \frac{\text{Absenteeism}}{100} \right) \right] \times 100. \end{aligned} \quad (1)$$

For women who remained employed during the trial follow-up, generalized estimating equation models with a Gaussian distribution and identity link were used to estimate absenteeism and presenteeism over 1 year of treatment by treatment arm. Women who became unemployed during the trial follow-up were assumed to have 100% absenteeism. The overall work productivity loss was calculated by the weighted sum of absenteeism for unemployed women (100%) and absenteeism and presenteeism for employed women (estimated from regression models).

Missed work hours per week before treatment (due to absenteeism, presenteeism, and overall work productivity loss) were calculated for the pooled cohort of fezolinetant- and placebo-treated women as the product of baseline WPAI-VMS outcomes and country-specific average weekly work hours and employment rate.

After 1 year of treatment, missed work hours per week due to absenteeism were calculated according to employment status during the trial follow-up periods as a weighted sum of formulas (2) and (3). Missed hours per week due to presenteeism after 1 year of treatment among employed women were calculated using formula (4). Missed work hours per week due to overall work productivity were the sum of missed work hours from absenteeism and presenteeism for both employed and

TABLE 1. Baseline characteristics of employed women with moderate to severe VMS in population 1^a and population 2^b

Parameter	Population 1		<i>P</i>	Population 2		<i>P</i>
	Fezolinetant 45 mg (n = 188)	Placebo (n = 171)		Fezolinetant 45 mg (n = 313)	Placebo (n = 301)	
Age, mean (SD), y	53.8 (5.1)	53.8 (4.1)	0.9707	54.1 (4.8)	53.7 (4.2)	0.2704
Race, n (%)			0.9439			0.6858
White	150 (79.8)	142 (83.0)		273 (87.2)	270 (89.7)	
Black/African American	31 (16.5)	24 (14.0)		32 (10.2)	23 (7.6)	
Other ^c	7 (3.7)	5 (2.9)		8 (2.6)	7 (2.3)	
Ethnicity, not Hispanic or Latino, n (%)	154 (81.9)	139 (81.3)	0.8328	129 (41.2)	124 (41.2)	0.9912
Time since amenorrhea onset, mo, mean (SD)	78.7 (75.0)	69.2 (75.5)	0.2390	70.8 (64.7)	61.6 (65.1)	0.0935
Time since hot flash onset, mo, mean (SD)	70.6 (66.6)	69.1 (62.4)	0.8285	64.1 (58.0)	64.7 (60.3)	0.8985
Severity ^d of moderate to severe VMS, mean (SD)	2.4 (0.3)	2.4 (0.3)	0.6013	2.4 (0.4)	2.4 (0.3)	0.5326
Frequency ^e of moderate to severe VMS, mean (SD)	11.1 (5.5)	11.2 (4.4)	0.8367	10.9 (4.8)	10.8 (4.0)	0.7157
Treatment history, n (%)			0.2167			0.2091
No prior HT	143 (76.1)	143 (83.6)		233 (74.4)	237 (78.7)	
HT unsuitable	158 (84.0)	152 (88.9)		NA	NA	
WPAI-VMS, mean (SD)						
Absenteeism	5.0 (12.3)	4.2 (11.0)	0.5180	4.6 (13.3)	3.6 (11.4)	0.3214
Presenteeism	42.7 (28.1)	46.0 (26.2)	0.2587	42.6 (27.6)	43.3 (26.2)	0.7496
Overall work productivity loss	44.7 (29.0)	47.8 (26.7)	0.2958	44.2 (28.3)	44.7 (26.8)	0.8134

HT, hormone therapy; NA, not applicable; VMS, vasomotor symptoms; WPAI-VMS, Work Productivity and Activity Impairment-Vasomotor Symptoms.

^aPopulation 1: Employed women from the SKYLIGHT 1 and SKYLIGHT 2 trials with moderate to severe VMS associated with menopause who received fezolinetant 45 mg or placebo at randomization and had a baseline WPAI-VMS assessment.

^bPopulation 2: Employed women from the SKYLIGHT 1, SKYLIGHT 2, and DAYLIGHT trials with moderate to severe VMS associated with menopause who received fezolinetant 45 mg or placebo at randomization were HT-unsuitable and had a baseline WPAI-VMS assessment.

^c“Other” includes American Indian/Alaska Natives, Asian/Pacific Islanders, other race, and those who selected >1 race.

^dBaseline VMS severity was calculated as the mean of nonmissing daily weighted average severities of moderate to severe VMS over the 10 days immediately preceding randomization and was scored on a scale from 0 (none) to 3 (severe).

^eBaseline VMS frequency was calculated as the mean of the nonmissing daily numbers of moderate to severe VMS recorded over the 10 days immediately preceding randomization.

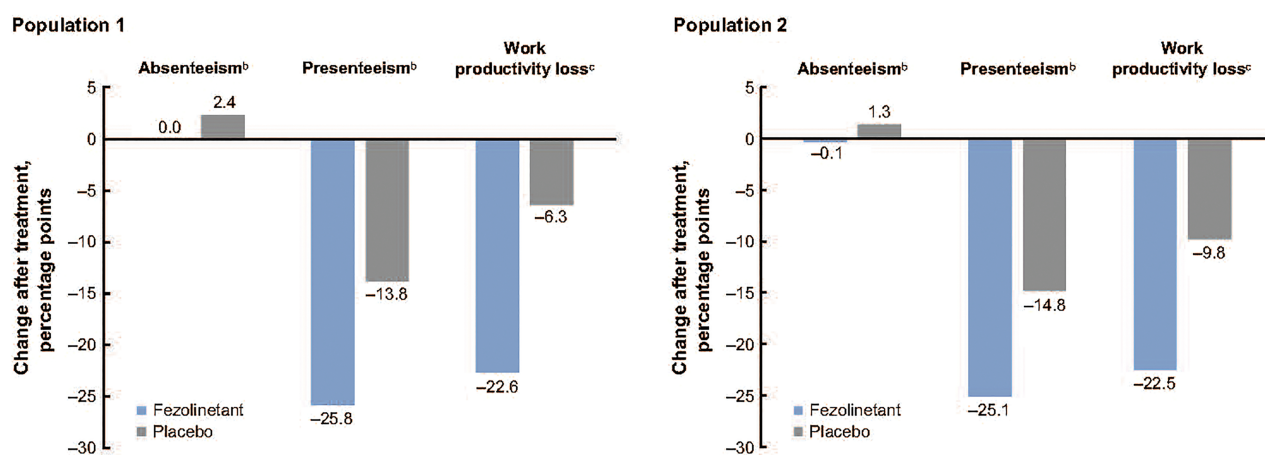


FIG. 2. WPAI-VMS^a after 1 year of treatment in women with moderate to severe VMS. ^aA positive change denotes a worsening in work productivity, while a negative change denotes an improvement in work productivity. ^bAbsenteeism and presenteeism were estimated using regression models for women who remained employed after treatment. ^cOverall work productivity loss was calculated as absenteeism + (1 – absenteeism) × presenteeism. VMS, vasomotor symptoms; WPAI-VMS, Work Productivity and Activity Impairment-Vasomotor Symptoms.

TABLE 2. Rates of any employment and full-time employment among women with moderate to severe VMS by country (from national statistics; not participant-reported)

Country	Employment rate, % ^a	Full-time employment, %	Employment rate year	Source
United States	68.3	84.1	2023	US Bureau of Labor Statistics ^{26,27}
Canada	70.3	78.9	2023	Statistics Canada ^{28,29}
United Kingdom	72.7	61.3	2023	Office for National Statistics ^{30,31}
Australia	67.4	50.8	2021	Australian Bureau of Statistics ³²
Germany	77.7	50.1	2023	Federal Statistics Office of Germany ^{33,34}
France	68.2	75.7	2021	French National Institute of Statistics and Economic Studies ^{35–37}
Brazil	50.2	71.8	2022	Brazilian Institute of Geography and Statistics ³⁸

VMS, vasomotor symptoms.

^aEmployment rates were calculated as the weighted average among women across available age groups in the United States (age 40–64 y), Canada (age 45–64 y), United Kingdom (age 40–64 y), Germany (age 40–64 y), France (age 40–64 y), Australia (age 40–64 y), and Brazil (age 50–59 y) to align with the age ranges of the trial populations (age 40–65 y).

unemployed women during the trial periods. Changes in missed work hours per week before and after 1 year of treatment were estimated for fezolinetant- and placebo-treated women, and differences in changes between treatment arms were reported.

Missed weekly work hours due to absenteeism (Unemployed)

$$\begin{aligned}
 &= \text{Average work hours per week} \\
 &\times \text{Employment rate} \\
 &\times \text{Absenteeism (100\% assumption).}
 \end{aligned}
 \tag{2}$$

Missed weekly work hours due to absenteeism (Employed)

$$\begin{aligned}
 &= \text{Average work hours per week} \\
 &\times \text{Employment rate} \\
 &\times \text{Absenteeism (estimated from regression models).}
 \end{aligned}
 \tag{3}$$

Missed weekly work hours due to presenteeism (Employed)

$$\begin{aligned}
 &= \text{Average work hours per week} \times \text{Employment rate} \\
 &\times \text{Presenteeism} \\
 &\times (1 - \text{Absenteeism}) \text{ (estimated from regression models).}
 \end{aligned}
 \tag{4}$$

Indirect costs were modeled estimates based on WPAI-VMS outcomes combined with national employment and wage data (not directly reported participant data). Specifically, annualized indirect costs were calculated as missed work hours per week multiplied by the country-specific number of work weeks per year and hourly wage. Similar to missed work hours, annualized indirect costs were estimated before treatment for the pooled cohort of fezolinetant- and placebo-treated women and, after 1 year of treatment, separately for fezolinetant- and placebo-treated women. Annualized indirect costs due to absenteeism, presenteeism, and overall work productivity were calculated based on formulas (5), (6), and (7), respectively. Changes in indirect costs before and after 1 year of treatment were estimated for fezolinetant- and placebo-treated women, and differences in changes between the two groups were reported. Unemployment was not directly assessed; however, WPAI sample sizes at each follow-up reflected employed participants, indicating that most women remained

employed and provided WPAI data throughout the trials.

Annualized indirect costs due to absenteeism

$$\begin{aligned}
 &= \text{Missed weekly work hours due to absenteeism} \\
 &\times \text{Hourly wage} \\
 &\times \text{Number of work weeks.}
 \end{aligned}
 \tag{5}$$

Annualized indirect costs due to presenteeism

$$\begin{aligned}
 &= \text{Missed weekly work hours due to presenteeism} \\
 &\times \text{Hourly wage} \\
 &\times \text{Number of work weeks.}
 \end{aligned}
 \tag{6}$$

Annualized indirect costs due to overall work productivity loss

$$\begin{aligned}
 &= \text{Missed weekly work hours due to overall work productivity loss} \\
 &\times \text{Hourly wage} \\
 &\times \text{Number of work weeks.}
 \end{aligned}
 \tag{7}$$

Missing data were handled using LOCF for patients who discontinued before week 52. Data processing, summarization, and analyses were performed in SAS version 9.4 or higher or RStudio and Excel on Windows.

RESULTS

Among 193 fezolinetant-treated and 186 placebo-treated women who met the inclusion criteria in population 1, 188 (97.4%) and 171 (91.9%), respectively, had ≥ 1 postbaseline WPAI-VMS measure and were included in the analyses; of these women, 5 (2.7%) and 15 (8.8%) became unemployed during trial follow-up in the fezolinetant and placebo arms, respectively (Supplemental Digital Content 2, <http://links.lww.com/MENO/B487>, sample selection flowchart, population 1). This pattern was consistent with WPAI sample sizes, which suggest that most participants remained employed and contributed data at each time point. Employed women had a mean age of 53.8 years, were predominantly white (81.3%), and had a mean VMS severity of 2.4 at baseline. There were no statistically significant differences between the two treatment arms at baseline in demographic or clinical variables (all $P > 0.05$) (Table 1).

TABLE 3. Annual and estimated hourly wages among women with moderate to severe VMS by country (from national statistics; not participant-reported)

Country	Annual wage in local currency ^a	Wage year	Annual wage in 2024 local currency ^b	Average work hours per week of full-time employees	Average work hours per week of part-time employees	Hourly wage in 2024 local currency ^c	Source for wage	Source for work hours
United States	64,700 USD	2022	69,288 USD	40.7	18.8	36 USD	US Census Bureau ³⁹	OECD ⁴⁰
Canada	59,034 CAD	2022	63,053 CAD	39.1	18.5	35 CAD	Statistics Canada ⁴¹	Statistics Canada ⁴²
United Kingdom	31,485 GBP	2023	32,597 GBP	39.1	19.0	20 GBP	Office for National Statistics ³⁰	OECD ⁴⁰
Australia	69,276 AUD	2021	80,800 AUD	39.2	19.0	53 AUD	Australian Bureau of Statistics ⁴³	OECD ⁴⁰
Germany	47,576 EUR	2023	48,721 EUR	37.2	17.6	34 EUR	Federal Statistics Office of Germany ⁴⁴	OECD ⁴⁰
France	30,652 ^d EUR	2021	34,695 EUR	38.3	18.1	20 EUR	French National Institute of Statistics and Economic Studies ⁴⁵⁻⁴⁸	OECD ⁴⁰
Brazil	30,424 ^d BRL	2022	33,136 BRL	40.8	17.4	19 BRL	Brazilian Institute of Geography and Statistics ³⁸	OECD ⁴⁰

AUD, Australian dollar; BRL, Brazilian real; CAD, Canadian dollar; EUR, Euro; GBP, Great Britain pound; OECD, Organisation for Economic Co-operation and Development; USD, United States dollar.

^aWages were calculated based on the weighted average among women across available age groups in the United States (age 45-64 y), Canada (age 45-64 y), the United Kingdom (age 40-59 y), Germany (age 40-64 y), France (age 40-59 y), Australia (age 45-64 y), and Brazil (age 50-59 y) to align with the age ranges of the trial populations (age 40-65 y).

^bWages in all countries were inflated to 2024 local currency based on country-specific consumer price indices retrieved from the Federal Reserve Bank of St. Louis (<https://fred.stlouisfed.org>).

^cEstimated hourly wages were calculated by dividing the annual wage by the average work hours per week among full-time and part-time employees, divided by 52 weeks.

^dThe annual wages in France and Brazil were calculated as their mean monthly wage multiplied by 12 months.

In population 2 (HT-unsuitable women across the SKYLIGHT 1, SKYLIGHT 2, and DAYLIGHT trials), 313 (97.8%) fezolinetant-treated and 301 (95.0%) placebo-treated women had ≥ 1 postbaseline WPAI-VMS measure and were included in the regression analysis (Supplemental Digital Content 3, <http://links.lww.com/MENO/B487>, sample selection flowchart, population 2). During follow-up, 7 (2.2%) and 16 (5%) became unemployed in the fezolinetant and placebo arms, respectively (Supplemental Digital Content 3, <http://links.lww.com/MENO/B487>, sample selection flowchart, population 2). Women in both populations had similar demographic and disease-related characteristics, including WPAI-VMS data, at baseline. Table 1 presents baseline characteristics for employed women in population 2 who were fezolinetant or placebo-treated during the trial follow-up periods.

WPAI-VMS data after treatment are summarized in Figure 2 for each population. Before treatment, mean baseline absenteeism, presenteeism, and overall work productivity loss were similar, yet numerically higher in population 1 versus population 2. After 1 year of treatment with fezolinetant or placebo, overall work productivity loss improved by 22.6 and 6.3 percentage points, respectively, in population 1 and by 22.5 and 9.8 percentage points, respectively, in population 2 (Fig. 2). Observed WPAI-VMS trends across SKYLIGHT and DAYLIGHT demonstrated that most improvements occurred within the first 4 weeks, with minimal changes thereafter (Supplemental Digital Content 4 and 5, <http://links.lww.com/MENO/B487>, trends in WPAI measures [population 1] and trends in WPAI measures [population 2]).

Employment rates ranged from 50.2% in Brazil to 77.7% in Germany, with the proportion employed full-time ranging from 50.1% (Germany) to 84.1% (United States), based on national labor statistics (Table 2).²⁶⁻³⁸ Annual wages in local currency, work hours per week for full- and part-time employees, and hourly wage per woman by country were obtained from national statistical agencies and are presented in Table 3.^{30,38-48} Overall, full-time employees worked between 37.2 (Germany) and 40.8 (Brazil) hours, with average hourly wages ranging from 19 BRL in Brazil to 53 AUD in Australia (2024 local currency).

Before treatment in population 1, the total missed work hours per week per woman due to overall work productivity loss ranged from 8.2 hours in Brazil to 12.0 hours in the United States (Supplemental Digital Content 6, <http://links.lww.com/MENO/B487>, missed work due to work productivity loss table). After 1 year of treatment, the women treated with fezolinetant reported notably low numbers of missed work hours (Table 4). In the United States, where total missed work hours were greatest, total missed work hours per week per woman were estimated to be 6.2 hours for fezolinetant versus 10.4 hours for placebo. In Brazil, total missed hours after 1 year of treatment were 4.2 hours per week per woman with fezolinetant and 7.1 hours per

TABLE 4. Missed work hours per week after 1 year of treatment due to work productivity loss per woman with moderate to severe VMS by country^a

Country	Population 1, per woman		Change from baseline	Population 2, per woman		Change from baseline
	Fezolinetant	Placebo	Fezolinetant/placebo	Fezolinetant	Placebo	Fezolinetant/placebo
United States						
Absenteeism						
Unemployed	0.7	2.1	0.6/2.0	0.6	1.3	0.5/1.2
Employed	1.1	1.6	0.0/0.6	1.0	1.3	0.0/0.3
Presenteeism	4.4	6.7	-6.4/-4.1	4.3	6.5	-6.3/-4.1
Overall work productivity loss	6.2	10.4	-5.8/-1.6	5.9	9.1	-5.8/-2.5
Canada						
Absenteeism						
Unemployed	0.6	2.0	0.6/1.9	0.5	1.2	0.5/1.2
Employed	1.1	1.6	0.0/0.5	1.0	1.3	0.0/0.3
Presenteeism	4.2	6.4	-6.2/-4.0	4.1	6.2	-6.0/-3.9
Overall work productivity loss	6.0	10.0	-5.6/-1.6	5.6	8.8	-5.5/-2.4
United Kingdom						
Absenteeism						
Unemployed	0.6	1.8	0.6/1.8	0.5	1.2	0.5/1.1
Employed	1.0	1.5	0.0/0.5	0.9	1.2	0.0/0.3
Presenteeism	3.9	6.0	-5.7/-3.7	3.8	5.8	-5.6/-3.6
Overall work productivity loss	5.5	9.3	-5.2/-1.4	5.2	8.1	-5.1/-2.3
Australia						
Absenteeism						
Unemployed	0.5	1.6	0.5/1.5	0.4	1.0	0.4/1.0
Employed	0.9	1.3	0.0/0.4	0.8	1.0	0.0/0.2
Presenteeism	3.4	5.2	-5.0/-3.2	3.3	5.0	-4.9/-3.2
Overall work productivity loss	4.8	8.1	-4.5/-1.3	4.5	7.1	-4.5/-2.0
Germany						
Absenteeism						
Unemployed	0.6	1.7	0.5/1.7	0.5	1.1	0.4/1.0
Employed	1.0	1.4	0.0/0.5	0.8	1.1	0.0/0.3
Presenteeism	3.7	5.6	-5.4/-3.5	3.6	5.4	-5.2/-3.4
Overall work productivity loss	5.2	8.7	-4.8/-1.4	4.9	7.6	-4.8/-2.1
France						
Absenteeism						
Unemployed	0.6	1.9	0.6/1.8	0.5	1.2	0.5/1.1
Employed	1.0	1.5	0.0/0.5	0.9	1.2	0.0/0.3
Presenteeism	4.0	6.0	-5.8/-3.7	3.9	5.8	-5.6/-3.7
Overall work productivity loss	5.6	9.3	-5.2/-1.5	5.3	8.2	-5.2/-2.3
Brazil						
Absenteeism						
Unemployed	0.5	1.4	0.4/1.3	0.4	0.9	0.4/0.8
Employed	0.8	1.1	0.0/0.4	0.7	0.9	0.0/0.2
Presenteeism	3.0	4.5	-4.4/-2.8	2.9	4.4	-4.3/-2.8
Overall work productivity loss	4.2	7.1	-3.9/-1.1	4.0	6.2	-3.9/-1.7

VMS, vasomotor symptoms.

^aWork hours based on country-specific statistics from the US Bureau of Labor Statistics, Statistics Canada, the Office for National Statistics (United Kingdom), the Federal Statistics Office of Germany, the National Institute of Statistics and Economic Studies (France), the Australian Bureau of Statistics, the Brazilian Institute of Geography and Statistics, and the Organization for Economic Co-operation and Development.

week per woman with placebo. Overall, this corresponded to an increase of 2.8 to 4.2 work hours per week per woman treated with fezolinetant versus placebo in population 1. A similar increase in work hours per week per woman treated with fezolinetant versus placebo was also observed in population 2. The increased work hours per week per woman due to overall work productivity loss in populations 1 and 2 are presented for each country in Figure 3.

Annualized estimated indirect costs due to work productivity loss before treatment per woman for populations 1 and 2 are presented by country in Supplemental Digital Content 7, <http://links.lww.com/MENO/B487>, indirect costs due to work productivity loss

table; corresponding modeled costs after treatment are included in Table 5 for comparison. Annualized estimated indirect costs due to overall work productivity loss before treatment ranged from 7,913 BRL per woman in Brazil to 25,727 AUD per woman in Australia for population 1 and from 7,656 BRL per woman to 24,893 AUD per woman for population 2. After 1 year of treatment, annualized indirect costs due to overall work productivity loss per woman in population 1 were estimated to be 13,305 AUD with fezolinetant and 22,259 AUD with placebo. On the lower end of the costs, annualized estimated indirect costs due to overall work productivity loss per woman in Brazil were 4,092 BRL with fezolinetant and 6,846 BRL with placebo in population 1. These re-

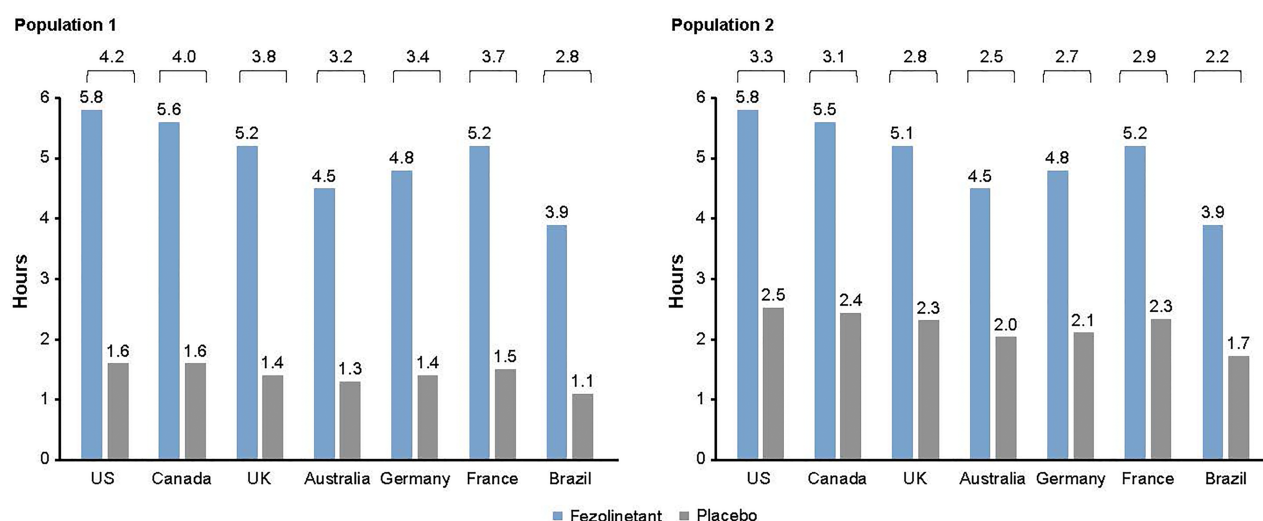


FIG. 3. Increase in work hours due to overall work productivity loss per woman per week after 1 year of treatment with fezolinetant versus placebo.

sults represent additional annualized cost savings of 8,953 AUD and 2,754 BRL with fezolinetant versus placebo in Australia and Brazil, respectively (Fig. 4). In population 2, additional annualized cost savings due to overall work productivity loss were similar to those in population 1 (Fig. 5).

DISCUSSION

This is the first study to evaluate the effect of fezolinetant on work productivity and estimated indirect costs among women with moderate to severe VMS associated with menopause in these seven countries. Compared with placebo, 1 year of treatment with fezolinetant was associated with greater improvements in work productivity, increased work hours, and greater reductions in estimated indirect costs.

Improvements in overall work productivity among women treated with fezolinetant were primarily due to sizeable changes in presenteeism compared with those treated with placebo. This phenomenon is confirmed by the Yuksel et al⁴⁹ study, which indicated that VMS-related work impairment is driven primarily by presenteeism. Women treated with fezolinetant in both populations also had lower absenteeism than those treated with a placebo, yet the differences were not substantial. In the SKYLIGHT 1 and 2 trials, improvements in overall work productivity, absenteeism, and presenteeism were observed with fezolinetant 45 mg versus placebo at week 12.⁵⁰ In the DAYLIGHT trial, fezolinetant was associated with improvements in presenteeism and overall productivity loss among women who were not suited for HT compared with those treated with placebo.¹⁶ Although improvements in absenteeism were not observed at week 24, the mean change from baseline was lower with fezolinetant versus

placebo (+0.94 vs. +2.39, respectively).¹⁶ These improvements were thought to be due to the positive impact of fezolinetant on improving VMS, thus promoting increased work productivity.⁵⁰

Multiple studies^{51–53} have shown that as the severity of VMS increases, so does their impact on overall work impairment (absenteeism and presenteeism), which may significantly impact indirect costs, especially among those who remain untreated. In the present study, annualized indirect costs before treatment ranged from 7,913 BRL per woman in Brazil to 25,727 AUD in Australia. In the United States, annualized indirect costs due to overall work productivity loss before treatment were estimated at 22,386 USD, with absenteeism accounting for 2,198 USD and presenteeism accounting for 20,188 USD. After 1 year of treatment, annualized costs due to overall work productivity loss were reduced to 11,577 USD with fezolinetant and to 19,368 USD with placebo. A 2015 study⁵⁴ of indirect costs among women with untreated VMS estimated that the incremental indirect costs of untreated VMS were 1,697 USD per person per year in 2011 USD (~2,377 in 2024 USD), primarily due to absenteeism. These costs are comparable with costs due to absenteeism within this study (2,198 USD), yet annualized indirect costs in this study were driven primarily by presenteeism.

Over the course of 1 year, treatment with fezolinetant was associated with a 48.3% reduction in annualized estimated indirect costs from baseline and an additional annualized estimated saving of 7,791 USD per woman versus placebo in the United States. Even after adjusting for differences in baseline characteristics, the benefit of treatment with fezolinetant remained the same regardless of a woman's suitability for HT compared with placebo.

TABLE 5. Estimated annualized indirect costs after 1 year of treatment due to work productivity loss per woman with moderate to severe VMS by country^a

Country	Population 1 ^b per woman (local currency)	Change from baseline Fezolinetant/placebo	Population 2 ^c per woman (local currency)	Change from baseline Fezolinetant/placebo
United States				
Absenteeism				
Unemployed	1,238.6 USD	3,855.5 USD	1,045.8 USD	2,413.1 USD
Employed	2,134.3 USD	3,058.6 USD	1,879.0 USD	2,454.5 USD
Presenteeism	8,204.6 USD	12,453.9 USD	8,002.0 USD	12,089.9 USD
Overall work productivity loss	11,577.5 USD	19,368.1 USD	10,926.9 USD	16,957.5 USD
Canada				
Absenteeism				
Unemployed	1,159.8 CAD	3,610.3 CAD	979.3 CAD	2,259.6 CAD
Employed	1,998.6 CAD	2,864.1 CAD	1,759.5 CAD	2,298.4 CAD
Presenteeism	7,682.7 CAD	11,661.7 CAD	7,493.0 CAD	11,320.9 CAD
Overall work productivity loss	10,841.0 CAD	18,136.1 CAD	10,231.8 CAD	15,878.8 CAD
United Kingdom				
Absenteeism				
Unemployed	616.5 GBP	1,919.0 GBP	520.5 GBP	1,201.1 GBP
Employed	1,062.3 GBP	1,522.4 GBP	935.3 GBP	1,221.7 GBP
Presenteeism	4,083.7 GBP	6,198.8 GBP	3,982.9 GBP	6,017.6 GBP
Overall work productivity loss	5,762.5 GBP	9,640.2 GBP	5,438.7 GBP	8,440.3 GBP
Australia				
Absenteeism				
Unemployed	1,423.4 AUD	4,431.0 AUD	1,201.9 AUD	2,773.2 AUD
Employed	2,452.9 AUD	3,515.1 AUD	2,159.5 AUD	2,820.8 AUD
Presenteeism	9,429.1 AUD	14,312.6 AUD	9,196.3 AUD	13,894.3 AUD
Overall work productivity loss	13,305.4 AUD	22,258.7 AUD	12,557.7 AUD	19,488.3 AUD
Germany				
Absenteeism				
Unemployed	984.5 EUR	3,064.7 EUR	831.3 EUR	1,918.1 EUR
Employed	1,696.5 EUR	2,431.2 EUR	1,493.6 EUR	1,951.0 EUR
Presenteeism	6,521.7 EUR	9,899.4 EUR	6,360.7 EUR	9,610.0 EUR
Overall work productivity loss	9,202.7 EUR	15,395.3 EUR	8,685.6 EUR	13,479.2 EUR
France				
Absenteeism				
Unemployed	620.2 EUR	1,930.6 EUR	523.7 EUR	1,208.3 EUR
Employed	1,068.7 EUR	1,531.6 EUR	940.9 EUR	1,229.1 EUR
Presenteeism	4,108.4 EUR	6,236.2 EUR	4,006.9 EUR	6,053.9 EUR
Overall work productivity loss	5,797.3 EUR	9,698.4 EUR	5,471.5 EUR	8,491.3 EUR
Brazil				
Absenteeism				
Unemployed	437.8 BRL	1,362.8 BRL	369.7 BRL	853.0 BRL
Employed	754.4 BRL	1,081.2 BRL	664.2 BRL	867.6 BRL
Presenteeism	2,900.1 BRL	4,402.2 BRL	2,828.5 BRL	4,273.5 BRL
Overall work productivity loss	4,092.4 BRL	6,846.2 BRL	3,862.4 BRL	5,994.1 BRL

AUD, Australian dollar; BRL, Brazilian real; CAD, Canadian dollar; EUR, Euro; GBP, Great Britain pound; HT, hormone therapy; USD, United States dollar; VMS, vasomotor symptoms; WPAI-VMS, Work Productivity and Activity Impairment-Vasomotor Symptoms.

^aIndirect costs based on country-specific employment, work hour, and wage statistics from the US Bureau of Labor Statistics, Statistics Canada, the Office for National Statistics (United Kingdom), the Federal Statistics Office of Germany, the National Institute of Statistics and Economic Studies (France), the Australian Bureau of Statistics, the Brazilian Institute of Geography and Statistics, and the Organization for Economic Co-operation and Development.

^bPopulation 1: Employed women from the SKYLIGHT 1 and SKYLIGHT 2 trials with moderate to severe VMS associated with menopause who received either fezolinetant 45 mg or placebo at randomization and had a baseline WPAI-VMS assessment.

^cPopulation 2: Employed women from the SKYLIGHT 1, SKYLIGHT 2, and DAYLIGHT trials with moderate to severe VMS associated with menopause who received fezolinetant 45 mg or placebo at randomization, were HT-unsuitable, and had a baseline WPAI-VMS assessment.

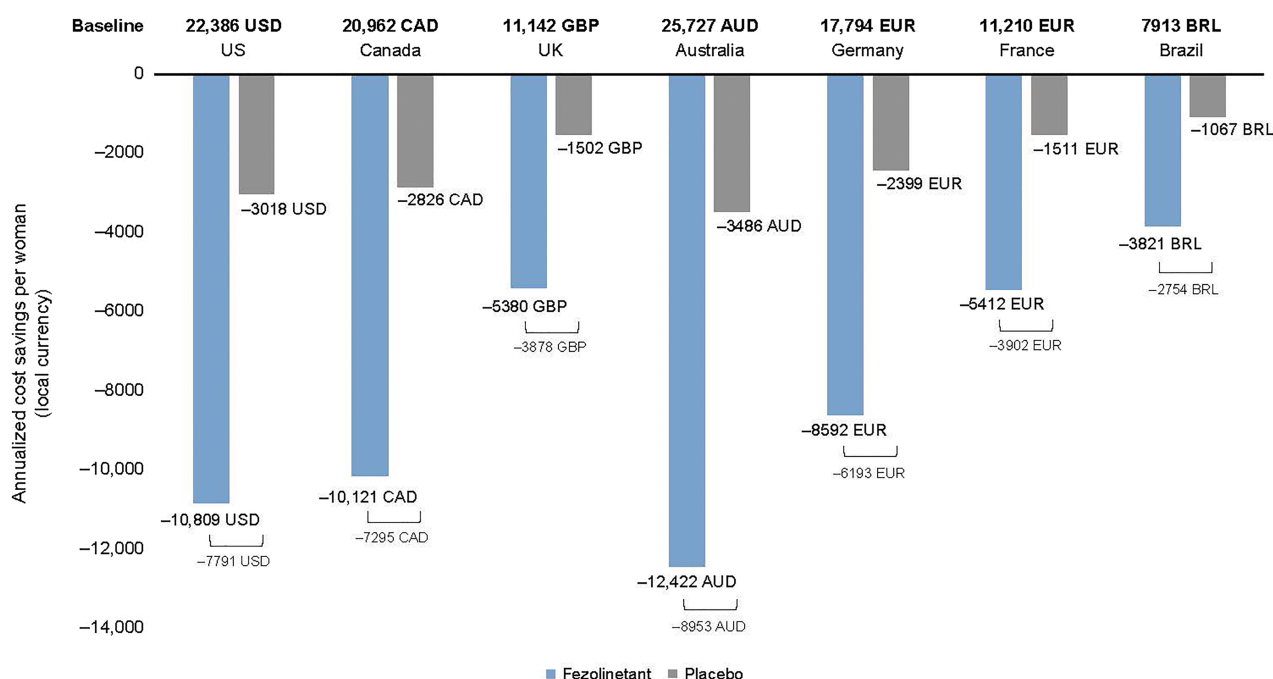


FIG. 4. Annualized cost savings per woman with moderate to severe VMS in population 1. AUD, Australian dollar; BRL, Brazilian real; CAD, Canadian dollar; EUR, Euro; GBP, Great Britain pound; USD, United States dollar; VMS, vasomotor symptoms.

Limitations

This study has several limitations. First, our indirect cost estimates relied on external employment and wage

data that may not fully reflect the specific study population. Follow-up duration varied across trials: placebo-treated women in SKYLIGHT 1 and SKY-

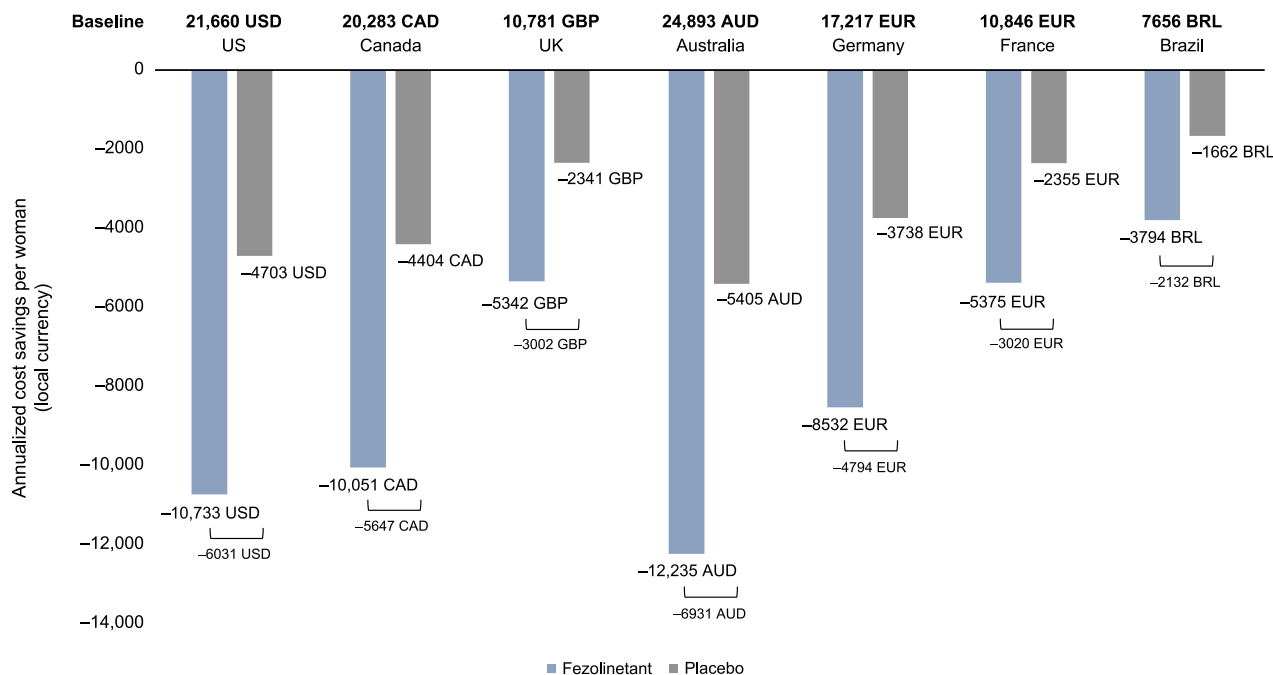


FIG. 5. Annualized cost savings per woman with moderate to severe VMS in population 2. AUD, Australian dollar; BRL, Brazilian real; CAD, Canadian dollar; EUR, Euro; GBP, Great Britain pound; USD, United States dollar; VMS, vasomotor symptoms.

LIGHT 2 had 12 weeks of follow-up, and fezolinetant- and placebo-treated women in DAYLIGHT had 24 weeks of follow-up. To enable 1-year analyses, missing WPAI-VMS data beyond these time points were imputed using the LOCF method (placebo arms in SKYLIGHT 1 and SKYLIGHT 2 from weeks 12 to 52; fezolinetant and placebo arms in DAYLIGHT from weeks 24 to 52). Since the most dramatic changes in overall work productivity loss and presenteeism occurred within the first 4 weeks of treatment and only slight changes were observed for absenteeism during trial follow-up, the LOCF method was considered a reasonable imputation approach. In addition, employment eligibility was defined at enrollment, and women were not censored if they became unemployed during follow-up, which may also be considered a limitation. Because the placebo follow-up ended at 12 weeks, the 12-week values were carried forward. Although this could bias results in favor of treatment, observed trends across trials suggest minimal changes beyond week 4, supporting the validity of this method.

Measures of WPAI-VMS rely on self-reported data, which may be subjective; therefore, repeated measures of WPAI-VMS were collected across follow-ups to account for recall bias. The treatment effect of fezolinetant may have been underestimated due to the placebo effect. This study classified women as unemployed if they were unemployed during the entire trial follow-up period. This may have contributed to the lower unemployment rates observed among fezolinetant- versus placebo-treated women (up to 52 wk vs. 12 wk). However, the impact on study results was likely minimal, as unemployment rates for women treated with fezolinetant changed only slightly when using 12-week versus 52-week data. Reasons for unemployment were not documented in the clinical trials; therefore, the percentage of VMS-related absenteeism for women who became unemployed during trial follow-up periods could not be assessed. Thus, a conservative assumption of 100% absenteeism for both fezolinetant and placebo treatment was used to estimate the effect of fezolinetant on indirect costs. Finally, the employment rate and wages used within this study were based on available data for the general population of women across multiple age groups (40–65 y). These values may deviate from the employment rate and wages of women with moderate to severe VMS.

Potential clinical value

Fezolinetant demonstrated a clear advantage over placebo in sustaining work productivity improvements and increasing hours worked among women with moderate to severe VMS, including those unsuitable for HT. These benefits may translate into higher productivity, fewer workdays lost, and lower indirect costs overall versus no treatment. Given the considerable burden of untreated VMS, these findings highlight the value of effective treatment, such as fezolinetant, to improve work productivity and lessen the economic burden of moderate to severe menopausal VMS.

CONCLUSIONS

Fezolinetant improved work productivity and reduced estimated indirect costs compared with placebo in women with moderate to severe VMS associated with menopause. Benefits were observed consistently across the overall population and in women unsuitable for HT. Reductions were largely driven by decreased presenteeism, with additional gains in absenteeism contributing to overall improvements in work productivity. These changes translated into meaningful reductions in missed work hours and annualized estimated indirect costs across multiple countries. While long-term placebo comparisons relied on imputation, the observed short-term improvements were maintained through modeling to 1 year. These findings highlight the potential role of fezolinetant as a valuable non-HT option, particularly for women unsuitable for HT, a population with high unmet need.

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