A Phase 3b, Randomized, Double-blind, Placebo-controlled, 24-week Study to Assess the Efficacy and Safety of Fezolinetant in Menopausal Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) and Considered Unsuitable for Hormone Replacement Therapy.

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PrimaryTo evaluate the efficacy of fezolinetant 45 mg versus placebo on the frequency of moderate to severe VMSKey secondaryTo evaluate the efficacy of fezolinetant 45 mg versus placebo on the severity of moderate to severe VMSSecondary• To evaluate...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52081

Source
ToetsingOnline

Brief title
Daylight

Condition

- Other condition
- Body temperature conditions

- Gender related factors

Synonym
Hot Flashes, Vasomotor Symptoms

Health condition

hot flashes

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma Global Development, Inc. (APGD)
Source(s) of monetary or material Support: The sponsor as described in question B6/B7

Intervention

Keyword: Fezolinetant, Hot flashes, Vasomotor Symptoms

Outcome measures

Primary outcome

Primary Endpoint:

Mean change in the frequency of moderate to severe VMS from baseline to week 24

Secondary outcome

Key Secondary

Mean change in the severity of moderate to severe VMS from baseline to week 24

Secondary

Mean change in the participant-reported sleep disturbance by the PROMIS SD SF

8b from baseline to week 24

• Mean change in the frequency of moderate to severe VMS from baseline to weeks

1, 4, 8, 12, 16 and 20

• Mean change in the severity of moderate to severe VMS from baseline to weeks 1, 4, 8, 12, 16 and 20

• Mean percent reduction in the frequency of moderate and severe VMS from baseline to weeks 1, 4, 8, 12, 16, 20 and 24

• Responder of percent reduction >= 50%, >= 75% and at 100% in the frequency of moderate and severe VMS from baseline to weeks 1, 4, 8, 12, 16, 20 and 24

• Frequency and severity of AEs, clinical laboratory assessments, vital signs and ECG

Exploratory

• Change in serum concentrations of sex hormones and SHBG from baseline to weeks 12 and 24

• Plasma concentration of fezolinetant and ES259564

• Mean change in the PROMIS SD SF 8b from baseline to week 4, 12, and 16

• Score on the PGI-S SD at each visit (weeks 4, 12, 16, and 24)

• Score on the PGI-C SD to each visit (weeks 4, 12, 16, and 24)

• Score on the PGI-C in VMS to at each visit (4, 12, 16, and 24)

• Mean change on the MENQOL total score from baseline to weeks 4, 12, 16, and 24

• Mean change on the MENQOL domain scores from baseline to weeks 4, 12, 16, and 24

• Mean change on the Euro-Qol 5D-5L (EQ-5D-5L) Visual Analog Scale (VAS) from baseline to weeks 4, 12, 16, and 24

• Mean change on the WPAI-VMS domain scores from baseline to each week up to weeks 4, 12, 16, and 24

• Mean change on the FSFI total score from baseline to weeks 4, 12, 16, and 24

• Mean change on the FSFI domain scores from baseline to weeks 4, 12, 16, and 24

• Mean change on PHQ-4 score from baseline to weeks 4, 12, 16, and 24

• Mean change in the frequency of mild, moderate and severe VMS from baseline to each week up to week 24

• Mean change in the severity of mild, moderate and severe VMS from baseline to each week up to week 24

• Daily mean change in the frequency of moderate to severe VMS from baseline (day 1) to days 2 to 7 (week 1)

• Daily mean change in the severity of moderate to severe VMS from baseline (day 1) to days 2 to 7 (week 1)

Study description

Background summary

Background
VMS, commonly known as hot flashes (HFs), are the most common complaint among women entering menopause and for many women, may continue to occur for up to 5 years (although around 20% of women will continue to experience them for up to 15 years) [Stearns et al, 2003; Rossouw et al, 2002; Kronenberg, 1994]. The large prospective cohort Study of Women's Health Across the Nation found that overall prevalence of VMS was approximately 70% [Thurston & Joffe, 2011].
VMS can have a significant negative impact on quality of life and are therefore a major reason for menopausal women to seek medical attention. Despite the vast numbers of individuals affected, the physiology of VMS is not fully understood, although a disturbance in normal thermoregulatory function is thought to be the main underlying cause. The primary presentation of VMS is a subjective and transient sensation of heat, flushing and sweating that usually last 4 to 10 min and may be followed by a feeling of being chilled. VMS may be accompanied by palpitations, feelings of anxiety and sleep disruption leading to fatigue or irritability; in rare occurrence, panic may occur [Kronenberg, 1994; Kronenberg, 1990].
The most effective and commonly used treatment for VMS is hormone replacement

therapy (HRT), commonly referred to as hormonal treatment (HT), but a Women*s Health Initiative study raised questions about the long-term safety of this treatment [Rossouw et al, 2002]. Thus, current guidelines recommend a limited duration of HRT due to associated risks of breast cancer (BC), coronary artery disease, stroke and thromboembolism [de Villiers et al, 2016; Rossouw et al, 2002]. Furthermore, the current safety data do not support the use of HRT in several groups of patients (e.g., those with a history of breast cancer/endometrial cancer) or those suffering from underlying medical conditions with a high risk for negative cardiovascular outcome (e.g., coronary heart disease, diabetes). Women may also stop HRT or make an informed decision to not take HRT after having a benefit-risk discussion with a healthcare professional. The perceived limitations of HRT, coupled with the limited efficacy and adverse effects observed with non-HT (e.g., selective serotonin reuptake inhibitors) have led clinicians to search for other treatment options for VMS. Therefore, a non-HT like fezolinetant may be beneficial in patients with VMS who for a variety of reason are unsuitable for HRT treatment.
A detailed description of the chemistry, pharmacology, as well as clinical efficacy and safety of fezolinetant is provided in the Investigator*s Brochure (IB).

Study objective

Primary
To evaluate the efficacy of fezolinetant 45 mg versus placebo on the frequency of moderate to severe VMS

Key secondary
To evaluate the efficacy of fezolinetant 45 mg versus placebo on the severity of moderate to severe VMS

Secondary
• To evaluate the effect of fezolinetant 45 mg versus placebo on participant-reported sleep disturbance
• To evaluate the efficacy of fezolinetant 45 mg versus placebo on the frequency and severity of moderate to severe VMS
• To evaluate the safety and tolerability of fezolinetant 45 mg.

Exploratory
• To evaluate the effect of fezolinetant on pharmacodynamic markers
• To evaluate the pharmacokinetics of fezolinetant and metabolite ES259564
• To evaluate QoL improvement with fezolinetant 45 mg versus placebo on participant-reported outcomes
• To evaluate the efficacy of fezolinetant 45 mg versus placebo on the frequency, severity and HF score of mild, moderate and severe VMS.

Study design

This is a 2-arm, randomized, 24-week double-blind, placebo-controlled, parallel group, multicenter study to assess the efficacy and safety of fezolinetant 45 mg in women suffering from moderate to severe VMS associated with menopause and considered unsuitable for HRT treatment.
Approximately 440 participants in total will be randomized in a 1:1 ratio across both treatment arms and stratified by smoking status (smoker or non-smoker) through IRT.
Participants who complete the 24 weeks of treatment will complete an end of treatment (EOT) visit and a safety follow-up visit 3 weeks after the end-of-treatment visit. Data from all remaining visits for participants who discontinue study investigational medicinal product (IMP) early will be collected, whenever possible. It is important for participants to complete an early discontinuation (ED) visit at the time of discontinuation of IMP and subsequently all planned visits, continue to complete the electronic daily diary, complete an end of treatment (EOT) visit, and safety follow-up visit. Home health care visits will be made available to accommodate participants who have stopped dosing.
Screening will occur up to 21 days prior to randomization. Eligibility during screening will be assessed via medical history and HRT questionnaire, physical examination, clinical laboratory testing and vital signs.
At randomization, participants must have a minimum average of 7 moderate to severe hot flashes (HFs) (VMS) per day. Participants are to record HFs for the entirety of the screening period. The electronic diary data will be reviewed by study site staff on Day 1 (visit 2) to confirm study eligibility.
During the 24-week treatment period, visits will be conducted at weeks 2, 4, 8, 12, 16, 20 and 24 as indicated in the schedule of assessments [Table 1]. Participants will record their VMS via an electronic diary on a daily basis. Site-based patient-reported outcome (PRO) measures will be self-administered via an electronic device as indicated in the schedule of assessments [Table 1]. Assessments on Day 1 (visit 2) must occur prior to randomization/first dosing; assessments at weeks 4, 12, 16, 20 and 24 must occur prior to dosing. All self-administered assessments will be performed first and prior to all other procedures.
A Data Monitoring Committee (DMC) and a Liver Safety Monitoring Panel (LSMP) will assess the safety of fezolinetant for the duration of the study.

Intervention

n/a

Study burden and risks

Please refer to section 6. *What side effects could you experience?* and section 7. *What are the pros and cons if you take part in the study?* in the Subject Information For Participation In Medical Research Form for an overview of the risks and side effects.

Contacts

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Scientific
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Northbrook IL 60062
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. IRB/IEC approved written informed consent and privacy language as per national regulations must be obtained from the participant prior to any study-related procedures.
2. Participant is born female, aged >= 40 years and <= 65 years of age at the screening visit
3. Participant must be seeking treatment or relief for VMS associated with menopause and confirmed as menopausal per one of the following criteria at the screening visit:
• Spontaneous amenorrhea for >= 12 consecutive months
• Spontaneous amenorrhea for >= 6 months with biochemical criterion of menopause (follicle-stimulating hormone [FSH] > 40 IU/L)
• Had bilateral oophorectomy >= 6 weeks prior to the screening visit (with or without hysterectomy)

• Had hysterectomy without oophorectomy and who meets the biochemical criterion of menopause (FSH > 40 IU/L)
4. Participant has VMS and is unsuitable to receive HRT (HRT contraindicated, HRT caution, HRT stoppers and HRT averse participants). The definitions for HRT unsuitable categories are provided below:
• HRT Contraindicated: participants with undiagnosed vaginal bleeding, history of breast cancer or estrogen dependent tumors; arterial thromboembolic disease (e.g., angina, myocardial infarction, cerebrovascular accident, transient ischemic attack, venous thrombophilic disorder [e.g., deep vein thrombosis, pulmonary embolism]); hypersensitivity to estrogen and progesterone therapy or any of the excipients; or porphyria. Note: Participants with undiagnosed vaginal bleeding will be allowed in the study after appropriate assessment has been performed at the investigator*s discretion.
• HRT Caution: participants with history of diabetes mellitus, hyperlipidemia, smoking (current), migraine, obesity (body mass index > 29.9 kg/m2), systemic lupus erythematosus, epilepsy, family history of breast cancer in the first degree relative or mutation of breast cancer gene (BRCA1 and BRCA2)
• HRT Stoppers: participants who have discontinued HRT due to lack of efficacy, HRT-related side effects, advised by healthcare provider to stop due to length of time on HRT or due to participant*s age >= 60 years old
• HRT Averse: participants who made an informed choice to not take HRT after a consultation about the benefit risks of HRT
For HRT Contraindicated and HRT Caution participants, written documentation regarding the conditions listed must be present in the medical files of participants to qualify under these definitions. For HRT Stoppers for lack of efficacy and HRT-related side effects, accurate and exhaustive documentation must be provided, for example (and as applicable) length of HRT treatment and reason for determining inefficacy, type and duration of HRT-related side effects, etc. For HRT Averse participants, documentation must be provided regarding the nature and extent of the participant*s consultation with her healthcare provider, participant*s reason not to take HRT, etc.
5. Participant has a minimum average of 7 moderate to severe HFs (VMS) per day as recorded in the electronic diary during the last 10 days prior to randomization.
6. Participant is in good general health as determined on the basis of medical history, general physical examination, laboratory and other medical assessments in the opinion of the investigator.
7. Participant has a negative serology panel (including hepatitis B surface antigen, hepatitis C virus antibody and human immunodeficiency virus antibody screens).

Exclusion criteria

1. Participant uses a prohibited therapy for VMS (e.g., prescription, over the-counter or herbal) prior to screening and for the duration of treatment

with IP. Refer to [Section 6.8 Concomitant Therapy and Section 10.4 Appendix 4: List of Excluded Concomitant Medications] for a list of prohibited therapies.
2. Participant has known documented substance abuse or alcohol addiction within 6 months of screening.
3. Participant has history of a malignant tumor within the last 5 years, except for basal cell carcinoma.
4. Participant has endometrial thickness > 8 mm on the locally read screening transvaginal ultrasound (TVU) or any clinically significant findings that that would make the participant ineligible in the opinion of the investigator.
5. Participant has history of severe allergy, hypersensitivity or intolerance to the IP and/or any of its excipients.
6. Participant has a history of seizures or other convulsive disorders unless well controlled.
7. Participant has a medical condition or chronic disease (including history of neurological [including cognitive], renal, cardiovascular, gastrointestinal, pulmonary [e.g., moderate asthma], endocrine or gynecological disease) or malignancy that could confound interpretation of the study outcome in the opinion of the investigator.
8. Participant has any of the following:
• active liver disease,
• jaundice,
• elevated liver aminotransferases at screening (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]),
• elevated total bilirubin (TBL) or direct bilirubin (DBL) >1.5 x upper limit of normal (ULN),
• elevated International Normalized Ratio (INR) >1.5 (unless participant is receiving anticoagulant therapy) or
• elevated alkaline phosphatase (ALP).
Participants with mildly elevated ALT or AST up to 1.5 × ULN can be enrolled if TBL and DBL are normal.
Participants with mildly elevated ALP (up to 1.5 × ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed.
Participants with Gilbert's syndrome with elevated TBL may be enrolled as long as DBL, hemoglobin and reticulocytes are normal.
9. Participant has creatinine > 1.5 × ULN or estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula <= 59 mL/min per 1.73 m2 at the screening visit.
10. Participant has a history of suicide attempt or suicidal behavior within the last 12 months.
11. Participant has participated in another interventional study within the last 30 days prior to screening and for the duration of the study.
12. Participant who has been previously enrolled in a clinical study with fezolinetant.
13. Participant is unable or unwilling to complete the study procedures.
14. Participant has any condition, which in the investigator*s opinion, makes

the participant unsuitable for study participation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-03-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fezolinetant
Generic name:	n/a

Ethics review

Approved WMO

Date:	08-09-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	20-12-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-10-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

(Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-001685-38-NL
CCMO	NL78137.100.21

Study results

Date completed: 16-03-2023

Results posted: 08-04-2024

First publication
13-10-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File