

ASTELLAS INVESTOR MEETING

**fezolinetant: A Novel Approach for Targeted
Menopausal Symptom Relief**



December 14, 2017

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING INFORMATION

In this material, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas Pharma. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

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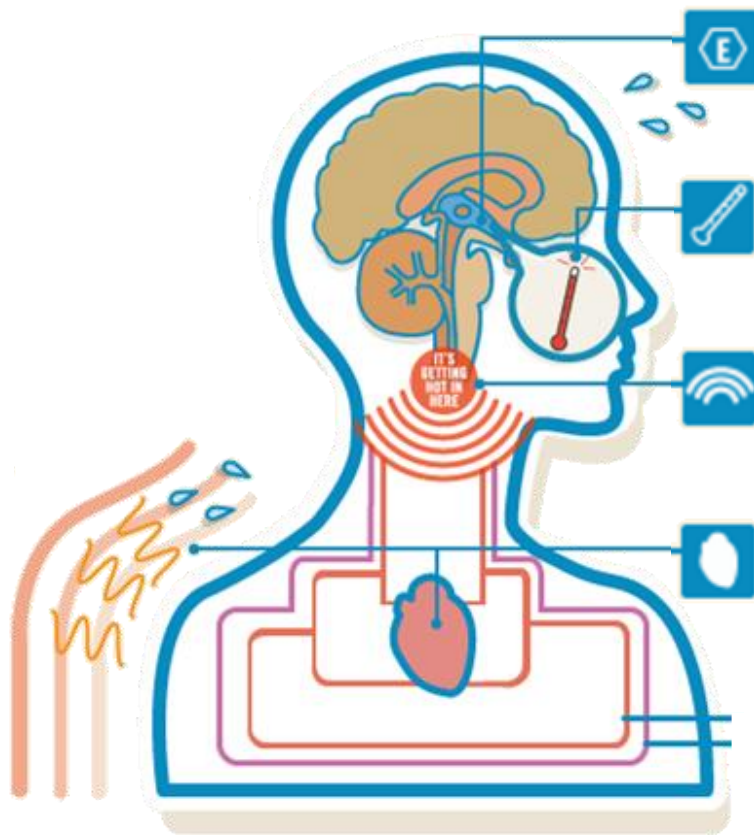
B. Zeiher, G. Fraser, J. Kern

VMS AND FEZOLINETANT

Graeme Fraser, PhD
Chief Scientific Officer
Ogeda SA

MECHANISM OF VASOMOTOR SYMPTOMS (VMS)

- **Vasomotor symptoms**, typically comprised of hot flashes and night sweats, are associated with decreases in reproductive hormones commonly associated with menopause (eg. MR-VMS) but also occurring in response to hormone-lowering therapies used for the treatment of benign or malignant conditions



A diminished amount of hormones, such as estrogen, affects the hypothalamus



This confuses the hypothalamus and makes it read “too hot”



The brain responds by relaying an alert to cool off

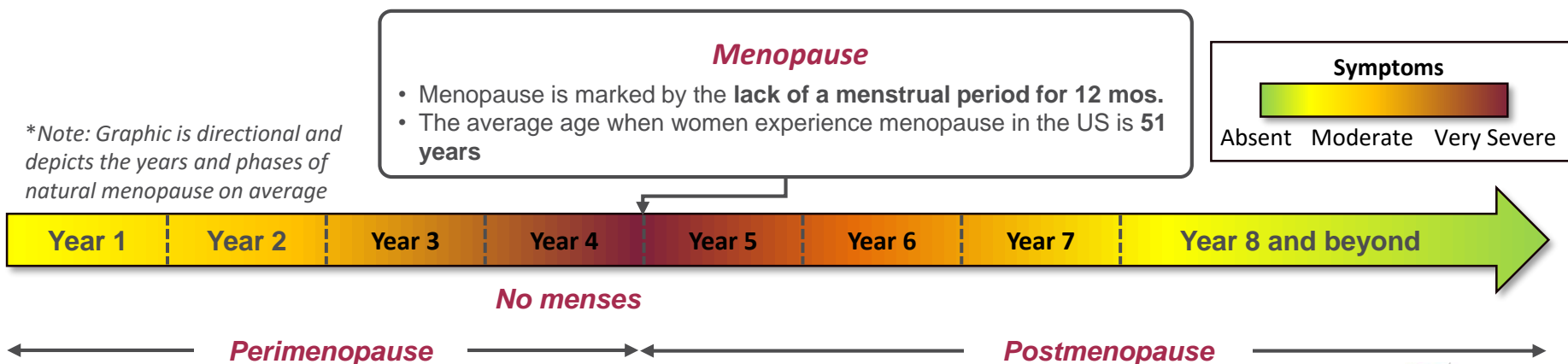


The body then tries to cool off by beginning to perspire

MENOPAUSE-RELATED VMS (MR-VMS): OVERVIEW

Vasomotor symptoms may vary from person to person:

- MR-VMS patients are women generally in **mid-40's to mid-60's**
- VMS experienced in **up to 80%** of menopausal women, prevalence depends on region
- According to a 2015 study, the **average duration of vasomotor symptoms is 7 years**
- May range in severity from discomfort to **debilitation**. 64% of women with VMS experience “moderate to severe” symptoms*
- Episodes may last from 30 seconds to **5 minutes**. Patients recruited to our clinical trials have 7 and more hot flashes per day
- Impact on patients: discomfort, sleep deprivation, anxiety due to sudden/unpredictable onset, inability to focus (work, leisure activities), and depressed mood/interpersonal relations



APPROVED TREATMENTS FOR MR-VMS

Guidelines (US, EU)

Both US (ACOG) and EU (NICE) guidelines recommend systemic hormonal replacement therapy (HRT) as the most effective therapy for VMS related to menopause

- ACOG recommends individualized dosing scheme for the lowest effective dose and the shortest duration given variable response to HRT and associated risks, while NICE only recommends to discuss short-term (up to 5 years) and longer-term benefit and risks with patients
- Non-hormonal agents such as SSRIs are recommended as alternatives for patients with contraindications to or concerns about HRT

Approved Treatment Options*		VMS indication	MoA in MR-VMS
Hormonal Replacement Therapy (HRT)	• Estrogen and progesterone combination for women who have not undergone a hysterectomy	Yes	Exogenous estrogen to replace naturally declining endogenous estrogen levels and thereby restore hypothalamic control to normalize the thermoregulatory set point
	• Conjugated equine estrogen with bazedoxifene for women with uterus	Yes	
Anti-depressants (SSRI)	• Paroxetine is the only approved non-hormonal agent for VMS; best suited for patients contraindicated for HRT.	Yes (US only)	Not determined

*Treatments approved for MR-VMS as an indication



WHI STUDY: THE LARGE LONG-TERM STUDY THAT CHANGED THE WOMEN'S HEALTH MARKET

Women's Health Initiative (WHI)^{1,2}

- In 1991, WHI was initiated in the US, designed to address major health issues in postmenopausal women
- It consisted of 3 clinical trials and an observational study
- Nearly 160,000 women between 50 and 79 participated, results were published in 2002



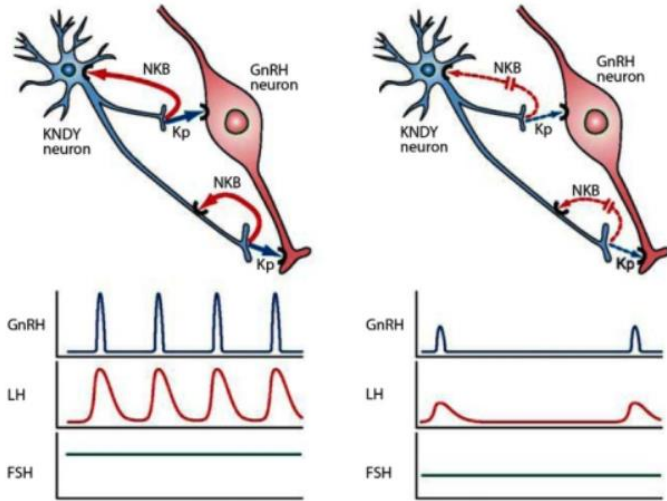
Conclusion: WHI hormone therapy studies do not support the use of hormone therapy for chronic disease prevention^{1,2}

- Hormone therapy increased the risk of stroke (41%), breast cancer (26%), coronary heart disease (29%) and several other serious illnesses¹
- The study of hormone therapy was halted 3 years earlier than designed due to the preliminary results³
- The study received huge media attention and led to a large drop in hormone therapy prescriptions

 **Since the WHI findings, no replacement for hormone therapy with similar efficacy and no significant safety concern as reported by WHI for HRT has been found and marketed, resulting in a huge unmet medical need**

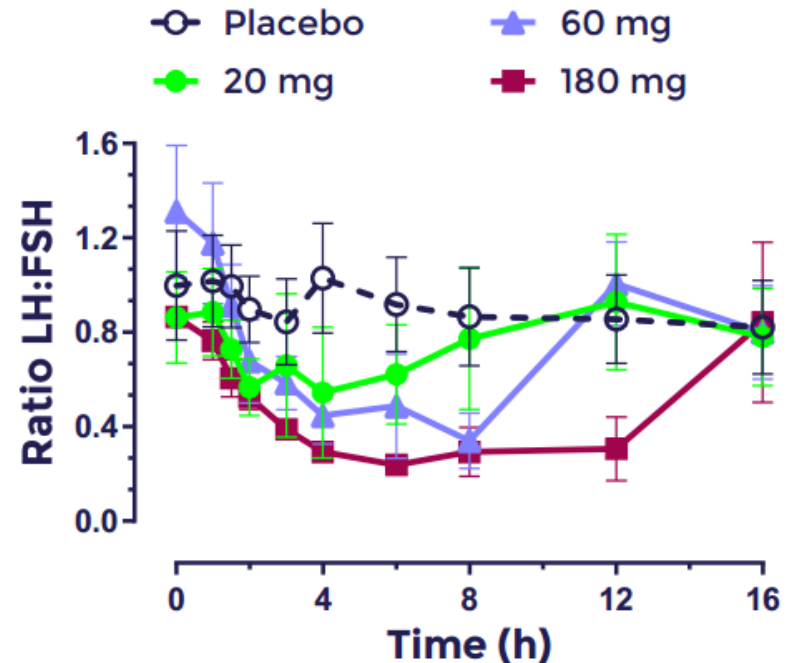
FEZOLINETANT (ESN364): MECHANISM OF ACTION

Theory



- fezolinetant is a Neurokinin-3 receptor antagonist, blocks Neurokinin B (NKB)
- Oral bioavailability, CNS penetrant for action in hypothalamus
- Consistent in vivo effects on LH suppression in rat and cynomolgus monkey models

Phase 1: Proof of Pharmacology



*p<0.05 at 4 hrs for all dose groups



Key References

Mittleman-Smith *et al.*, *PNAS* 2012 & *Endocrinology* 2015

- Neurokinin-3 receptor (NK3R) expressing KNDy & preoptic area (POA) neurons modulate heat dissipation in ovariectomized rat

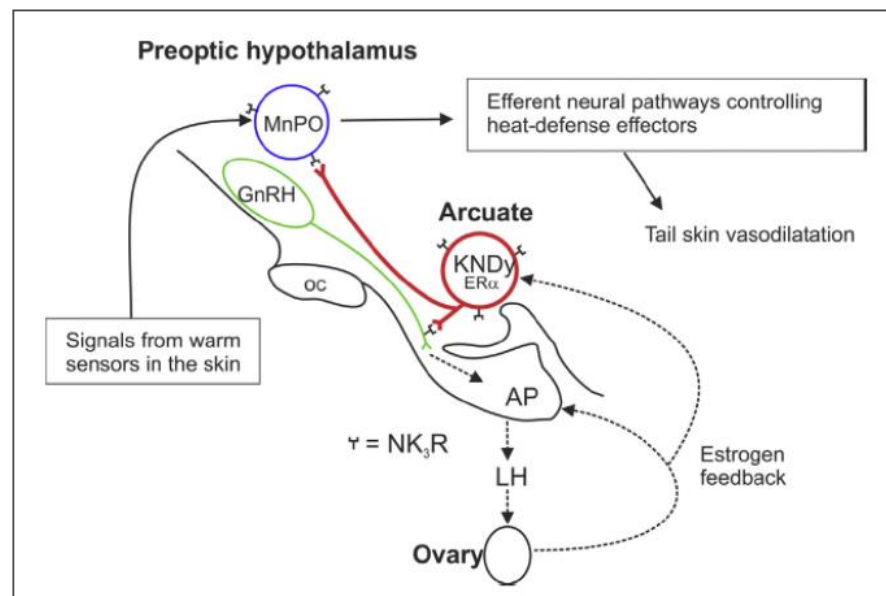
Jayasena *et al.*, *SciRep* 2015

- Neurokinin B (NKB) induces hot flashes in premenopausal women

Crandall *et al.*, *Menopause* 2017

- Genetic variation in *Tacr3* ('NK3R') associated with hot flashes in menopausal women

Rance *et al.* (2013) *Front Neuroendocrinol* 34:211



*Figure used with author permission

KNDy: Kisspeptin-NKB-Dynorphin
LH: Luteinizing hormone
MnPO: Median preoptic nucleus
GnRH: Gonadotropin releasing hormone
AP: Area postrema

Phase 1 Studies:

ESN-364-CPK-101¹ : First-in-human, single and multiple ascending doses up to 180 mg in 64 healthy male and female individuals (10 days in males, 21 days in females)

- Few TEAEs. Nausea and headache were more frequently reported in fezolinetant group compared to placebo. 1 non-related SAE (fezolinetant: foot fracture –fall from ladder)

ESN-364-CPK-102 : Exploration of maximum tolerated dose(MTD) in healthy female and healthy male volunteers with dose range between 180 mg and 900 mg tested as single doses and doses up to 720 mg as multiple dose for 7 consecutive days (single dose for male, multiple dose for 7 days in females)

- An increase with dose in incidence of TEAEs [headache, dizziness and (circumoral) paresthesia].
- Well-tolerated during both single-dose escalation up to 900 mg (900mg single dose = MTD) and the multiple-dose escalation up to 720mg
- No clinically significant changes across dose groups in any of the lab parameters, vital signs (including orthostatic vital signs), and/or ECG measurements

FEZOLINETANT: POC STUDY IN MR-VMS

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Study design

Double
blind

8
Sites*

12
Weeks

80
Patients

2
Cohorts:
90mg (BID) vs. PBO

Patients with ≥ 49
moderate/severe
HF/week at baseline

Endpoints

Primary Endpoint (FDA Guidance**)

- HF Frequency and Severity at wks 4, 12

Secondary Endpoints

- Patient Questionnaires:
QoL, Sleep, Bother, Productivity
- Safety and Pharmacokinetics
- Hormones: LH, FSH, estradiol, SHBG

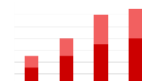
Timing

Baseline
Sampling

PK/hormones
wk-12

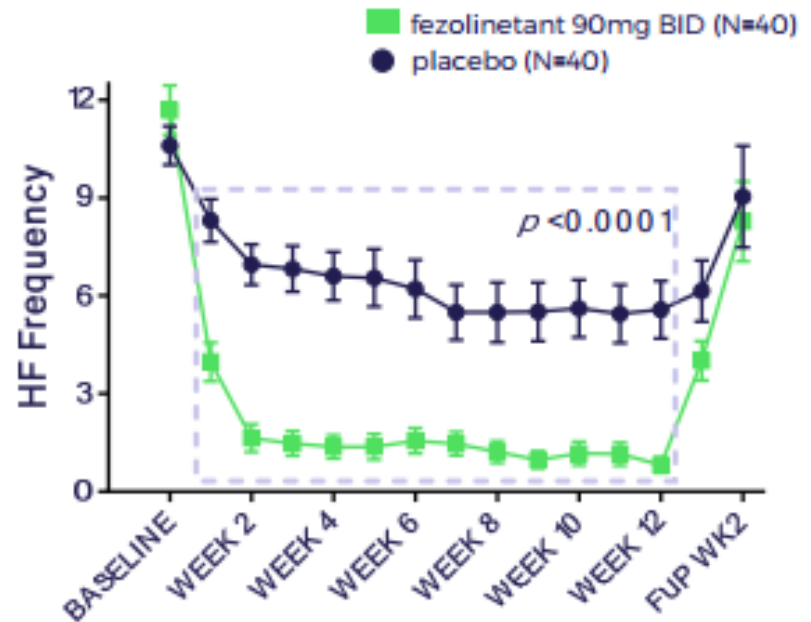
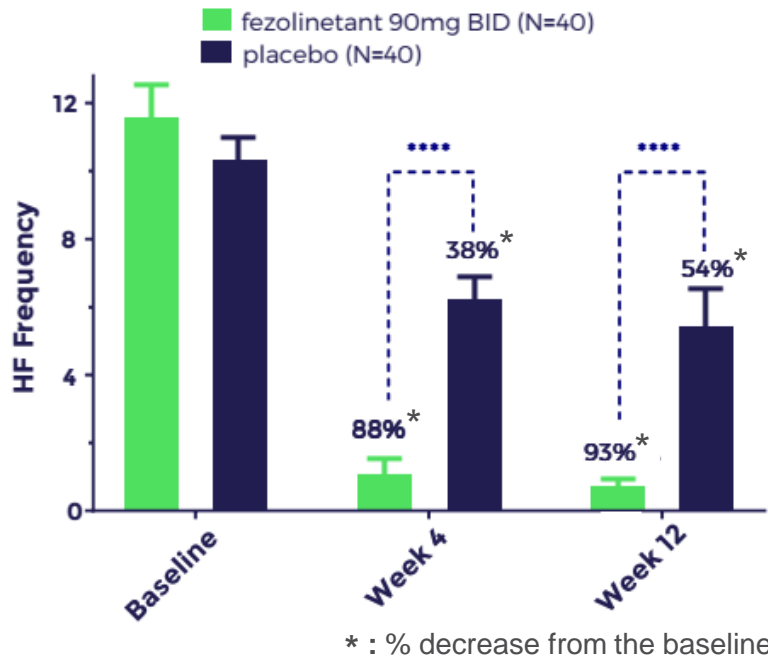


Daily self-reporting of HF with
weekly data compilation



Study results were presented
at ENDO 2017¹

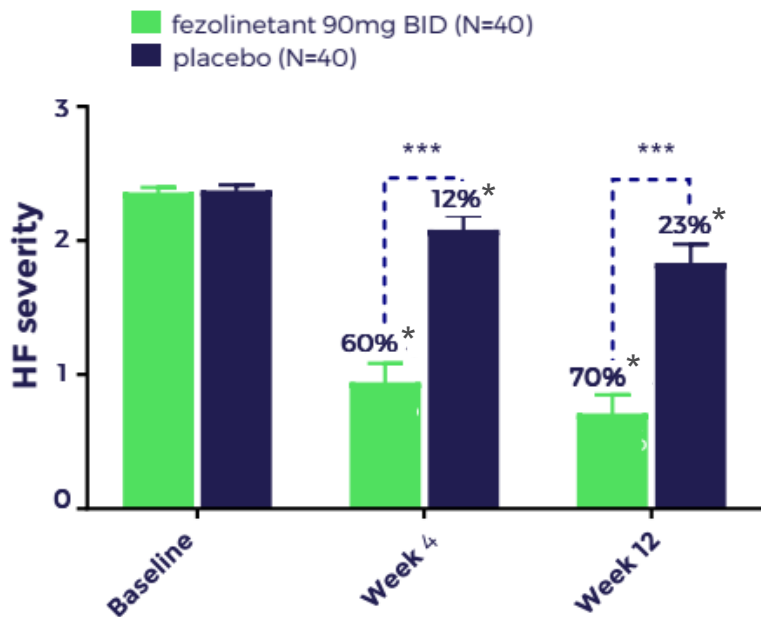
Average Daily Hot Flash Frequency Reported as per FDA Guidance



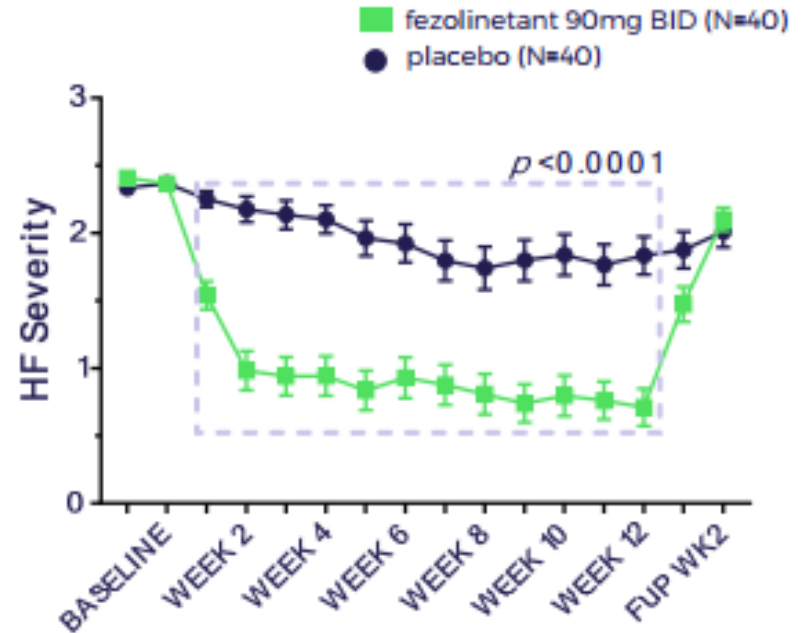
At Week 4:

- *fezolinetant group: 14/40 patients have ZERO hot flash*
- *placebo group: 2/40 patients have ZERO hot flash*

Score of average severity of Hot Flash, irrespective of frequency of Hot Flash



* : % decrease from the baseline

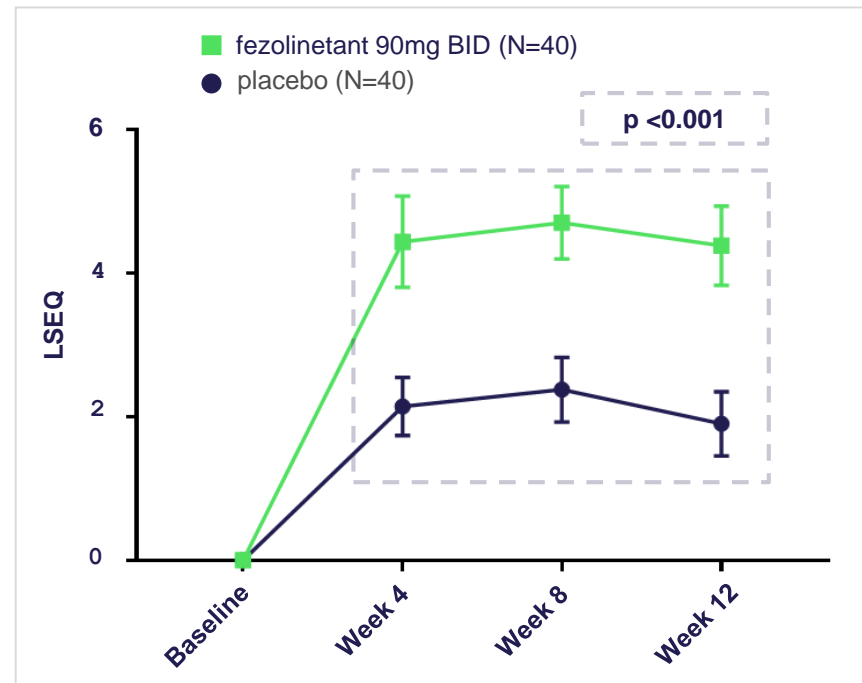


- 1 - **Mild:** sensation of heat without sweating
- 2 - **Moderate:** heat with sweating, but able to continue activity
- 3 - **Severe:** heat with sweating, causing cessation of activity

Leeds Sleep Evaluation Questionnaire (LSEQ)

- **Getting to sleep (GTS)** How would you compare getting sleep using the medicine with how you usually get to sleep without the medicine? $p < 0.01$
- **Quality of sleep (QOS)** How would you compare the quality of sleep using the medicine with your usual sleep? $p < 0.001$
- **Awakening from sleep (AFS)** How did your awakening feel after being medicated compared with your usual pattern of awakening without the medicine? $p < 0.05$
- **Behaviour following wakening (BFW)** How did you feel when you woke up? $p = 0.08$

LSEQ: Quality of Sleep \pm SEM



Safety Data: adverse event profile

Total number of subjects with:	Placebo		fezolinetant 90 mg BID	
	n	%	n	%
At least one treatment emergent adverse event (TEAE)	35	79.5	29	67.4
At least one serious TEAE	1	2.3	0	0.0
At least one mild TEAE as worst severity	20	45.5	19	44.2
At least one moderate TEAE as worst severity	15	34.1	10	23.3
At least one TEAE where treatment was stopped	0	0.0	2	4.7
At least one TEAE considered to be treatment related	11	25.0	13	30.2

- More patients reported TEAE in the placebo group than in fezolinetant group
- Treatment-related TEAEs were reported in 13 (30.2%) subjects in the fezolinetant group and in 11 (25.0%) subjects in the placebo group
- Most treatment-related TEAEs were gastrointestinal disorders (SOC), reported for 6 (14.0%) subjects in the fezolinetant group and for none of the subjects administered placebo

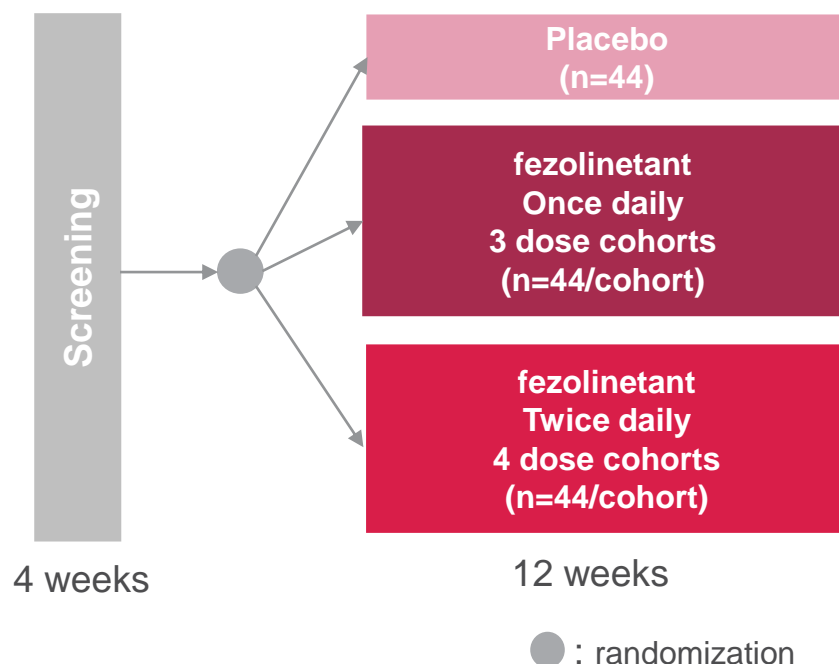
FEZOLINETANT: PHASE 2B STUDY IN MR-VMS

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Target patient

- Post menopausal women suffering from at least 50 moderate to severe vasomotor symptoms per week (n=352)

Study Design



Co-primary endpoints

- Change from baseline in the mean number of hot flashes (moderate and severe) per day
 - to Week 4
 - to Week 12
- Change from baseline in the mean severity of hot flashes (moderate and severe) per day
 - to Week 4
 - to Week 12

Plan

- Study completion in Aug 2018*

MARKET OVERVIEW

JEFFREY KERN

VP, MARKETING STRATEGY

ASTELLAS PHARMA US, INC.

MR-VMS: HISTORY AND UNMET MEDICAL NEEDS IN US

Menopause-related vasomotor symptom (MR-VMS) treatment has a well characterized history and there is a resurgent demonstration of medical needs

**Prior to 2001,
HRT was standard of care
for VMS**

- **Hormone Replacement Therapy (HRT)** was widely used for VMS for decades
- ~50-year-old **Premarin® is traditional segment leader**; #1 prescribed drug in U.S. (1998) ¹
- By 2000, 40 % of U.S. female cohort on Premarin®/Prempro®**

**In 2001, Women's Health
Initiative Fundamentally
Alters Market**

- Though effective in treating VMS, WHI links HRT to **increased risk of breast cancer, coronary artery disease, stroke, and VTE**²
- Many women are **ineligible for or uncomfortable with HRT** and its associated risks

**No good replacement for
HRT exists to treat VMS
so women suffer in silence**

- **Alternatives to HRT are limited** and have not been extensively studied
- Brisdelle® (paroxetine) is the **only approved non-hormonal** therapy
- Even after introduction of new non-hormonal agent, the unmet medical needs still remain
- Given the preference to avoid HRTs, patients may rely on lifestyle modifications or **alternative medicine to adequately mitigate symptoms, many patients report little efficacy**



APPROVED THERAPIES AND DEVELOPMENT PROGRAMS

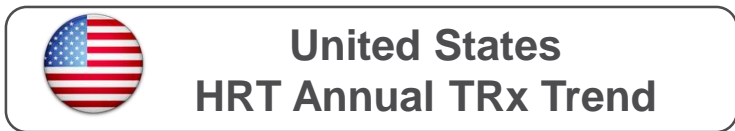
With the existing treatments, there is still high unmet medical needs. fezolinetant is first-in-class development compound in MR-VMS

Hormone Replacement Therapy (HRT)							
Existing treatments	Company	Product	MoA	Development	Company	Compound	MoA
	Pfizer	Premarin	conjugated estrogen		Mithra	estetrol	estrogen
		Duavee	SERM+Premarin			Ausio	AUS131
	Novo Nordisk	Activelle	progestogen+estrogen				
	Bayer	Climara	estradiol				
Teva	Cenestin	conjugated estrogen					

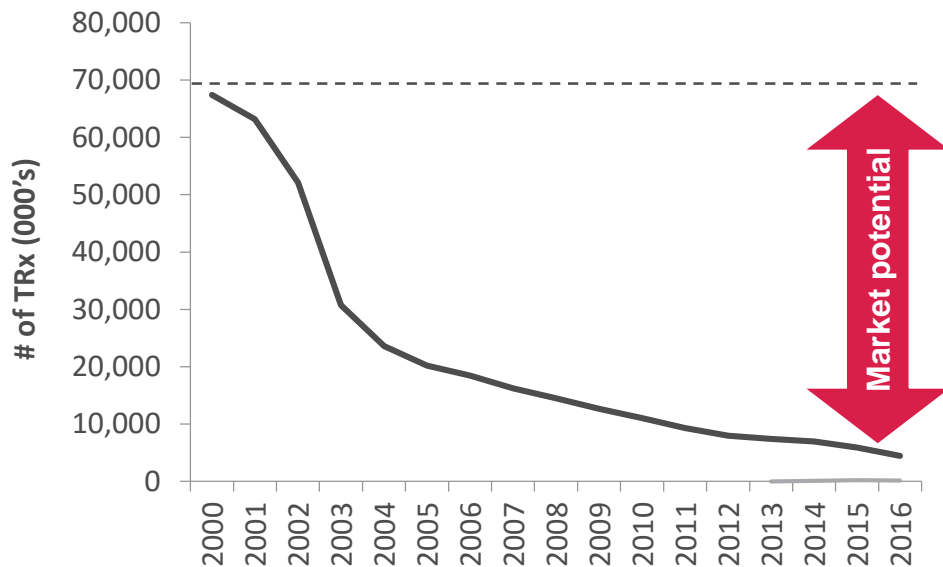
Non-hormone Replacement Therapy							
Existing treatments	Company	Product	MoA	Development	Company	Compound	MoA
	Hisamitsu/ Noven	Brisdelle	SSRI		KaNDY	NT-814	NK1/3 antagonist
						Pherin	salubrin
					QUE Oncology	Q-122	CXCR4 inhibition
					Tanabe Mitsubishi	MT-8554	Undisclosed

US MARKET

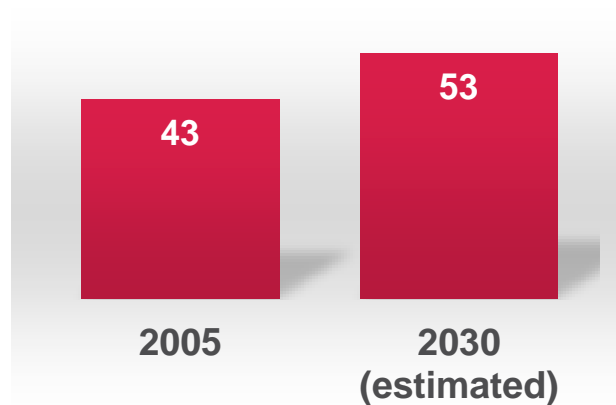
Growth in patient population and precipitous drop in hormone replace therapy shows re-emergence of unmet need and market potential



2016 MR-VMS market: approx. \$1B USD¹



Female Population, Age 45-69²
(in millions)



- Approximately 51% of menopausal women experience moderate to severe VMS³



1: IQVIA NPA –Premarin, Prempro, Minivelle, 2: Epi Database©. Kantar Health. Available from www.epidb.com. Accessed 08 11 2017.

3: Acsel Health Market Research – February 2017, HRT: hormonal replacement therapy, TRx: total prescription, MR-VMS: menopause related vasomotor symptoms, B: billion

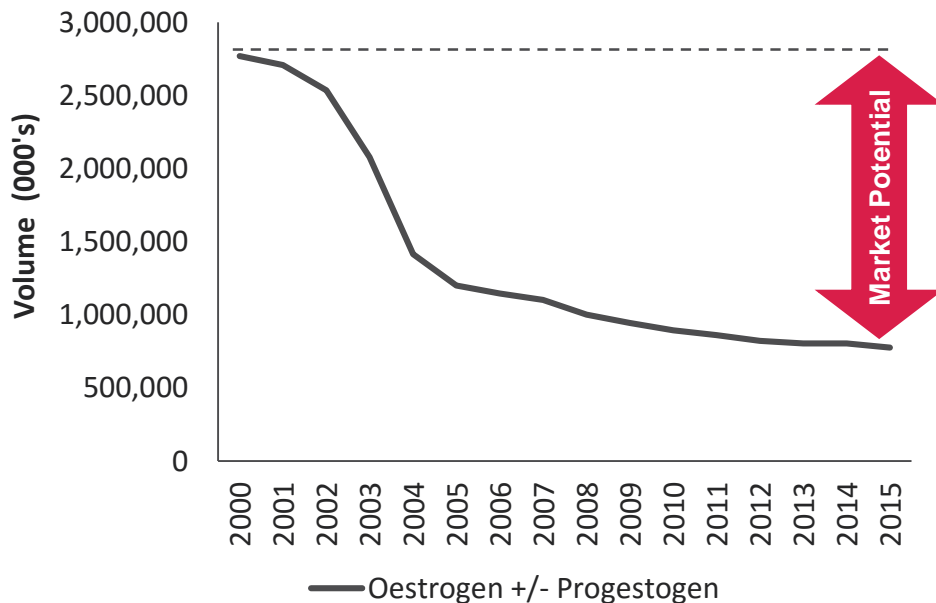
EU MARKET

Growth in patient population and precipitous drop in hormone replace therapy shows re-emergence of unmet need and market potential



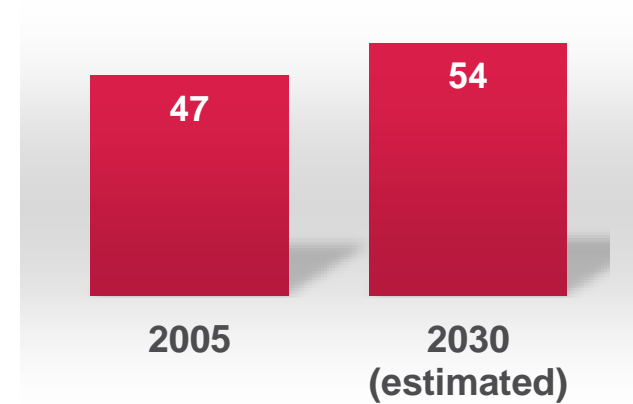
EU5 Countries HRT Annual Volume Trend

2016 MR-VMS market: approx. 110M euro¹



Female Population, Ages 45-69²

EU5: France, Spain, Italy, German, UK
(in millions)



- Approximately 40% of menopausal women experience moderate to severe VMS^{3,4}



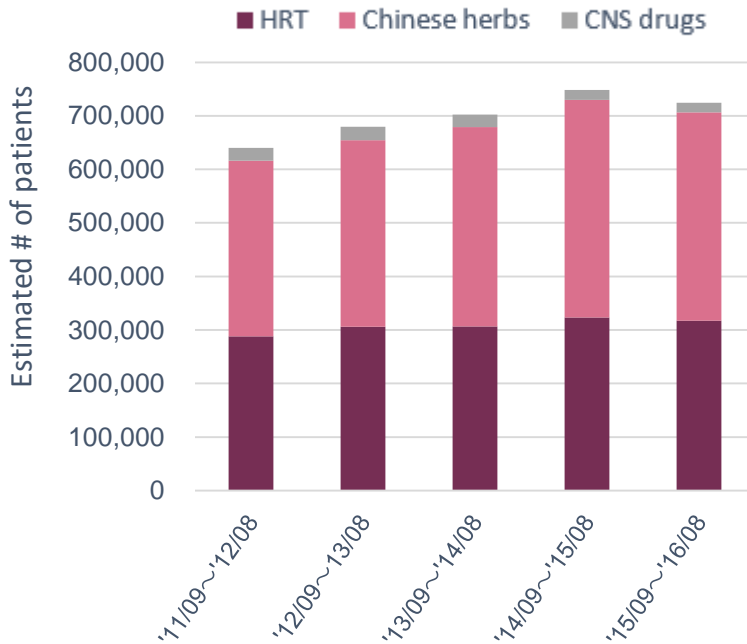
Unlike US and EU, proportion of patients who are diagnosed/treated is limited in JP; however, a market development opportunity exists for a novel agent

Japan

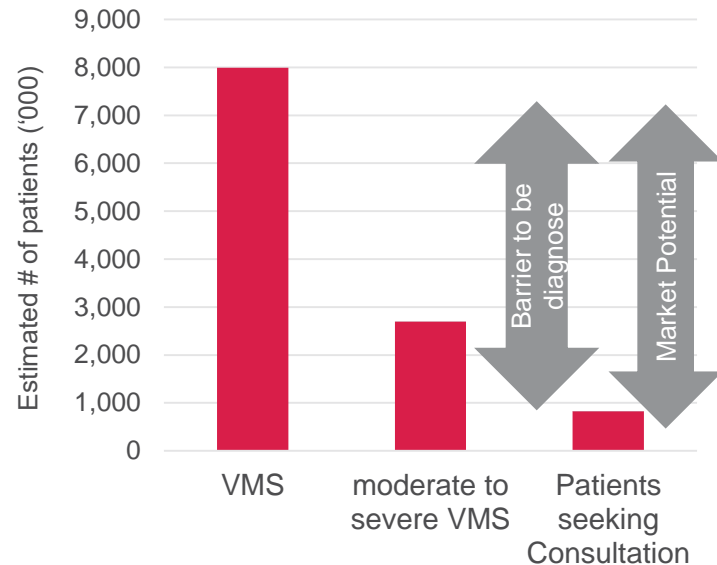
MR-VMS Treatment Trend

2016 HRT market: ~ 50 oku yen

Estimated # of patients with menopausal disorder and breakdown of drug treatment



MR-VMS patients in Japan (2016) ^{3,4,5}



- In 2005, total female population age 45-64 was 18M and expected to be 17M in 2030⁴
- Approximately 33% of women ages 45-65 who experience VMS consider it to be moderate to severe⁵



1: IQVIA JPM (2005-2015), 2: JMDC (2011/09-2016/08), 3: Statistics of Japan – 2017/4/1 data, 4: Epi Database®. Kantar Health. Available from www.epidb.com. Accessed 08 11 2017. 5: IPSOS Healthcare Market Research – Japan – September 2017

HRT: hormonal replacement therapy, MR-VMS: menopause related vasomotor symptoms, M: million

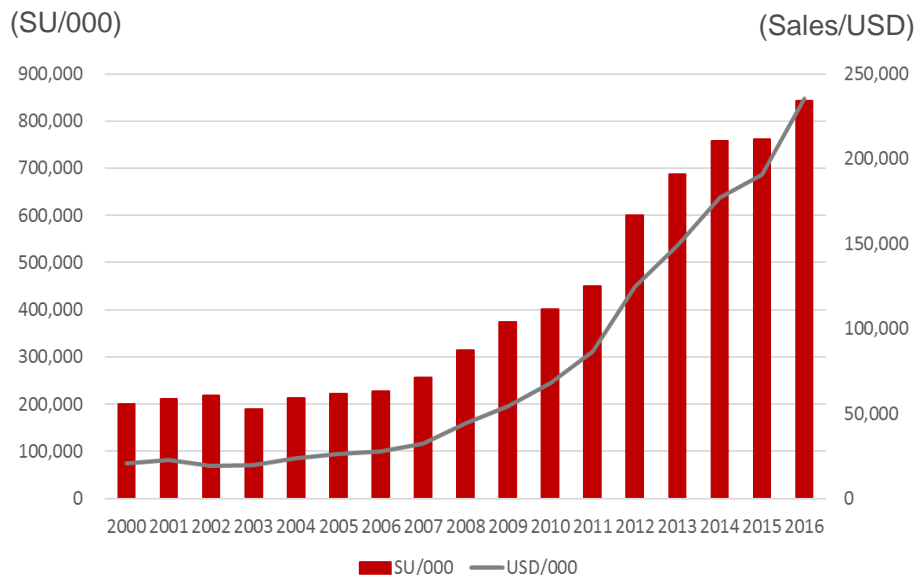
CHINA MARKET

Due to the lack of awareness of MR-VMS treatments, only 24% moderate-severe VMS patients are currently treated. Unlike US/EU, HRT market has been increasing in China

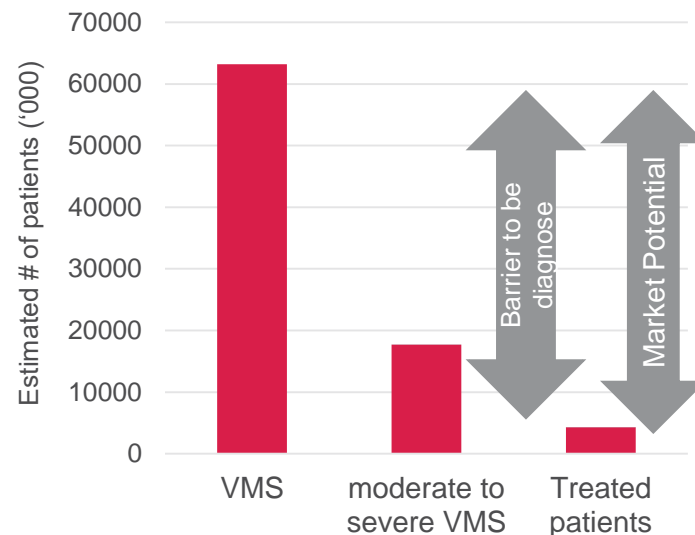


China HRT Annual TRx Trend

2016 MR-VMS market: ~\$235M USD¹



MR-VMS patients in urban region (2016)^{1,2,3}



- In 2005, total urban female population in age 40-64 was **77M**, expected to be **183M** in 2030⁴
- 12.7% of urban women (age 40-65) would experience moderate to severe VMS³



UNMET MEDICAL NEEDS FROM MR-VMS PATIENTS' VIEW

Patients around the world are waiting for the next innovation



"It is like someone **turned the heat on high**. You break out in to a horrible sweat and end up soaked. They wake me up in the middle of the night because they are so strong"



"There are times when I feel like I am going to faint. I have to strip my clothes off to try to cool down. My **whole life has changed** because of hot flashes"



"I find it **hard to cope** with it, because I don't practically sleep any more without waking up every 2 hours to uncover myself and cover up again I have cold sweats, this is horrible in my daily life"



"You suddenly start sweating mid-conversation, this is embarrassing. You have **trouble sleeping at night**, and feel knocked out the entire day. And you never feel like being fresh, not even right after a shower. And the clothes are always soaked"



"I **perspired heavily while I was working** serving customers, and they gave me a questionable look"



"I **perspire so heavily** that I was afraid to use public transportation like trains and busses"



"I perspired heavily as I was being examined by the doctor and became **embarrassed** when he asked, 'Did it rain?'"



"Horrible; **unpredictable; little understanding; taboo** subject"



"A situation of **continual anxiety**, you never know when they might occur and if you will be able to handle them when they do. They cause problems at work, social problems and prevent you from resting at night. You can't catch a break"



UNMET MEDICAL NEEDS FROM PHYSICIANS' VIEW

Likewise, physicians want to help their patients by providing an effective, well-studied non-hormonal treatment option



OB
GYN

*"Because of my personal experiences I can say that its **very impactful, but it's not appreciated.** I was recently at a conference where a male stood up in the audience and suggested hot flashes were a no big deal, and I immediately got up and said, 'sir once you experience a hot flash you can say that'"*



GYN

*"In Japan, patients tend to think **HRT is not safe** and thus are negative about using it"*



GYN

*"The main impact is on relationships with family members or at work, because women **feel ashamed and feel different**"*



PCP

*"It diminishes their relationships, not just sexual relations. They stop going out and stay at home with the air conditioning, so no one can see them. It's very embarrassing if you are talking with someone and they are seeing you sweat like mad! **It takes away their self confidence.** Not sleeping exhausts them"*



KOL

*"**The burden is significant.** It can impact a patients' coping skills, their ability to function, their quality of life, their relationships, and work to a certain degree; women say they get **embarrassed** and don't want to be in a public place during a hot flash, a lot of the burden can also be traced to **low quality sleep** due to their VMS"*



GYN

*"The women really suffer from the nocturnal hot flashes in particular, they can't sleep. And if you can't sleep during the night, you can't work during the day. You won't be able to cope with your everyday chores. **Sleep deprivation is a torturing method** on the WHO-list. It is very brutal in the long-term"*



GYN

*"Some patients prefer herbal medicine. Herbal medicine works well for a certain patients, but **physicians think placebo effect is related**"*



SYNERGY WITH OAB FRANCHISE

We have category leadership in reaching this patient population, which aligns with that of our OAB franchise, through similar specialty/PCP providers

After 13 years of OAB experience in the US:

- We know these patients:**

OAB is a condition that affects women beginning around age 40 and VMS affects women in mid-40's to mid-60's

- We know these providers:**

Almost 400 sales representatives are currently dedicated to reaching more than 50,000 PCP and OB/GYN providers annually for our current OAB franchise

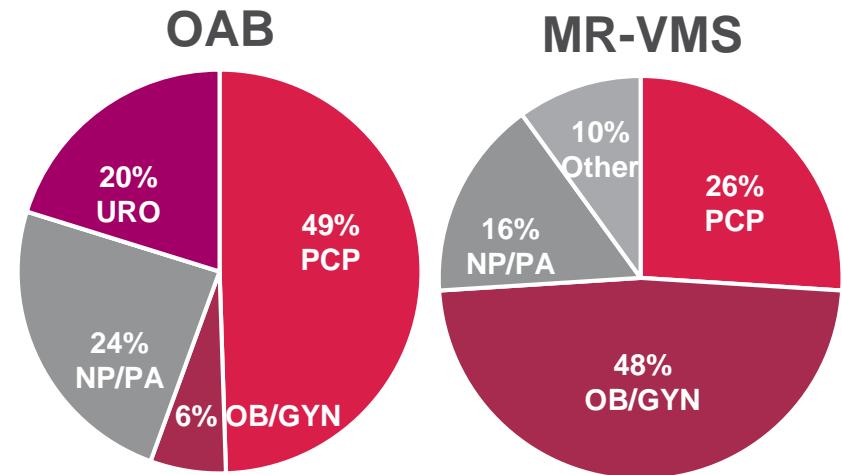
- We know the right marketing mix:**

More than 10 marketing professionals are assigned to our OAB franchise

Synergy with OAB Franchise

Treating Physicians in 2016

(% of Total Prescriptions, Deciles 4-10)



Source: IQVIA NPA (2000-2016), IQVIA NSP (2000-2016). (3 HTs and SSRI) NAMS 2015 Position Statement, IQVIA Open Claims Dec 2015-Dec 2016;

*Based on deciles 4-10 Transaction announced; completion pending

OAB: Over active bladder, PCP: Primary care physician, OB/GYN: Obstetrician/Gynecologist, NP/PA: Nurse practitioners/Physician assistants

VMS TREATMENT DECISIONS ARE DRIVEN BY A TRIAD: OB/GYN, PCP AND THE PATIENT

Patient engagement is important since current VMS diagnosis is reliant on self-assessment by patients; Patients are the decision maker in treatment selection

Patients	OB/GYN	PCP
<p>Decision Maker</p> <p>Significant impact on QoL (Hot Flashes and Night Sweats disrupt normal daily activities & can lead to lifestyle modifications to cope)</p> <p>HRT offers a complicated risk/benefit profile</p> <p>Herbal Supplements, OTCs, and other alternative treatment options provide minimal relief</p> <p>Diagnosis and Decision to Treat is Patient Driven</p>	<p>Specialty Prescriber</p> <p>Patients see OB/GYN at annual exams and physician discusses MR-VMS symptoms</p> <p>OB/GYN presents therapy options to patients</p> <p>Defer to the Patient to make the decision regarding treatment</p>	<p>Prescriber</p> <p>Patients see PCP throughout Menopause</p> <p>Presents therapy options to patient or refers patient to OBGYN</p> <p>Defer to the Patient to make the decision regarding treatment</p>

- Prior to 2001, the market was satisfied using HRT as a treatment option for VMS
- After the WHI HRT Study, the treatment paradigm changed as patients and physicians reassessed the risks and benefits of using HRT
- This reassessment by millions of patients and physicians has resulted in a significant unmet need around the world
- Astellas research indicates that globally both patients and physicians remain concerned about HRTs and alternative treatments have not fully satisfied the needs for those seeking VMS relief
- fezolinetant: A novel, targeted NK3 antagonist has the potential to change the treatment paradigm again and fulfilling the Astellas Mission...

Turn innovative science into value for patients by
**delivering paradigm changing
treatment options.**

Fezolinetant and MR-VMS

Target indication	<ul style="list-style-type: none"> • MR-VMS
MoA	<ul style="list-style-type: none"> • NK-3 inhibitor • First-in-class • In non-clinical studies, it was reported that NK-3 receptor in KNDy neuron to be an effective target to treat MR-VMS
Unmet Medical Needs	<ul style="list-style-type: none"> • According to the finding in WHI studies, HRT is not recommended for long-term use and not for patients with previous history of cancer • Even after the non-HRT treatment (i.e. SSRI) was approved, the high unmet medical needs still exist and patients and physicians have been seeking for alternative treatments
Current treatment option	<ul style="list-style-type: none"> • Hormone Replacement Therapy (HRT) • Anti-depressant (i.e. SSRI) • Others (i.e. Chinese herbs)
Market size	<ul style="list-style-type: none"> • According to IMS data of currently available treatments for MR-VMS <ul style="list-style-type: none"> - US: ~\$1 billion USD - EU5: ~110 million euro - JP: ~ 50 oku yen (HRT only) - China: ~ \$235 million USD • Due to the findings in WHI studies in 2001, the prescription of HRT dropped significantly (US/EU) • In JP and China, there are still huge proportion of patients who are not diagnosed and not treated for MR-VMS