fezolinetant: A Novel Approach for Targeted Menopausal Symptom Relief

December 14, 2017
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Information about pharmaceutical products (including products currently in development) which is included in this material is not intended to constitute an advertisement or medical advice.
AGENDA

I. VMS and fezolinetant
   Graeme Fraser, PhD

II. Market Overview
    Jeffrey Kern

III. Questions & Answers
     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 (e.g. 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

*Note: Graphic is directional and depicts the years and phases of natural menopause on average*

**Menopause**
- Menopause is marked by the **lack of a menstrual period for 12 mos.**
- The average age when women experience menopause in the US is **51 years**

Source: US market research by Acsel health; Vasomotor symptoms Opportunity Assessment, February 2017, Up to Date (Literature review current through: June 2017)
*Prevalence of women with moderate to severe VMS varies by reports*
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

<table>
<thead>
<tr>
<th>Approved Treatment Options*</th>
<th>VMS indication</th>
<th>MoA in MR-VMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal Replacement Therapy (HRT)</td>
<td>• Estrogen and progesterone combination for women who have not undergone a hysterectomy</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>• Conjugated equine estrogen with bazedoxifene for women with uterus</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-depressants (SSRI)</td>
<td>• Paroxetine is the only approved non-hormonal agent for VMS; best suited for patients contraindicated for HRT.</td>
<td>Yes (US only)</td>
</tr>
</tbody>
</table>

*Treatments approved for MR-VMS as an indication

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 illnesses\(^1\)
- The study of hormone therapy was halted 3 years earlier than designed due to the preliminary results\(^3\)
- 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

• 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


*p<0.05 at 4 hrs for all dose groups
PATHOPHYSIOLOGY OF VMS: NEW UNDERSTANDING

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

- 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
FEZOLINETANT: SAFETY PROFILE FROM PHASE 1

Phase 1 Studies:

**ESN-364-CPK-101**

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

1: J Clin Endocrinol Metab. 2016;101(2):417-426
FEZOLINETANT: POC STUDY IN MR-VMS

<table>
<thead>
<tr>
<th>Study design</th>
</tr>
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<tbody>
<tr>
<td>Double blind</td>
</tr>
<tr>
<td>12 Weeks</td>
</tr>
<tr>
<td>2 Cohorts: 90mg (BID) vs. PBO</td>
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<tr>
<th>Endpoints</th>
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<tbody>
<tr>
<td>Primary Endpoint (FDA Guidance**)</td>
</tr>
<tr>
<td>• HF Frequency and Severity at wks 4, 12</td>
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<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
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</thead>
<tbody>
<tr>
<td>• Patient Questionnaires: QoL, Sleep, Bother, Productivity</td>
</tr>
<tr>
<td>• Safety and Pharmacokinetics</td>
</tr>
<tr>
<td>• Hormones: LH, FSH, estradiol, SHBG</td>
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<thead>
<tr>
<th>Timing</th>
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<tbody>
<tr>
<td>Baseline Sampling</td>
</tr>
<tr>
<td>PK/hormones wk-12</td>
</tr>
<tr>
<td>12w Treatment 2w FUP</td>
</tr>
<tr>
<td>Daily self-reporting of HF with weekly data compilation</td>
</tr>
<tr>
<td>Study results were presented at ENDO 2017¹</td>
</tr>
</tbody>
</table>

*All sites were in Belgium. POC: Proof of Concept, BID: twice daily, PBO: placebo, HF: hot flash, PK: pharmacokinetics, QoL: quality of life, LH: luteinizing hormone, FSH: follicle stimulating hormone, SHBG: sex hormone-binding globulin, 1: Herman Depypere et al., ENDO2017 **Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation
FEZOLINETANT: POC STUDY IN MR-VMS

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

* : % decrease from the baseline
FEZOLINETANT: POC STUDY IN MR-VMS

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

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

* : % decrease from the baseline

POC: Proof of concept, MR-VMS: Menopause-related vasomotor symptoms, HF: hot flash

Herman Depypere *et al.*, ENDO2017
FEZOLINETANT: POC STUDY IN MR-VMS

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 ± SEM

Herman Depypere *et al.*, ENDO2017,
POC: Proof of concept, MR-VMS: Menopause-related vasomotor symptoms
FEZOLINETANT: POC STUDY IN MR-VMS

Safety Data: adverse event profile

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

• 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

Target patient

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

Study Design

- Placebo (n=44)
  - 4 weeks
- Fezolinetant Once daily
  - 3 dose cohorts (n=44/cohort)
  - 12 weeks
- Fezolinetant Twice daily
  - 4 dose cohorts (n=44/cohort)
  - 12 weeks

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*

*: from ClinicalTrial.gov (Study number: NCT03192176)
MARKET OVERVIEW

JEFFREY KERN
VP, MARKETING STRATEGY
ASTELLAS PHARMA US, INC.
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 VTE²
- 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

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

### APPROVED THERAPIES AND DEVELOPMENT PROGRAMS

#### Hormone Replacement Therapy (HRT)

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>MoA</th>
<th>Company</th>
<th>Compound</th>
<th>MoA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>Premarin</td>
<td>conjugated estrogen</td>
<td>Mithra</td>
<td>estetrol</td>
<td>estrogen</td>
</tr>
<tr>
<td></td>
<td>Duavee</td>
<td>SERM+Premarin</td>
<td>Ausio</td>
<td>AUS131</td>
<td>estrogen receptor agonist</td>
</tr>
<tr>
<td>Novo Nordisk</td>
<td>Activelle</td>
<td>progestogen+estrogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayer</td>
<td>Climara</td>
<td>estradiol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teva</td>
<td>Cenestin</td>
<td>conjugated estrogen</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

#### Non-hormone Replacement Therapy

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>MoA</th>
<th>Company</th>
<th>Compound</th>
<th>MoA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hisamitsu/Noven</td>
<td>Brisdelle</td>
<td>SSRI</td>
<td>KaNDY</td>
<td>NT-814</td>
<td>NK1/3 antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pherin</td>
<td>salubrin</td>
<td>Undisclosed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QUE Oncology</td>
<td>Q-122</td>
<td>CXCR4 inhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tanabe Mitsubishi</td>
<td>MT-8554</td>
<td>Undisclosed</td>
</tr>
</tbody>
</table>
**US MARKET**

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

**United States**  
**HRT Annual TRx Trend**

**2016 MR-VMS market: approx. $1B USD**

- **Female Population, Age 45-69**
  - (in millions)
  - 2005: 43  
  - 2030 (estimated): 53

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

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**EU MARKET**

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

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**EU5 Countries HRT Annual Volume Trend**

**2016 MR-VMS market: approx. 110M euro**

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**Female Population, Ages 45-69**

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

2005: 47

2030 (estimated): 54

• Approximately 40% of menopausal women experience moderate to severe VMS

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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.

- In 2005, total female population age 45-64 was 18M and expected to be 17M in 2030\(^4\)
- Approximately 33% of women ages 45-65 who experience VMS consider it to be moderate to severe\(^5\)


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.

2016 MR-VMS market: ~$235M USD

In 2005, total urban female population in age 40-64 was 77M, expected to be 183M in 2030.

12.7% of urban women (age 40-65) would experience moderate to severe VMS.
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 perspired 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”

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

*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*

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

HRT: hormone replacement therapy, OB/GYN: Obstetrician/Gynecologist, PCP: Primary care physician, QoL: Quality of life, OTC: over the counter
SUMMARY

- 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.
## SUMMARY

### Fezolinetant and MR-VMS

<table>
<thead>
<tr>
<th>Target indication</th>
<th>• MR-VMS</th>
</tr>
</thead>
</table>
| **MoA**           | • 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** | • 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** | • Hormone Replacement Therapy (HRT)  
|                   | • Anti-depressant (i.e. SSRI)  
|                   | • Others (i.e. Chinese herbs) |
| **Market size** | • According to IMS data of currently available treatments for MR-VMS  
|                   | - 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 |