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# NOE-PMM-201, Results Of Phase 2a Study Of NOE-115 For The Treatment of Vasomotor Symptoms In Menopause

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## SUMMARY

1. **Recent advances in managing VMS pharmacologically have focused on antagonism of the NK1/3 receptor leaving unaddressed many co-occurring symptoms: depression, weight gain/food craving, and fatigue.**
2. **Cendifensine (NOE-115) modulates serotonin, norepinephrine, and dopamine simultaneously; in this open-label trial, such modulation was expected to improve VMS and well as other associated symptoms of menopause.**
3. **Large, clinically meaningful reductions from baseline were reported in moderate-to-severe hot flash frequency (82% at Week4; 92% at Week 12) and severity (42% at Week4; 59% at Week 12) with cendifensine 30 mg daily; similar improvement was seen with the 60 mg cohort.**
4. **Cendifensine improved symptoms of depression, food cravings, fatigue, and weight gain, consistent with its mechanism of action and nonclinical model.**
5. **Cendifensine 30 mg was well tolerated, with no serious events and no clinically significant changes in laboratories or ECGs; transient BP elevation during the first 28 days that attenuated with continued treatment.**

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## INTRODUCTION & OBJECTIVE

- Vasomotor symptoms (VMS), including hot flashes and night sweats, affect over 80% of peri- and postmenopausal women.[1] Up to 40% experience moderate-to-severe VMS requiring treatment, yet many of these remain undertreated due to contraindications or reluctance to use hormonal therapy.[2] Approved / off-label non-hormonal options, such as low dose paroxetine (Selective Serotonin Reuptake Inhibitor - SSRI), venlafaxine and desvenlafaxine (Serotonin–Norepinephrine Reuptake Inhibitor - SNRIs) provide limited reduction of VMS and some improvement of the menopause-associated symptoms. NK1/3 receptor antagonists, primarily targeting thermoregulatory pathways, do not fully address the broader constellation of menopause-associated symptoms, including low mood, fatigue, food craving/body weight gain, and cognitive complaints.[3–5]
- Declining estrogen levels during menopause disrupt serotonergic (SE), noradrenergic (NE), and dopaminergic (DA) neurotransmission, narrowing the thermoregulatory zone and simultaneously impairing cortical and hypothalamic domains controlling mood, appetite, sleep, and cognition.[6]
- Cendifensine (NOE-115) is a novel, investigational broad-spectrum monoamine regulator modulating the serotonin transporter (SERT), norepinephrine transporter (NET), and dopamine transporter (DAT). Cendifensine is designed to restore thermoregulatory balance while also addressing associated menopausal symptoms.

### OBJECTIVE

To evaluate the safety, tolerability, and preliminary efficacy of cendifensine (NOE-115) 15–60 mg QD for 12 weeks in postmenopausal women with moderate-to-severe VMS.

## METHODS

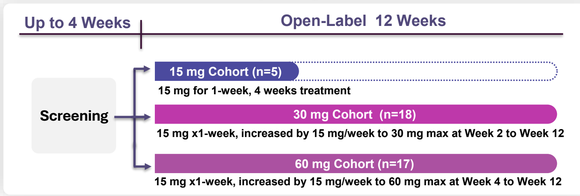
### DESIGN

- NOE-PMM-201 was a Phase 2a, single-arm, open-label, multicenter study conducted at 5 sites in the United States (April 2024–August 2025) (FIGURE1).
- The study comprised 3 sequential cohorts: 15 mg 4-week treatment cohort (n=5), 60 mg 12-week treatment cohort (n=17), 30 mg 12-week treatment cohort (n=18)

### ENDPOINTS

- **Primary (safety):** Proportion of participants discontinuing study intervention due to treatment-emergent adverse events (TEAEs), with 95% CI (Clopper-Pearson)
- **Secondary (safety):** Adverse events (AEs) including serious adverse events (SAEs); adverse events of special interest (AESIs: euphoria, hypertension, tachycardia); suicidal ideation/behavior (Columbia–Suicide Severity Rating Scale C-SSRS); withdrawal symptoms (Penn Physician Withdrawal Checklist - Penn PWC); nature, frequency, and temporality of TEAEs; weight (kg)
- **Secondary (efficacy):** Mean change from baseline at Weeks 4 and 12 in:
  - Daily frequency and daily severity of moderate-to-severe VMS (Hot Flash Diary)
  - Clinical Global Impression–Severity (CGI-S)
  - Proportion of responders (≥ 30% frequency or severity reduction from baseline)
- **Exploratory:** MENO-D (Depression in Menopause scale), FCQ-T-R (Food Craving Questionnaire-Trait-Revised), BFI (Brief Fatigue Inventory), pharmacokinetics

**FIGURE 1. NOE-PMM-201 study design**




## RESULTS

### Population Characteristics & Disposition

- Of 121 women screened, 40 were enrolled across 5 sites (81 screen failures). The study population was racially diverse (TABLE 1). Baseline VMS burden was substantial, with a mean of 12.7 (SD 5.6) moderate-to-severe hot flashes per day.

**TABLE 1. Baseline Demographics and Disease Characteristics (Safety Analysis Set)**

| Characteristic | Cohort 30 mg 12-week (n=18) | Cohort 60 mg 12-week (n=17) | Overall (n=40)[a] |
|---|---|---|---|
| **Age, years - mean (SD)** | **54.2 (2.6)** | **54.2 (4.6)** | **54.1 (3.7)** |
| **BMI, kg/m² - mean (SD)** | **28.2 (5.2)** | **29.2 (4.4)** | **29.3 (5.2)** |
| **Weight, kg - mean (SD)** | **75.0 (16.3)** | **79.6 (13.8)** | **78.7 (15.5)** |
| **Race** | | | |
| Black or African American | 5 (27.8) | 10 (58.8) | 18 (45.0) |
| White | 9 (50.0) | 4 (23.5) | 15 (37.5) |
| Asian | 2 (11.1) | 2 (11.8) | 4 (10.0) |
| Other[b] | 2 (11.1) | 1 (5.9) | 3 (7.5) |
| **Baseline moderate-to-severe VMS/day - mean (SD)** | **12.4 (3.7)** | **12.3 (6.0)** | **12.7 (5.6)** |
| **Baseline VMS severity score - mean (SD)** | **2.4 (0.4)** | **2.6 (0.4)** | **2.5 (0.4)** |

[a] Overall includes 15 mg 4-week Cohort (n=5). [b] Includes American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, and Other.
BMI = body mass index; SD = standard deviation; VMS = vasomotor symptoms.

### Disposition & Exposure

- Overall, 57.5% of participants (23/40) completed the study. In the 17 patients who discontinued, 9 discontinued for adverse events, 6 withdrawals of consent, 1 lost of follow-up and 1 protocol deviation.
- Cendifensine treatment exposure is presented in TABLE 2

**TABLE 2. Cendifensine Treatment Exposure (Safety Analysis Set)**

| Characteristic | Cohort 30 mg 12-week (n=18) | Cohort 60 mg 12-week (n=17) | Overall (N=40)[a] |
|---|---|---|---|
| **Median treatment exposure, days (range)** | 83 (7–89) | 61 (1–87) | 61 (1–89) |
| **Highest dose received — n (%)** | | | |
| 15 mg | 4 (22.2) | 2 (11.8) | 11 (27.5) |
| 30 mg | 14 (77.8) | 3 (17.6) | 17 (42.5) |
| 45 mg | - | 1 (5.9) | 1 (2.5) |
| 60 mg | - | 11 (64.7) | 11 (27.5) |

[a] Overall includes Cohort 15 mg 4-week (n=5).

### Efficacy – Changes in Moderate-to-Severe daily VMS

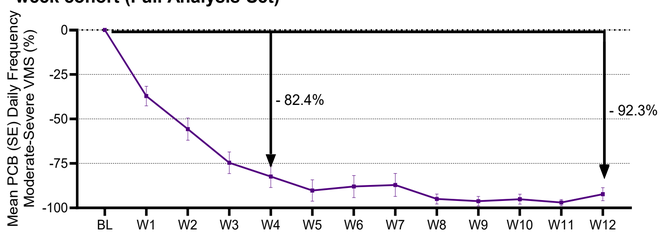
- Large, clinically meaningful and statistically significant within-group reductions from baseline in both daily VMS frequency and severity were observed at all post-baseline timepoints for participants in the 12-Week 30 mg and 60 mg cohorts (TABLE 3, FIGURE 2).
- The 30 mg cohort showed numerically greater improvements than the 60 mg cohort across all key efficacy parameters, with:
  - Moderate-to-Severe daily VMS Frequency: 92.3% reduction at Week 12 vs Baseline
  - VMS Severity: 59.2% reduction at Week 12 vs Baseline

**TABLE 3. VMS Frequency and Severity Changes (Full Analysis Set)**

| Percent Change From Baseline (p within group change) | Cohort 30 mg 12-week (n=18) | Cohort 60 mg 12-week (n=17) |
|---|---|---|
| VMS Moderate-to-Severe Frequency | | |
| Week 4 | - 82.4% (p<0.001) | - 67.5%% (p<0.001) |
| Week 12 | - 92.3% (p<0.001) | - 78.1%% (p=0.016) |
| VMS Severity | | |
| Week 4 | - 41.8% (p<0.001) | - 41.6% (p<0.001) |
| Week 12 | - 59.2% (p<0.001) | - 45.6% (p=0.031) |

VMS = vasomotor symptoms.

**FIGURE 2. Percent change From Baseline, VMS frequency, 30 mg 12-week cohort (Full Analysis Set)**




PCB = percent change from baseline, SE = standard error, VMS = vasomotor symptoms

- Sensitivity analyses (LOCF imputation, per protocol analyses) show consistent improvement in Moderate-to-Severe daily frequency and VMS severity.
- Responder analyses showed that most of participants improved by 75% or more (Daily Moderate-to-Severe VMS Frequency).

### Efficacy – VMS Co-occurring symptoms

- Depression: Among the subgroup of patients with baseline MENO-D above the median, the MENO-D total score mean (SD) was 19.6 (4.5), consistent with mild depression. Patients reported a mean 12.9-point reduction at Week 12.
- Food craving and weight: Among the subgroup of patients with baseline Food Craving Questionnaire (FCQ-T-R) score ≥ 50 (n=11), a baseline mean score (SD) of 63.5 (11.6) was reported, consistent with clinically significant food craving abnormalities. Patients reported a mean 22.8-point reduction at Week 12 (n=6, p<0.001). The 30mg cohort reported a median reduction in weight of 2.5 kg.
- Fatigue: Among the subgroup of patients with baseline BFI score above the median (n=11), the baseline BFI total score mean (SD) was 5.9 (0.6), consistent with moderate fatigue. Patients reported an improvement at week 12 vs baseline of -4.32 (n=5, p<0.05).

### Safety

- No deaths, no SAEs were reported.
- No suicidal ideation or behavior was reported at any timepoint (C-SSRS).
- No clinically meaningful findings in chemistry, hematology, coagulation, urinalysis, liver function tests, or ECG parameters.
- No clinically significant withdrawal symptoms were observed during treatment or follow-up (Penn PWC).
- AESIs comprised hypertension (n=3) and tachycardia (n=1); all were mild or moderate, mostly resolved, all considered possibly treatment related.
- Most frequently reported AEs: dry month, headache, insomnia, constipation, dizziness.
- Vital signs: nominal blood pressure elevation during Weeks 1–4 with accommodation; negligible change at steady state (Week 12). Modest pulse rate increase consistent with cendifensine's pharmacology. No clinically significant blood pressure or hear rate AEs at steady state.

## CONCLUSIONS

- **Cendifensine 30 mg daily demonstrated robust reductions in both the frequency (92%) and severity (59%) of moderate-to-severe VMS over 12 weeks in postmenopausal women with substantial baseline symptom burden.**
- **Improvements measured in mood, food craving, fatigue, and body weight consistent with cendifensine mechanism of action.**
- **These Phase 2a open-label results support advancement to a randomized, placebo-controlled Phase 2b trial to confirm the efficacy and safety of cendifensine for VMS and other menopause-associated symptoms.**