MACE study
Summary

1. **Study Title:**

   Major Adverse Cardiovascular Event Risk in Menopausal Women Treated With Oral Estradiol/Micronized Progesterone Versus Conjugated Estrogens/Medroxyprogesterone: US Claims Data Analysis

2. **Study Sponsor:**
   Theramex Ltd, 5th Floor 50 Broadway, London, SW1H 0BL

3. **Study Objective:**

   To compare the risk of major adverse cardiovascular events (MACE) between two combined oral therapies available to women in U.S: estradiol/micronized progesterone (E2/P4) and conjugated equine estrogens/medroxyprogesterone acetate (CEE/MPA) using real-world data.

4. Study Design:
Study type: observational, retrospective longitudinal, non-interventional study of a US claims Symphony database (04/2019 to 06/2021)

5. Study Population:
- E2/P4 cohort included 6,520 women
- CEE/MPA cohort included 29,426 women
- Total: 35,673 participants

6. Methodology:
- Women were eligible if they met the following criteria:
    a. no MACE events (hospitalization with MI, stroke, or heart failure diagnosis) before or on the index date (first prescription fill)
    b. ≥ 1 medical claim and ≥ 1 pharmacy claim during the baseline period date
    c. continuous medical and pharmacy-based activity for ≥ 6 months after the index date for (E2/P4) or (CEE/MPA)

- Outcomes were measured from the index date to the earliest of the day before switch to the comparator treatment, the data cut-off date in June 2021, or the end of clinical activity (observation period; ≥6 months by design).

- MACE Measures:
    a. events included hospitalization (based on medical claims) for:
        - Acute myocardial infarction
        - Ischemic or hemorrhagic stroke
        - Heart failure
        - Revascularization procedures indicative of MI observed during or the day before a hospitalization

- Statistical analysis

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- MACE risk was compared between E2/P4 and CEE/MPA using Cox and Poisson/negative binomial regression models.
- Confounding factors were controlled using inverse probability of treatment (IPT) weighting. **7.**

Study Locations:

United States

8. Regulatory Information:

- N/A

9. Results Summary:

- In the IPT-weighted analyses, MACE events rates were 23.5 and 85.4 per 10,000 women-years among women receiving E2/P4 and CEE/MPA, respectively (IPT-weighted incidence rate ratio [IRR] 0.28, 95% CI 0.17 - 0.45)
- In analyses stratified by type of MACE event, each type of MACE event were associated with significantly lower relative risks for E2/P4 as compared to CEE/MPA (IPT-weighted IRRs 0.24, 0.22, and 0.32 for heart failure, acute MI, and stroke, respectively; all p< 0.001

10. Safety and Adverse Events:

- No safety concerns or adverse events reported during the study.

11. Conclusions:

- In IPT time to event analyses, the probability of experiencing a MACE event was significantly lower for women receiving E2/P4 than for those receiving CEE/MPA (IPT-weighted hazard ratio [HR] 0.28, 95% CI 0.17 – 0.46)

12. Publication Plans:

- The study results are submitted to peer-reviewed journal (*Climacteric*); expected publication in Q1 2025

13. Contact Information:

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14. References:

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MACE study
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