NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Treatment patterns of menopausal hormone therapy in South Korea: a nationwide cohort study
Protocol number	B2311076
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Active substance	Conjugated estrogens and bazedoxifene (G03CC07)
Medicinal product	Duavive® tablet 0.45mg/20mg
Research question and objectives	Research question: What are the real-world usage patterns of menopausal hormone therapy in South Korea? Objectives 1. To estimate the prevalence of menopausal hormone therapy by treatment class, age group, menopausal symptoms, and the type of administration 2. To describe the baseline characteristics of patients prescribed with or without menopausal hormone therapy 3. To examine treatment patterns, adherence, and persistence among patients with menopausal hormone therapy
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CCI	Charlson Comorbidity Index
EPT	Estrogen-Progestin Therapy
ET	Estrogen Therapy
HIRA	Health Insurance and Review Assessment
HT	Hormone Therapy
ICD	International Statistical Classification of Diseases and Related Health Problems
IRB	Institutional Review Board
KCD	Korean Standard Classification of Disease
KOSIS	Korean Statistical Information Service
MHT	Menopausal Hormone Therapy
MPR	Medication Possession Ratio
NHIS	National Health Insurance Service
SERM	Selective Estrogen Receptor Modulator
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD, RPh, MPH	Non-Interventional Study Lead	Pfizer Korea	Seoul, Korea
PPD, MD, PhD	Principal Investigator	Konkuk University	Seoul, Korea
PPD, PhD	Principal Inversitator, PPD	Sungkyunkwan University (SKKU)	Suwon, Korea
PPD, MD, PhD	Principal Investigator	Inje University	Busan, Korea

4. ABSTRACT

- **Title**

Treatment patterns of menopausal hormone therapy in South Korea: a nationwide cohort study

- **Rationale and Background**

Women experiencing menopause may undergo various changes, such as vasomotor, bone and joint, genitourinary, and psychological symptoms due to ovarian failure and sex hormone deficiency. Treatment guidelines recommend menopausal hormone therapy (MHT) for vasomotor symptoms and prevention of osteoporosis in women under 60 years of age or within 10 years of menopause and without contraindications. However, since the Women's Health Initiative report and the Million Women Study were published, the use of MHT has declined rapidly. Also, many studies have reported a potential link between MHT and increased risk of cardiovascular disease, breast cancer, and endometrial hyperplasia. Therefore, many menopausal individuals also seek treatment alternatives to MHT, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and clonidine, although some of them have limited effectiveness and are also associated with specific adverse effects. Recently, in light of the position statement on MHT, several menopause societies concur on the necessity of individualized MHT. Given that there is limited evidence on latest MHT usage pattern using the most recent data in South Korea, we aim to estimate the prevalence of MHT among menopausal women and understand treatment patterns, adherence, and persistence among patients with MHT in South Korea using the nationwide claims database from 2011 to 2020.

- **Research Question and Objectives**
  - Research question: What are the real-world usage patterns of MHT in South Korea?
  - Objectives
    1. To estimate the prevalence of MHT by treatment class, age group, menopausal symptoms and the type of administration
    2. To describe the baseline characteristics of patients prescribed with or without MHT
    3. To examine treatment patterns, adherence, and persistence among patients with MHT

- **Study design**

A retrospective observational study using the administrative healthcare claims data

- **Study Population Eligibility Criteria**
  - Inclusion criteria
    - Patients aged 40-59 years at cohort entry date.
    - Patients who had at least one inpatient or outpatient diagnosis of menopausal symptoms between January 1, 2012 and December 31, 2019.
  - Exclusion criteria
    - Patients diagnosed with breast cancer (C50, D05), endometrial cancer (C54.1) and granulosa cell tumor (C56) within 1 year prior to the index date.
    - Patients diagnosed with coronary heart disease (I20-I25, I51.6), stroke (I60-64), and VTE (I80.2, I80.3 I26) within 1 year prior to the index date.
    - Patients diagnosed with viral hepatitis (B16-B19), cirrhosis (K70.2-K70.4, K71.7, K72.0-K72.1, K72.9, K74.0–K74.6, K76.1, K76.6–K76.7, R18, I85.0, I85.9, I86.4, I86.8, I98.2-I98.3), and hepatic cancer (C22) within 1 year prior to the index date.
    - Patients diagnosed with gallbladder disease (K80, K81, K82, K83, K85.1), gallbladder cancer (C23), extrahepatic bile duct cancer (C24) within 1 year prior to the index date.

- **Variables**
  - Exposures
    - Estrogen therapy (ET)
    - Estrogen plus Progestin therapy (EPT)
    - Tibolone
  - Outcomes
    - Prevalence of menopausal symptoms and use of MHT among women aged 40-59 years
    - Prevalence of each menopausal symptom among patients with MHT
    - Secular trend in the prevalence of MHT by treatment class, age group, menopausal symptoms and the type of administration
    - Treatment regimens change of MHT across time at 3-, 6-, 9-, and 12-month

- Time to switch and discontinuation of MHT
- Adherence and persistence of MHT during the follow-up

- Baseline characteristics
  - Demographic characteristics (age, insurance type)
  - Medical institution type
  - Proxies of health status: Charlson Comorbidity Index (CCI), No. of outpatient visits, No. of hospitalization
  - Comorbidities
  - Concomitant medications
  - Type of administration

- **Data sources**
  - The Health Insurance and Review Assessment (HIRA) claims database
  - Korean Statistical Information Service (KOSIS)

- **Study size**

We estimated the expected number of eligible patients using a medical claims volume search tool operated by HIRA (available at: http://opendata.hira.or.kr/op/opc/olap3thDsInfo.do). We retrieved the number of patients with menopausal and other perimenopausal disorders (N95) recorded as primary diagnosis codes and the number of patients with menopausal and other perimenopausal disorders was identified as 4,293,747 from 2012 to 2019 which is likely to have sufficient power for the study.

- **Data analysis**
  - Annual time-series prevalence of menopausal symptoms and use of MHT will separately be calculated among total women aged 40-59 years.
  - Prevalence of each menopausal symptom including vasomotor symptoms, bone and joint symptoms, genitourinary symptoms, and psychosomatic symptoms will be calculated among patients with MHT.

- Within final study cohort, prevalence of menopausal hormone therapy by treatment class, age group, menopausal symptoms and the type of administration will be calculated for each year.
- Baseline characteristics including demographic characteristics, medical institution type, proxies of health status, comorbidities, and concomitant medications will be assessed on cohort entry date or within 365 days prior to cohort entry date. Type of administration will be assessed on index date. The baseline characteristics of patients with menopausal symptoms will be presented in frequency (proportion) for categorical variables and mean (standard deviation, SD) or median (interquartile ranges, IQR) for continuous variables.
- All outcome variables will be summarized descriptively through tables or graphical forms, including means, medians, ranges, and standard deviations of continuous variables, as well as frequency distributions of categorical variables.
- We will evaluate annual and quarterly time-series trends in the prevalence of MHT between 2012 and 2020 from 4 dimensions: 1) treatment class of MHT: ET (estrogen therapy), EPT (estrogen-progestin therapy), and tibolone. 2) age group: all, 40-44, 45-49, 50-54, and 55-59. 3) menopausal symptoms: vasomotor symptoms, bone and joint symptoms, genitourinary symptoms, and psychosomatic symptoms. 4) type of administration: systemic HT (oral), systemic HT (transdermal), and local HT (transvaginal).
- For treatment change pattern analysis, the treatment will be categorized and the proportional flows of patients switching the treatment classes will be demonstrated by Sankey diagram.
- Kaplan-Meier survival curves will be generated to calculate the time to non-persistence events including switch and discontinuation. Discontinuation will be defined as no subsequent prescriptions within 2 months of last prescription date.
- Treatment persistence is calculated by the average length of treatment of the drugs prescribed at the index date. Persistence rate at 3-, 6-, 9-, and 12-month were also calculated.
- Treatment adherence will be evaluated using medication possession ratio (MPR) calculated as the total number of days of medication supply divided by the number of days in the follow-up period.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	June 27, 2023	Study Title	Modification of the details of expression	To represent the characteristics of the study
		6. Milestones	Delay of protocol approval, and start of data collection	To amend protocol
		7. Rationale and background	Modification of background explanation and addition of references	To explain rationale and background of the study
		8. Research question and Objectives	Modification of research question and reprioritization of objectives	To represent the characteristics of the study
		9.1. Study design	Modification and specification of study design	To represent the characteristics of the study and describe the study period
		9.2. Setting	Modification of target population and the study period	To establish a cohort with representativeness, reliability, and efficiency
		9.3. Variables	Modification, specification, and systematization of variables and their operational definitions, and addition of sensitivity analysis	To analyze the data set within improved validity and reliability
		9.4. Data sources	Addition of a supplementary data source, and explanation of data sources	To analyze the data set within improved validity and reliability

		9.5. Study size	Revision of estimation method of the expected number of patients	To confirm if the power of the study is sufficient
		9.6. Data management	Modification of description	To describe the data management and statistical software in detail
		9.7. Data analysis	Modification, specification, and systematization of data analysis methods	To analyze the data set within improved validity and reliability
		9.8. Quality control	Modification of description	To describe the rationale for the unnecessity of quality control and the qualifications of the research group
		9.9. Strengths and limitations of the research methods	Modification of description	To refine description
		10.3. IRB/IEC	Modification of description	To include standard text for studies requiring IRB/IEC approval
		10.4. Ethical conduct of the study	Addition and deletion of guidance documents	To include only relevant guidance used in the study
		12. Plans for disseminating and communicating study results	Modification of description	To refine description
		13. References	Addition and deletion of references	To include all references cited in the protocol

		14. List of tables	Addition of Table 3~7	To describe variables and their operational definitions in detail, and provide evidence of estimation of the expected number of patients
		15. List of figures	Addition of Figure 2	To show the study flow visually

6. MILESTONES

Milestone	Planned date
Study proposal approval	4Q 2022
Study protocol approval	2Q 2023
Start of data collection: application submission to the HIRA	3Q 2023
End of data collection: data acquisition and analysis	4Q 2023~1Q 2024
Statistical analysis report	4Q 2023~1Q 2024
Final study report	2Q 2024~3Q 2024

7. RATIONALE AND BACKGROUND

Women at menopause may experience various changes due to ovarian failure and sex hormone deficiency[1]. Globally, more than half of women aged 40-64 years experience menopausal symptoms such as hot flushes, night sweating, palpitation, sexual dysfunction, depression, insomnia and osteoporosis[2]. These symptoms can disrupt various aspects of a person's life such as their ability to sleep, concentrate, maintain a good mood, feel energetic, carry out work, and engage in leisure or social activities[3]. Furthermore, the burden of medical treatment for menopausal symptoms is substantial and keeps increasing, highlighting the need for effective solutions to improve the quality of life for these population[4].

Treatment guidelines recommend MHT for vasomotor symptoms and prevention of osteoporosis in women under 60 years of age or within 10 years of menopause and without contraindications[5]. However, since the Women's Health Initiative report and the Million Women Study were published, the use of MHT has declined rapidly[6,7]. Also, many studies have reported a potential link between MHT and increased risk of cardiovascular disease, breast cancer, and endometrial hyperplasia[8-10]. Therefore, many menopausal individuals also seek treatment alternatives to MHT, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, and clonidine[11], although some of them have limited effectiveness and are also associated with specific adverse effects[12].

Recently, in light of the position statement on MHT, several menopause societies concur on the necessity of individualized MHT [13,14]. Given that there is limited evidence on the latest MHT usage pattern using the most recent data in South Korea, we aim to estimate the prevalence of MHT among menopausal women and understand treatment patterns, adherence, and persistence among patients with menopausal hormone therapy in South Korea using the nationwide claims database from 2011 to 2020.

8. RESEARCH QUESTION AND OBJECTIVES

- Research question: What are the real-world usage patterns of menopausal hormone therapy in South Korea?
- Objectives

1. To estimate the prevalence of MHT by treatment class, age group, menopausal symptoms, and the type of administration
2. To describe the baseline characteristics of patients prescribed with or without MHT
3. To examine treatment patterns, adherence, and persistence among patients with MHT

9. RESEARCH METHODS

9.1. Study design

A retrospective observational study will be conducted to examine the prevalence, treatment patterns, persistence, and adherence of commonly used MHT in South Korea, using the HIRA database from January 1, 2011 to December 31, 2020.

9.2. Setting

The study cohort will include patients aged 40-59 years who were firstly diagnosed with menopausal symptoms and initiated MHT between January 1, 2012 and December 31, 2019. Patients with menopausal symptoms will be defined as at least one inpatient or outpatient claim with any of the following diagnosis codes (Table 1), restricted to primary and secondary diagnosis. The cohort entry date will be defined as the date of first diagnosis of menopausal symptoms and the index date will be defined as the date of the first prescription for MHT.

The exclusion assessment window will be defined as the year before the index date. Patients meeting any of the following criteria will be excluded: 1) patients diagnosed with breast cancer (C50, D05), endometrial cancer (C54.1), or granulosa cell tumor (C56); 2) patients diagnosed with coronary heart disease (I20-I25, I51.6), stroke (I60-64), or VTE (I80.2, I80.3 I26); 3) Patients diagnosed with viral hepatitis (B16-B19), cirrhosis (K70.2-K70.4, K71.7, K72.0-K72.1, K72.9, K74.0–K74.6, K76.1, K76.6–K76.7, R18, I85.0, I85.9, I86.4, I86.8, I98.2-I98.3), and hepatic cancer (C22); 4) patients diagnosed with gallbladder disease (K80, K81, K82, K83, K85.1), gallbladder cancer (C23), extrahepatic bile duct cancer (C24) within 1 year prior to the index date. Baseline characteristics including demographic characteristics, and medical institution type will be assessed on cohort entry date and comorbidities, concomitant medications and proxies of health status will be assessed within 1 year prior to cohort entry date. Menopausal symptoms will be assessed within 90 days after cohort entry date. Type of administration will be assessed on index date. (Figure 1).

In the identified study cohort, we will examine treatment patterns, adherence, and persistence of MHT during the follow-up window, which will be defined from the index date (date of first prescription for MHT) to the end of the study period (December 31, 2020).

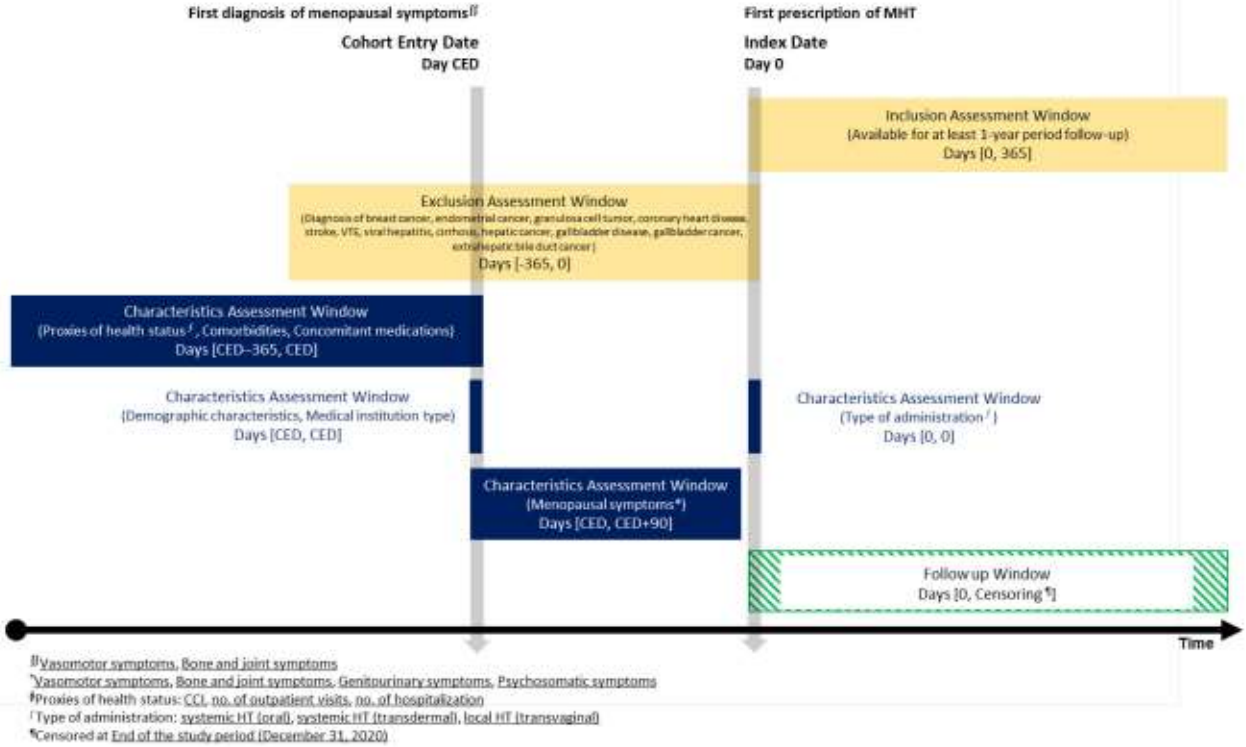

Figure 1. Study design scheme

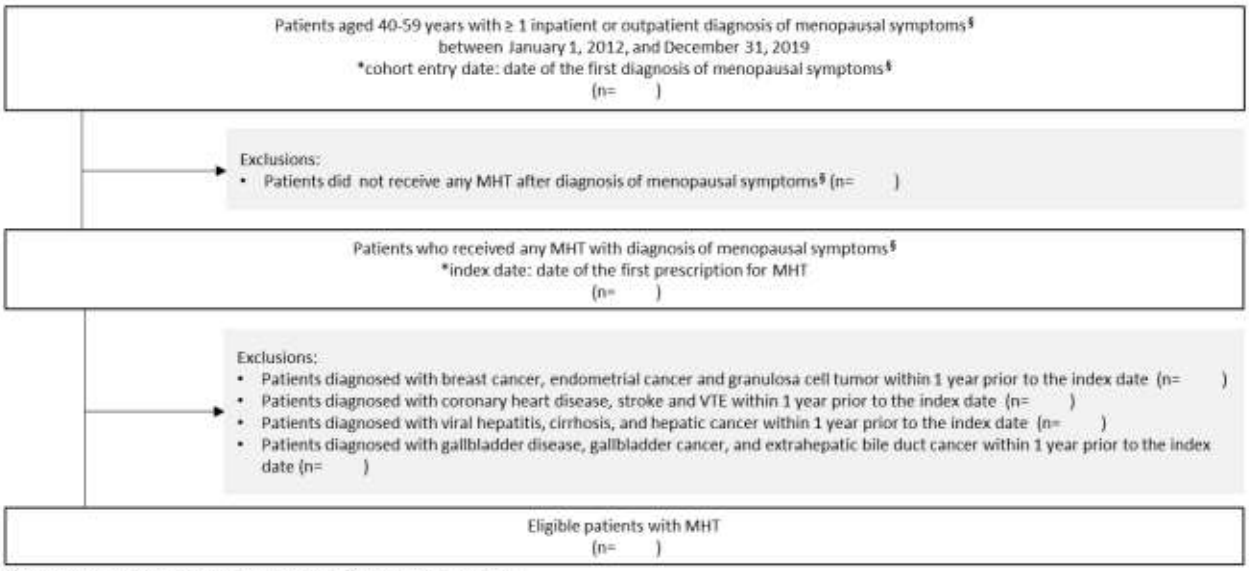

Figure 2. Study Flowchart

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

Using the HIRA database, which covers the entire Korean population of ≥ 50million, we will include patients who meet all the following the inclusion criteria.

1. Patients aged 40-59 years at cohort entry date.
2. Patients who had at least one inpatient or outpatient diagnosis of menopausal symptoms (detailed below) between January 1, 2012 and December 31, 2019.

Table 1. Diagnosis codes for inclusion

KCD-8* code	Description
N95.1	Menopausal and female climacteric states
N95.2	Postmenopausal atrophic vaginitis
N95.3	States associated with artificial menopause
N95.8	Other specified menopausal and perimenopausal disorders
N95.9	Menopausal and perimenopausal disorder, unspecified
M80.0	Postmenopausal osteoporosis with pathological fracture
M81.0	Postmenopausal osteoporosis
M81.99	Osteoporosis, unspecified, site unspecified; Osteopenia

M85.99	Disorder of bone density and structure, unspecified, site unspecified; Osteopenia, mild; Osteopenia, moderate; Osteopenia, severe

*KCD-8 (Korean standard classification of disease, 8th revision): Korean version of ICD-10 (International statistical classification of diseases and related health problems, 10th revision)

9.2.2. Exclusion criteria

1. Patients diagnosed with breast cancer (C50, D05), endometrial cancer (C54.1), and granulosa cell tumor (C56) within 1 year prior to the index date.
2. Patients diagnosed with coronary heart disease (I20-I25, I51.6), stroke (I60-64), and VTE (I80.2, I80.3 I26) within 1 year prior to the index date.
3. Patients diagnosed with viral hepatitis (B16-B19), cirrhosis (K70.2-K70.4, K71.7, K72.0-K72.1, K72.9, K74.0–K74.6, K76.1, K76.6–K76.7, R18, I85.0, I85.9, I86.4, I86.8, I98.2-I98.3), and hepatic cancer (C22) within 1 year prior to the index date.
4. Patients diagnosed with gallbladder disease (K80, K81, K82, K83, K85.1), gallbladder cancer (C23), extrahepatic bile duct cancer (C24) within 1 year prior to the index date.

9.3. Variables

9.3.1 Exposure

As our main goal of this study is to understand current treatment patterns of MHT, exposure will be defined as the medications prescribed most likely to treat menopausal symptoms based on current treatment guideline. We will classify treatment classes of MHT as below:

Table 2. Prescription drugs for inclusion

MHT type	Ingredient	Ingredient code
Estrogen therapy (ET)	Estradiol hemihydrate	154901ATB 154902CCM 154903ATB 154904CPC 154905CPC 154906CPC 154907CSI 154908CCM 154908COM

		154930CCM 154931CCM 154932CCM
	Estradiol valerate	155001ATB 155002ATB
	Conjugated estrogens	155301ATB 155303CCM 155401ATB 155402ATB 155402CCM 155404ATB 155430CCM
	Estriol	155201CCM 155202CSP
	Estriol/Lactobacillus Acidophilus	507700CTB
	Ethynylestradiol	156401ATB
	Estradiol	154601CPC 154602CPC 154603CPC 154604CPC 154605CPC 154606CPC
	Estradiol/Lactobacillus Acidophilus	336200CTB
	Estropipate	155501ATB 155502ATB 155502CCM
	Promestriene	219001CCS 219001CCM 219030CCM 336100CTB
Estrogen + Progestin Therapy (EPT)*	Estradiol hemihydrate/Norethisterone acetate	297000ATB 297100ATB 298200ATB
	Estrodiol or Estradiol hemihydrate/Dydrogesterone	297400ATB 433700ATB 433800ATB
	Estrodiol hemihydrate/Drospirenone	490400ATB
	Estradiol valerate/Norethisterone acetate	507600ATB

	Estradiol valerate/Medroxyprogesterone acetate	297600ATB 297700ATB 433900ATB 434000ATB 434100ATB 441800ATB
	Estradiol valerate/Cyproterone acetate	297800ATB 398400ATB
	Estradiol valerate/Levonorgestrel	297500ATB 298000ATB
	Estradiol valerate/Norgestrel	297900ATB
	Conjugated estrogen/Medroxyprogesterone acetate	297200ATB 297300ATB 298100ATB 424600ATB 424700ATB 424800ATB 424900ATB 453500ATB 465500ATB
	Estradiol/Norethindrone acetate	335900CPC
	Estradiol/Norethistrone acetate	336000CPC
	Dydrogesterone†	150501ATB
	Medroxyprogesterone acetate†	188901ATB 188903ATB 188904ATB 188905ATB 188906ATB
	Micronized progesterone †	195001ACS
	Cyproterone acetate†	139401ATB
	Norethisterone†	203201ATB
Tibolone	Tibolone	239001ATB

*Estrogen and progestin in combination and estrogen monotherapy plus progestin monotherapy will be included.

†Regarding Estrogen monotherapy plus Progestin monotherapy, only both estrogen and progestin within the same prescription will be considered as progestin therapy is only approved for use in combination with estrogen.

9.3.2 Outcomes

We will examine the treatment patterns of patients with MHT.

1) Prevalence of menopausal symptoms and use of MHT among women aged 40 – 59 years.

- The annual prevalence of menopausal symptoms will be calculated as the number of women diagnosed with menopausal symptoms divided by the mid-year population of women aged 40 – 59 years.
- The annual prevalence of menopausal symptoms with MHT will be calculated as the number of women diagnosed with menopausal symptoms and prescribed with MHT divided by the mid-year population of women aged 40 – 59 years.

2) Prevalence of each menopausal symptom among patients with MHT.

- Menopausal symptoms will be classified into 4 categories: vasomotor symptoms, bone and joint symptoms, genitourinary symptoms, and psychosomatic symptoms. (Table 3)
- The prevalence of each menopausal symptom among patients with MHT will be calculated as the number of patients diagnosed with each menopausal symptom divided by the number of patients prescribed for MHT.

Table 3. Menopausal symptoms

Menopausal symptoms	KCD-8 code
Vasomotor symptoms	N95.1 (Menopausal and female climacteric states) N95.3 (States associated with artificial menopause) N95.8 (Other specified menopausal and perimenopausal disorders) N95.9 (Menopausal and perimenopausal disorder, unspecified) R23.2 (Flushing) §
Bone and joint symptoms	M80.0 (Osteoporosis with pathological fracture) M81.0 (Postmenopausal osteoporosis) M81.99 (Osteoporosis, unspecified, site unspecified; Osteopenia)

	M85.99 (Disorder of bone density and structure, unspecified, site unspecified; Osteopenia, mild; Osteopenia, moderate; Osteopenia, severe)
Genitourinary symptoms	N94.1 (Dyspareunia) N95.0 (Postmenopausal bleeding) N95.2 (Postmenopausal atrophic vaginitis) F52.6 (Nonorganic dyspareunia)§
Psychosomatic symptoms	F32 (Depressive episode)§ F33 (Recurrent depressive disorder)§ F51 (Nonorganic sleep disorders)§ G47 (Sleep disorders) §

§R23.2, F32, F33, F51, F52.6, G47 are considered as diagnosis codes for menopausal symptoms only when they are obtained by obstetrics and gynecology specialists. (DGSBJT_CD:10)

3) Secular trend in the prevalence of MHT by treatment class, age group, menopausal symptoms, and the type of administration

- We will examine annual and quarterly time-series trends in the prevalence of MHT between January 1, 2012, and December 31, 2020.
- First, we will examine trends by 3 classes of MHT: ET (estrogen therapy), EPT (estrogen-progestin therapy) and tibolone. The time-series trend will be presented as the proportion of each class of MHT quarterly, calculated as the number of patients receiving each class of MHT divided by the total number of patients prescribed with MHT.
- Second, we will examine trends by age group: all, 40-44, 45-49, 50-54, and 55-59. The time-series trend will be presented as the proportion of MHT use by each age group, calculated as the number of patients in each age group divided by the total number of patients prescribed with MHT.
- Third, we will examine trends by menopausal symptoms: vasomotor symptoms, bone and joint symptoms, genitourinary symptoms, and psychosomatic symptoms. The time-series trend will be presented as the proportion of MHT use by each menopausal symptom, calculated as the

number of patients with each menopausal symptom divided by the total number of patients prescribed with MHT.

- Fourth, we will examine trends by the type of administration: systemic HT (oral), systemic HT (transdermal) and local HT (transvaginal). The type of administration of MHT will be classified as follows (Table 4). The time-series trend will be presented as the proportion of MHT use by each type of administration, calculated as the number of patients with MHT by each type of administration divided by the total number of patients prescribed with MHT.

Table 4. Type of administrations

Type of administrations	Ingredient code
Systemic HT (oral)	All ingredient codes except those for systemic HT (transdermal) and local HT (transvaginal)
Systemic HT (transdermal)	154902CCM 154904CPC 154905CPC 154906CPC 154907CSI 154908CCM 154908COM 154930CCM 154931CCM 154932CCM 154601CPC 154602CPC 154603CPC 154604CPC 154605CPC 154606CPC 335900CPC 336000CPC

Local HT (transvaginal)	155303CCM 155402CCM 155430CCM 155201CCM 155202CSP 507700CTB 336200CTB 155502CCM 219001CCS 219001CCM 219030CCM 336100CTB

4) Treatment regimens change of MHT across time

- We will depict treatment switch and discontinuation patterns across time by measuring the number of different treatments, including ET, EPT and tibolone, at time points of 3, 6, 9, and 12 months from the index date. Switching and discontinuation of MHT across time will be presented with a Sankey diagram.

5) Time to switch and discontinuation of MHT

- Over time since the index date (initiation of MHT), Kaplan-Meier survival curves will be generated to calculate the time to non-persistence events including switch and discontinuation. Discontinuation will be defined as no subsequent prescriptions within 2 months of last prescription date.
- Switching MHT for any other treatment classes. (i.e. Switch will be defined as when a patient initiating a ET is prescribed a tibolone or EPT)

6) Treatment persistence and adherence

- Treatment persistence is calculated by the average length of treatment of the drugs prescribed at the index date. Persistence rate at 3-, 6-, 9-, and 12-month will also be calculated.

- Treatment adherence will be evaluated using medication possession ratio (MPR), calculated as the total number of days of medication supply divided by the number of days in the follow-up period.

9.3.3 Baseline characteristics

We will identify the demographic and clinical characteristics of patients with menopausal hormone therapies.

- On cohort entry date
  - Age (40-44, 45-49, 50-54, 55-59)
  - Insurance type (national health insurance, medical aid)
  - Medical institution type (tertiary hospital, hospital, clinic)
- During 1-year prior to cohort entry date
  - CCI (Charlson Comorbidity Index)
  - No. of outpatient visits
  - No. of hospitalization
  - Comorbidities (diabetes mellitus, hypertension, dyslipidemia, cancer, anemia)

Table 5. Comorbidities

Comorbidities	KCD-8 code
Diabetes mellitus	E10-E14
Hypertension	I10-I15
Dyslipidemia	E78
Cancer	C00-C97 (except C22, C23, C24, C50, C54.1, C56)
Anemia	D50-D53, D55-D64

  - Concomitant medications (bisphosphonate, denosumab, teriparatide, SERM, vitamin D, calcium)

Table 6. Concomitant medications

Ingredient	Ingredient code

Ibandronic acid*	480301BIJ 480302BIJ 480303BIJ 480304ATB 480330BIJ 487901ATB 523900ATB
Zoledronic acid*	420701BIJ 420702BIJ 420730BIJ 420731BIJ 420732BIJ
Risedronic acid*	442301ATB 442302ATB 500901ATB 442303ATB 511200ATB 518400ATB 442302ATE 442330ATB
Pamidronic acid*	207901ACS 207902BIJ 207903BIJ 207930BIJ
Alendronic acid*	228302ATB 228301ATB 228303ATB 468000ATE 481100ATR 500200ATB 481100ATB 228303ALQ 228305ATB 228306ALQ 228307ALQ
Etidronic acid*	147401ATB
Clodronic acid*	136101ACH 136102BIJ
Denosumab	629001BIJ

	629002BIJ
Teriparatide	487502BIJ 646301BIJ
Bazedoxifene[§]	617101ATB 674500ATB
Raloxifene[§]	358001ATB 358002ATB 659200ACH 659200ATB 698200ATB
Vitamin D	121401ACS 121402ACS 121601ACS 121602BIJ 121603BIJ 121604ACS 121604ATB 121630BIJ 316800BIJ 316900BIJ 317000BIJ 387900ACS 468000ATE 481100ATB 481100ATR 500200ATB 511200ATB 518400ATB 523900ATB 659200ACH 659200ATB 674500ATB 698200ATB
Calcium	357900ATB

*Following medications will be categorized as bisphosphonate: Ibandronic acid, Zoledronic acid, Risedronic acid, Pamidronic acid, Alendronic acid, Etidronic acid, Clodronic acid

§Following medications will be categorized as SERM: Bazedoxifene, Raloxifene

- On index date

- Type of administration (systemic HT (oral), systemic HT (transdermal), local HT (transvaginal)) (Table 4)

9.3.4 Sensitivity analyses

We will conduct sensitivity analyses as follows:

1. Discontinuation will be defined as no subsequent prescriptions within 4 months of last prescription date.
2. Treatment patterns of medication use for MHT by index treatment classes with patients for 2 years of follow-up.

9.4. Data sources

Health Insurance Review and Assessment service (HIRA) database

This study will use the claims data of HIRA from January 1, 2011 to December 31, 2020. The National Health Insurance in South Korea covers approximately 98% of the entire Korean population. Under the terms of universal health coverage, all the claims data for reimbursement filed by healthcare providers are collected in HIRA database. This database contains a comprehensive information for healthcare services provided to beneficiaries such as diagnoses, treatment, procedures, surgical history, and prescription drugs. It includes an anonymized identifier, which represents the individuals in claims data, with age, sex, inpatient and outpatient diagnoses and drug prescriptions. The diagnoses are coded in compliance with KCD-8 which is a modified codes based on the International Classification of Disease, 10th revision (ICD-10). Information on prescribed drugs included generic name, prescription date, duration, and type of administration. Previous validation studies have been conducted to compare the diagnoses entered in the claims database with the actual diagnoses recorded in the patients' medical records from hospital or clinic chart review. The overall positive predictive value of the diagnoses in the South Korean healthcare database is 82%.

Korean Statistical Information Service (KOSIS)

The KOSIS was established by the Korean National Statistic Office in July 2007 under the national information strategy scheme. It is a statistical information system open to public that provides a

convenient access to wide variety of statistics. It currently provides more than 343 types of statistics produced by 120 organizations in South Korea. Moreover, KOSIS releases 100 major indicators of Korea, which provides information on health indicators and social status including mid-year population of each year and census population for each year.

9.5. Study size

The objectives of the analysis are descriptive in nature. Therefore, the sample size calculations are not applicable, Instead, we estimated the expected number of patients with MHT using a medical claims volume search tool operated by HIRA (available at:
http://opendata.hira.or.kr/op/opc/olap3thDsInfo.do)

This search tool provides the number of diagnosis codes filed for reimbursement to HIRA classified by age and sex of beneficiaries. We retrieved the number of patients between age of 40-59 with menopausal and other perimenopausal disorders (KCD-8 code: N95) recorded as primary diagnosis codes from 2012 to 2019 via this public search tool (Table 7). The number of patients with menopausal and other perimenopausal disorders was similar over the recent 4 years, and we identified 4,293,747 female patients with menopausal and other perimenopausal disorders in total as of 2012 to 2019.

We plan to include patients who were diagnosed with menopausal symptoms between January 1, 2012 and December 31, 2019 as our study cohort study which is likely to have sufficient power for the study.

Table 7. Number of diagnosis code (KCD-8: N95) filed for reimbursement to HIRA from 2012 to 2019

age	2012	2013	2014	2015	2016	2017	2018	2019
40 - 44	23,651	22,014	19,679	17,840	16,928	15,733	14,432	13,477
45 - 49	117,078	109,784	101,951	95,700	93,679	91,211	86,927	84,398
50 - 54	264,843	257,496	235,877	223,231	211,798	204,688	198,718	203,940
55 - 59	186,203	185,308	185,719	190,210	199,122	206,497	207,747	207,868
Total	591,775	574,602	543,226	526,981	521,527	518,129	507,824	509,683

9.6. Data management

A Principal Investigator will obtain a customized HIRA database between January 1, 2011 and December 31, 2020. It is secondary data in which events or outcomes already had occurred at the time of data collection. As the information of subjects in the database is all de-identified, this study is free of any personal information issues. Access to the database is only permitted to individuals who submit the registration form to HIRA. All data management will be conducted on secure servers with regular backups. We will perform all statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Sungkyunkwan University's Institutional Review Board (SKKU-IRB- 2022-11-005).

9.7. Data analysis

We will investigate the baseline characteristics of patients with MHT. Baseline characteristics such as age, insurance type and income levels, and medical institution type will be assessed on cohort entry date. Baseline characteristics such as CCI, no. of outpatient visits/hospitalization, comorbidities and concomitant medications will be assessed on during a 1-year period before cohort entry date. Type of administration will be assessed on index date. The results will be presented in frequency (proportion) for categorical variables and mean (SD) or median (IQR) for continuous variables.

All outcome variables will be summarized descriptively through the tabular or graphical form of means, medians, ranges, and standard deviations of continuous variables and frequency distributions of categorical variables.

Annual time-series prevalence of menopausal symptoms and use of MHT will separately be calculated among total women aged 40-59.

The prevalence of each menopausal symptom among patients with MHT will be calculated as the number of patients diagnosed with each menopausal symptom divided by the number of patients diagnosed and prescribed for MHT. Menopausal symptoms, assessed within 90 days after the cohort entry date, will be classified into 4 categories: vasomotor symptoms, bone and joint symptoms, genitourinary symptoms, and psychosomatic symptoms.

We will examine annual and quarter time-series trends in the prevalence of use for MHT by treatment class, age group, menopausal symptoms, and the type of administration between 2012 and 2020.

We will examine annual and quarterly time-series trends in the prevalence of MHT use by 3 types of MHT: ET (estrogen therapy), EPT (estrogen-progestin therapy), and tibolone. The time-series trend will be presented as the proportion of each type of MHT quarterly, calculated as the number of patients receiving each type of MHT divided by the total number of patients prescribed with MHT.
We will examine annual time-series trends in the prevalence of MHT use by age group: all ages, 40-44, 45-49, 50-54, and 55-59. The time-series trend will be presented as the proportion of MHT use by each age group, calculated as the number of patients in each age group divided by the total number of patients prescribed with MHT.
We will examine annual time-series trends in the prevalence of use for MHT by menopausal symptoms: vasomotor symptoms, bone and joint symptoms, genitourinary symptoms, and psychosomatic symptoms. The time-series trend will be presented as the proportion of MHT use by each menopausal symptom, calculated as the number of patients with each menopausal symptom divided by the total number of patients prescribed with MHT.
We will examine annual time-series trends in the prevalence of use for MHT by the type of administration: systemic HT (oral), systemic HT (transdermal) and local HT (transvaginal). The time-series trend will be presented as the proportion of MHT use by each type of administration, calculated as the number of patients with MHT by each type of administration divided by the total number of patients prescribed with MHT.
Switching and discontinuation of MHT for any other MTH type will be shown by using Kaplan-Meier curve. Discontinuation will be defined as no subsequent prescriptions within 2 months of last prescription date. We will conduct a sensitivity analysis where discontinuation of MHT is defined as a 4-month period without any MHT.
Treatment persistence is calculated by the average length of treatment of the drugs that were prescribed at the index date. Treatment adherence will be shown by calculating MPR (medication possession ratio), calculated as a total number of days of supply of medication divided by the number of days of the follow-up period.

9.8. Quality control

The HIRA data is first generated in the process of reimbursement under the National Health Insurance Service, a government agency, in South Korea. Claims for which reimbursement decision

has been completed are collected in the database, managed regularly by the HIRA, and then processed to be provided for research purposes. Thus, the general requirements for quality control in clinical trials are unnecessary for this study. All data will be checked for completeness and outlying values by a research group with requisite background and experiences in pharmacoepidemiology. The statistical analysis will be independently conducted by two researchers who are skilled in using the SAS program and cross-checked to guarantee the accuracy of the analysis. We will archive all data files, data management, and statistical programs for quality control.

9.9. Strengths and limitations of the research methods

Due largely to its nature of medical claims data, there are some inbuilt limitations. Firstly, discrepancies occur between diagnoses entered in HIRA data and diseases that a patient actually has in reality. Such discrepancies may arise from the inherent nature of claims data, in which the diagnostic codes used for reimbursement might reflect suspected clinical diagnoses rather than confirmed clinical diagnoses. In addition, there is a lack of clinical laboratory data and other clinical markers. Lastly, claims data only provide information on filled prescriptions, not medications actually used. It is also applicable for non-reimbursable diagnosis, treatment or medications. These limitations are generally undetectable or unsolvable, but the dominant majority of data is valid according to the previous studies on the feasibility of the NHIS (National Health Insurance Service) and the HIRA claims data in South Korea. Despite these limitations, we will use HIRA data because it has enormous valuable information representing the entire population of South Korea. We expect to produce real-world evidence on current trends in MHT in South Korea.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in 'Good Outcomes Research Practices' and 'Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making' published by International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and in the 1964 Helsinki declaration and its later amendments.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study are planned to be submitted for publication in a peer-reviewed journal related to this study.

Authorship of any publications reported as results of this study will be determined in accordance with recommendations of the International Committee of Medical Journal Editors (ICJME) for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. The Recommendations of ICJME mentioned that authorship should be satisfied on following all 4 criteria: Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data (2) drafting the article or revising it critically for important intellectual content (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

1. Lee HW, Choi TY, Lee MS, et al. Prescription patterns of herbal medicine for menopausal disorders in major Korean medicine hospitals: a multicenter retrospective study. *Integr Med Res.* 2021;10(3):100706.
2. Stute P, Cano A, Thurston RC, et al. Evaluation of the impact, treatment patterns, and patient and physician perceptions of vasomotor symptoms associated with menopause in Europe and the United States. *Maturitas.* 2022;164:38-45.
3. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA internal medicine.* 2015;175(4):531-539.
4. Assaf AR, Bushmakin AG, Joyce N, Louie MJ, Flores M, Moffatt M. The Relative Burden of Menopausal and Postmenopausal Symptoms versus Other Major Conditions: A Retrospective Analysis of the Medical Expenditure Panel Survey Data. *American health & drug benefits.* 2017;10(6):311-321.

5. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause (New York, NY).* 2022;29(7):767-794.
6. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet (London, England).* 2003;362(9382):419-427.
7. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama.* 2002;288(3):321-333.
8. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *The Cochrane database of systematic reviews.* 2012;2012(8):Cd000402.
9. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet (London, England).* 2019;394(10204):1159-1168.
10. Bath PM, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *BMJ (Clinical research ed).* 2005;330(7487):342.
11. Mintziori G, Lambrinoudaki I, Goulis DG, et al. EMAS position statement: Non-hormonal management of menopausal vasomotor symptoms. *Maturitas.* 2015;81(3):410-413.
12. Kiran A, Schultz NM, Siddiqui E, et al. Epidemiology and treatment patterns of UK women diagnosed with vasomotor symptoms: Findings from the Clinical Practice Research Datalink GOLD database. *Maturitas.* 2022;164:1-8.
13. Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric : the journal of the International Menopause Society.* 2016;19(2):109-150.
14. Cobin RH, Goodman NF. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON MENOPAUSE-2017 UPDATE. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2017;23(7):869-880.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.