March 12, 2025

ASKA Pharmaceutical Co., Ltd.
R&D Presentation for Investors

Securities code : 4886 (TSE)

ASKA Pharmaceutical Holdings Co., Ltd.

Introduction

Sohta Yamaguchi
Senior Managing Member of the Board of Directors, Representative Director
ASKA Pharmaceutical Holdings Co., Ltd.

Enhancement of Drug Discovery Research Structure

Shuzo Watanabe
Corporate Officer, Innovative Drug Discovery Division Director
ASKA Pharmaceutical Co., Ltd.

Self-introduction

Shuzo Watanabe Ph. D. (Agricuture)

- Education:
  - Master of Agricultural Chemistry, the Graduate School of Agriculture, Shizuoka University （1992）
  - Ph. D. in Science of Biological Resources, the United Graduate School of Agricultural Science, Gifu University（2002）

- Work Experience:
  - Pfizer Pharmaceutical Japan Inc. (Currently Pfizer Japan Inc.) （1992 - 2008）
  - RaQualia Pharma Inc.（2008 - 2022）
  - Fujita Health University (2022 - 2023)
  - Remiges Ventures (2022 - 2023)
  - **ASKA Pharmaceutical Co., Ltd. (2023 - Present)**

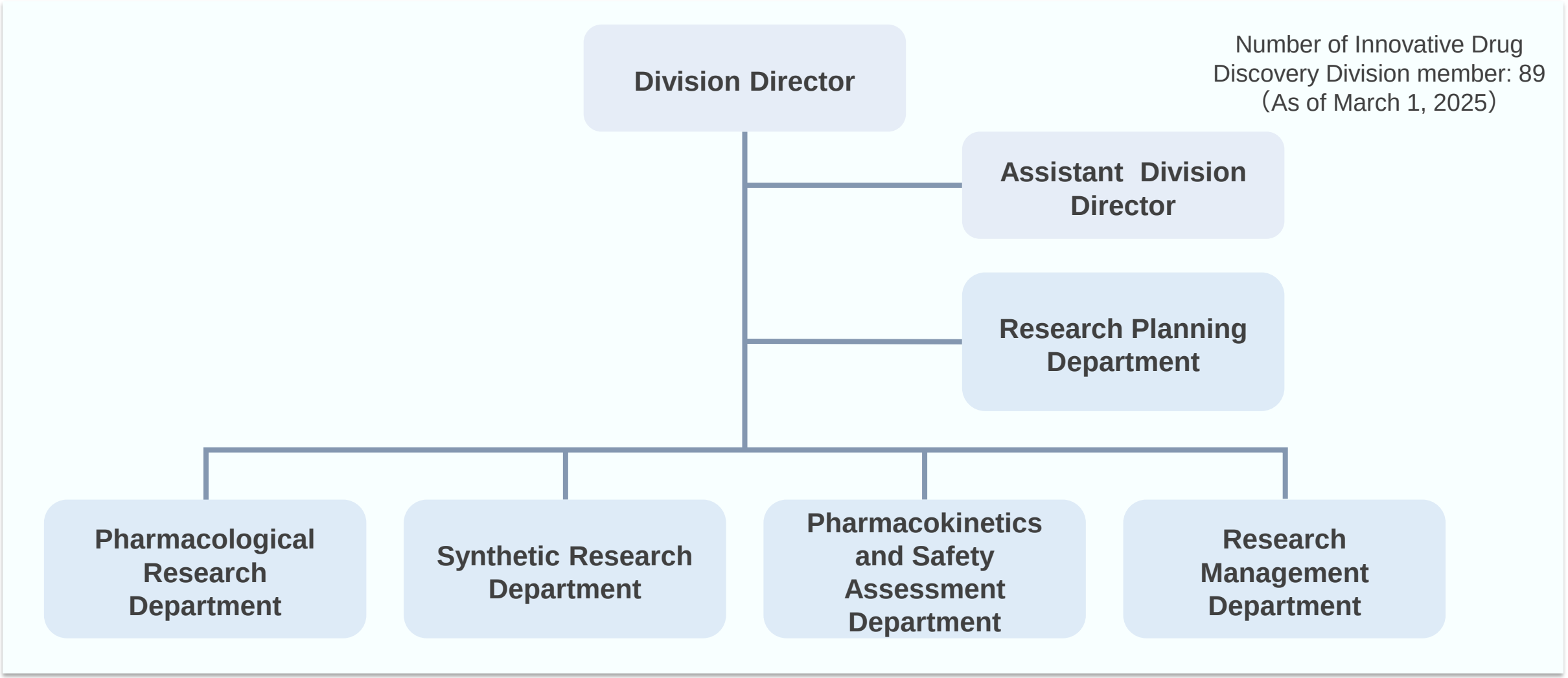
- Expertise: Pharmacology, Neuroscience (particularly pain), Ion Channel Drug Discovery

About Shonan Research Center

- With the aim of strengthening drug discovery research, the Kawasaki Research Center was closed in April 2020 and relocated to the Shonan Health Innovation Park (Shonan iPark)

  Shonan iPark is Japan's first pharmaceutical-initiated science park which is currently home to about 190 companies, including 64 member companies, and more than 2,500 people (as of February 2025) from not only the pharmaceutical industry but also next-generation medicine, cell agriculture, AI, government, and other fields, forming an ecosystem.

Innovative Drug Discovery Structure



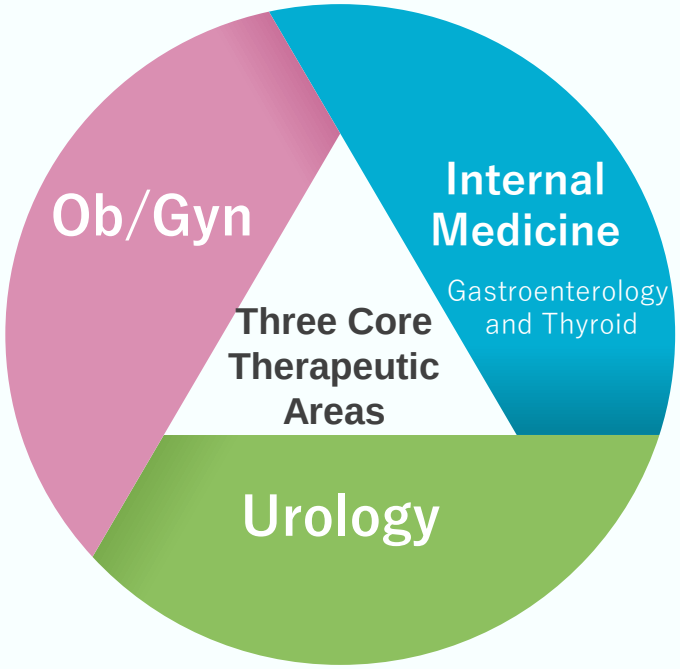
Conventional Drug Discovery Research Activities and Achievements

Focusing on internal medicine (gastrointestinal and thyroid medicine), obstetrics and gynecology, and urology as the prioritized fields, drug discovery research has been conducted mainly to create products that should be developed in Japan.

AKP-009 (novel androgen receptor modulator)
It is an in-house-created compound discovered based on endocrine hormone research, our strength, and is under joint development with Kyorin Pharmaceutical as a therapeutic drug for benign prostatic hyperplasia (P2a).

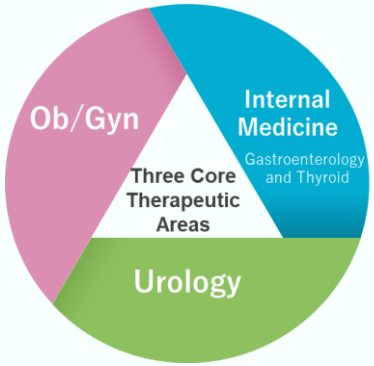
AKP-021 (mPGES-1 inhibitor)
It is an in-house-created compound and is currently under P1.

AKP-017 (tranasal testosterone)
We have obtained formulation patents involving particle size and water-soluble polymers to solve issues with the route of administration (oral administration is unavailable) and are preparing the development of the drug.



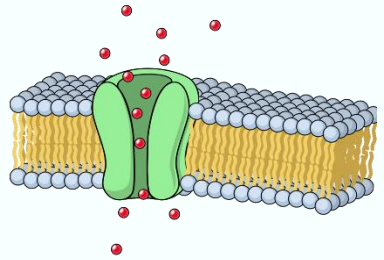
New Drug Discovery Research Activities

- Among the fields that will be continuously prioritized as has been the case to date, basic drug discovery technology in the field of obstetrics and gynecology will be further strengthened.
- In addition to the prioritized fields, unmet medical needs (UMNs) in new fields will be addressed through active utilization of open innovation.
- As a new drug discovery platform, basic drug discovery technologies for ion channels will be introduced.



+

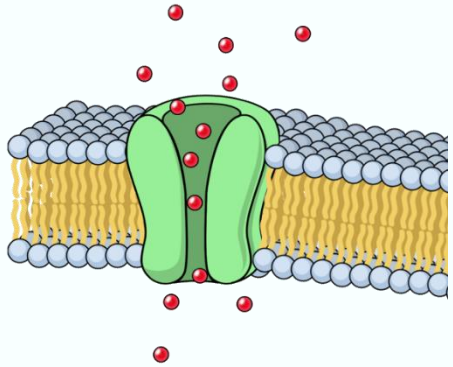
UMNs



Ion Channel Drug Discovery

What are ion channels?

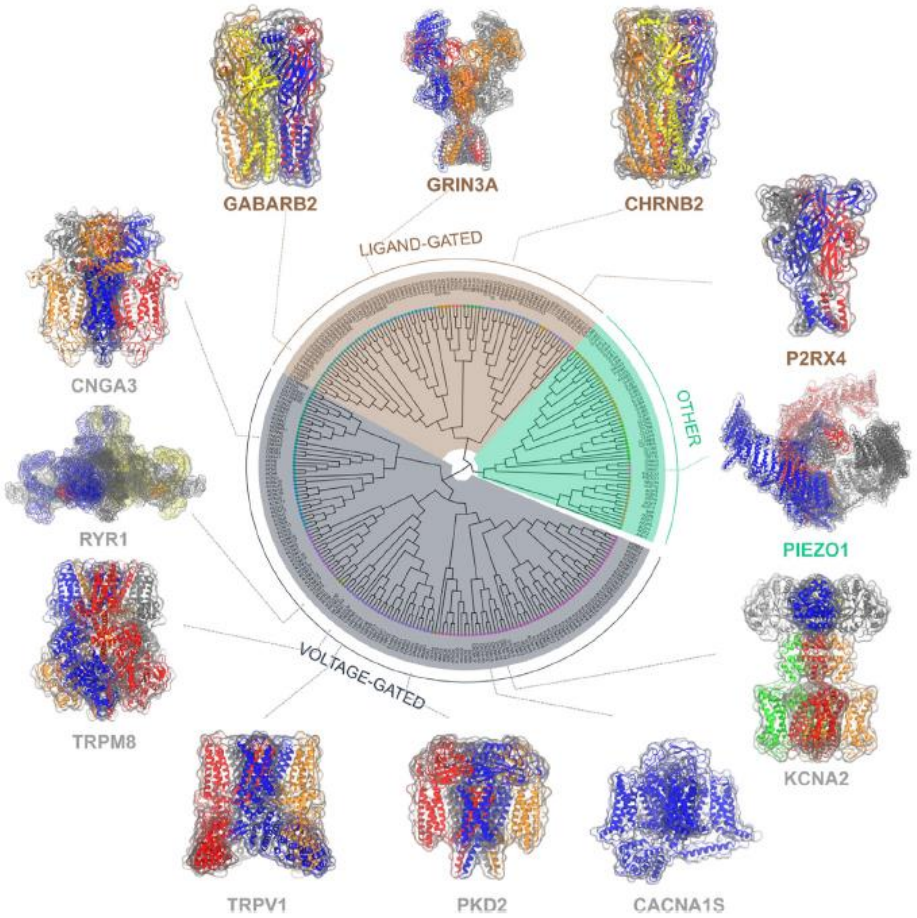
- membrane proteins passing ions across cell membranes
- involving the release of chemical transmitters, control of hormone secretion, etc.
- attractive target molecules for a variety of disease conditions



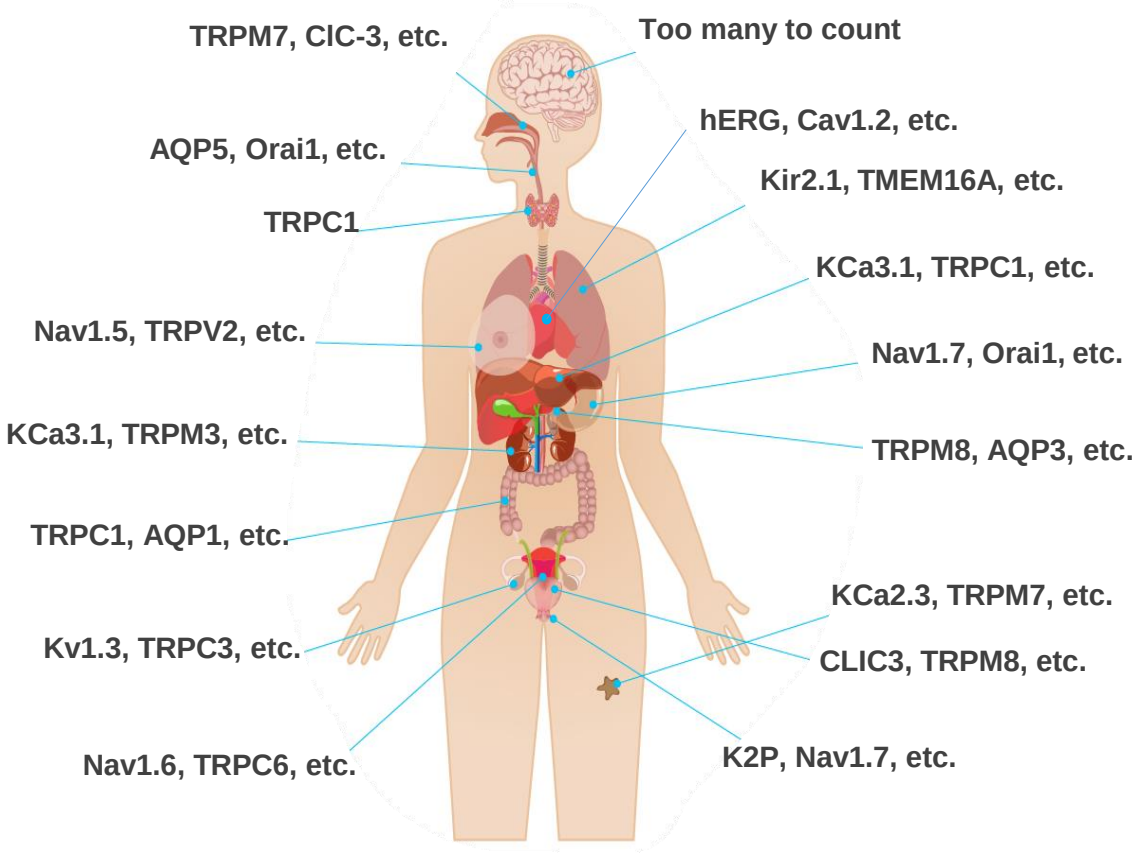
Type	Condition
Ca^{2+} channel	Arrhythmia, diabetes, muscular dystrophy, epilepsy, hypertension, migraine, muscular dysgenesis, cerebral infarction, pain
Cl^- channel	Cystic fibrosis, nephrolithiasis, myotonia
K^+ channel	Arrhythmia, bronchial asthma, ataxia, hypertension, myocardial infarction, deafness, diabetes, epilepsy, cancer, glaucoma, immunosuppression
Na^+ channel	Arrhythmia, epilepsy, migraine, myotonia, sharp pain, paralysis, cerebral infarction
Ligand-gated ion channel	Allergic diseases, bronchial asthma, epilepsy, reflux esophagitis, migraine, Parkinson's disease, Huntington's disease, pain, cerebral infarction, gastric ulcer, constipation

Modified from: Ion Channels as Therapeutic Targets for Multiple Diseases (2002)

Types and Distribution of Ion Channels in the Body



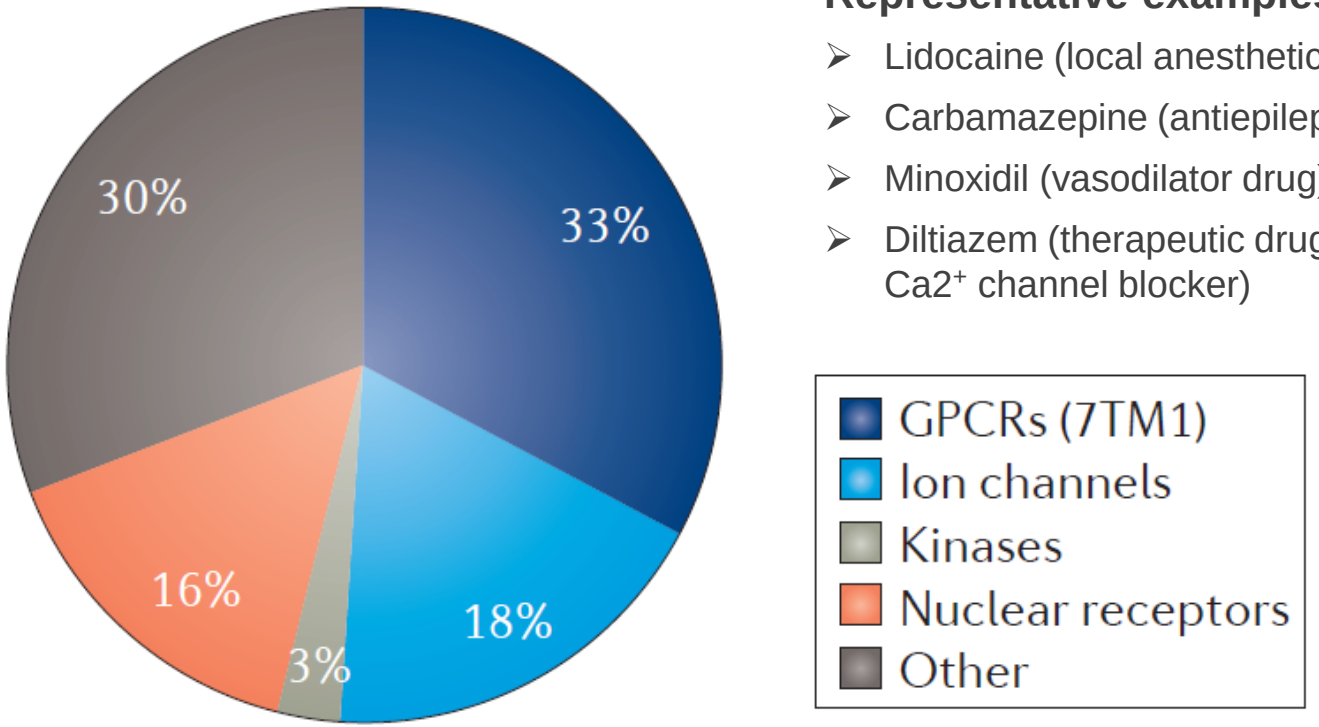
Front. Pharmacol. Vol.13:939555.



Modified from the Sophion Bioscience Corporation website.

Ion channels are widely distributed throughout the body, and **about 400 types** of genes have been identified.

The Proportion of Ion Channel-Targeted Drugs among Approved Drugs (Small Molecules)



Representative examples of ion channel-targeted drugs

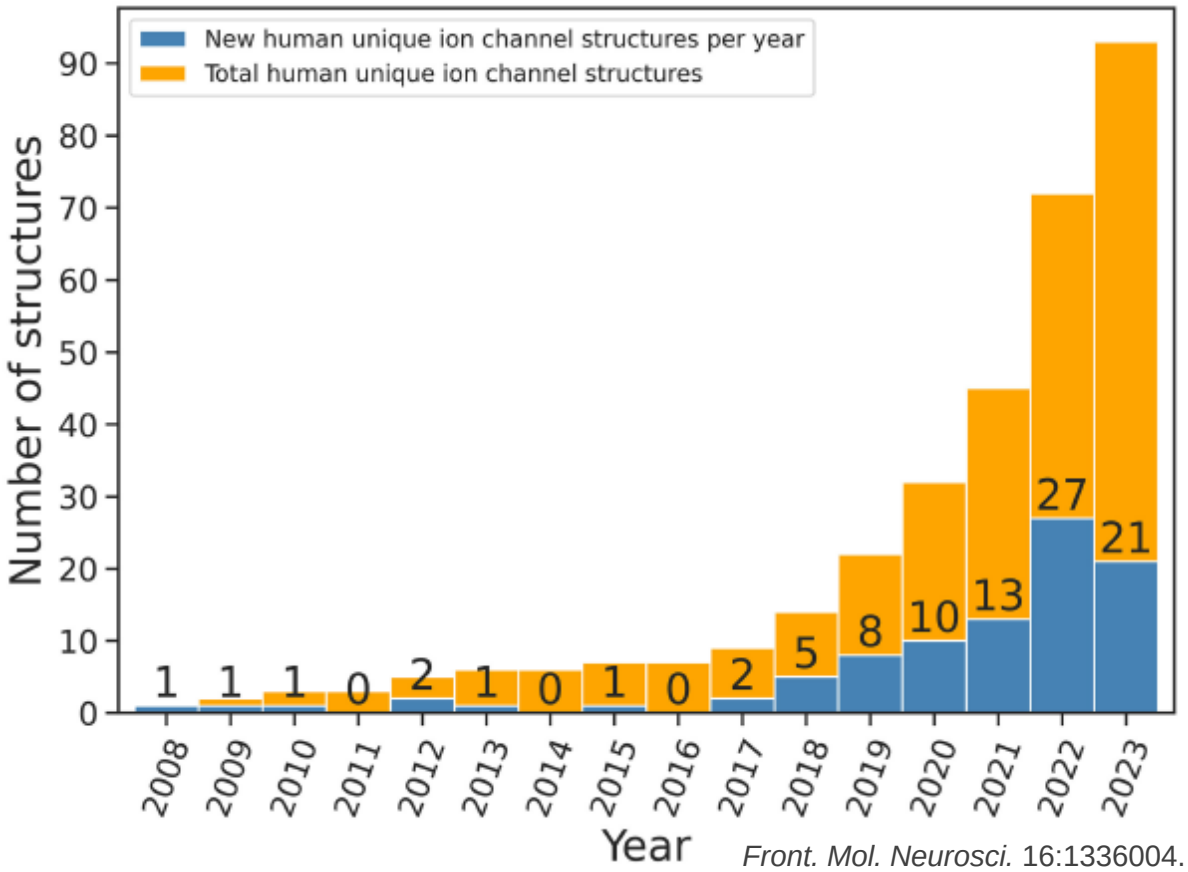
- Lidocaine (local anesthetic/antiarrhythmic drug; Na^+ channel blocker)
- Carbamazepine (antiepileptic drug; Na^+ channel blocker)
- Minoxidil (vasodilator drug); K^+ channel opener)
- Diltiazem (therapeutic drug for angina pectoris and hypertension; $Ca2^+$ channel blocker)

Nature Review Drug Discovery. 2017, 16, 19.

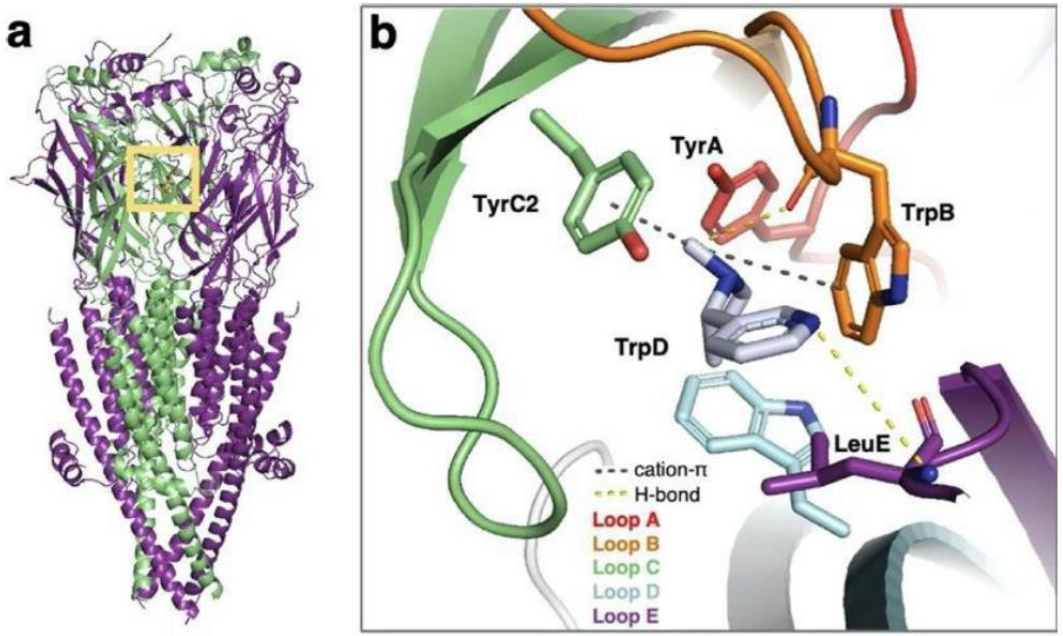
The proportion of ion channel-targeted drugs among approved drugs has remained as low as **18%**. One reason for this is a delay in elucidating the three-dimensional structure, which immensely complicates drug discovery.

Why Ion Channels?

- Technological Advances in the Analysis of the Three-Dimensional Structure of Ion Channels -



Front. Mol. Neurosci. 16:1336004.



Electron microscopic analysis of nicotinic acetylcholine receptors

Int. J. Mol. Sci. 2023, 24, 9226.

Technological advances in X-ray and electron microscopy have increased the number of analyzed three-dimensional structures of ion channels.

➡ Drug discovery targeting ion channels, which has been complicated until now, is becoming possible.

Tackling the Challenge of Developing Ion Channel Drugs Using New Modalities

We have started research and development of new therapeutic drugs using Veneno's technology for creating medium-sized compounds (disulfide-rich peptides) for ion channels, which have been difficult to create with low-molecular-weight compounds that show selective and excellent medicinal effects.

VENENO TECHNOLOGIES

ASKA Pharmaceutical Co., Ltd.

Veneno Technologies and ASKA Signed a Joint Research Agreement for the Development of Novel Ion Channel Therapeutics

Veneno Technologies Co. Ltd.(Head Office: Tsukuba City, Ibaraki/President: Kazunori Yoshikawa; hereinafter "Veneno Technologies") and ASKA Pharmaceutical Co., Ltd. (Head Office: Minato-ku, Tokyo/Representative Director: Sohta Yamaguchi, "ASKA") announced that they have entered into a joint research agreement to conduct a drug discovery program to obtain functional disulfide-rich peptides (DRPs) for ion channels selected by both companies using Veneno Technologies' next-generation peptide discovery technology, PERISS™, with the aim of developing new therapeutic drugs.

Veneno's Website

Further Initiatives

- Promote open innovation and accelerate drug discovery research by introducing external technologies and drug discovery seeds, while also working to enhance our pipeline.
- Strengthen the drug discovery platform technology and enhance collaboration with domestic and international pharmaceutical companies.
  - Establish unique drug discovery platform technology in Ob/Gyn.
  - Build a drug discovery platform for ion channels.
- Aim to continuously create global development products and out-license them to major pharmaceutical companies.

Pipeline

Masaya Takanashi
Corporate Officer, Development Division Director
ASKA Pharmaceutical Co., Ltd.

Pipeline

R&D Status (as of March 2025)

Development code (generic name) Indication	Research[1]	Non-clinical[1]	Ph Ⅰ	Ph Ⅱ	Ph Ⅲ	Application	Approval
LF111 (drospirenone) Contraception							Filed
AKP-022 (Relugolix combination tablet) Uterine fibroids					Ph III Ongoing		
AKP-022 (Relugolix combination tablet) Endometriosis					Preparing clinical trials		
LPRI-CF113 (drospirenone) Dysmenorrhea				Ph I/II Ongoing			
AKP-SMD106 (Digital therapeutics app) PMS/PMDD[2]				Specified Clinical Trial ongoing			
Theme A / Ob/Gyn							
Theme B / Ob/Gyn							
TRM-270 (adhesion barrier) Gastroenterology and Ob/Gyn					Ph III Ongoing		
Theme C / Internal Medicine							
AKP-009 (ludaterone acetate) Benign prostatic hyperplasia				PhIIa Completed[3]			
AKP-021 (mPGES-1 inhibitor agent) Interstitial Cystitis/Bladder Pain Syndrome			Ph I Ongoing				
AKP-017 (transnasal testosterone)			Preparing clinical trials				

1. Details of research are not disclosed because it is non-clinical 2. Premenstrual syndrome/premenstrual dysphoric disorder
3. Next steps are being considered based on the results of the re-conducted Phase I trial.

Pipeline Status of Main Products in Ob/Gyn Field

✓ **LF111**	- Contraception: Application for approval filed
✓ **AKP-022**	- Uterine fibroids: Phase III initiated - Endometriosis: Under development
✓ **LCPI-CF113**	- Dysmenorrhea: Phase I/II initiated

LF111
（Contraception）

LF111 (Oral Contraceptive)

LF111 Overview

Nonproprietary name	Drospirenone
Indication	Contraception
Characteristics	Progesterone-only pill (POP) with the ingredient drospirenone. Conventional oral contraceptives contain two female hormones, estrogen and progesterone. Although the frequency of occurrence is low, there is a risk of thrombosis due to estrogen. **Since this is a progestogen-only oral contraceptive, the risk of thrombosis can be expected to be lower.**
Significance of development	**Provides a new option for women who desire contraception and are not suitable candidates for COC use** for reasons of age, smoking, and obesity.

Filed in June 2024, expected to be launched in 2Q FY2025.

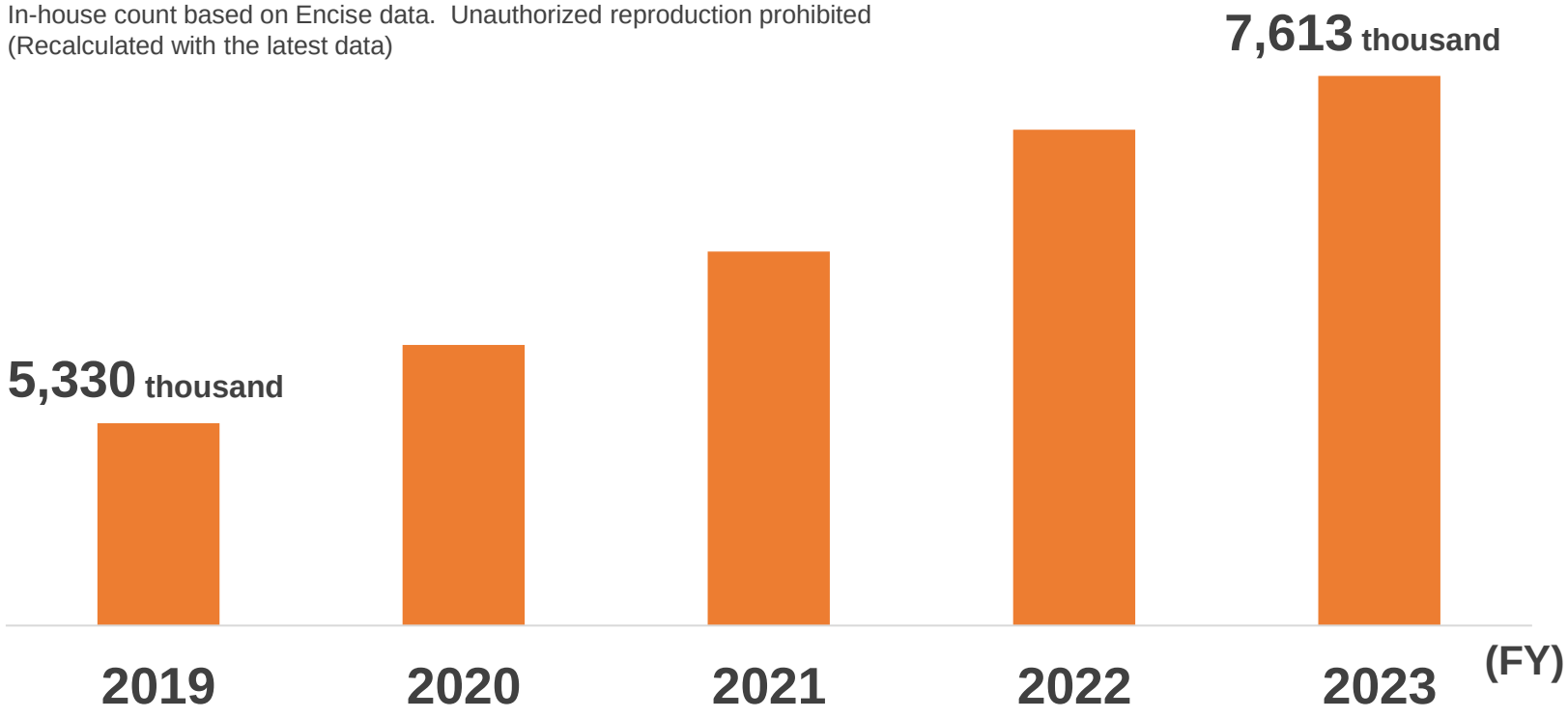
Change in Oral Contraceptive Market Over Time

Prevalence rate[1] of OCs among developed countries

France	33.1%
Germany	31.7%
Canada	28.5%
United States	13.7%
South Korea	3.3%
Japan	**2.9%**

Change in COC market over time (unit: 1000 sheets)

In-house count based on Encise data. Unauthorized reproduction prohibited
(Recalculated with the latest data)



The domestic market is tending to expand

1. United Nations：Contraceptive Use by Method 2019「Estimated prevalence of contraceptive use among women of reproductive age (15-49 years), 2019」

AKP-022
（Uterine Fibroids/Endometriosis）

AKP-022 (Therapeutic Agent for Uterine Fibroids/Endometriosis)

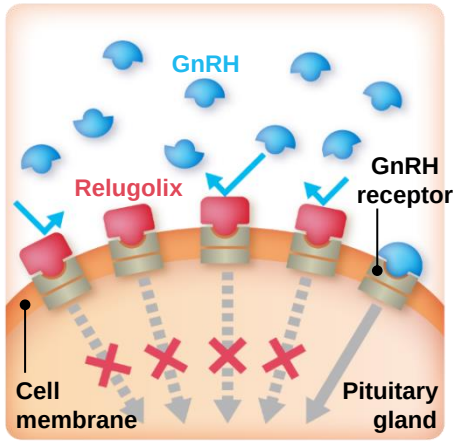
Overview of AKP-022 (planned)

Nonproprietary name	Relugolix, ethinylestradiol, norethisterone acetate
Therapeutic category	GnRH antagonist
Indication	Uterine fibroids, endometriosis
Characteristics	These drugs combine relugolix, which inhibits the production of estradiol and progestogen, with ethinylestradiol, which inhibits bone loss, and norethisterone acetate, which inhibits endometrial proliferation.
Significance of development	This drug is now under development. The relugolix in this combination improves symptoms associated with uterine fibroids, the ethinylestradiol keeps E2 levels within the range where symptoms of uterine fibroids are not exacerbated and menopausal symptoms (hot flashes, bone mass decreased) do not occur, and the progestogen inhibits the development of E2-induced endometrial proliferation. Together, **these actions are expected to make long-term administration possible.** This drug represents a new option for the treatment of uterine fibroids/endometriosis.

Overseas approval status of AKP-022, relugolix combination tablet (as of Jan. 2025)

It has been approved in 48 countries worldwide, including the United States (2021), the United Kingdom (2021), and EU member states (2021).

Mechanism of action of relugolix



Competitively binds to GnRH receptors

↓

Inhibits FSH/LH secretion

↓

Inhibits follicular development and ovulation

↓

Inhibits E_2/P_4 production

↓

Improves various symptoms of uterine fibroids

GnRH (gonadotropin-releasing hormone), FSH (follicle-stimulating hormone), LH (luteinizing hormone), E2 (estrogen), P4 (progesterone)

AKP-022 (Therapeutic Agent for Uterine Fibroids/Endometriosis)

AKP-022 Overview of Ph III（LUNA[1] program: uterine fibroids）

Study name	LUNA1 Study
Research objective	To evaluate the superiority of AKP-022 over placebo in patients with uterine fibroids accompanied by hypermenorrhea, using the primary endpoint to verify the efficacy of AKP-022.
Study phase	III
Study period	**December 2024 - December 2026**
Target sample size	75
Study design	Randomized, double blind, placebo control, parallel assignment
Intervention	Oral administration of AKP-022, placebo or relugolix
Primary outcome	Proportion of participants with a total PBAC[2] score of < 10 from Week 18 to Week 24 of study treatment

1. LUNA=**L**ong-term **U**terine fibroid treatment with **N**ew relugolix combination **A**ssessment in Japan
2. PBAC Score=**P**ictorial **B**lood loss **A**ssessment **C**hart Score; A total score based on the degree of bleeding on sanitary products and the size of blood clots, etc.

AKP-022 (Therapeutic Agent for Uterine Fibroids/Endometriosis)

AKP-022 Overview of Ph III（LUNA program: uterine fibroids）

Study name	LUNA2 Study
Research objectives	- To verify the effect of long-term administration of AKP-022 on the suppression of bone mass loss in patients with uterine fibroids accompanied by hypermenorrhea - To verify the effect of long-term administration of AKP-022 on the suppression of the occurrence of endometrial hyperplasia in patients with uterine fibroids accompanied by hypermenorrhea
Study phase	III
Study period	**December 2024 - December 2026**
Target sample size	350
Study design	Open(masking not used), single arm
Intervention	Oral administration of AKP-022
Primary outcome	- Percent change in BMD[1] from baseline at week 52 of study treatment - Incidence rate of endometrial hyperplasia up to week 52 of study treatment

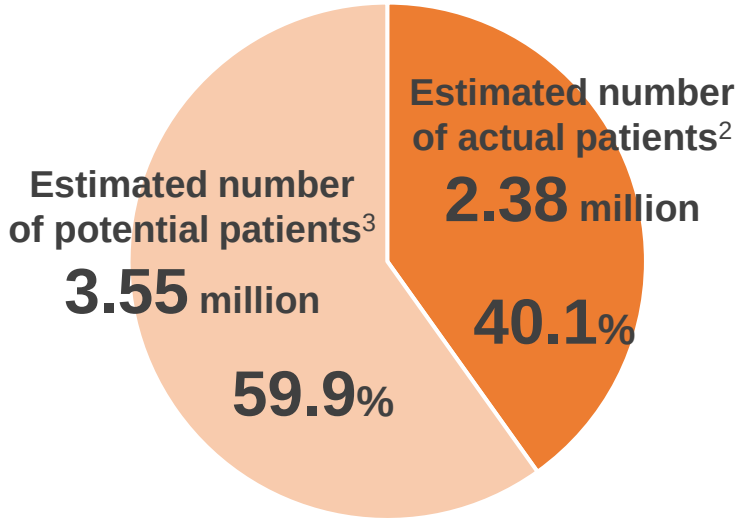
Under development as a successor to RELUMINA

1. BMD=Bone Mineral Density

Estimated Number of Patients in Gynecological Diseases
(in-house estimates from external data)

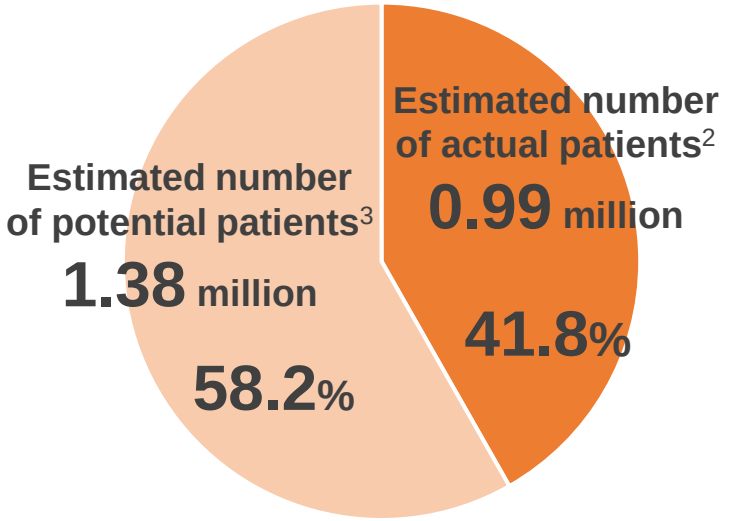
Estimated number of patients with uterine fibroids[1]

5.93 million



Estimated number of patients with endometriosis[1]

2.37 million



Offer a new option for the treatment of uterine fibroids and endometriosis

1. Calculated based on the assumption that the population of women aged 15-49 is 23.73 million and that the incidence rates of endometriosis and uterine fibroids are 10% and 25%, respectively, based on various reports.
2. JMDC Corporation survey (expanded estimates from electronic receipt data, period: January 2023 - December 2023)
3. Estimated number of potential patients = estimated number of patients - estimated number of actual patients

LPRI-CF113
(Dysmenorrhea)

What is Dysmenorrhea?

Dysmenorrhea is a condition in which symptoms causing discomfort such as lower abdominal pain, low back pain, nausea, headache, fatigue/weakness, and irritation associated with menstruation become so severe that daily life is affected.
Dysmenorrhea can be divided into functional and organic dysmenorrhea, respectively.

[Functional Dysmenorrhea]

Cause of pain Excessive contraction of the uterus caused by prostaglandin

Although there may be not be a specific causative disease, a substance called prostaglandin, which is produced in the endometrium during menstruation, may cause excessive contraction of the uterus and induce symptoms such as pain.

Onset period: Within 1 to 3 years after the menarche
The time when pain is felt: Days 1 to 2 of menstruation

[Organic Dysmenorrhea]

Cause of pain Diseases related to the uterus

Symptoms, including pain, may occur due to diseases involving the uterus, such as endometriosis, uterine adenomyosis, and uterine fibroids.

Onset period: Several years after the menarche
The time when pain is felt: From several days before the start of menstruation through the end of menstruation

Quoted from our company's treatment support tool

Treatment of Dysmenorrhea

Treatment of dysmenorrhea is mainly medicinal. Medications are selected depending on the symptoms and the patient's desire to become pregnant. In the case of organic dysmenorrhoea, the causative disease is also treated concomitantly.

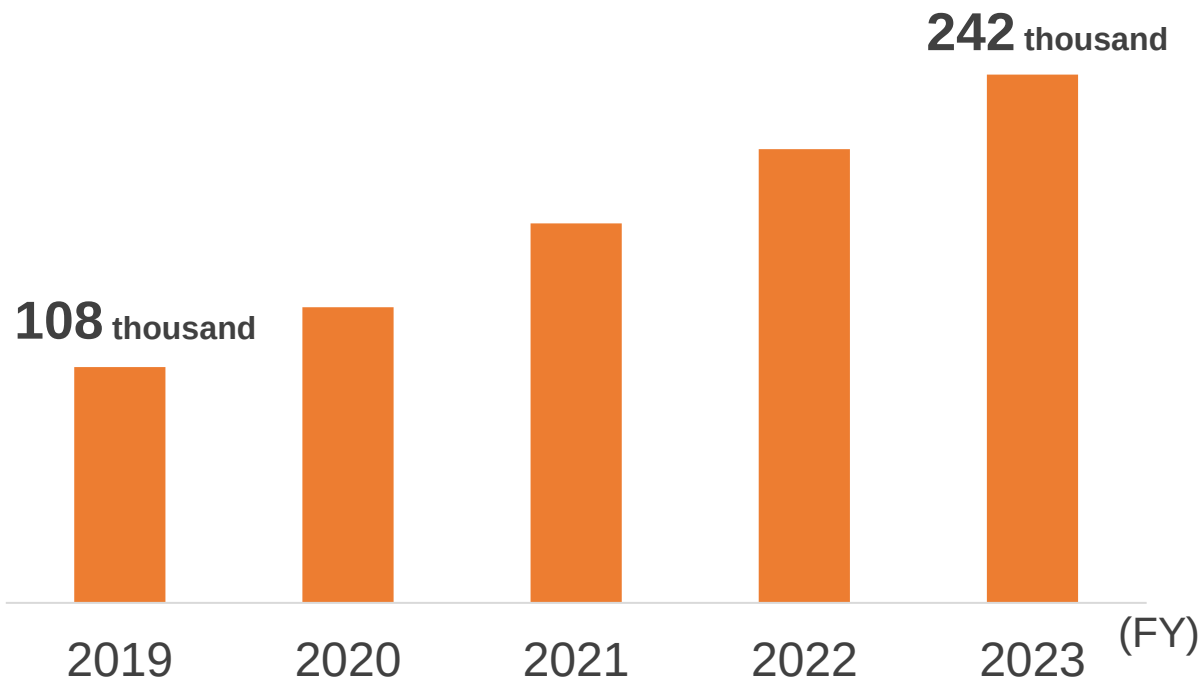
Type	Effect
Analgesics	Analgesics suppress the production of prostaglandin, which is a cause of pain, and thus alleviate menstrual pain.
LEP (low-dose estrogen/ progestin) agents	LEPs are combination drugs of low-dose estrogen and progestin. LEPs inhibit ovulation, prevent thickening of the endometrium, and suppress the production of prostaglandin to reduce menstrual pain.
Progestin agents	Progestin suppresses proliferation of the endometrium and reduces menstrual pain.
Progestin-releasing intrauterine system	Placement of an intrauterine system that releases progestin in the uterus suppresses the proliferation of the endometrium and reduces menstrual pain and blood loss.
Traditional oriental (kampo) medicine	Kampo medicines relieve symptoms associated with dysmenorrhea, such as pain, swelling, and constipation.

Quoted from our company's treatment support tool

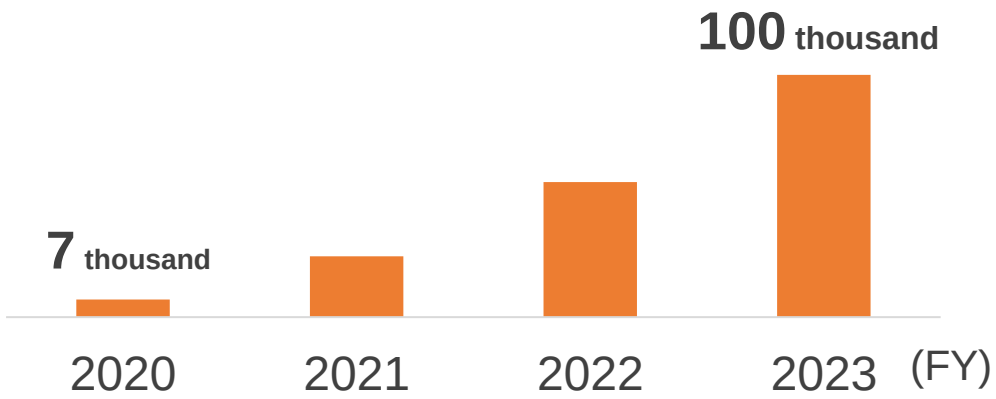
Estimated Number of Patients Taking Progestin Agent
(Dienogest Agent)

In-house analysis based on date of Encise Inc.
(unauthorized reproduction prohibited)

Estimated number of patients taking 1mg agent



Estimated number of patients taking 0.5mg agent



The number of patients taking progestin agents is continuing to increase

LPRI-CF113（Dysmenorrhea Agent）

Overview of LPRI-CF113 (planned)

Nonproprietary name	Drospirenone
Mechanism of action	The drug shows selective agonist activity on progesterone receptors, and suppresses prostaglandin production by inhibiting ovarian function and suppressing the proliferation of endometrial cells, indicating its effectiveness in treating dysmenorrhea.
Indication	Dysmenorrhea
Characteristics	A continuously administered progestin agent
Significance of development	**A once-daily progestin agent**
Status	Ph I/II ongoing

LPRI-CF113（Dysmenorrhea Agent）

LPRI-CF113　Overview of Ph I/II

Research objective	The pharmacokinetics, pharmacodynamics, and safety of repeated administration of LPRI-CF113 will be compared with those of a control drug in healthy adult women before menopause.
Study phase	Ph I/II
Study period	February 2025 - January 2026
Target sample size	30
Study design	Randomized, double blind, active-control, parallel assignment
Intervention	3 cycles of 28-day periods
Primary outcome	Blood drug concentration and pharmacokinetic parameters, ovarian function, blood hormone concentration, uterine bleeding, adverse events, etc.

Overseas approval status of LPRI-CF113

This drug is being developed for an indication for treatment of moderate to severe pelvic pain in women suffering from endometriosis seeking contraception in Europe, and for the prevention of pregnancy in women of reproductive potential in the United States.

Pipeline - Summary of Characteristics

- ✓ **LF111 (contraception)**
  First progesterone only oral contraceptive in Japan. Under development **with the expectation of reducing the risk of thrombosis**.

- ✓ **AKP-022 (uterine fibroids/endometriosis)**
  Combines estradiol and norethindrone acetate with relugolix. Under development **with the expectation that long-term administration for 6 months or longer will be possible**.

- ✓ **LPRI-CF113 (dysmenorrhea)**
  Under development as a **once-daily** progestin agent.

ASKA Pharmaceutical Holdings Group

Corporate Message

For a Healthy Tomorrow and Future.

ASKA Pharmaceutical Holdings Co., Ltd.

Forward Looking Statement

- The forward-looking statements contained in this presentation are based on the Company's assumptions and beliefs in the light of information currently available to it and involves known and unknown risks and uncertainties.
- Accordingly, there is a possibility that actual results and development programs may differ largely from these forecasts, due to a variety of factors.
- This report contains information on Pharmaceuticals Products (including those under development), and the content of this report is not intended for medical promotion or medical advice.
- This translation is provided solely as a reference material. In the case of any discrepancy between the two versions, the original Japanese version shall prevail.

Appendix

Increase in the Number of Menstrual Cycles due to Changes in Life Events

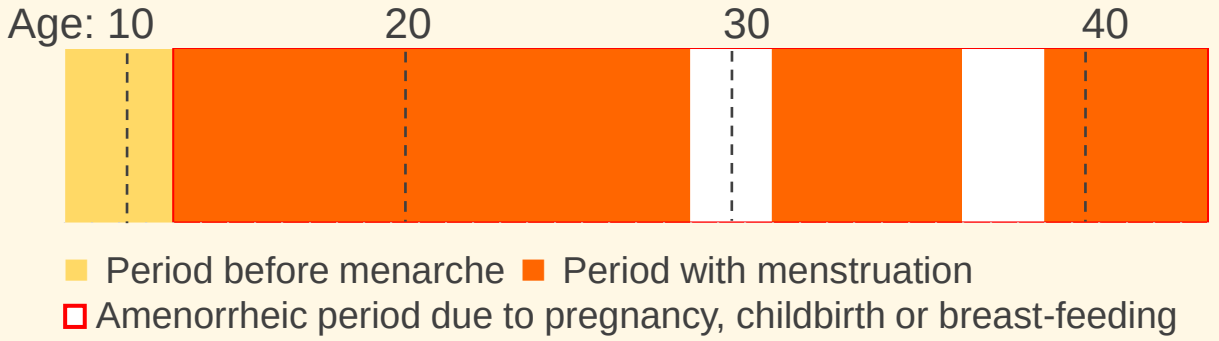
Many of Women today experience their first menstruation earlier, tend to marry later, and experience fewer childbirths than women in past generations. The increase in the number of menstrual cycles (MCs) experienced in women's lifetime is considered a factor for the increase in dysmenorrhea and other menstrual problems.

Number of MCs experienced by women today

Number of lifetime MCs: **Approx. 450**

Number of lifetime childbirths: **Approx. 2**

Menstrual periods of women today

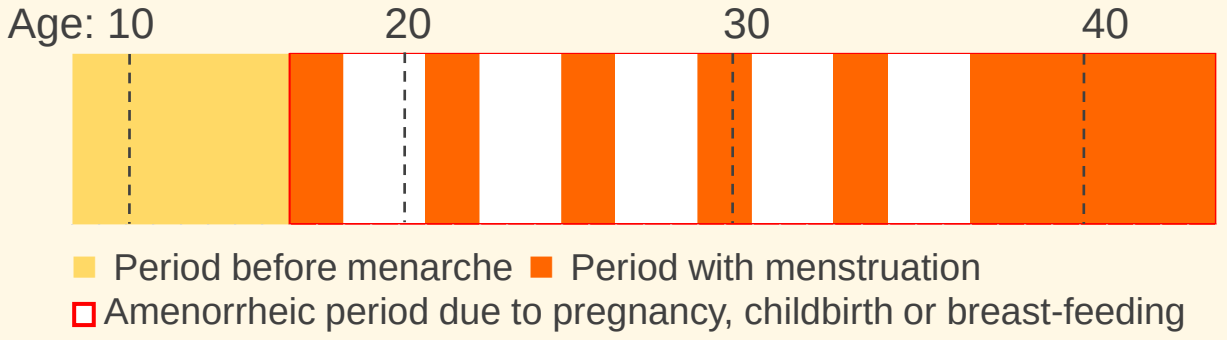


Number of MCs experienced by women in past generations

Number of lifetime MCs: **Approx. 50**

Number of lifetime childbirths: **Approx. 5**

Menstrual periods of women in past generations

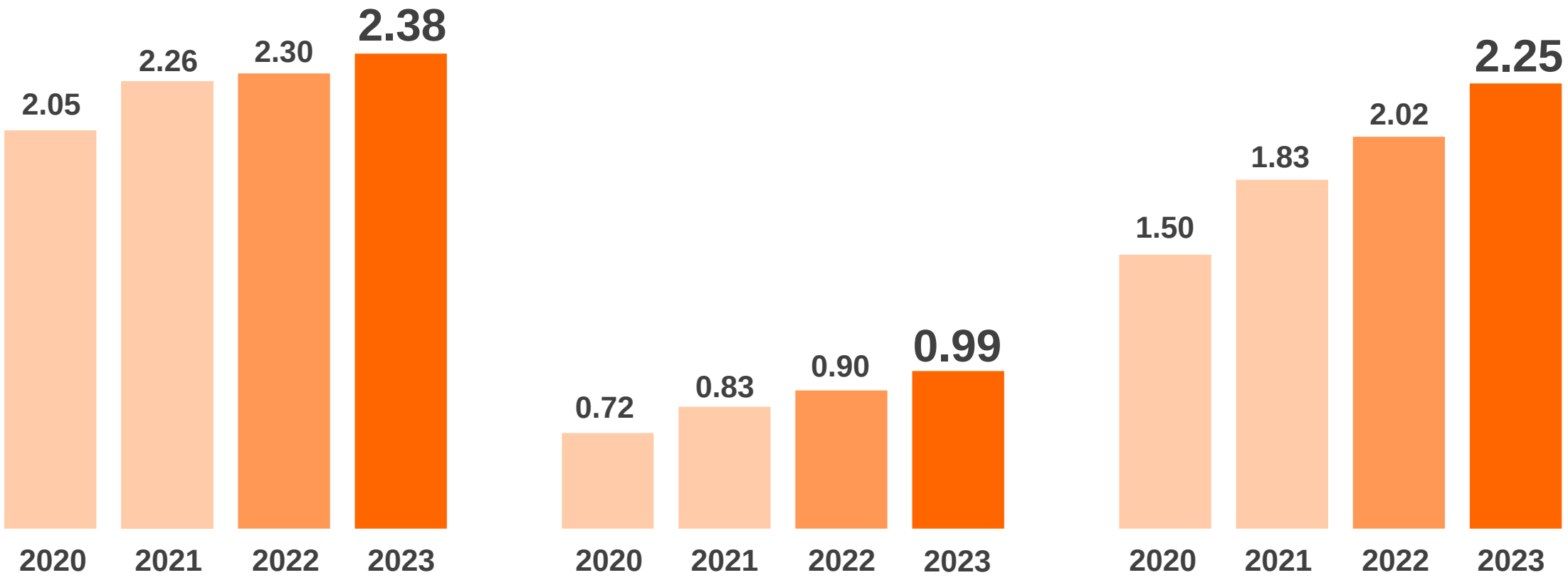


Modified from source: Short RV: Rroc. R. Soc. Lond B. Biol. Sci. 1976; 195, 3-24.

Number of Uterine Fibroids/Endometriosis/Dysmenorrhea Patients

(Extended estimates from electronic receipt data, 12 months from January of each year to December of the following year)

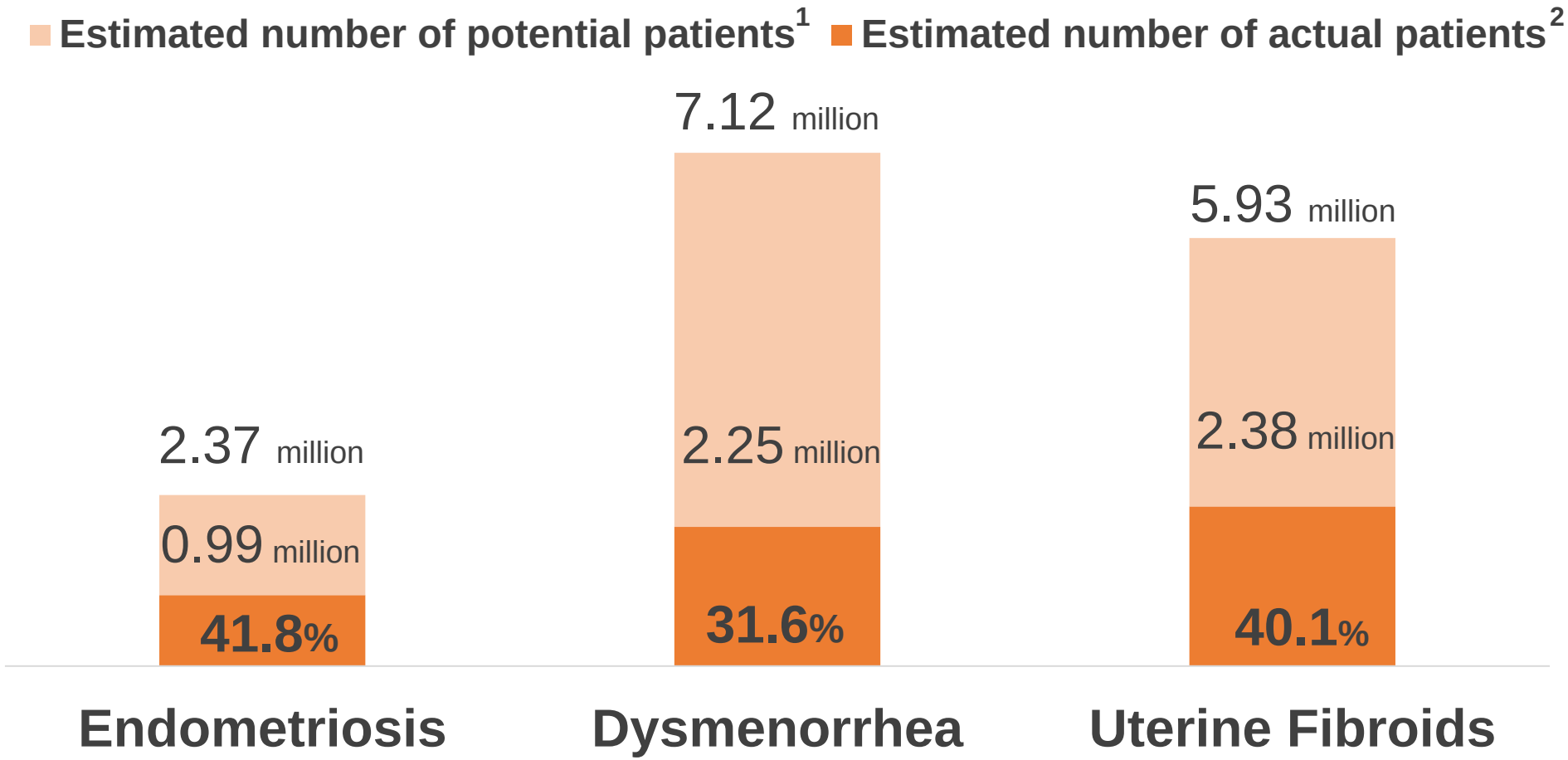
(Million of patients)



Source: JMDC Claims Database

Estimated Number of Patients in Gynecological Diseases
(in-house estimates from external data)

(Extended estimates from electronic receipt data, 12 months from January of each year to December of the following year)



1 JMDC Corporation survey (expanded estimates from electronic receipt data, period: January 2022 - December 2022)
2 Calculated based on the assumption that the population of women aged 15-49 is 24.12 million and that the incidence rates of endometriosis, dysmenorrhea, and uterine fibroids are 10%, 30%, and 25%, respectively, based on various reports.

Contribution to ESG 11 Material Issues and Women's Health

Environmental

- Environmental protection and continuous reduction of environmental impact

Social

- **Contribution to women's health**
- **Contribution to animal health**
- Human resource development
- Employee engagement
- Creation of innovative products
- Expanding access to healthcare
- Stable supply of high-quality products
- Promotion of proper use of products

Governance

- Corporate governance
- Secure compliance with laws and regulations, enforcement of compliance

Issues we are addressing to help women live fulfilling lives

Economic loss related to menstrual symptoms as estimated by the Company*

Contributed to 42.8 billion yen reduction in economic loss through the provision of ASKA Pharmaceutical products

Solving social issues related to women's health as a "leading company in the field of obstetrics and gynecology"

1. Calculated based on the Ministry of Economy, Trade and Industry's "Estimation of economic loss due to female-specific health issues and necessity of health management"
2. The Company's estimate Reduction in annual economic loss due to ASKA's pharmaceuticals = Reduction in annual economic loss due to medical care for women's menstrual symptoms x Percentage of annual economic loss avoided through ASKA's pharmaceuticals, Percentage of annual economic loss avoided through ASKA's pharmaceuticals = Number of people taking ASKA's pharmaceuticals ÷ Number of female workers who have symptoms associated with menstruation and take actions

Inquiries

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