TSUMURA

R&D Briefing Session

December 4, 2025
TSUMURA &CO.

THE BEST OF NATURE AND SCIENCE

Speakers

TSUMURA

Director Co-COO
Kei Sugii

CFO and Head of Corporate Management Division
Kaoru Kobayashi

CTO and Head of Research & Development Division
Akihito Konda

Deputy Head of Research & Development Division
Yukinori Katori

Deputy Head of Research & Development Division
Jun Kosaka

Head of CMC Development Research Laboratories
Takahiro Toyoshima

Head of TSUMURA Kampo Research Laboratories
Yoshiki Ikeda

Head of TSUMURA Advanced Technology Research Laboratories
Akinori Nishi

Head of International Pharmaceutical Planning Department
Eriko Yamashita

Head of International Pharmaceutical Research Department
Hiroshi Degami

TSUMURA

R&D Briefing Opening Remarks

CTO and Head of Research & Development Division
Akihito Konda

THE BEST OF NATURE AND SCIENCE

I am Konda. Thank you for your time today.

The Origin of Tsumura's Basic Corporate Philosophy

TSUMURA

Second President:
Jusha Tsumura

“Kampo is prescientific, and as medical science advances and science and technology progresses, it will surely come to be elucidated scientifically.”

Corporate Value

The Best of Nature and Science

Corporate Mission

To contribute to the unparalleled medical therapeutic power of the combination of Kampo medicine and Western medicine

By utilizing the characteristics of both traditional Kampo medicine and Western medicine, we aim to achieve well-being state (Cho-WA).

Mr. Keisetsu Otsuka

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The basic philosophy of the TSUMURA Group consists of Corporate Value and Corporate Mission.

The Corporate Value, "The Best of Nature and Science," originates from the second-President, Jusha Tsumura's saying, " Kampo is prescientific, and as medical science advances and science and technology progresses, it will surely come to be elucidated scientifically," which is the starting point of the so-called "Scientific approach to Kampo."

Also, the Corporate Mission "To contribute to the unparalleled medical therapeutic power of the combination of Kampo medicine and Western medicine" is based on the origin being " By utilizing the characteristics of both traditional Kampo medicine and Western medicine, we aim to achieve well-being state (CHO-WA).," as stated by the eminent Kampo expert of the Showa era, Dr. Keisetsu Otsuka.

Agenda

TSUMURA

1. The evolution and Vision of our company's R&D activities

2. Domestic Research & Development Activities

-A New Challenge for the Treatment of Cardio-Renal Diseases Using Goreisan

-Proposal of New "Treatment (of health issues)" Methods and Challenge in the Area of Pre-symptomatic Diseases (Disorder)

3. Research & Development Activities for Globalization

-Efforts for TU-100 Development in the United States and Future Policies

-Initiatives in Europe, ASEAN Regions, etc.

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To embody this fundamental Corporate Philosophy, the long-term management Vision "Tsumura Vision 'Cho-WA' 2031" aims to expand the standardization of Kampo treatment and advance individualized Kampo treatment in the field of health treatment.
At the same time, we are challenging scientific elucidation in the field of pre-symptomatic diseases and disorders.

Furthermore, leveraging our accumulated know-how, we are considering global expansion.

Next, we will explain the progress of our company's research and development.

TSUMURA

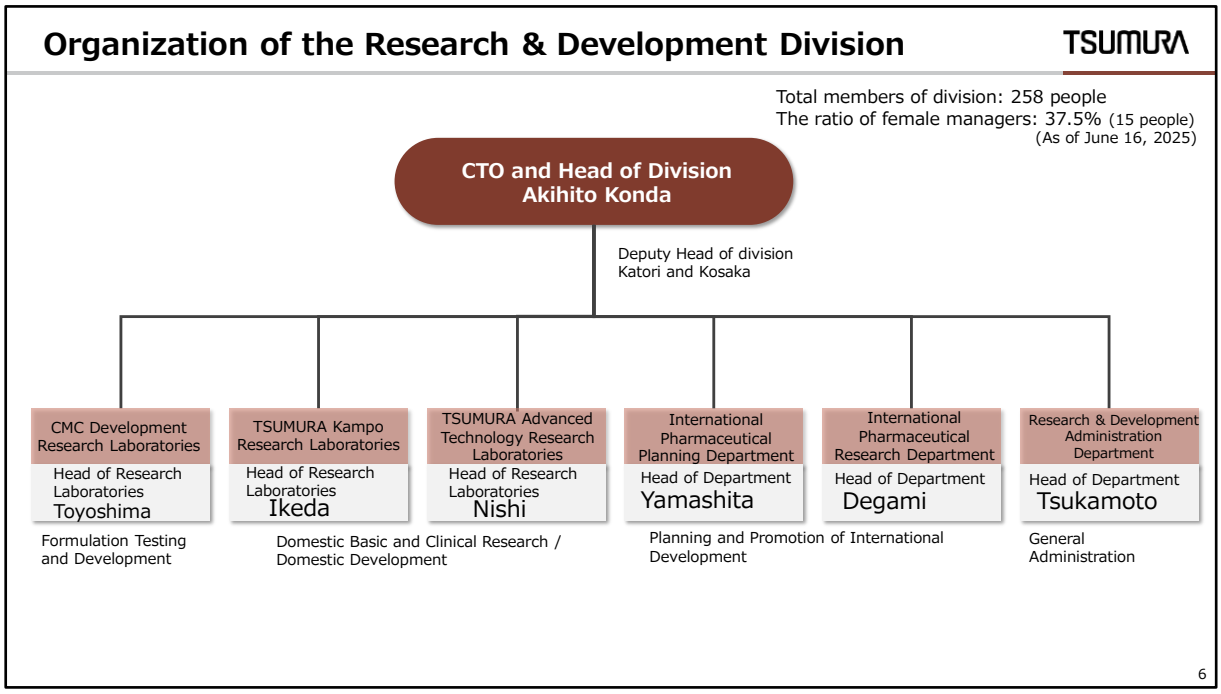
The Evolution and Vision of Our Company's R&D Activities

Deputy Head of Research & Development Division
Yukinori Katori

THE BEST OF NATURE AND SCIENCE

I'm Yukinori Katori from the Research & Development Division.
It's a pleasure to be here today.

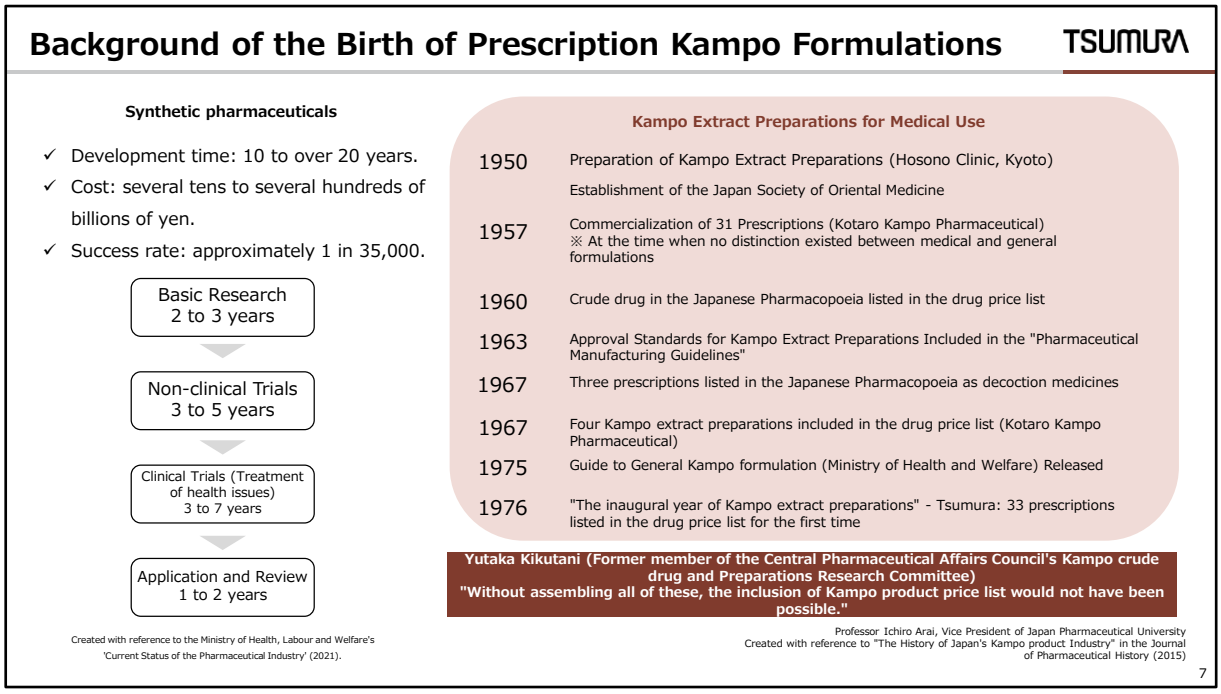
I will explain "The evolution and Vision of our company's R&D activities."
Before entering the main topic, I will introduce the organization of our Research & Development Division and the background of the birth of prescription Kampo formulations.



Let me introduce the organization of the Research & Development Division. From the far right, the Research & Development Administration Department manages the business resources related to research and development across the company and monitors the progress of each research.

The International Pharmaceutical Research Department and the International Pharmaceutical Planning Department are responsible for the research and development for the internationalization of Kampo medicines.

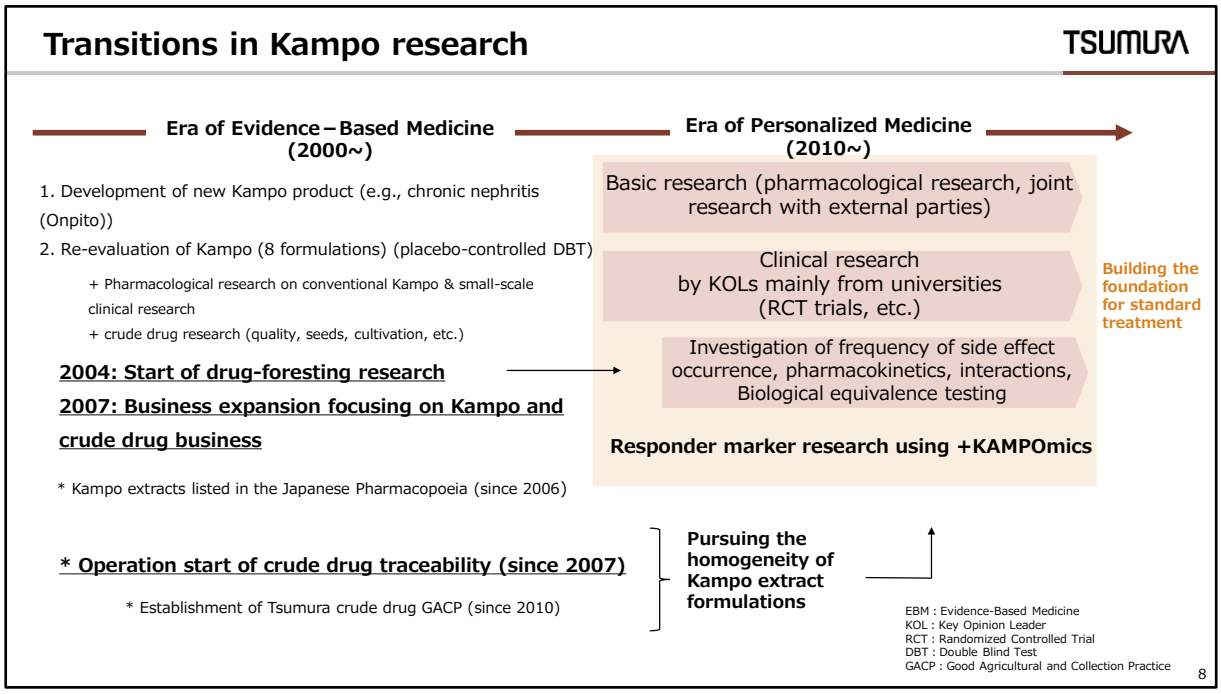
Tsumura Advanced Technology Research Laboratories are challenging the fields of pre-symptomatic diseases and disorders and individualized medicine, while the Tsumura Kampo Research Laboratories are responsible for generating various types of evidence to contribute to the standardization of Kampo treatment.



This slide summarizes the background of the birth of prescription Kampo formulations. On the left side of this slide, the general process of pharmaceutical development and the required time and costs are summarized.

On the other side, the history and other aspects of prescription Kampo formulations are summarized with reference to "The History of the Kampo Product Industry in Japan" by Professor Ichiro Arai, Vice President of Nihon Pharmaceutical University.
The advent of Kampo extract formulations dates to 1950.
This year marked the successful formulation of extracted products with various benefits, such as portability, unlike the traditional "Yuzai" or hot water decoction.
In the same year, the Japan Society for Oriental Medicine was established, and since then, Kampo products have been developed in various ways as one of the treatment methods used by physicians.
In 1963, the approval standards for Kampo extract products were listed in the "Pharmaceutical Manufacturing Guidelines," and in 1967, Kotaro Kampo Pharmaceutical had four Kampo extract prescriptions listed in the official drug price list.
Furthermore, in 1975, the Ministry of Health and Welfare at the time published guidelines for general Kampo formulation use, and since then, approval applications for prescription Kampo formulations have been proceeded based on these guidelines, with successive approvals and price listing being granted.
In particular, 1976 is referred to as the "first year of Kampo extract formulation," and at TSUMURA, 33 formulations were listed in the drug price list for the first time that year.

Dr. Kikutani, a former member of the Kampo and crude drug formulation investigation committee in the Central Pharmaceutical Affairs Council reflects, "The inclusion of prescription Kampo formulations in drug price listings would probably never have been possible without all these factors such as the technological development of Kampo extraction, the existence of the Kampo industry, social and medical backgrounds, the advancement of Kampo medicine research, the publication of pharmaceutical manufacturing guidelines, the establishment of 210 formulations, and charismatic figures such as Dr. Taro Takemi, the president of the Japan Medical Association, coming together,." I hope you'll understand that the listing of Kampo product prices was realized through the accumulation of various events and efforts.



From here, I will explain the transition and Vision of TSUMURA's R&D activities.
In the past, research and development mainly involved the development of new Kampo products and clinical research accompanying the reevaluation of Kampo formulations.
In addition, we have engaged in pharmacological research using existing prescription Kampo formulations, small-scale clinical research, and crude drug research.

As I mentioned earlier, in the development of new Kampo medicines under the review and approval standards based on chemical drugs, we experienced not only the difficulties in research, but also various challenges such as pharmaceutical administration aspects, for example, concepts of quality, efficacy, and safety in multi-component herbal medicines.
At that time, a primary reason why doctors did not use Kampo was that it has "no scientific evidence" to support it. To focus on solving those issues, we have been conducting drug-fostering research since 2004.
Regarding our efforts in drug-fostering research, in addition to in-house research, we engaged in clinical research led by KOLs and various safety studies.
Kampo extracts were listed in the Japanese Pharmacopoeia in 2006. The inclusion of Kampo extracts in the national official pharmacopoeia is highly significant, and as of now, 40 formulations have been listed.
In addition, in order to achieve even greater uniformity in the quality of Kampo products composed of multiple ingredients, we at TSUMURA, have implemented crude drug traceability since 2007 and been operating TSUMURA crude drug GACP from 2010.
By pursuing uniformity in Kampo extract products in this way, the construction of evidence has gradually progressed.

Efforts in drug-fostering pharmaceutical research

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Considering recent disease structures, we established scientific evidence in areas of high medical need, focusing on diseases for which new drug treatments are difficult but Kampo products demonstrate specific efficacy.

2004 — 2009 — 2011 — 2017 — 2021

Response to "Kampo formulations have no scientific evidence"

Start of drug-foresting
(3 prescriptions)

Rikkunshito
Yokukansan
Daikenchuto

Accumulation of basic and clinical evidence

Evidence Package	Meta-analysis	RCT (Randomized Controlled Trial)	Pharmacokinetics	Side Effects Incidence Survey
Rikkunshito	○	○	○	○
Yokukansan	○	○	○	○
Daikenchuto	○	○	○	○

Building the foundation for standard treatment

◆ Expansion of Treatment guideline
(Number of Publications/Recommendation Level) (From 2009)

◆The term 'Kampo medicines' included in the Model Core Curriculum (since 2011)

◆Science of Kampo (2017)

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The definition of TSUMURA's drug-fostering research is shown here.
As part of evidence accumulation, in addition to various efficacy evidence, we have also accumulated safety evidence, including a survey on the frequency of side effect occurrence involving approximately 3,000 cases.

Running parallel to these efforts, there have been expansions of the Treatment guideline, inclusion in the educational model and core curricula of medical schools, and the publication of "Science of Kampo", resulting in the establishment of foundation for the standard treatment based on these outcomes.

Enhancement of evidence and inclusion in Treatment guideline

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Enhancement of the evidence package

Evidence Package	Meta-analysis Analysis	RCT (Randomized Controlled Trial)	Drug Kinetics	Side Effects Incidence Rate Survey
Rikkunshito	○	○	○	○
Yokukansan	○	○	○	○
Daikenchuto	○	○	○	○
・・・	○	○	○	○

Enhancement of prescriptions / areas / types of evidence

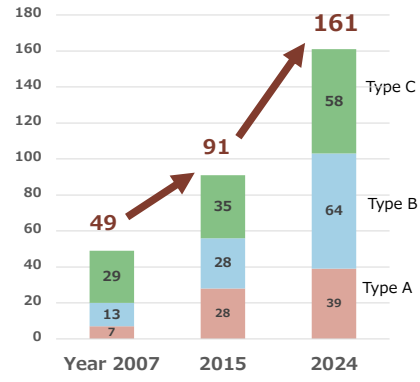
Quality improvement

Improvement of recommendation levels of listed prescriptions/diseases in treatment guideline

Quantitative expansion

New inclusions of unlisted prescriptions/diseases in treatment guideline

Number of inclusions in treatment guidelines



*From the "Treatment guideline Task Force" by the EBM Committee of the Japan Society for Oriental Medicine
Type A: There are cited papers, and it includes grading of evidence and recommendation.
Type B: There are cited papers, but it lacks grading of evidence and recommendation.
Type C: Those without cited papers, nor evidence grading and recommendation grading.

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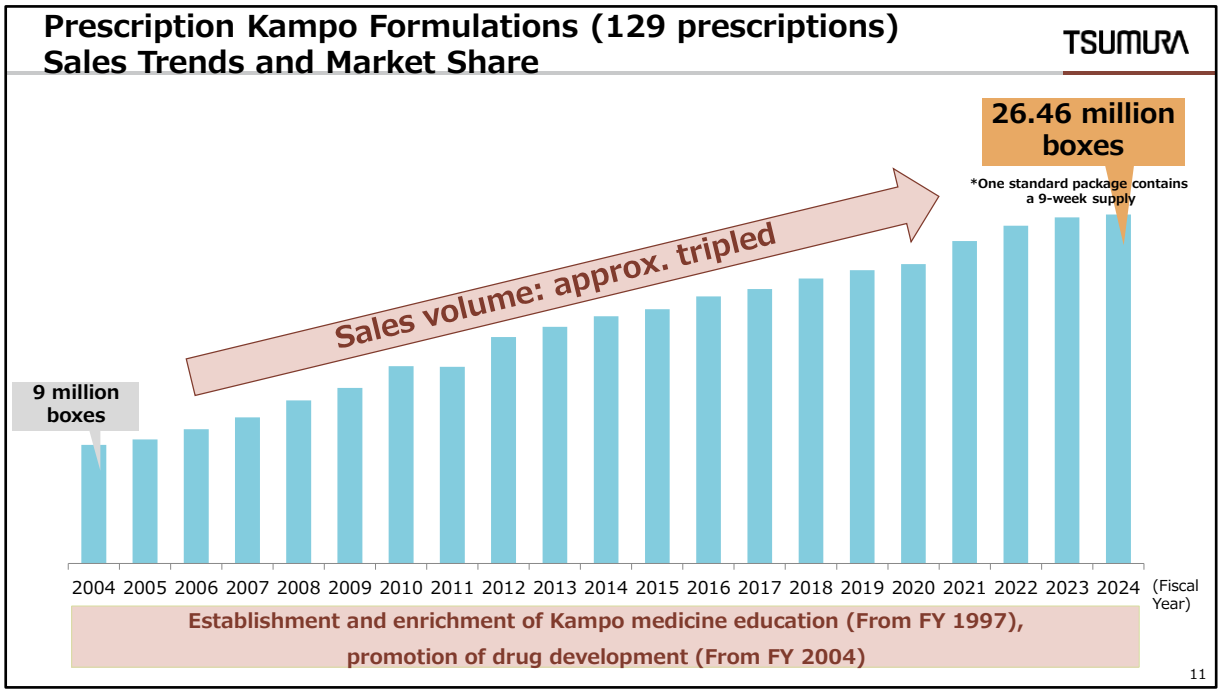
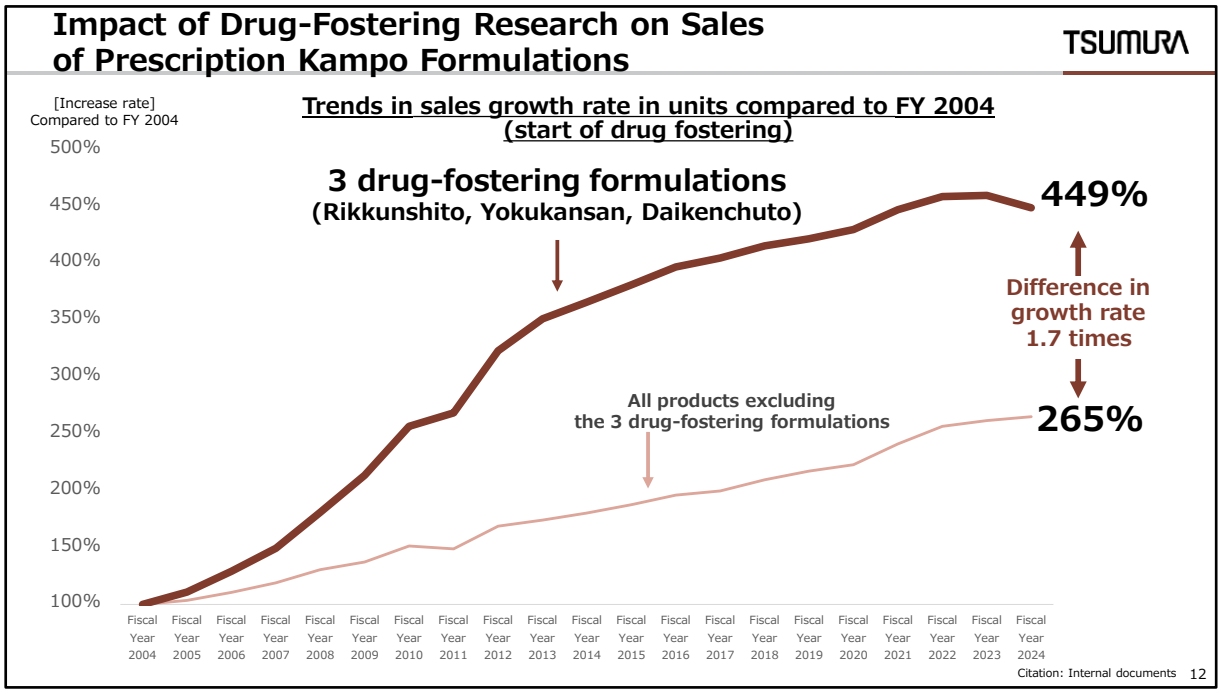
We have defined priority domains and key prescriptions, have been extensively accumulating diverse evidence, and have compiled it into an evidence package, providing information that supports its appropriate use.

As a result, the number of inclusions in treatment guidelines increased from 49 in 2007, when the survey began, to 91 in 2015, and most recently to 161. In addition, the number of Type A recommendations has also increased to 39.



I will explain the contribution of drug-fostering research to sales.

First, this is the trend of the total sales volume of TSUMURA prescription Kampo formulations. Drug-fostering research has been promoted, and a threefold increase in quantity has been confirmed.



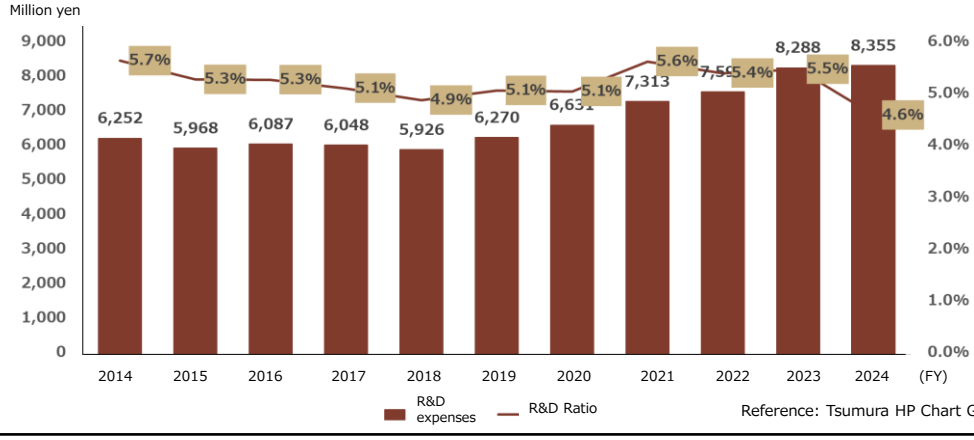
In the previous slide, I showed a threefold increase on an overall quantity basis.

When we compare the growth rates of sales volume between the three drug-fostering prescriptions and all other products, starting from 2004, when drug-fostering research was initiated, it is confirmed that there is a 1.7 times difference in their growth rates.

Tsumura's Research & Development Division expenses and the trend of R&D expense ratio

TSUMURA

- Our company's research and development encompasses a wide range of areas beyond pharmaceutical R&D, including crude drug herb cultivation and seedling research, formulation technology research, quality testing research, and contamination control research.
- The ratio of research and development expenses to consolidated net sales remains at about 5% (The second mid-term management plan also assumes the same level)



Reference: Tsumura HP Chart Generator

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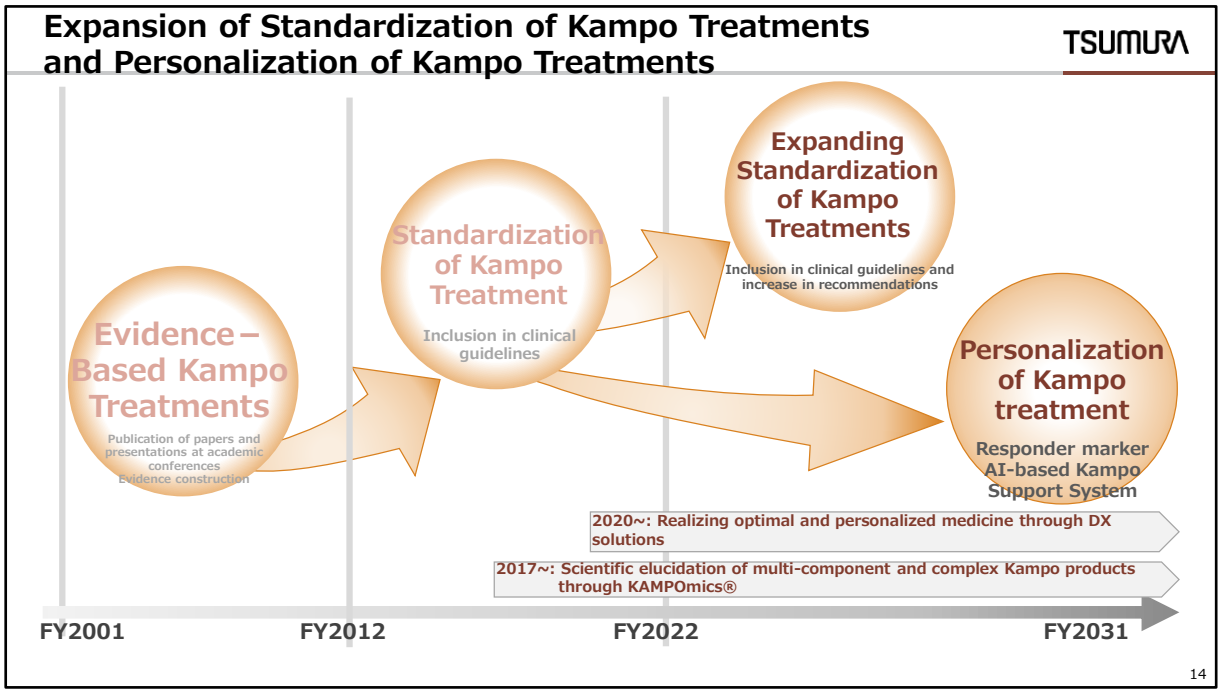
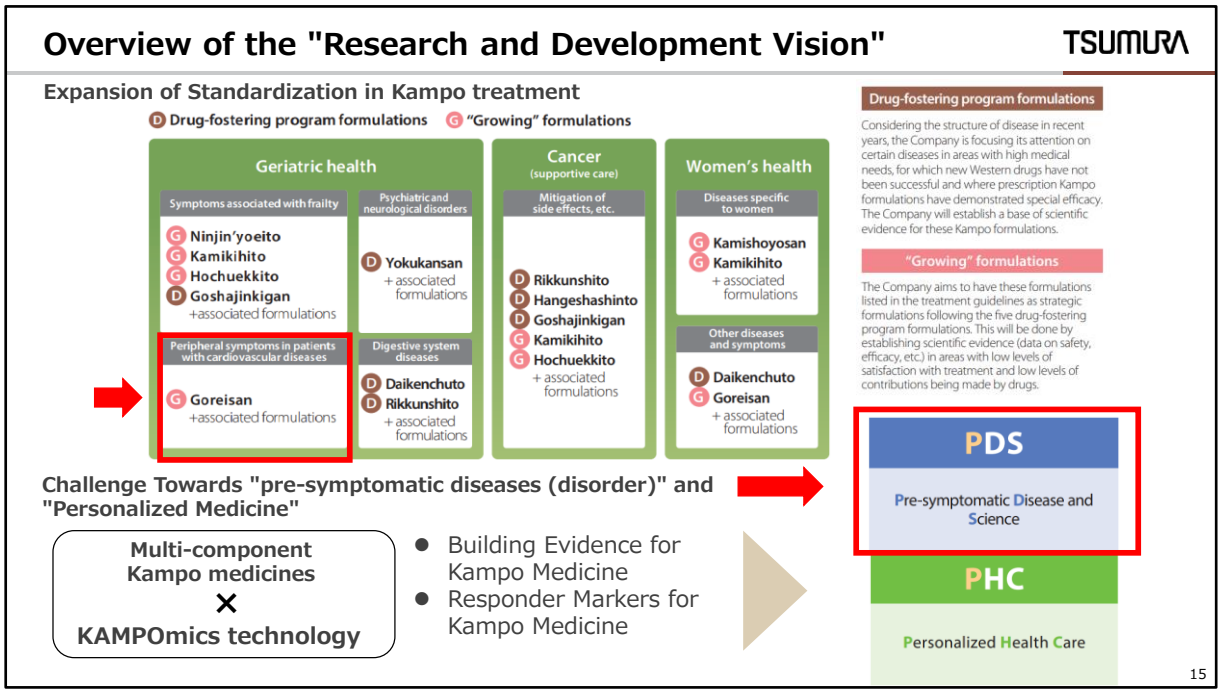
This graph shows the trend of TSUMURA's research and development expenses.

First, our company's research and development covers a wide range of fields beyond pharmaceutical research and development, including crude drug herb cultivation, formulation technology research, and quality testing research.
Within this context, the actual research and development expense percentage has remained within 5% of consolidated sales, and the second mid-term management plan also assumes the same level.



Regarding the standardization of Kampo treatment, we aim to enhance the evidence across various fields and prescriptions, and to further expand it. In addition, we have established KAMPOmics as our proprietary research package by integrating advanced technologies cultivated through prior Kampo research, such as metabolomics and genetics.

Leveraging this KAMPOmics technology as TSUMURA's strength, we will continue to advance the personalization of Kampo treatment and the establishment of the science of pre-symptomatic diseases and disorders.

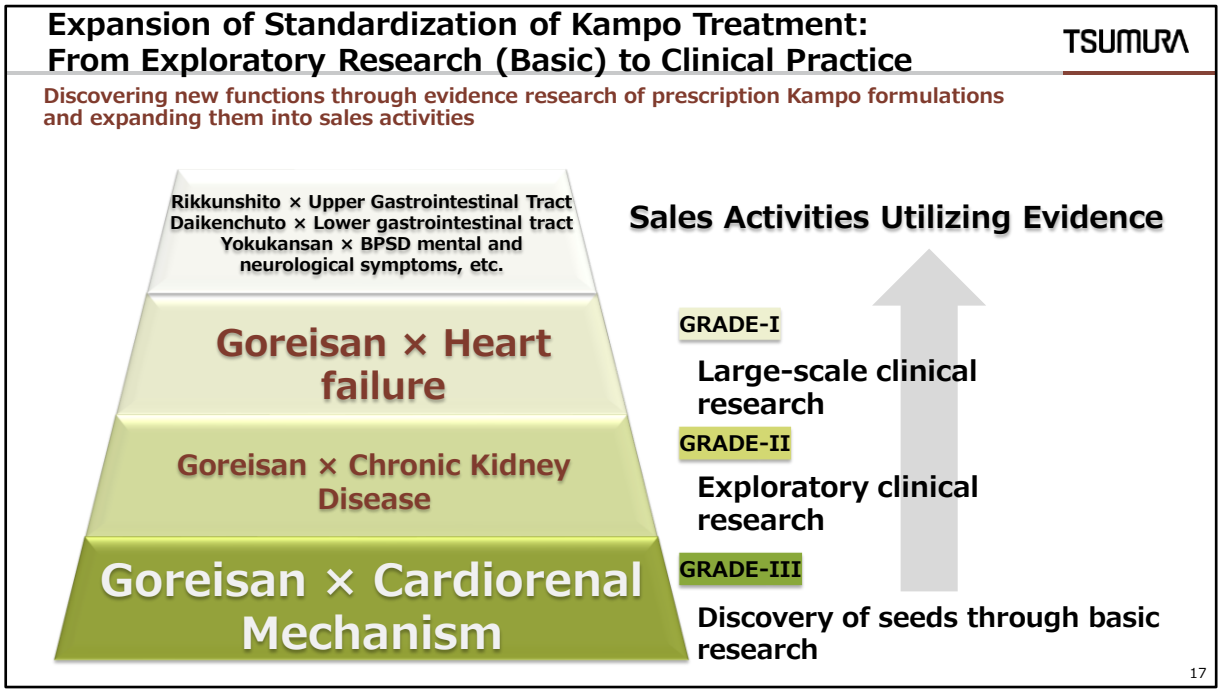


This is the final slide.

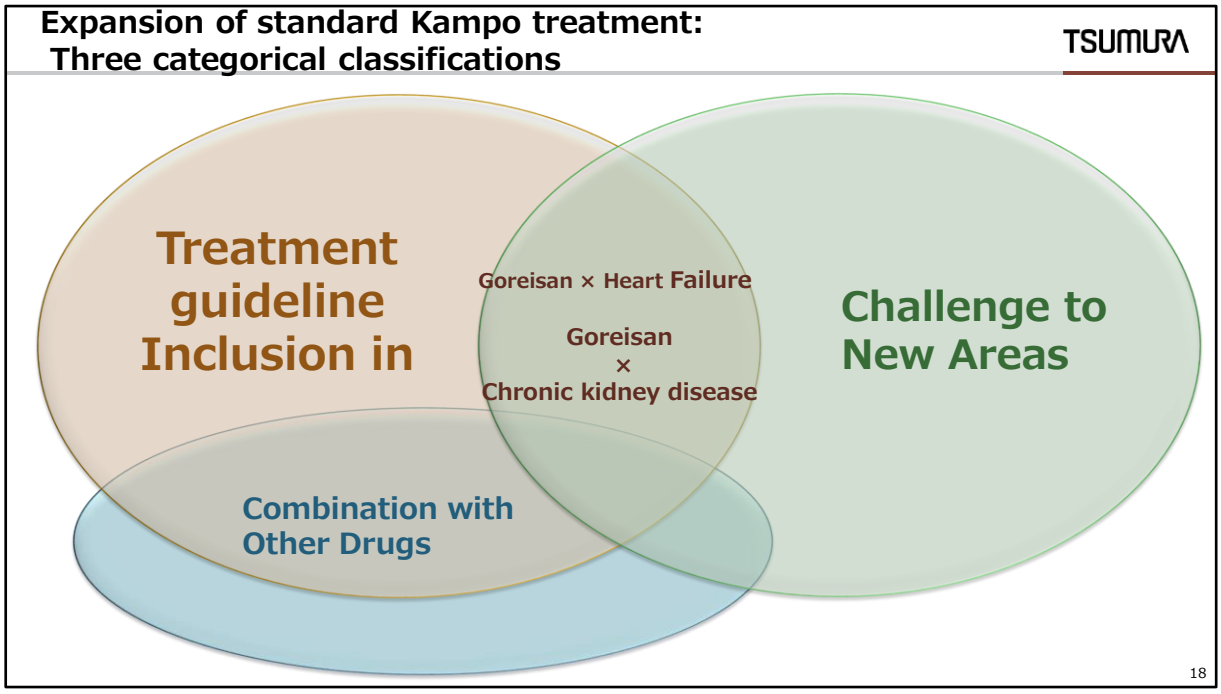
Regarding the expansion of the standardization of Kampo treatment, Ikeda, the head of the Tsumura Kampo Research Laboratories, and Nishi, the head of the Tsumura Advanced Technology Research Laboratories will explain the challenges to “pre-symptomatic diseases and disorders” and "personalized medicine" respectively after this.
Due to time constraints today, we are going to explain only the sections enclosed in the red frame in the slides.

I'm Ikeda from the Tsumura Kampo Research Laboratories.

I will speak on the theme of domestic research and development activities titled "A new challenge to the treatment of cardiorenal diseases with Goreisan."



First, regarding the efforts to expand the standardization of Kampo treatments.
We aim to expand the standardization of Kampo treatments in the fields of geriatrics, cancer supportive care, and women's health.
As shown in this pyramid, we proceed with the idea of moving from discovery of seeds through basic research (GRADE-III) to exploratory clinical studies (GRADE-II), and then to larger-scale studies (GRADE-I).
This time, I will talk about the heart-kidney mechanism of Goreisan (GRADE-III), chronic kidney disease treated with Goreisan (GRADE-II), and heart failure treated with Goreisan (GRADE-I).
As you may know, it takes 5 to 10 years to progress from GRADE-III, II to GRADE-I.



Our research is divided into three areas. The first is the challenge of inclusion in existing diagnostic treatment guidelines, the second is the challenge of expansion through combination with other drugs in anticancer treatment, and the third is the challenge of applying it to new fields (uses that have not been seen before) within the scope of indications.
Especially for cardiovascular and renal diseases, which I'll talk about today, we are challenging the inclusion of Goreisan in existing treatment guidelines and its entry into new fields (unseen uses).

Cardiorenal Diseases: Market Environment for treatment

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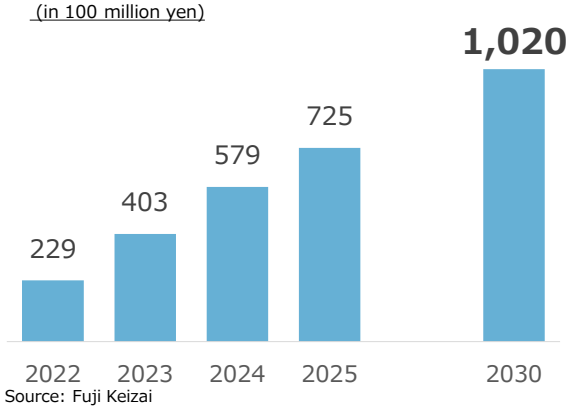
Domestic Market Size of Heart Failure Treatments

- Market Size **Increasing Year by Year**
- **Forecasted to Exceed 100 Billion Yen by 2030**

Domestic market size of heart failure treatments (in 100 million yen)

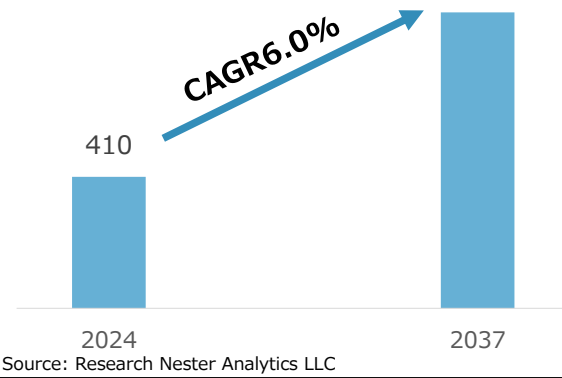


Source: Fuji Keizai

Global Market Size of Chronic Kidney Disease Treatments

- **41 Billion USD as of 2024**
- **CAGR Forecasted to be 6.0% until 2037**

Global market size of chronic kidney disease treatments (in 100 million USD)



Source: Research Nester Analytics LLC

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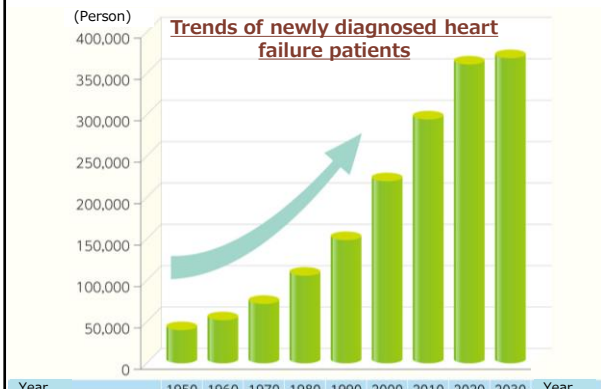
I'm going to talk about the marketability of drugs for cardiovascular and renal disease treatment. First, the market size of drugs for heart failure in Japan has been steadily increasing since 2022, and is expected to reach the 100 billion yen range by 2030. Also, the market size of drugs for chronic kidney disease is expected to grow globally until 2037, and the domestic market is said to have a similar trend. In other words, the markets for drugs for cardiovascular and renal disease are expanding.

Cardiorenal diseases: Increase in heart failure patients and cardiorenal connection

TSUMURA

Increase in patients with heart failure

- Currently, there are **1.2 million** heart failure patients, and annual medical costs **exceed 2 trillion yen**
- The number of new heart failure patients is expected to continue increasing, surpassing **1.3 million**

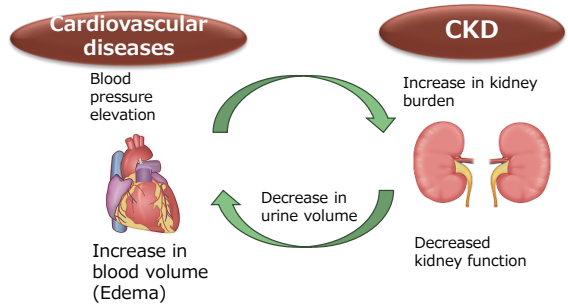


Year	1950	1960	1970	1980	1990	2000	2010	2020	2030	Year
% of elderly people (65 years and older)	4.9	5.7	7.1	9.1	12.1	17.4	23.0	29.1	31.6	(%)
Total population	83.2	93.4	103.7	117.1	123.6	126.9	128.1	124.1	116.6	Million people

Shimokawa H et al. Eur J Heart Fail 2015;17:884-892

Cardiorenal connection

- **Chronic kidney disease (CKD)** and cardiovascular diseases (such as myocardial infarction, angina, **heart failure,** and stroke) are closely related.
- CKD often complicates cardiovascular diseases, and cardiovascular diseases often complicate CKD



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Currently, there are 1.2 million heart failure patients in Japan, and it is said that the number of new patients will increase to exceed 1.3 million in the future. Annual medical expenses exceed 2 trillion yen. Heart failure has a close relationship with the kidneys, which is called the cardiorenal syndrome.

When blood pressure rises in the heart, it puts a burden on the kidneys, leading to impaired kidney function. As a result, urine volume decreases, blood volume increases, and the elevation of blood pressure accelerates. This vicious cycle is the cardiorenal syndrome.

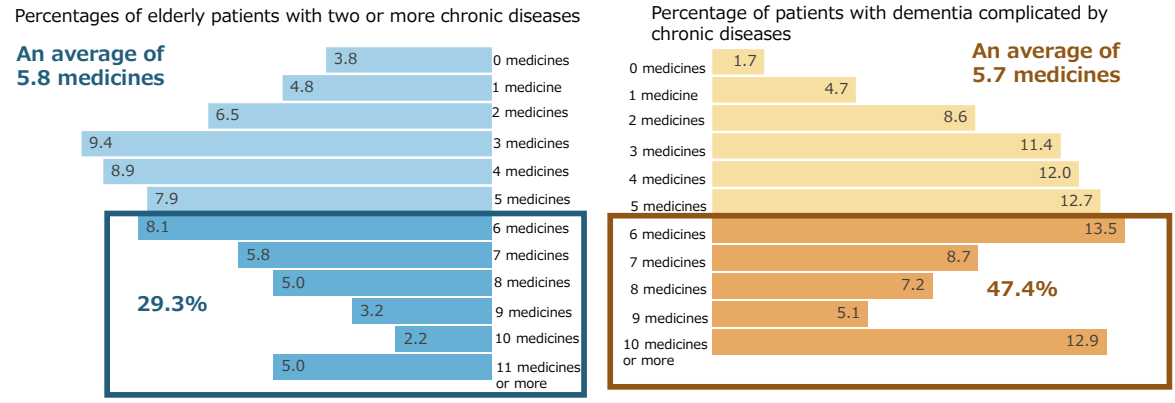
Cardiorenal Diseases: Challenges in the Pharmacological Treatment of Heart Failure

TSUMURA

- **Difficulty in drug management due to polypharmacy**
- **Restrictions on drug use due to decreased renal function***
- **High drug costs and medical financial burden**

*Approximately 70% of heart failure patients have eGFR levels below 60 (indicating decreased renal function)

Number of oral medicines for elderly patients



Source: Created based on materials from the Ministry of Health, Labour and Welfare's "Study Group on the Proper Use of Medicines for the Elderly"

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Elderly patients with heart failure face numerous challenges. One issue is that elderly people often have polypharmacy, meaning they take many oral medications.

Patients with dementia, elderly individuals with two or more chronic diseases, and those with heart failure are also considered to fall into this category, as they take an average of 6 medications, making management difficult due to polypharmacy. Furthermore, as mentioned earlier about the cardiorenal syndrome, it is said that about 70% of heart failure patients have impaired renal function, which imposes restrictions on drug use. Additionally, due to polypharmacy, there are new drugs that are more expensive than Kampo medicines, leading to a financial burden in terms of drug costs and healthcare economics.

Efficacy and Effects of Goreisan

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Goreisan: Indicated for symptoms associated with cardio-renal diseases

TSUMURA Goreisan Extract Granules for Ethical Use

Listed in the Drug Price Standards

Revised in December 2023
Source: Shanghan Lun, Jin Gui Yao Lue

Description

Composition	7.5 g of TSUMURA Goreisan extract granules (hereafter TJ-17) contains 2.0 g of a dried extract of the following mixed crude drugs. JP Alisma Rhizome ..... 4.0 g JP Atractylodes Lancea Rhizome ..... 3.0 g JP Polyporus Sclerotium ..... 3.0 g JP Poria Sclerotium ..... 3.0 g JP Cinnamon Bark ..... 1.5 g (JP: The Japanese Pharmacopoeia)
Inactive ingredients	JP Magnesium Stearate JP Lactose Hydrate

Dosage and Administration

The usual adult dose is 7.5 g/day orally in 2 or 3 divided doses before or between meals. The dosage may be adjusted according to the patient's age and body weight, and symptoms.

Indications

TJ-17 is indicated for the relief of the following symptoms of those patients with oral dryness and decreased urine volume:
Edema, nephrosis, alcoholic hangover, acute gastrointestinal catarrh, diarrhea, nausea, vomiting, dizziness, water retention in the stomach, headache, uremia, heat-stroke, and diabetes mellitus

Side effects (excerpt)

Other side effects

	Frequency unknown
Hypersensitivity	Rash, Redness, Pruritus, etc.
Hepatic	Abnormality of hepatic function [Increased AST (GOT) , ALT (GPT) and γ-GTP etc]

*For other precautions and information, please refer to the product's electronic package insert:
https://www.tsumura.co.jp/english/products/pi/JPR_T017.pdf

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Now, I will explain Goreisan.

Goreisan consists of five crude drugs and is a formula indicated for conditions related to cardiovascular and renal diseases.

Current Prescribing Status of Goreisan

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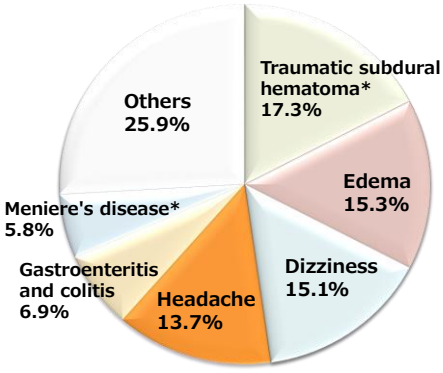
Prescription status of Goreisan (FY 2023)



IQVIA_MDI January 2021 to December 2023

*Off-label use: Not related to our promotional activities, Spread through physicians

Prescription status of Goreisan by treatment area (FY 2024)

Treatment area	Sales volume (boxes)
General Medicine	**166,318**
Otorhinolaryngology	76,662
Gastroenterology	31,286
Psychiatry	28,993
Orthopedics and pain management	27,542
Neurosurgery	27,407
Cardiology	**21,363**
Obstetrics and gynecology	19,126
Dermatology	13,197
Pediatrics	11,068
Neurology	10,913
Respiratory	8,718
Urology	7,965
Unclassified	6,766
Metabolism and endocrinology	3,560
Nephrology	**2,709**
Cancer	1,598
Rehabilitation	595

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As for the actual use of Goreisan, it is frequently used for traumatic subdural hematoma. This is an off-label use and has spread not through our company's promotional activities but via doctors. Following that, it is used for edema, dizziness, and headaches.

Compared to the general medicine area, Goreisan is a minor prescription in the cardiovascular and nephrology treatment areas based on the number of prescription boxes.

Goreisan's Potential of Future Market Expansion

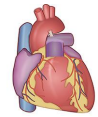
TSUMURA

Currently, Goreisan is scarcely used for the treatment of cardiorenal diseases

Heart failure April 2024 - March 2025 (About 500 DPC facilities) MDV data

Patients diagnosed with congestive heart failure:
521,118 people

Among them, **patients taking Goreisan:**
3,312 people (0.64%)

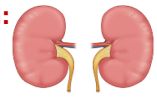


*Congestive heart failure: Patients with edema or subdural hematoma are excluded.

Chronic kidney disease April 2024 - March 2025 (About 500 DPC facilities) MDV data

Patients diagnosed with renal failure:
594,633 people

Among them, **Patients taking Goreisan:**
3,034 people (0.51%)



*Renal failure: Patients with edema or subdural hematoma are excluded.

Prescribing could increase significantly depending on research results

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Based on MDV data from about 500 DPC facilities for FY2024, the rate of heart failure patients taking Goreisan is 0.6% and that of renal failure patients is 0.5%. Currently, sales are over seven billion yen, but depending on the research results in the heart-kidney treatment area, there is potential for an increase in new prescriptions.

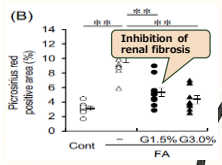
Possible Application of Goreisan to Cardiorenal Diseases (Basic Research)

TSUMURA

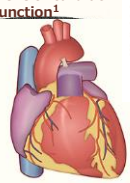
Seed research (GRADE-III)

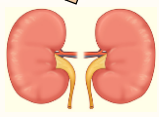
[CKD model]
- Reduction of creatinine[6]
- Increased urine volume[6]
- Suppression of renal fibrosis[2]

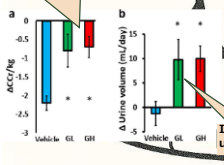
[Heart failure model]
- Improvement of cardiac hypertrophy[1, 3]
- Improvement of cardiac diastolic function[1]

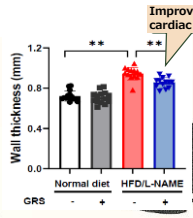


Cardiorenal Syndrome

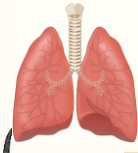








[Mechanism of action]
- Inhibition of Aquaporin[2] membrane translocation[4]
- Inhibition of Aquaporin 4[5]



[Heart Failure Model]
- Improvement of pulmonary edema[1]
- Reduction of interstitial fluid[1]

1) Shojima-Isayama Y et al., Hypertension Res. 2025; in press
2) Suenaga A et al., J Pharmacol Sci. 2023; 153: 31-37
3) Funamoto M et al., J Pharmacol Sci. 2015; 157: 104-1124)
Ogura K et al., Scientific Reports. 2024; 14: 29650.
5) Shimizu T et al., Tradit Kampo Med. 2023; 10: 168–176.
6) The Japanese Society of Nephrology Journal 64 (3) Page:293 (2022)

25

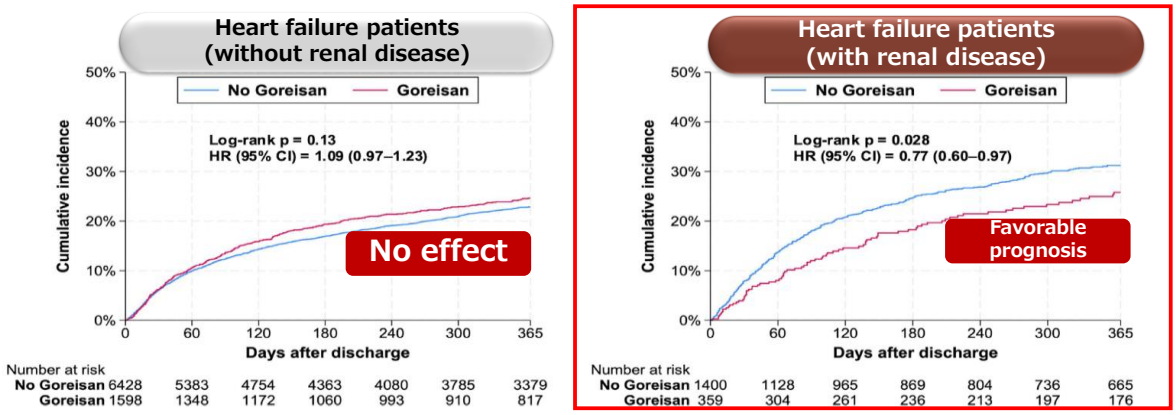
At the beginning, I talked about the pyramid of seed exploration. Goreisan has shown positive results for cardiovascular and renal diseases in basic research, with its mechanism also being clarified. So, I feel it has great potential as a seed.

Possible Application of Goreisan to Cardiorenal Diseases (Clinical Database Research)

TSUMURA

Clinical database research (GRADE-III)

Goreisan may be well suited for patients with heart failure having kidney disease



Kaplan-Meier curves showing **the cumulative incidence of heart failure rehospitalization** in the subgroups stratified by the presence or absence of renal disease in the propensity score-matched cohort

Isogai T, et al., J Cardiol 2024.; https://doi.org/10.1016/j.jjcc.2024.09.010

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We examined a study using a database to confirm the clinical effects of Goreisan on patients with heart failure.

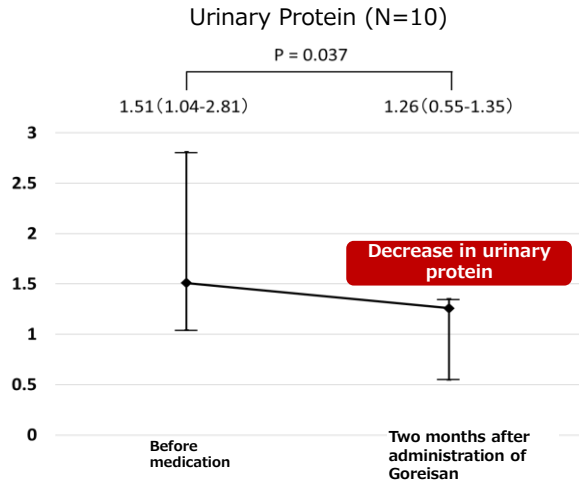
Goreisan did not affect the prognosis in heart failure patients without renal disease. But in patients with renal disease, the prognosis improved in terms of the rate of rehospitalization.
We are interested in the compatibility of Goreisan with patients having kidney diseases.

Possible Application of Goreisan to Cardiorenal Diseases (Retrospective Study)

TSUMURA

Decreases in the urinary protein level, an indicator for renal function evaluation, due to administration of Goreisan

Changes in urinary protein levels due to Goreisan administration



Nanako Terada et al., Japanese Society for Peritoneal Dialysis, 2023

27

Next, Goreisan was retrospectively examined in patients with chronic kidney disease, and although the number was small, kidney function was examined. By taking Goreisan for two months, the amount of urinary protein, which is an evaluation marker for kidney function, was reduced.

Possible Application of Goreisan to Cardiorenal Diseases (Clinical Research)

TSUMURA

① Possesses basic research and retrospective clinical data that serve as seeds

- Kidney failure model (J. Pharmacol. Sci., 2023)
- Nephrotic syndrome model (under submission)
- Chronic kidney disease (Japanese Journal of Nephrology, 2023)

② Within the scope of indications

- Nephrosis, uremia, edema, diabetes

③ Difficulty with treatment using existing drug (unmet medical needs)

- Establishing its position as a drug for prognostic management in cardio-renal diseases

If symptom reliefs such as dehydration and water balance adjustment, as well as effects like reducing the diuretic load—which places a significant burden on the kidneys—can be clinically proven to reduce readmissions and mortality, there is potential for its contribution in health economics.

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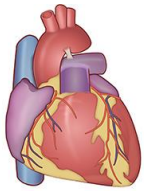
Goreisan shows interesting results both in basic research for seed exploration and retrospective clinical data for chronic kidney disease.

If Goreisan is clinically proven to alleviate symptoms such as dehydration and fluid balance regulation, there might be a possibility of contributing to medical economics. We are finally moving into the consideration of clinical research (GRADE-I, II).

Large-Scale Clinical Study of Goreisan in Heart Failure (GRADE-I)

TSUMURA

A study to examine the efficacy of additional administration of Goreisan on edema in patients with congestive heart failure (cardiac edema) (GOREISAN-HF Trial)



1. Research Objective
The number of heart failure patients hospitalized in Japan is increasing at a pace of approximately 10,000 per year. To treat this condition, it is important to maintain good control of fluid retention without causing kidney function worsening or electrolyte imbalances and to reduce the frequency of hospitalizations. However, the loop diuretics currently mainly used are less effective.

Therefore, this study aims to evaluate the efficacy of Tsumura Goreisan Extract Granules (for medical use) TJ-17 on edema and the composite endpoint of all-cause mortality and rehospitalization in patients with acute congestive heart failure (cardiac edema).

2. Research Operations Manager: Dr. Hidenori Yaku
Currently Heart Failure Department, Heart Failure and Transplant Division, National Cerebral and Cardiovascular Center/Visiting Researcher at Northwestern University,
and previously Kyoto University Hospital

3. Chief Investigator: Dr. Tsuyoshi Kimura
Currently Director of Hirakata Kohsai Hospital, and previously Professor at Kyoto University Hospital

4. Principal Investigator: Dr. Wataru Ono
Professor at Kyoto University Hospital

jRCTs051200101

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This is a large-scale clinical study on heart failure (GRADE-I).
It is a study centered at Kyoto University called the GOREISAN-HF Trial, which examines the efficacy of adding Goreisan to congestive heart failure (cardiac edema) patients for edema.

The significance of large-scale clinical research on Goreisan in heart failure

TSUMURA

Diuretic treatment is gaining renewed attention

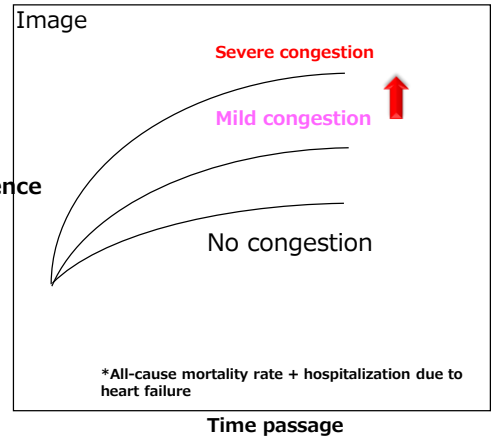
Types of heart failure and options for treatment (Class I recommendation)

	Types of heart failure		
	HFrEF	HFmrEF	HFpEF
ACE inhibitors / ARBs	○		
ARNI	○		
MRA	○		
SGLT2 inhibitors	○	○	○
Diuretics for congestion	○	○	○

Administration of diuretics for congestion are recommended in all types of heart failure

Adapted from
the Heart Failure Treatment Guideline revised in 2025

Poor prognosis due to residual congestion



Adapted from Andrew P. Et al. European Heart Journal (2013)34, 835–843

30

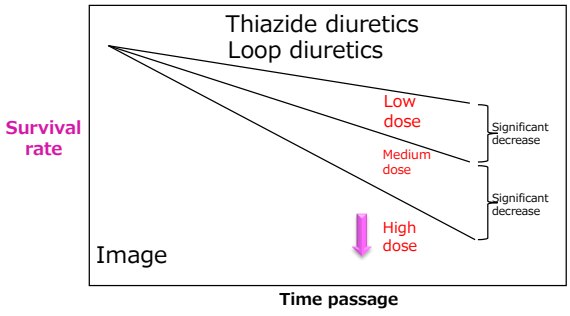
The reason for conducting this research is that diuretics are receiving renewed attention.
The use of diuretics for congestion is agreed upon as a common treatment even in the latest guidelines. It has been evidence-based proven that if congestion remains, the prognosis is poor.

Challenges of existing drugs in heart failure and the potential of Goreisan

TSUMURA

Conventional diuretics have a worse prognosis at higher doses.

Survival rate decreases with higher doses.



Adapted from Imamura T. et al., Int Heart J, September 2016

How to deal with treatment (of health issues)-resistant congestion?

The potential of Kampo (Goreisan) is

Diuresis: forced ✕

Fluid regulation: corrective ○

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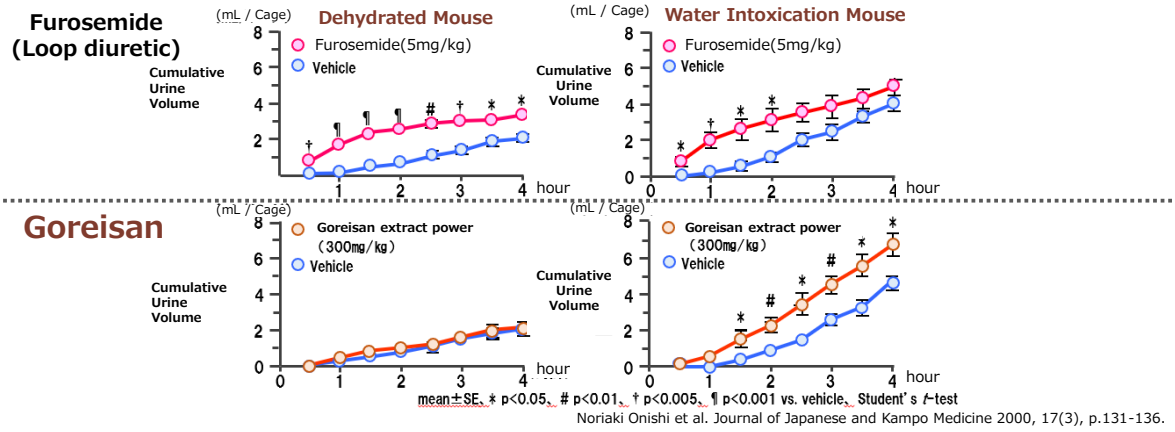
However, with conventional diuretics, the higher the dose, the lower the survival rate. So, how should we approach treatment-resistant congestion? Is there a potential role for Goreisan? Diuretics forcibly discharge fluids.

Kampo includes the concept of "fluid regulation," which essentially means that "fluid regulation" acts as a corrective remediation in the right direction. This is the effect of Goreisan.

Characteristics of Goreisan's diuretic (water-draining) effect

TSUMURA

Goreisan does not affect urine volume when there is water depletion but increases urine volume only when water is excessive



mean±SE, * p<0.05, # p<0.01, † p<0.005, ¶ p<0.001 vs. vehicle, Student's *t*-test

Noriaki Onishi et al. Journal of Japanese and Kampo Medicine 2000, 17(3), p.131-136.

Congestion treatment drugs, especially in the elderly, could reduce the dosage of loop diuretics.

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The fluid regulation effect of Goreisan can be discussed based on evidence from basic research.

The traditional diuretic furosemide forces an increase in urine output regardless of whether there is fluid in the body or not. On the other hand, Goreisan does not promote urine excretion when fluids are depleted and only promotes urine excretion when there is an excess of fluids. In other words, Goreisan does not affect urine volume in a dehydrated state. A reduction in diuretics dosage is expected.

Indication and Positioning of Goreisan Determined by Investigators Conducting the GOREISAN-HF study

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Chronic congestion management drugs for congestive heart failure (cardiac edema) (to adjust fluid balance and avoid dehydration)

- Despite of no subjective symptoms yet, move towards fluid regulation if a congestive tendency appears
- Despite of no subjective symptoms yet, move towards fluid retention and regulation if there is a tendency toward dehydration

Aspects of patients considered for prescribing Goreisan

- Elderly heart failure patients with mild renal dysfunction without coldness and accompanied by thirst who need management of cardiac edema
- Those with remaining cardiac edema (particularly cases with residual pleural effusion), despite of adding tolvaptan in addition to existing diuretics
- Heart failure patients with a history of hospitalization due to dehydration who need management of cardiac edema

In cases where dehydration, renal dysfunction, and electrolyte abnormalities are less likely to occur, Goreisan will be handy to administer and helpful to manage chronic congestion of the increasing number of elderly heart failure patients in in-home settings or at care centers in the future.

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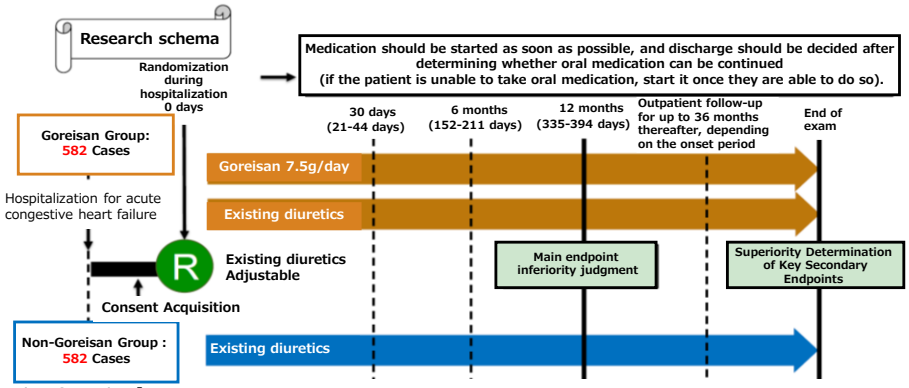
The feature of Goreisan, as considered by the investigators who participated in the GOREISAN-HF Trial, is that it is a medication for managing chronic congestion, which may be useful for patients in in-home settings and at care facilities.

Research schema of the GOREISAN-HF Trial

TSUMURA



[Implementation Overview]

- ✓ Primary endpoint: Edema improvement rate 12 months after enrollment (non-inferiority evaluation)
- ✓ Important secondary endpoint: Composite endpoint of all-cause mortality/all-cause readmission until the end of the trial (superiority evaluation)
- ✓ Participating facilities: 84 facilities nationwide; Target enrollment cases: **1,164 cases** (Enrollment period: until December 21, 2025)
- ✓ Subjects: 582 cases in the Kampo Goreisan group; 582 cases in the non-Goreisan group (As of December 3, 2025, a total of 1,111 cases registered in both groups)

⇨ Results are scheduled to be disclosed in FY 2027

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The schema of the GOREISAN-HF Trial is such that the baseline existing diuretics are given to both groups, and the evaluation is performed with or without Goreisan.

The target number of cases for this large trial is exceeding 1,000 cases, unprecedented in Kampo research, and the results are expected to be disclosed in FY 2027.

Target in the GOREISAN-HF Trial

TSUMURA

HFpEF (heart failure with preserved ejection fraction) has a large patient population and low treatment satisfaction.

Type of HF		HFrEF	HFmrEF	HFpEF (about half of the elderly patients)
Criteria	1	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
	2	Left ventricular ejection fraction < 40%	Left ventricular ejection fraction 40-49%	Left ventricular ejection fraction ≥ 50%
	3	-	1. Elevated sodium diuretic peptide levels 2. At least one additional criterion a) Obvious structural heart disease (left ventricular hypertrophy and/or left atrial enlargement) b) Diastolic dysfunction	

Treatment Drugs	- Angiotensin converting enzyme [ACE] inhibitor - Angiotensin II receptor blocker [ARB] - Mineralocorticoid receptor antagonist - Beta blocker	**SGLT2 inhibitors (some non-responders existing)** **There are issues in congestion management** Loop diuretics → factors worsening prognosis Tolvaptan → medication management, high drug cost

Examining the following effects of Goreisan
- Reduction in rehospitalization and mortality rates - Improvement in QOL - Changes in the amount of loop diuretics used
- Renal composite endpoints - Changes in eGFR - Adverse events - Reduction in drug costs

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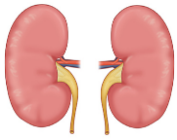
There are three major types of heart failure, and the "diastolic dysfunction type" called the HFpEF type accounts for about half of elderly heart failure patients. Some medications for this type has issues in congestion management, and its treatment options are still limited.

This GOREISAN-HF Trial is a study aimed at obtaining evidence on these matters.

Exploratory Clinical Study of Goreisan for Chronic Kidney Disease (GRADE-II)

TSUMURA



A Randomized, Open-Label, Parallel-Group Comparative Exploratory Clinical Trial of Goreisan for Uremia in Chronic Kidney Disease Patients
Exploratory Clinical Trial (GENERAL Study)

jRCTs051230192

[Research Overview]

Principal Medical Institution: Department of Nephrology and two other institutions, Kobe University Hospital

Principal Investigator: Hideki Fujii, Associate Professor

Research Design: Specific Clinical Research (Exploratory Study)

Subjects: Uremic patients with chronic kidney disease aged 18 and older

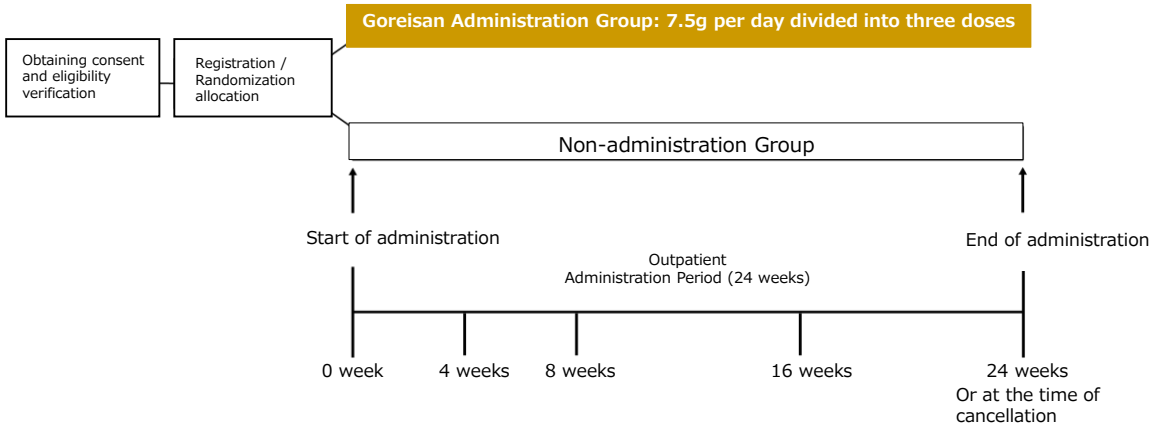
Research Period: From the jRCT publication date to October 31, 2027

36

Next is the clinical research on chronic kidney disease.
This study is being conducted mainly by Kobe University.

Study Schema and Evaluation Items of the GENERAL Study

TSUMURA



Target number of cases: 130 cases (registration completed)

Evaluation points: Primary endpoint; effect on uremia (urinary protein level)

Secondary endpoints; renal function (eGFR), edema, etc.

⇨ Analysis will be completed in FY2026; results to be disclosed

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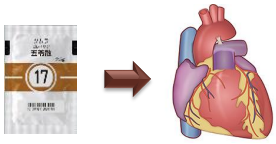
The research schema applies existing treatment for chronic kidney disease to both groups and evaluates them with or without Goreisan. The target number of cases is 130, which is also a large sample size for Kampo research. The endpoints mainly focus on kidney function.

The registration of 130 cases has already been completed, and the results are scheduled to be disclosed in FY 2026. The results of these two major clinical studies are eagerly awaited.

Challenges to Establishing Kampo (Goreisan) as a Standard Treatment for Cardiorenal Diseases (Expert Comments)

TSUMURA



Diuretics are essential in the cardiovascular treatment area. If Goreisan responders are clearly identified, the demand will increase, and it could become a viable treatment option.

- **There isn't a single doctor without issues with loop diuretics.**
  There are no cardiologists who do not require diuretics.
- **Goreisan is not for acute diuretic effect, but for "chronic congestion management", which means it works as a long-term fluid metabolism balance regulator that does not cause either fluid overload or dehydration.**
- **If responders are identified in the GOREISAN-HF trial, the demand for Goreisan will increase.**
- **Currently, the users of Goreisan is less than 1% of more than 1.2 million heart failure patients. However, it could be used in 20 to 30% of them depending on the trial results.**

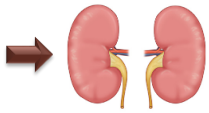
38

I will introduce comments regarding Goreisan from a heart failure specialist. Diuretics are essential in the cardiovascular treatment area.

If Goreisan responders are clearly identified, the demand will increase, and it could become a viable treatment option. There are no cardiologists who do not require diuretics. Goreisan is a long-term fluid metabolism balance regulator. It was suggested that if responders can be identified in the GOREISAN-HF trial, Goreisan usage in heart failure patients could increase to around 20-30%.

Challenges to Establishing Kampo (Goreisan) as a Standard Treatment for Cardiorenal Diseases (Expert Comments)

TSUMURA



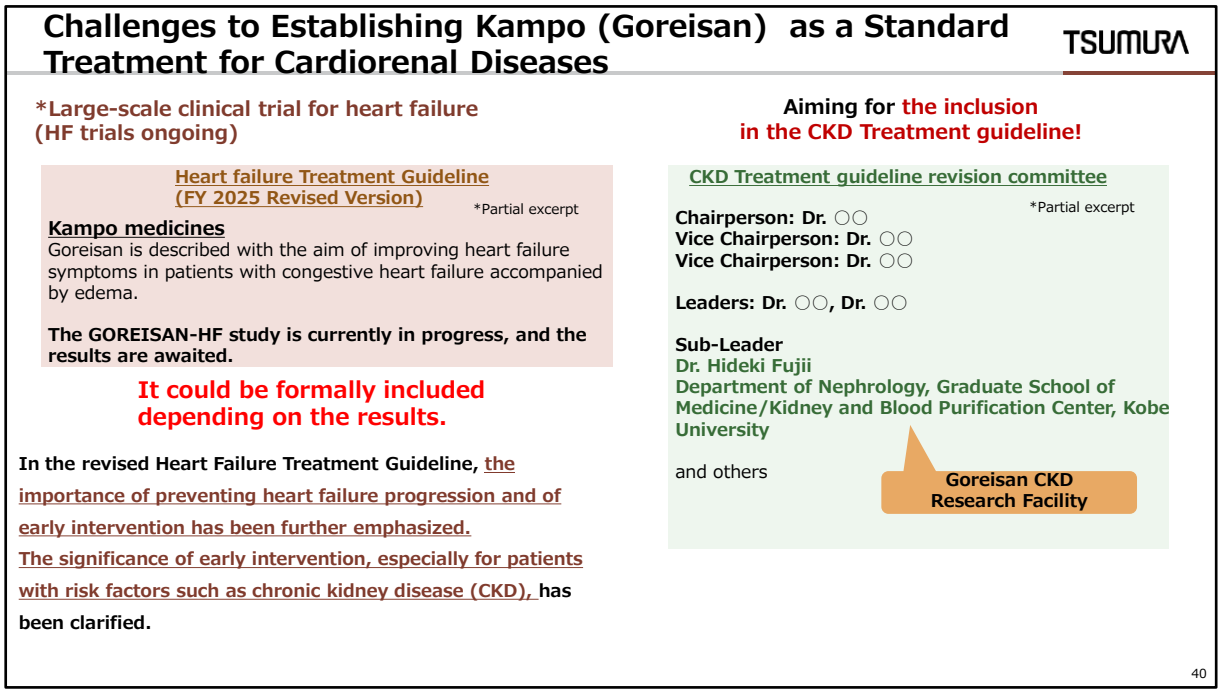
Diuretics are used in the kidney treatment. But when management does not go well, Kampo medicine Goreisan is indispensable. Evidence becomes important.

- **Goreisan is used as a third-line drug for the treatment of edema. It is used when fluid management with these diuretics does not go well although, first, loop diuretics, then SGLT2 inhibitors, and RA system inhibitors are used. Goreisan is a medicine that balances fluid without causing dehydration.**
- **Goreisan is a medicine that can be effective when used long-term. It could help reduce the dosage of other diuretics.**
- **It can become a medicine to suppress the worsening of kidney function. In the GENERAL Study, as the observation period is short, the suppression of eGFR decline cannot be seen directly. However, it is possible to predict renal function deterioration by calculating the eGFR slope (change). This approach will be adopted for analysis in this study as well. Evidence is the key.**

39

Next, I will share the comments on Goreisan from specialists in chronic kidney disease.

Diuretics are used in the kidney field. But when management does not go well, Goreisan is indispensable. Evidence is therefore important for that purpose. Goreisan is a third-line drug for the treatment of edema and is a medicine that balances fluid without causing dehydration. It could help reduce the dosage of other diuretics, and it may serve as a medicine to alleviate worsening of kidney function. Evidence is important in any case.



As we stated at the beginning, we are engaged in activities to establish the position of Kampo as a standard treatment.

One of the strategies we are considering is inclusion in Treatment guidelines. In the Heart Failure Treatment guideline, the implementation of the GOREISAN-HF trial is already mentioned, and depending on the results, we are quite hopeful that the medicine is highly likely to be formally included in the guideline.

Furthermore, this content emphasizes the importance of early treatment intervention and prevention of progression in heart failure, particularly highlighting the significance of early intervention for patients with risk factors such as chronic kidney disease (CKD). We aim for the inclusion of Goreisan in the treatment guideline for chronic kidney disease, and Dr. Fujii from Kobe University, which is the institution where the Goreisan CKD study mentioned earlier is taking place, is also one of the editors. Once the results are out, he will promptly review them.

Possibility of Application of Goreisan to Cardiorenal Diseases (Summary)

TSUMURA

Effectiveness in basic data, elucidation of the mechanism, and the potential in the clinical database have already been demonstrated.

Establishing evidence for the improvement of cardiac and renal functions by Goreisan and its use as a disease management drug could significantly contribute to medical care.

The time has come

- Deployment in heart failure research and (large-scale) clinical studies
  (Kyoto University and over 80 other institutions)
- Deployment in clinical studies
  (Department of Nephrology and two other institutions at Kobe University Hospital)

⇨ **Spread it with a new function and efficacy (evidence-based)**

⇨ **Aim for new listing in treatment guidelines**

⇨ **Establish Goreisan as a standard treatment**

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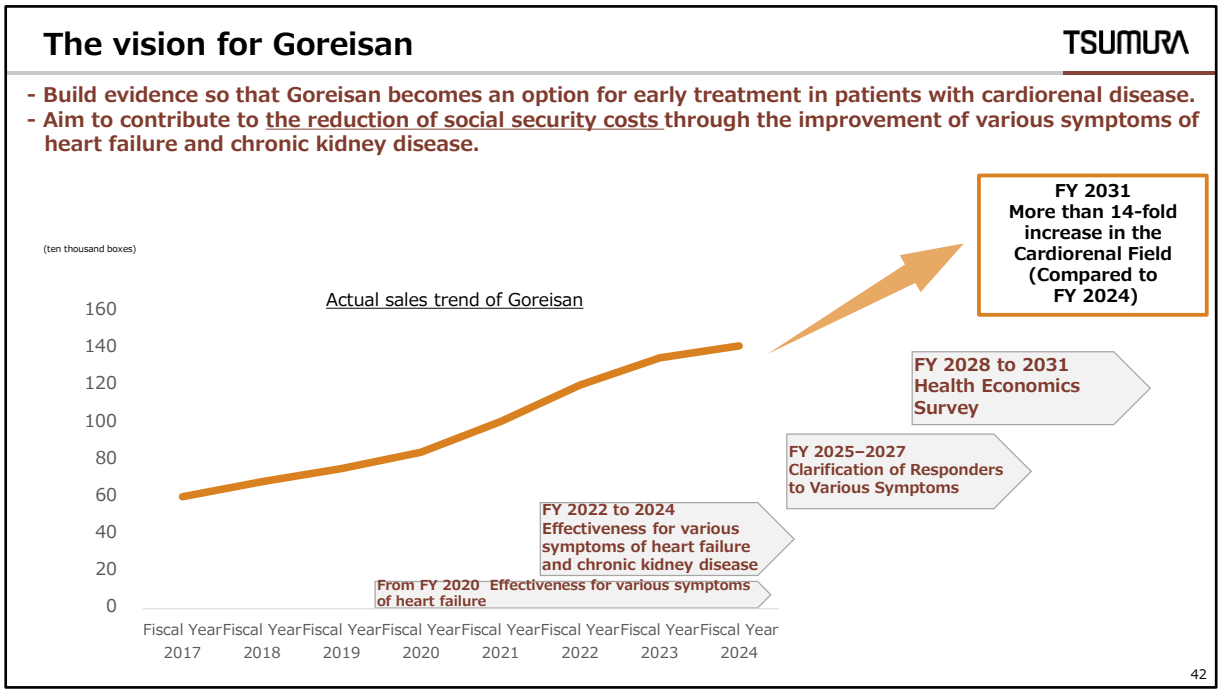
To summarize, the effectiveness in basic data, elucidation of the mechanism, and potential in clinical database have already been obtained.

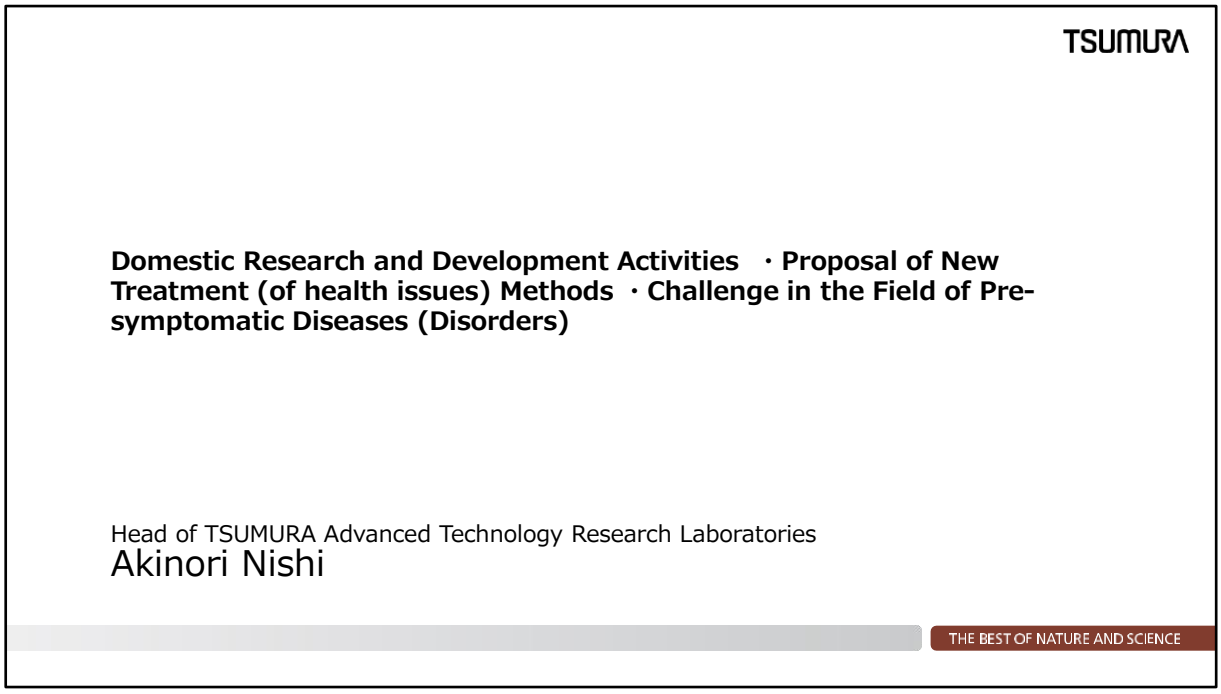
It will be a significant contribution to the healthcare environment, including polypharmacy and medical economics, to establish evidence that Goreisan improves cardiac and renal function and acts as a disease management drug. For that reason, clinical evidence from these two studies are absolutely essential.

We aim to spread it with a new function and efficacy, to newly include it in Treatment guidelines, and to make Goreisan the standard treatment.



This is the Vision that Goreisan aims for. Targeting the 2031 Vision, we aim to contribute to reducing social security costs through the improvement of various symptoms of heart failure and chronic kidney disease with Goreisan.

We aim to increase the number of Goreisan prescriptions in the cardio-renal field to more than 14 times by FY2031, a field that has not been an indication for use until now. We will build evidence to support recommending Goreisan as an option for early treatment of patients with cardio-renal disease in the treatment guideline mentioned earlier.
That concludes my explanation.



I'm Nishi from the Tsumura Advanced Technology Research Laboratories.

I will explain our efforts regarding "pre-symptomatic diseases and disorders" and "personalized medicine."

Challenging the Fields of “Pre-symptomatic Diseases (Disorders)” and “Personalized Medicine”

TSUMURA

Challenges identified from the past efforts

- Evaluating efficacy uniformly using Western medicine criteria makes it difficult to showcase the advantages of Kampo medicines.
- The strength of Kampo lies in its selective use, and the patterns based on the unique diagnostic methods of Kampo should be taken into consideration.
- In actual research, there were types that worked well and types that did not, which affected the results

Differentiation by symptoms, pathologies, and stages

KAMPOmics®

KAMPOmics® is our proprietary research system established by combining advanced technological fields cultivated by Tsumura (such as metabolomics, genetics, gut microbiota, and systems biology) to integratively understand Kampo medicine, traditional Japanese medicine, and the complex mechanisms of multi-component Kampo medicines.

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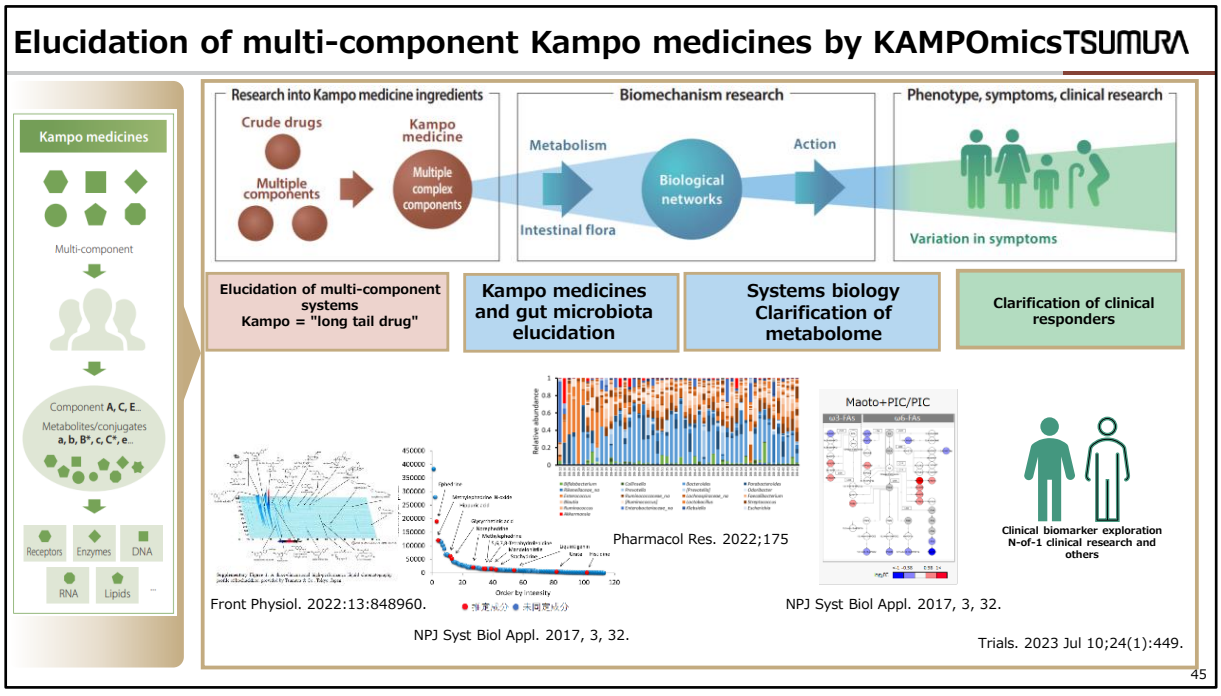
Within the accumulation of evidence for the standardization of traditional Kampo treatment so far, issues have become evident.

For example,
-Evaluating efficacy uniformly using Western medicine criteria makes it difficult to showcase the advantages of Kampo medicines.
-The strength of Kampo lies in its selective use, and the patterns based on the unique diagnostic methods of Kampo should be taken into consideration. In actual research, there were types that worked well and types that did not, which affected the results.

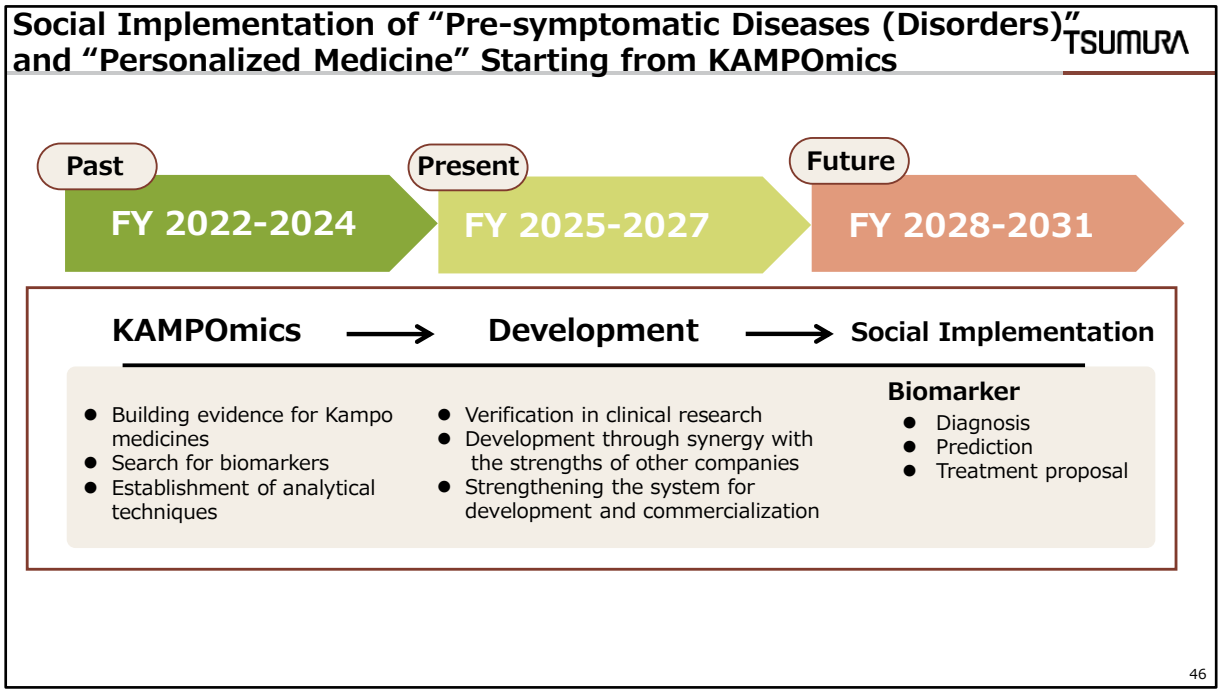
With regard to these points, thus far, we have focused on how to scientifically clarify the strengths of multi-component Kampo medicines, which are characterized by differentiated use according to the patient's constitution, symptoms, pathological states, and stages, and how to deliver the evidence to clinical practice.
For that reason, we have built a proprietary research system called 'KAMPOmics®' that integrates cutting-edge technologies. From this initiative, we are advancing research and development toward the social implementation of personalized medicine and the science of pre-symptomatic diseases and disorders.



This is the overview of KAMPOmics.

In order to clarify the complex and characteristic mechanisms of action of multi-component Kampo medicines, we start from the identification of the diverse active ingredients they contain. And we work on elucidating the metabolism of Kampo medicine components by intestinal bacteria and the body, the pharmacokinetics, and the interactions between Kampo medicines and the intestinal flora, which has recently been shown to play an important role in human health. And we conduct metabolomic and systems biology analyses to clarify how the various components of Kampo medicines act on complex biological networks and exert their effects.

Then, to investigate the influence of individual constitution on the efficacy of Kampo medicines, we are advancing the search for biomarkers of the actions of Kampo medicines, based on responders participating in clinical trials.



Our company's strengths lie in evidence creation, biomarker exploration, and the establishment of analytical technologies. So, starting with KAMPOmic, we aim to advance development stages through validation in clinical research, leveraging other companies' strengths into development, and strengthening systems for development and commercialization.

As for the social implementation, we aim to realize healthcare for pre-symptomatic diseases and disorders and personalized medicine by creating biomarkers that enable diagnosis, prediction, and treatment proposals. Today, I will focus on our challenge in the field of healthcare for “pre-symptomatic diseases and disorders".

Challenge in the field of "pre-symptomatic diseases (disorders)" TSUMURA

"Background"

- In Kampo medicine, there are the concept of pre-symptomatic diseases (disorders) and the prescriptions (treatment) for them, highlighting the importance of systematically improving pre-symptomatic disease (disorder) conditions, as indicated in the Huangdi Neijing.
- Science definition and treatment of pre-symptomatic diseases (disorders) based on evidence have not been established.

"Purpose and significance"

Contributing to the realization of a healthy society by providing diagnosis of pre-symptomatic diseases (disorders) defined based on evidence and methods for improving pre-symptomatic diseases suitable for each individual

"Establishing the science of pre-symptomatic diseases (disorders)"

- Establishing a scientific benchmark for the "pre-symptomatic disease (disorder) state" and comprehensively understanding the body's condition as it progresses from pre-symptomatic diseases (disorders) to disease.
- Focusing on research on biomarkers, which serve as indicators that can objectively measure the effects of Kampo medicines prescriptions such as pre-symptomatic treatment, prevention of aggravation, and prevention of relapses.

Collaborative research
Dr. Norihiro Okada
Kitasato University Laboratory of genomics for health and longevity, Emeritus Professor at Tokyo Institute of Technology (now Institute of Science Tokyo)

Focusing on intron retention (IR) as a marker for pre-symptomatic diseases (disorders)

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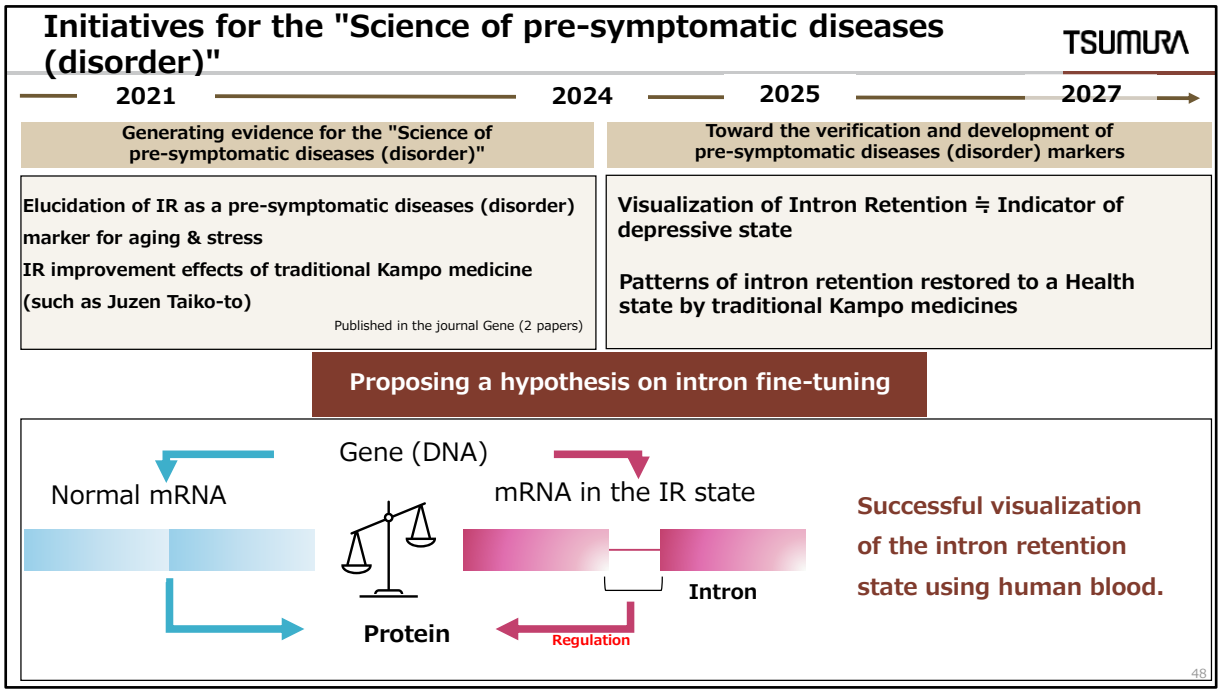
I'll start with the background for the field of healthcare for pre-symptomatic diseases and disorders. In Kampo medicine, there is the concept of "mibyou," meaning pre-symptomatic diseases and disorders and its prescriptions for treatment, emphasizing the importance of systematically improving the pre-symptomatic state.
On the other hand, , their scientific definitions and treatment based on evidence have yet to be established.

We are working to contribute to the realization of a Health-oriented society by providing diagnoses of pre-symptomatic diseases and disorders, defined based on evidence, and methods to improve them tailored to each individual.
First, to establish the science of pre-symptomatic conditions, we are trying to create a scientific standard for the "pre-symptomatic state" and to comprehensively understand the body's condition as it progresses from pre-symptomatic states to illness.
Then, we are making efforts to focus on research into biomarkers, which are objective indicators that can assess the effects of treatments such as Kampo medicines prescriptions on pre-symptomatic treatment, and preventing aggravation and relapses.

Among these, we are particularly focusing on a new marker for pre-symptomatic diseases disorders called intron retention (IR), which was discovered through joint research with Dr. Okada of the Health Longevity Genome Department at Kitasato University. We are working with the doctors to scientifically verify the diagnostic use of IR and the therapeutic effects of Kampo medicines, aiming to advance these results into development.



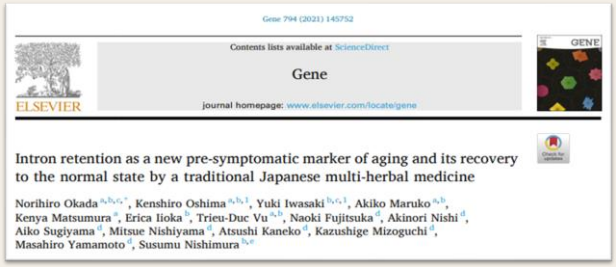
Intron retention is one of the states of mRNA during the process in which genes are translated into proteins, referring to the condition, where gene sequences that are not translated into proteins, are included within the mRNA. Previous research has revealed that this intron retention functions as a regulatory mechanism, and that by capturing changes in this regulatory mechanism, it becomes possible to detect early changes within the body. Our previous research on intron retention, using a senescence-accelerated animal models, showed that the state of intron retention could serve as a pre-symptomatic disease marker for aging and stress.

We also clarified that traditional Kampo medicines can improve aging-related intron retention. Furthermore, at the subsequent clinical research stage, we succeeded in visualizing intron retention using human blood, discovering its potential as an indicator of depressive states. We also showed that Kampo medicines restored the pattern of intron retention to a healthy type.

'Intron Retention (IR) as a pre-symptomatic diseases (disorder) Marker of Aging' Discovered

TSUMURA

2021


Gene 794 (2021) 145752

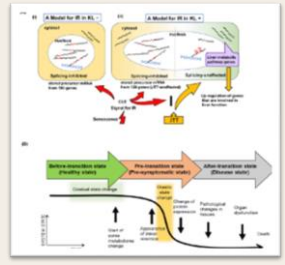
Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Intron retention as a new pre-symptomatic marker of aging and its recovery to the normal state by a traditional Japanese multi-herbal medicine

Norihiro Okada [a,b,c,*], Kenshiro Oshima [a,b,1], Yuki Iwasaki [b,c,1], Akiko Maruko [a,b], Kenya Matsumura [a], Erica Iioka [b], Trieu-Duc Vu [a,b], Naoki Fujitsuka [d], Akinori Nishi [d], Aiko Sugiyama [d], Mitsue Nishiyama [d], Atsushi Kaneko [d], Kazushige Mizoguchi [d], Masahiro Yamamoto [d], Susumu Nishimura [b,e]



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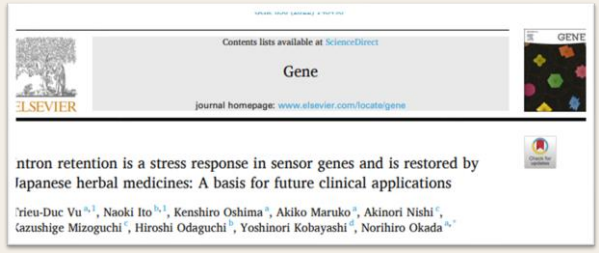
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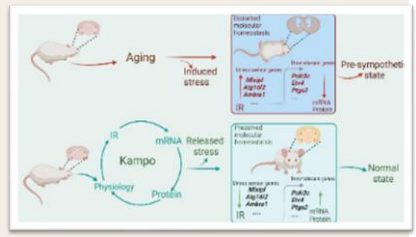
Gene

journal homepage: www.elsevier.com/locate/gene

ntron retention is a stress response in sensor genes and is restored by Japanese herbal medicines: A basis for future clinical applications

Trieu-Duc Vu [a,1], Naoki Ito [b,1], Kenshiro Oshima [a], Akiko Maruko [a], Akinori Nishi [c], Kazushige Mizoguchi [c], Hiroshi Odaguchi [b], Yoshinori Kobayashi [d], Norihiro Okada [a,*]



Basic Papers on pre-symptomatic diseases (disorder) Intron Retention (Published in Genes Journal in 2021 and 2022)

49

The achievement of discovering that this intron retention (IR) can serve as a pre-symptomatic disease marker for aging has been published in the journal Gene.

Effects of Kampo Medicines on IR (Basic Research Using Aging-Related Animals)

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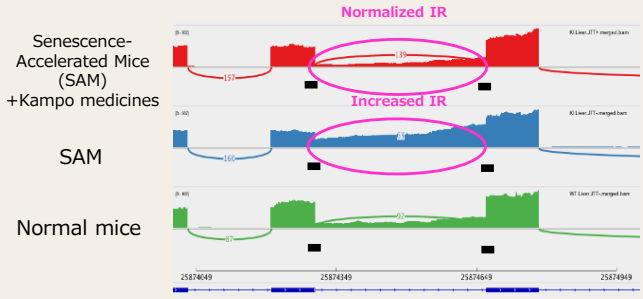
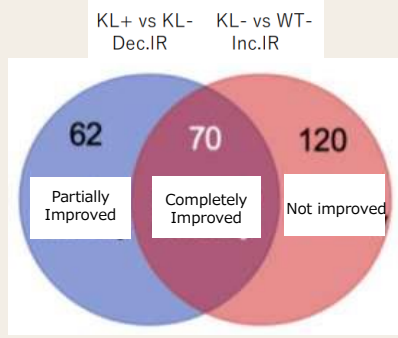
Kampo Medicines Normalizes IR Increased by Aging

Anxa11: IR



Okada et al. (2021) Gene

IR Improved by Kampo medicines Number of genes (liver)



The first report of intron normalization by medication

50

Regarding the overview of the research, basic research using senescence-accelerated mice confirmed that the Kampo medicines (Juzentaihoto) normalizes IR. This is the first report showing that introns can be normalized by medication, indicating a new potential for Kampo medicines.

Proposing the intron fine-tuning hypothesis

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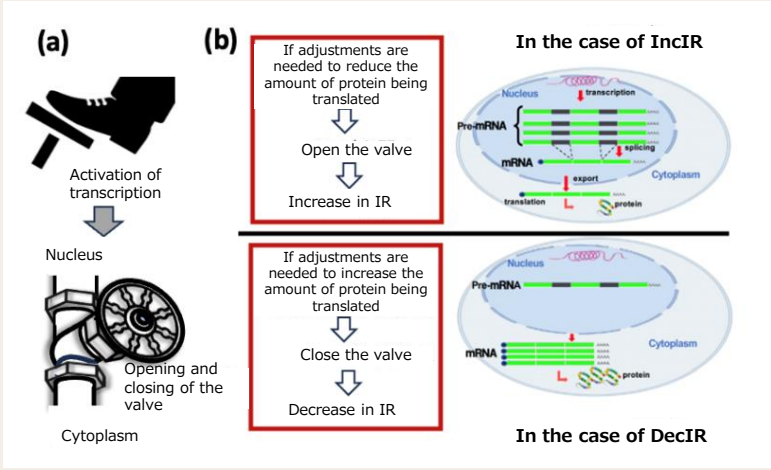
It has been found that IR is a monitoring mechanism for maintaining protein homeostasis in the cytoplasm



Stress causes changes in the appropriate amount of protein in the cytoplasm

IR has a role in surveillance and regulation

Okada et al. BioRxiv (2024)

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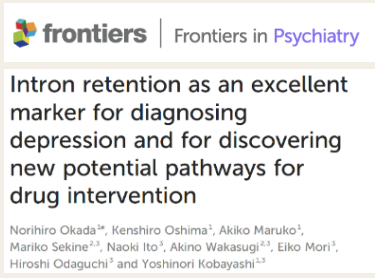
Through such research findings, it has been discovered that IR is a mechanism for monitoring protein levels in the cytoplasm and plays a role in regulating (tuning) changes caused by stress. Thus, from the intron fine-tuning hypothesis, the physiological significance of IR is gradually being clarified.

Clinical Research Evidence of IR as a Marker for Depression

TSUMURA

- **Intron retention is an excellent marker for the diagnosis of depressive disorders.**
- **This finding helps discover new biological pathways for drug intervention.**


frontiers | Frontiers in Psychiatry

Intron retention as an excellent marker for diagnosing depression and for discovering new potential pathways for drug intervention

Norihiro Okada[1*], Kenshiro Oshima[1], Akiko Maruko[1], Mariko Sekine[2,3], Naoki Ito[3], Akino Wakasugi[2,3], Eiko Mori[3], Hiroshi Odaguchi[3] and Yoshinori Kobayashi[2,3]

Front Psychiatry. 2024 Sep 19:15:1450708.


北里大学

プレスリリース

2024年9月30日

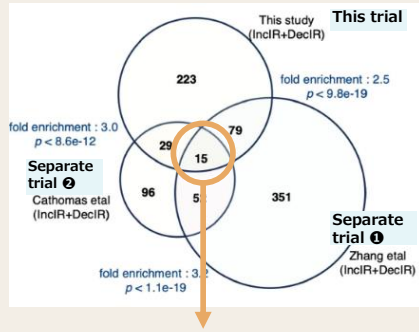
報道関係者各位

北里大学

うつのマーカーを発見

概要

From Kitasato University press release



15 genes common to three studies

Potential marker for overall depression

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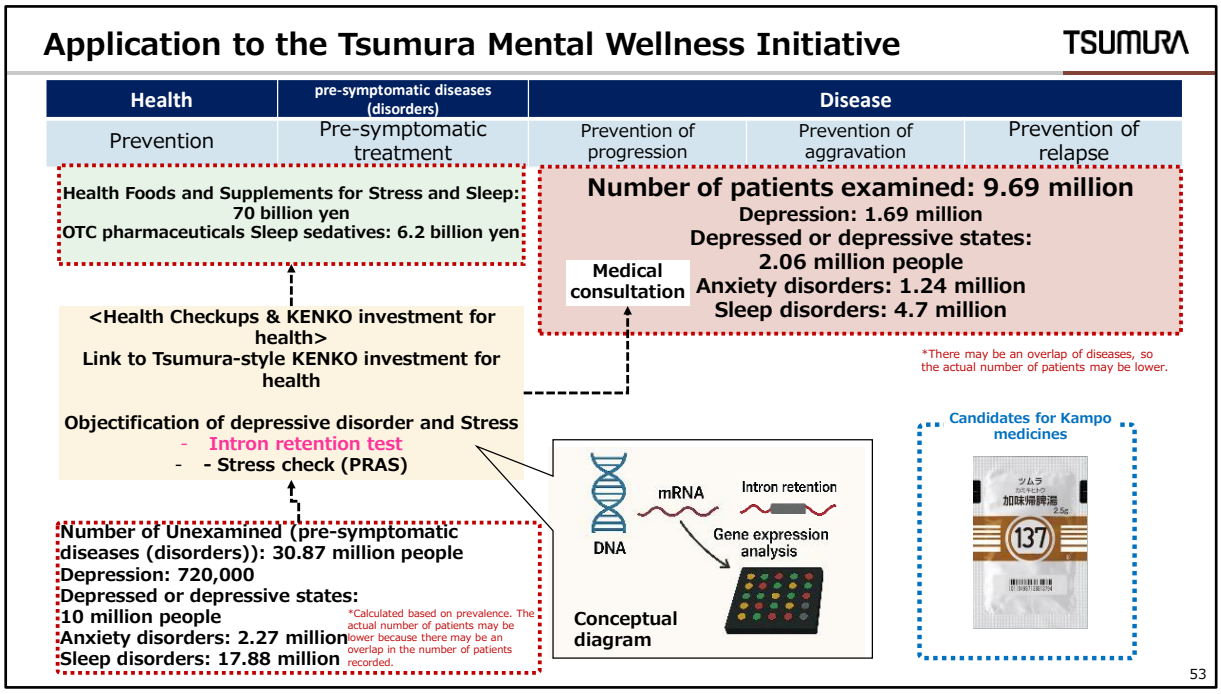
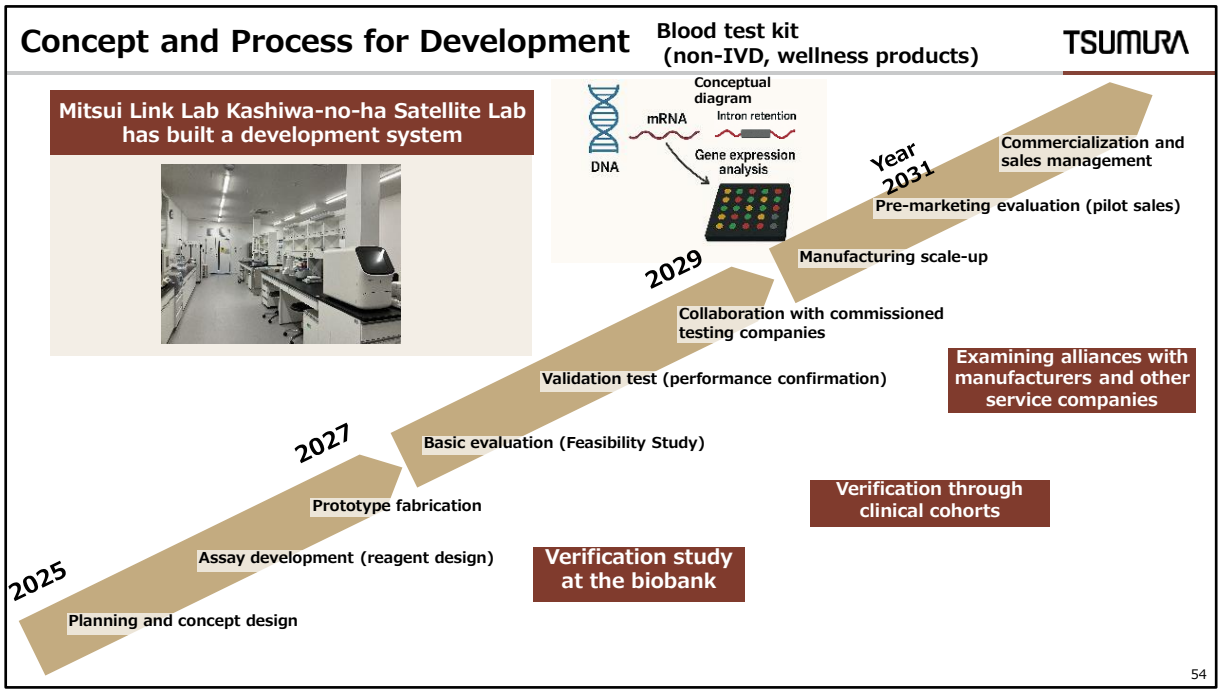
Based on these research findings, the visualization of IR using human blood revealed the potential of intron retention as an indicator of depressive states and demonstrated that the pattern of intron retention recovers to a healthy type when Kampo medicines are used.

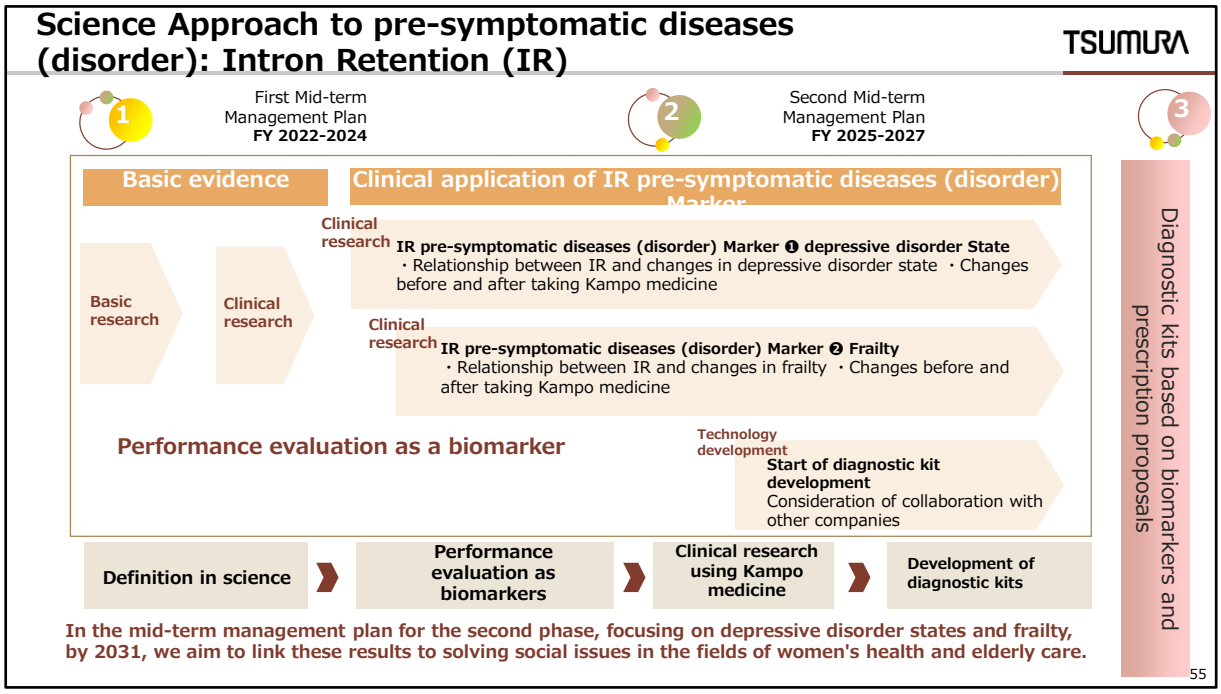
These findings provide clinical research evidence for IR as a marker of depression. Moreover, this study identified genes common to multiple clinical studies, suggesting that IR may become a useful marker for diagnosing depression.



Going forward, we would like to apply these results to the field of mental wellness, where it is said that 30 million people remain untreated, by testing pre-symptomatic depression through intron retention, properly detecting it, and thereby linking it to prevention, early treatment, and full-fledged treatment with Kampo medicine.



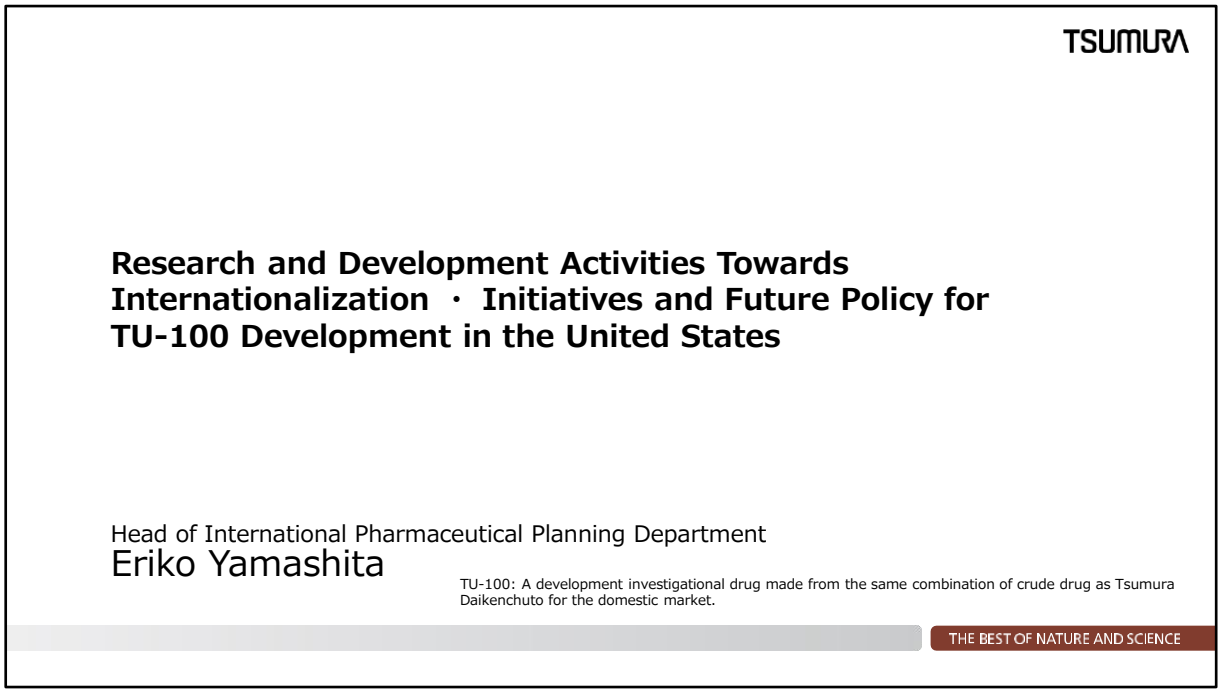
Currently, regarding the development of diagnostic kits for pre-symptomatic diseases and disorders, we have built this roadmap and established a system for development at Mitsui Link Lab Kashiwa-no-ha starting this fiscal year. Utilizing this as a hub, we are also considering verification through clinical cohorts and alliances with other companies.



Lastly, in the second mid-term management plan, we will advance the clinical application of IR as markers for pre-symptomatic disease and disorder, focusing on depressive states and frailty, and simultaneously promote the development of technology that combines diagnostic kits with prescription proposals.

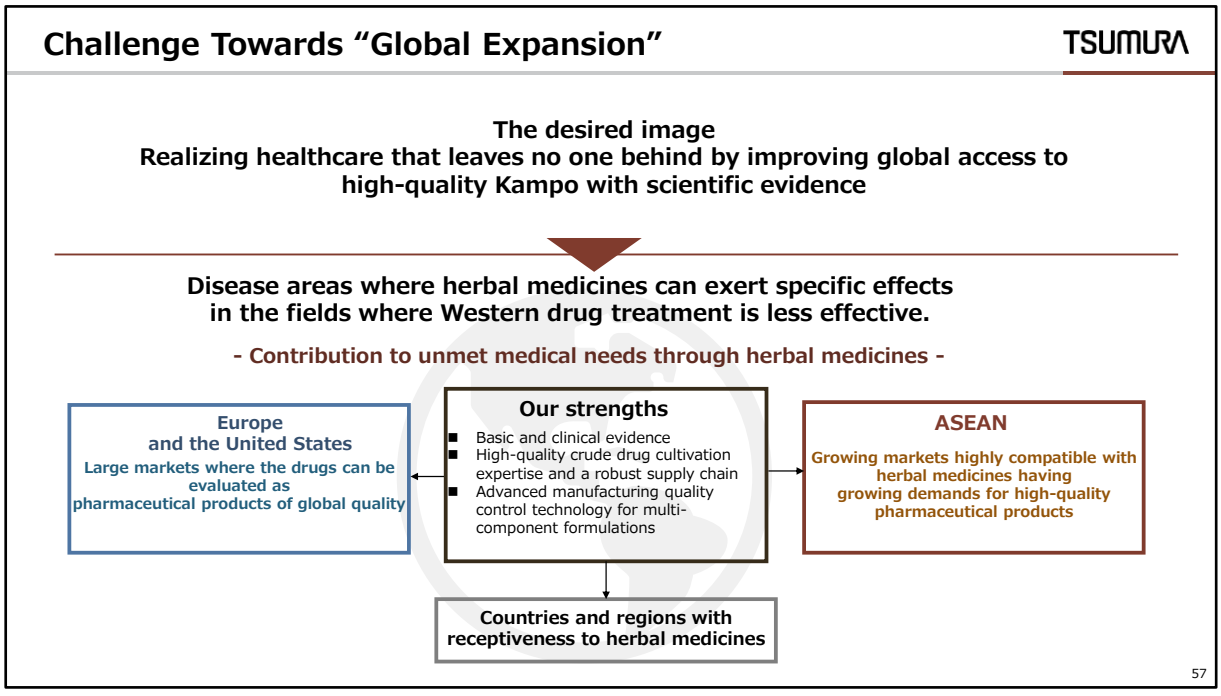
Through these measures, we aim to focus on IR and contribute to solving social issues related to the elderly and mental health.
This concludes my explanation.

Next, I would like to invite Yamashita to take over.



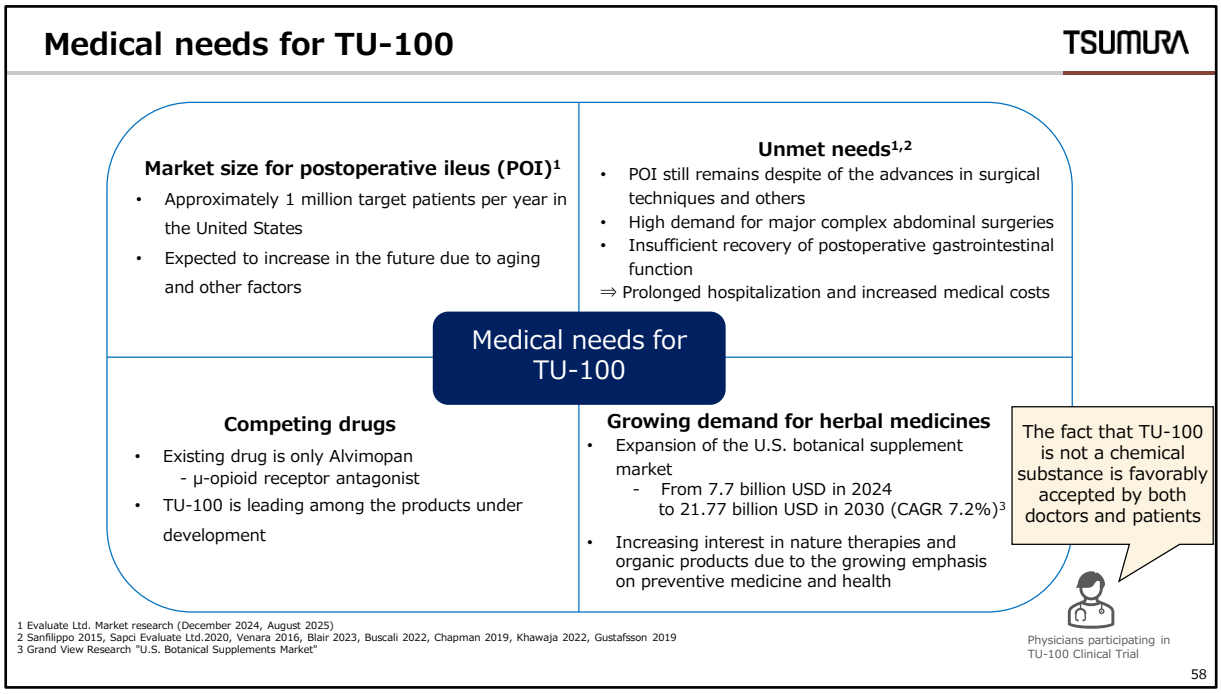
I'm Yamashita from the International Pharmaceutical Planning Department.

As part of our research and development activities toward the internationalization of herbal formulations, I will explain our efforts in developing TU-100 in the United States and our future policies.



Our challenge is to improve global access to high-quality herbal formulations with scientific evidence, thereby realizing healthcare that leaves no one behind.

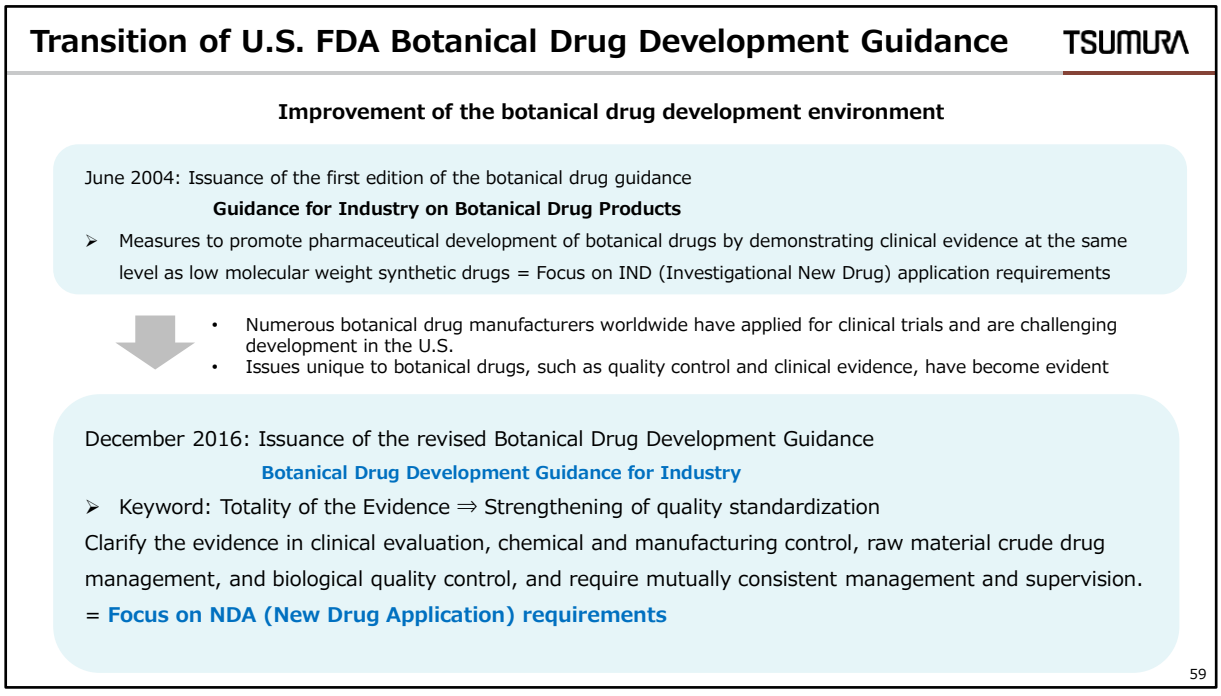
In other words, leveraging our strengths in "basic and clinical evidence," "high-quality crude drug supply chains," and "advanced manufacturing quality control technologies," we aim to enter the European and American markets with TU-100 as a globally qualified pharmaceutical product. Moreover, we will contribute to meeting with unmet medical needs in the ASEAN region, where there is a high affinity for herbal medicines and expected growth, as well as other countries receptive to herbal medicines. Finally, Head of ~division Imada will explain the overall research portfolio.



I will explain the past efforts and future plans regarding the development of TU-100 for postoperative ileus, or POI for short, in the United States.
POI remains an unmet need in the United States, which has an advanced medical environment, and the target patient population of approximately one million people per year is expected to increase with aging.

The existing drug alvimopan has a mechanism of action that directly causes opioid-induced gastrointestinal dysfunction. As the factors involved in postoperative gastrointestinal dysfunction are complex, there is growing expectation for drugs like TU-100 that can approach from a different mechanism of action.

Under these circumstances, TU-100 is leading others in the development phase. Also, the fact that it is a herbal medicine is favorably accepted by both doctors and patients, which serves as a factor supporting its development and market launch.



Furthermore, the development environment for botanical drugs has been established with the issuance of the guidance on botanical drug development by the FDA, the regulatory authority of the United States.

In the 2016 revised version, a method called "Totality of the evidence" was introduced as a quality control strategy unique to botanical drugs. It evaluates the quality of all botanical drugs through a multifaceted approach and defines the path for only high-quality botanical drugs to file new drug approval applications.
Since the revised version was issued, no botanical drugs have been approved, and if a Kampo medicine is approved by the FDA, it would be the world's first case and would represent a breakthrough proving the true value of Kampo medicine.

We are leveraging our accumulated know-how to not only demonstrate efficacy and safety but also to improve quality control technologies and continue challenges to meet expectations both domestically and internationally.

Major results and external opinions of the TU-100 P2T4 trial

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Major results of the TU100 P2T4 trial

- Randomized double-blind placebo-controlled Phase II trial (36 institutions, 402 intestinal resection patients)
- No significant difference in the primary endpoint [time to recovery of gastrointestinal function]
- Significant differences in multiple secondary endpoints [proportion of patients with recovered gastrointestinal function, length of hospital stay, etc.] in the TU-100 7.5g group

- **The FDA and U.S. KOL recognized a trend of effectiveness with the daily administration of 7.5g of TU-100**
- **In October 2025, a paper was published online in the Diseases of the Colon and Rectum (DC&R).**

Views of U.S. Key Opinion Leaders (KOL) and others

- Despite relatively short hospitalization periods and other conditions, the TU-100 7.5g group showed a favorable benefit-risk profile.
- A one-day reduction in hospitalization period is clinically significant.
- It was suggested that multiple mechanisms are involved in the effects of TU-100.

FDA's perspective

- There was a trend indicating effectiveness with a daily dose of 7.5g of TU-100.
- No new safety concerns were identified.

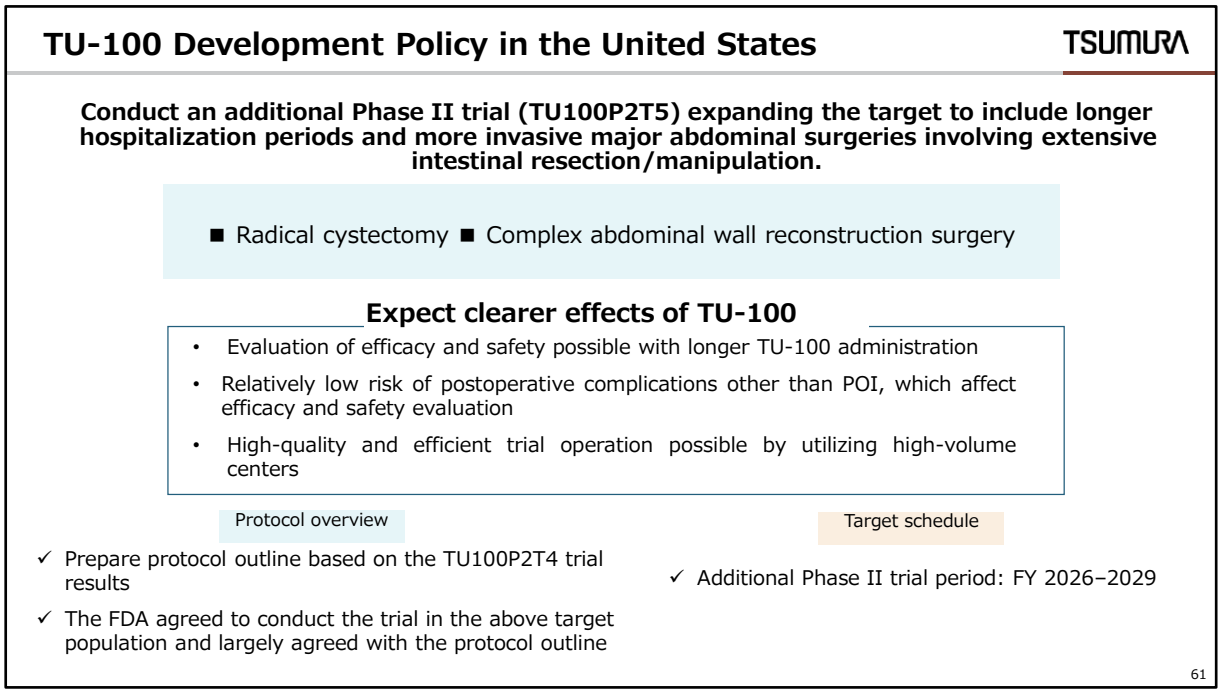
DC&R: Diseases of the Colon and Rectum is a peer-reviewed academic journal published by the American Society of Colon and Rectal Surgeons (ASCRS).

Nedeljkovic, S. S., Silinsky, J. D., Nagle, D., et al. (October 2025). Evaluation of TU-100 (Daikenchuto), a traditional Japanese Kampo medicine, as an adjunct to enhanced recovery after surgery, for acceleration of gastrointestinal recovery after bowel resection: Results of a proof-of-concept, phase 2, randomized, double-blind, placebo-controlled trial. Diseases of the Colon & Rectum. Advance online publication. https://doi.org/10.1097/DCR.0000000000003990

While promoting development in the United States, in May 2024, we completed a large-scale randomized double-blind placebo-controlled Phase 2 trial involving 402 patients who underwent intestinal resection surgery.

The unexpected COVID-19 pandemic created a difficult situation where the periods of hospitalization and administration of the investigational drug were shortened, but in response to the results of this trial, the FDA and US KOL recognized the trend of efficacy with TU-100 7.5g administration.

Furthermore, on October 20, a paper on the P2T4 trial was published in the Diseases of the Colon and Rectum, a peer-reviewed journal influential globally, especially in the field of gastrointestinal surgery mainly in the US and was publicized as evidence in an important area.



Meanwhile, considering future medical needs, the future policy is to conduct an additional Phase 2 trial targeting major invasive abdominal surgery with higher invasiveness, including longer hospitalization periods and more extensive intestinal resection and manipulation. Specifically, the participants will be those undergoing radical cystectomy or complex abdominal wall reconstruction.

After repeated discussions with key opinion leaders and consultants in the United States and Japan, we concluded that TU-100 can be administered to this group for a longer period, and because the factors affecting the evaluation of efficacy and safety are limited, clearer effects can be expected. The FDA has also agreed to conduct the trial with this trial group.

Furthermore, thanks to a consortium called SUO-CTC, involving more than 500 physicians, which promotes clinical trials for urologic cancer, showing strong interest in this trial and expressing their support for it, smooth preparations for the trial implementation is steadily proceeding.
The Phase 2 trial period is planned from fiscal 2026 to fiscal 2029.

Strategy to Acquire Indications

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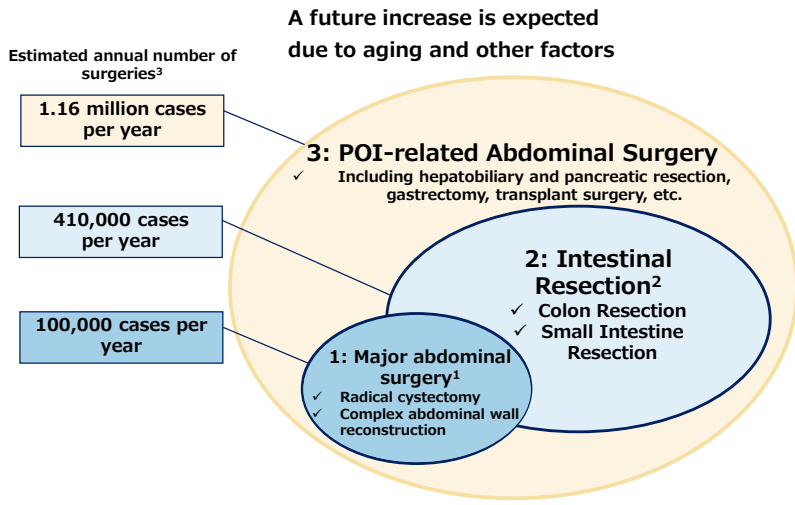

Clear results can be obtained and indications can be acquired through P2T5 and PIII trials targeting patients undergoing **1: major abdominal surgery**, where there is a high demand for POI treatment and more definitive effects of TU-100 can be expected.

+

By asserting the similarity in surgical characteristics with 1: major abdominal surgery, acquired indications can be acquired for **2: intestinal resection** patients targeted in the P2T4 trial

+

Indications can be acquired for a broader range of **3: POI-related abdominal surgery** patients

or

Possible use in a broader range of **3:POI-related abdominal surgery** patients[4]

1: P2T5 (next planned Phase II trial) target area
2: P2T4 (completed Phase II Trial) target area
3: Nationwide Inpatient Data from AHRQ (Agency for Healthcare Research and Quality, USA)
4: Evaluate Ltd. Market Research (December 2024, February 2025)

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Regarding indications, we aim to securely obtain the indications for the trial population shown in item 1, which are patients undergoing major abdominal surgery. Also, as for the patients who received intestinal resection surgery and were the subjects of the previous trial indicated in 2, we plan to obtain indications at the same time based on the similarity of surgical characteristics with major abdominal surgery.

Furthermore, by demonstrating postoperative usefulness through evidence obtained in 1 and 2, we aim to acquire comprehensive indications for a wide range of patients who received POI-related abdominal surgery, including those undergoing hepatobiliary pancreatic resection and gastrectomy. Even if it is difficult, we have confirmed through external market research that there is a possibility of widespread use.

Regarding investment evaluation, various scenarios are regularly examined. At this point, it is predicted that all investment costs, including capital expenditures, can be recovered.
Also, the company’s research and development expense ratio against sales is at a level of 5%, which is expected to be maintained even considering the US development costs.

Results Obtained from the Development of TU-100 in the US and its Ripple Effects

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Results	Ripple effects	
1. Clinical trials of safety and efficacy	Obtaining evidence for TU-100 and understanding its pharmacological effects and mechanisms	
2. Research on intestinal bacteria	Accumulating know-how in intestinal bacteria research	Expansion to/ application for other Kampo medicines
3. Human blood pharmacokinetics study	Pioneer in applying the same testing methods to herbal extract preparations → Enhancing the package insert	
4. Investigation of frequency of adverse effects	Quantification of safety information about Kampo medicines based on data from 3,000 cases	
5. Building the reference data base of crude drugs	Establishment of lot analysis and production processes of crude drug through the measurement of indicator components for management	Quality improvement of Kampo products
6. Establishment of quality control system in accordance with global standards	Promotion of PIC/S GMP and GACP compliance in Kampo medicine manufacturing	

PIC/S : Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme. Pharmaceutical Inspection Agreement and Joint Pharmaceutical Inspection Scheme
GMP: Good Manufacturing Practice. Standards for Manufacture Control and Quality Control GACP: Good Agricultural and Collection Practice. Good Agricultural Practice for Medicinal Plants

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Improvements in quality and evidence through development in the United States not only help in recouping investments directly in the US market but also lead to international technological innovation, which is being applied to other Kampo products.

Results Obtained from the Development of TU-100 in the US and its Ripple Effects

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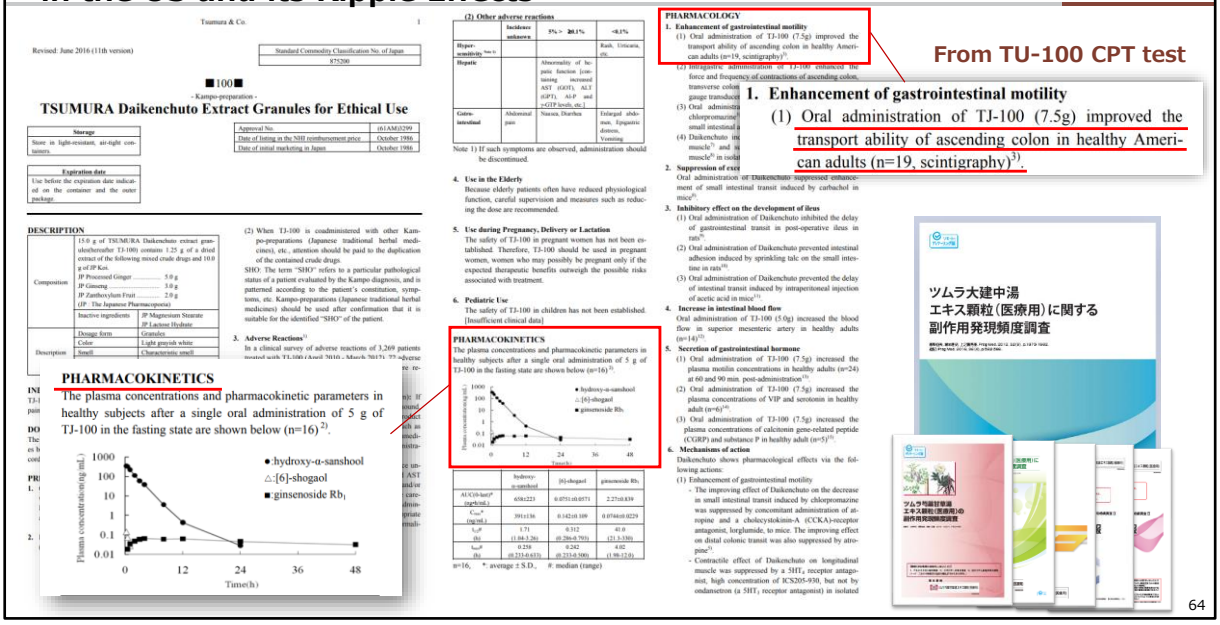
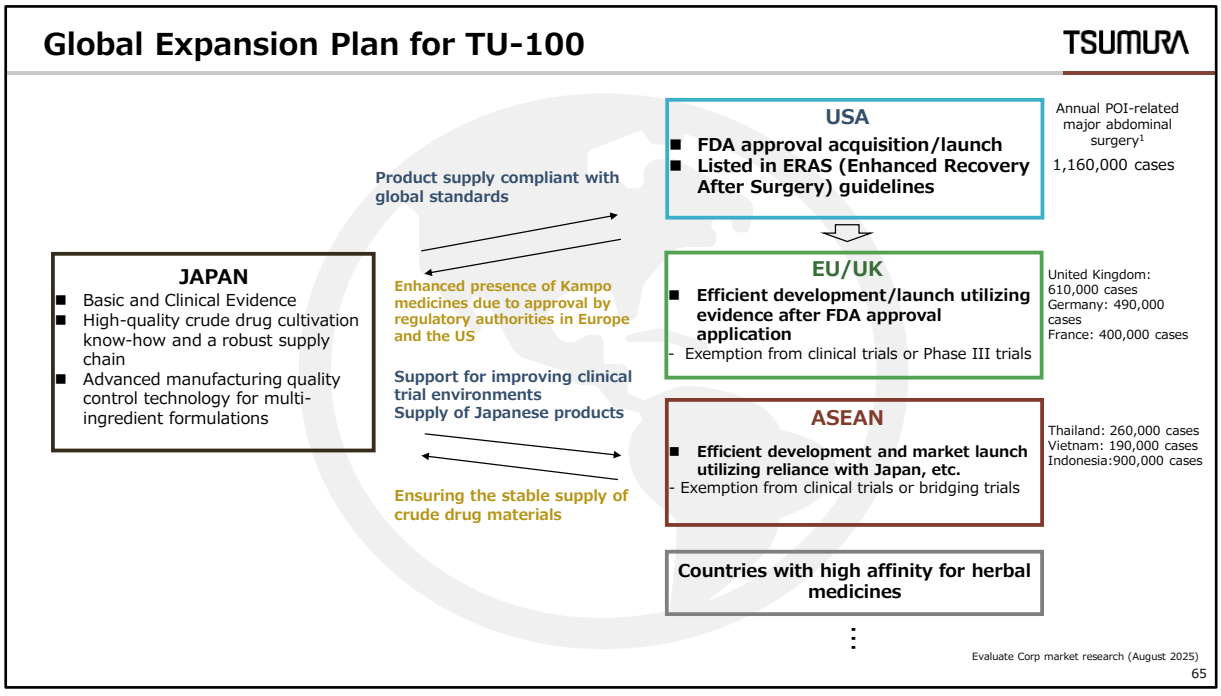


As an example, the domestic package insert of Daikenchuto contains the results of pharmacokinetics studies and information on clinical trials conducted in the United States.
The survey on the frequency of side effects also started with Daikenchuto triggered by its development in the United States, and it is now applied to other Kampo products, helping to promote their appropriate use.



Leveraging the evidence and know-how obtained in the United States, we are also considering the possibility of overseas expansion in the future. POI is an unmet need even in Europe, which has a medical environment similar to that of the United States, and efficient development utilizing U.S. data is expected. In particular, there is a possibility of utilizing preferential regulatory review in the UK.

In the ASEAN region, demand for high-quality pharmaceuticals is increasing alongside economic development, and with a cultural background that deeply trusts traditional medicine, we believe there is a foundation for our products to be accepted.

Also, there are countries that can utilize data from the Japanese Pharmacopoeia, which is expected to create a favorable environment for promoting reliance locally. In addition, some of the crude drugs used in our products are procured from the ASEAN region, which we believe contributes not only to medical care but also to local communities through the cultivation of crude drug herbs.

And within Japan, we hope it will be a good opportunity for the doctors who support the launch in the United States to once again recognize the value of Kampo products acknowledged worldwide.

Global Trends in Traditional Medicine

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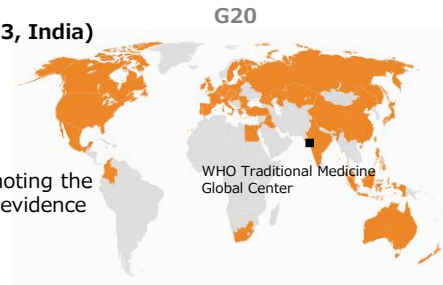
The First WHO Traditional Medicine Global Summit (August 2023, India)

- Co-hosted by WHO and the Indian government, held as part of the G20 Health Ministers' Meeting
- The Summit outcome document "Gujarat Declaration" adopted

Guidelines for reevaluating the value of traditional medicine, promoting the policy formation and international cooperation based on scientific evidence



Our Strengths are created from
Extensive clinical experience of Kampo product in Japan, Activities aimed at obtaining US FDA approval for TU-100, and Activities through cooperation in the development of traditional Chinese medicine

- **Abundant basic and clinical evidence**
- **Know-how of cultivating high-quality crude drugs and robust supply chains**
- **Advanced manufacturing quality control technology for multicomponent formulations**

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The concept for the overseas expansion of TU-100 aligns with the direction of WHO's initiative to re-evaluate the value of traditional medicine.
At the 1st WHO Traditional Medicine Global Summit held in India in 2023, the "Gujarat Declaration" was adopted, which provided guidelines for re-evaluating the value of traditional medicine, promoting policy-making based on scientific evidence, and fostering international cooperation. Since this summit was held jointly with the G20 Health Ministers' Meeting, it became an important venue to draw political commitment.

In terms of building scientific evidence, it is expected that countries with many achievements, such as China and Japan, will demonstrate leadership. Our company has accumulated a wealth of know-how not only through development in the United States but also through extensive practical clinical use in Japan and activities cooperating in the development of traditional Chinese medicine as part of our China business. We aim to share these strengths globally and contribute to providing the best medical care by integrating traditional medicine and Western medicine.

Next, following the TU-100 development in the United States, we will talk on initiatives in Europe and the ASEAN regions.

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Research and development activities for globalization
Initiatives in Europe and ASEAN regions

Head of International Pharmaceutical Research Department
Hiroshi Degami

THE BEST OF NATURE AND SCIENCE

I'm Degami from the International Pharmaceutical Research Department. I will explain our initiatives in the Europe and ASEAN regions.

Investigator-initiated Clinical Research of Rikkunshito for Functional Dyspepsia (FD) Treatment

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Objective of this Study
Strengthening evidence for domestic doctors through clinical research in Europe (Belgium)
(Inclusion in clinical practice guidelines)

Name of study: Placebo-controlled, randomized, double-blind trial to evaluate efficacy and safety for upper gastrointestinal symptoms in FD patients

Principal Investigator: Professor Jan Tack, KU Leuven, Kingdom of Belgium

- **A world-leading expert in the diagnosis and research of FD.**
- **Chairman of the ROME criteria development organization.**
- **Highly values the potential of Liu Jun Zi Tang as a treatment for FD.**

*ROME Criteria: International Diagnostic Criteria for Functional Gastrointestinal Disorders

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This study is investigator-initiated clinical research on the effectiveness of Rikkushinto for functional dyspepsia, or FD for short. By promoting this study, we believe it will also contribute to strengthening the evidence in the guidelines.

Professor Jan Tack of KU Leuven, a global leader in the area of FD treatment and research and serves as the General Manager of the organization that established the ROME criteria, which are the global diagnostic standards for functional gastrointestinal disorders, is leading the study.
The trial is a placebo-controlled, double-blind study of Rikkunshito in patients with functional gastrointestinal disorders, specifically functional dyspepsia (FD), conducted at KU Leuven.
This study was realized based on Professor Tack's high evaluation of the usefulness of Rikkunshito in the treatment of FD.

What is Functional Dyspepsia (FD)?

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Definition (From Rome IV, revised in 2016)
Diseases presenting abdominal symptoms mainly centered around the epigastric area, such as epigastric pain or stomach heaviness, which cause patients to feel chronic discomfort, despite the absence of organic, systemic, or metabolic diseases as causes

Prevalence (from the Gastrointestinal Functional Disease Guidelines 2021)

- 11-17% in Japan (health checkup receivers)
- Corresponding to 45-53% of hospital visitors complaining upper gastrointestinal symptoms in Japan
- **Estimated that one in ten Japanese people are affected.**
- Reported prevalence overseas is 11-23% in Europe and 15% in the United States.

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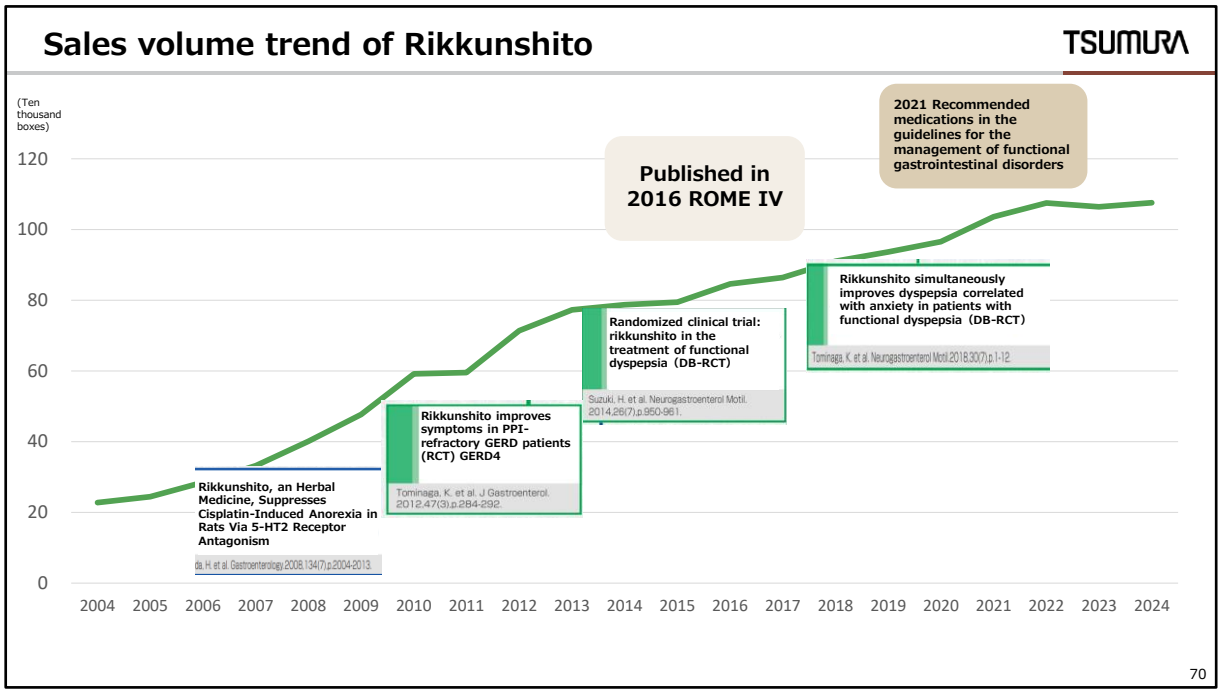
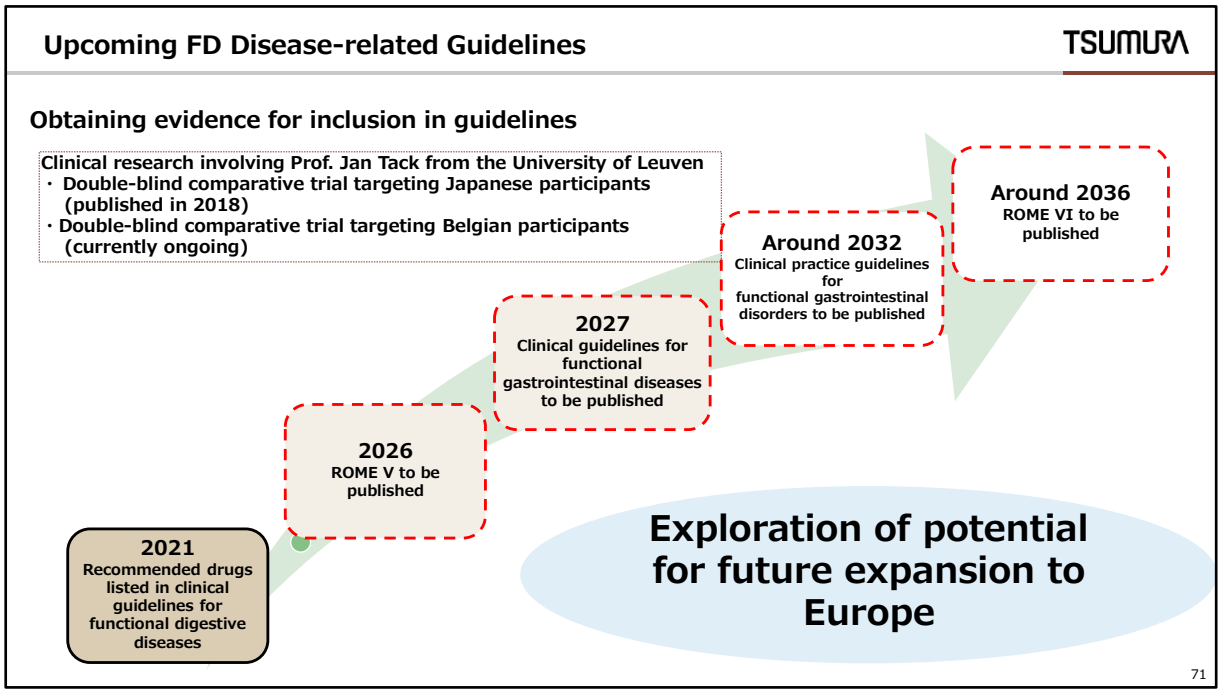
FD is a condition characterized by chronic abdominal symptoms centered around the epigastrium, such as epigastric pain and stomach discomfort, despite the absence of organic, systemic, or metabolic diseases.

The prevalence in Japan is between 11% and 17%, meaning that more than one in ten people are affected. In overseas regions, the prevalence is reported to be approximately 10–20% in Europe and about 15% in the United States. Because the causes and manifestations of symptoms vary from patient to patient, effective treatment tailored to the individual pathologies have not yet been adequately established. Therefore, FD is considered a disease with high unmet medical needs globally.
Especially in Europe, concerns about the safety of long-term use of proton pump inhibitors, which are used to treat functional dyspepsia (FD), have been growing, and the number of doctors expecting effectiveness of Rikkunshito is increasing.



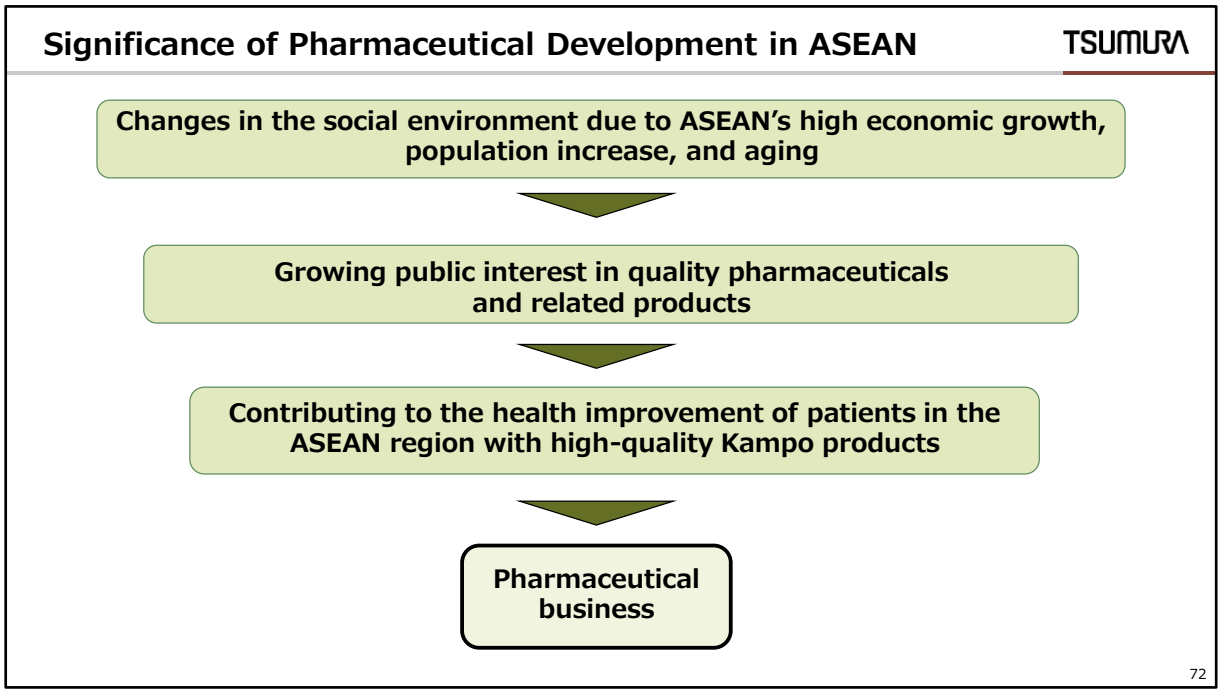
Next, this is a graph showing the trend in the sales volume of Rikkunshito. Rikkunshito began to be promoted as one of the drug-fostering program formulations in 2004, and as a result of focused efforts, its sales volume increased more than fivefold over about 20 years, from 200,000 units to over 1 million units. In the background, it is believed that contributions from basic and clinical research have helped build the evidence.

Furthermore, evidence based on clinical research has led to its inclusion in the Rome diagnostic criteria and the guidelines for functional gastrointestinal disorders, which is thought to have contributed to the increased sales.



This is the upcoming publication schedule for the FD disease-related guidelines. Inclusions in Treatment guidelines require clinical evidence as bases. The clinical research conducted at the KU Leuven that was mentioned earlier is expected to contribute to future inclusions in Treatment guidelines.

We will also consider future development in Europe based on the results of the trial.



Next, I will explain the pharmaceutical development in ASEAN.

In the ASEAN region, while population growth and economic development continue, the social environment is undergoing significant changes due to aging. Amid these changes, people's interest in high-quality pharmaceuticals is increasing. We aim to contribute to the health of patients in the ASEAN region through high-quality Kampo products.

Changes in regulatory environment in ASEAN

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- In ASEAN countries, the **“Reliance System”** utilizing Japan’s review results has been introduced.
- **The Simplification** of the approval process for pharmaceuticals and medical devices is being **promoted**.
- **PMDA Asia Office** has been established.
- The penetration of Japanese pharmaceutical regulations and **the use of simplified review systems are being promoted** in ASEAN countries.

Japan as a reference country in major countries and regions

Pharmaceuticals

Country	System
Thailand	・Acceleration of pharmaceutical review (2015) ・Reference to the Japanese Pharmacopoeia (2019)
Indonesia	・Acceleration of pharmaceutical review (2000)
Malaysia	・Acceleration of additional review for adaptation (2004) ・Acceleration of pharmaceutical review (2024)
Vietnam	・Reference to the Japanese Pharmacopoeia (2018)
Philippines	・Acceleration of pharmaceutical review (2022)

The approval/certification system for medical devices in Japan is recommended by the WHO as a "Global model framework" (a regulatory system to be referenced).

*Excerpted from PMDA "List of major countries and regions for which Japan is a reference country system, etc."

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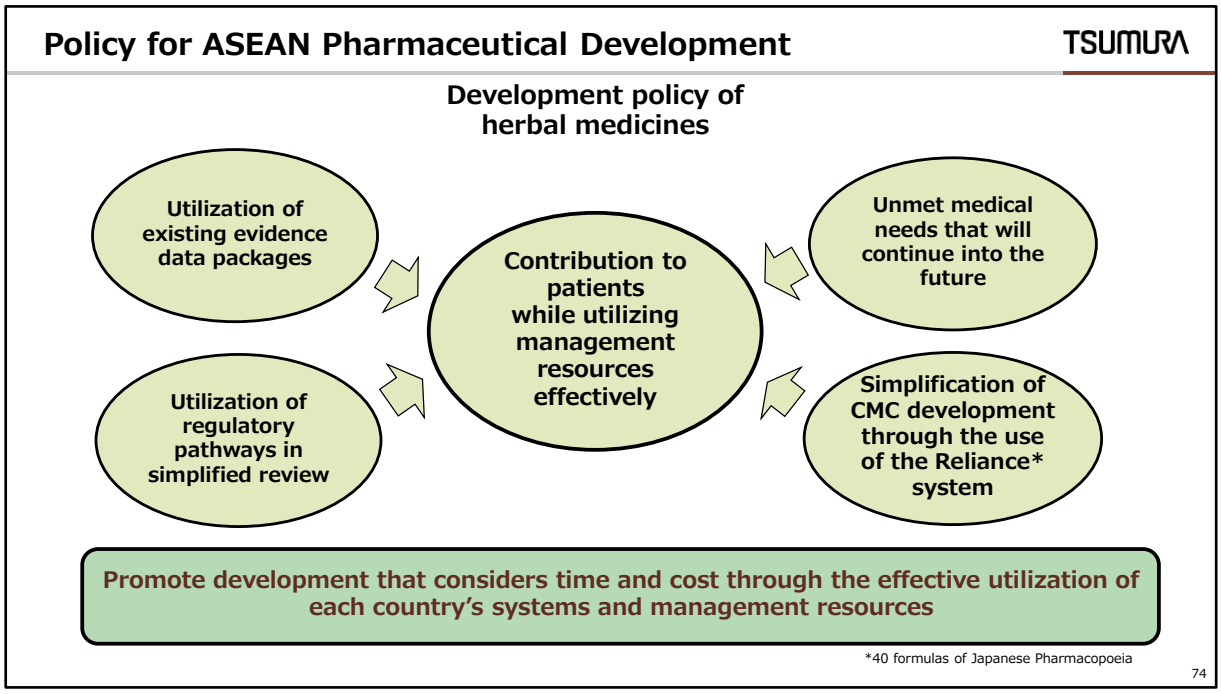
In the ASEAN countries, the "Reliance System" utilizing Japan's examination results has been introduced, simplifying the approval process for pharmaceuticals and medical devices.

Japan is also promoting the penetration of Japanese pharmaceutical regulations and the facilitation of the simplified review system through the establishment of the PMDA Asia Office and discussions with regulatory authorities in ASEAN countries.

As shown in the table on the right, Japan is a reference country under the system in five countries, including Thailand.



In this situation, the pharmaceutical development policy in ASEAN aims to address unmet medical needs that are difficult to meet with Western medicines by utilizing each country's reliance system and simplified review pathways.

By making full use of the evidence packages cultivated in Japan, we proceed with development in a way that avoids large-scale investments such as capital expenditures, effectively utilizes management resources, and reduces time and cost.

Challenge Towards “Global Expansion”

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The desired image
Realizing healthcare that leaves no one behind by improving global access to high-quality Kampo with scientific evidence

Disease areas where herbal medicines can exert specific effects in the fields where Western drug treatment is less effective.

- Contribution to unmet medical needs through herbal medicines -

Europe and the United States
Large markets where the drugs can be evaluated as pharmaceutical products of global quality

Our strengths
- Basic and clinical evidence
- High-quality crude drug cultivation expertise and a robust supply chain
- Advanced manufacturing quality control technology for multi-component formulations

ASEAN
Growing markets highly compatible with herbal medicines having growing demands for high-quality pharmaceutical products

Countries and regions with receptiveness to herbal medicines

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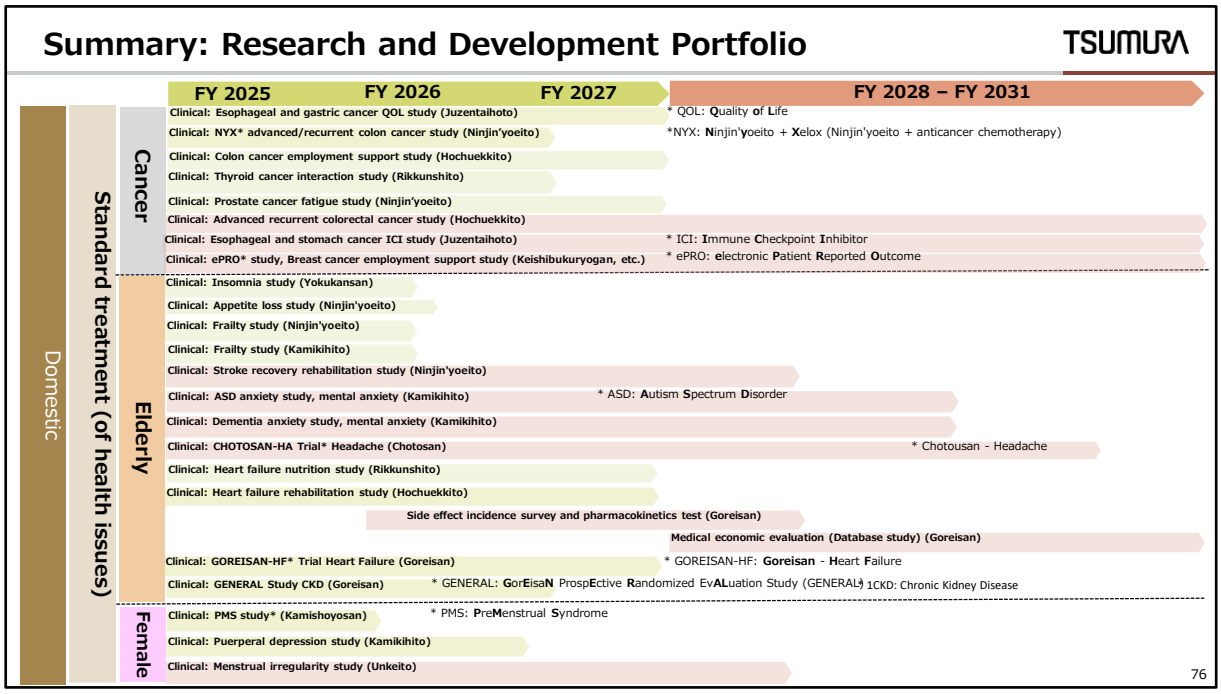
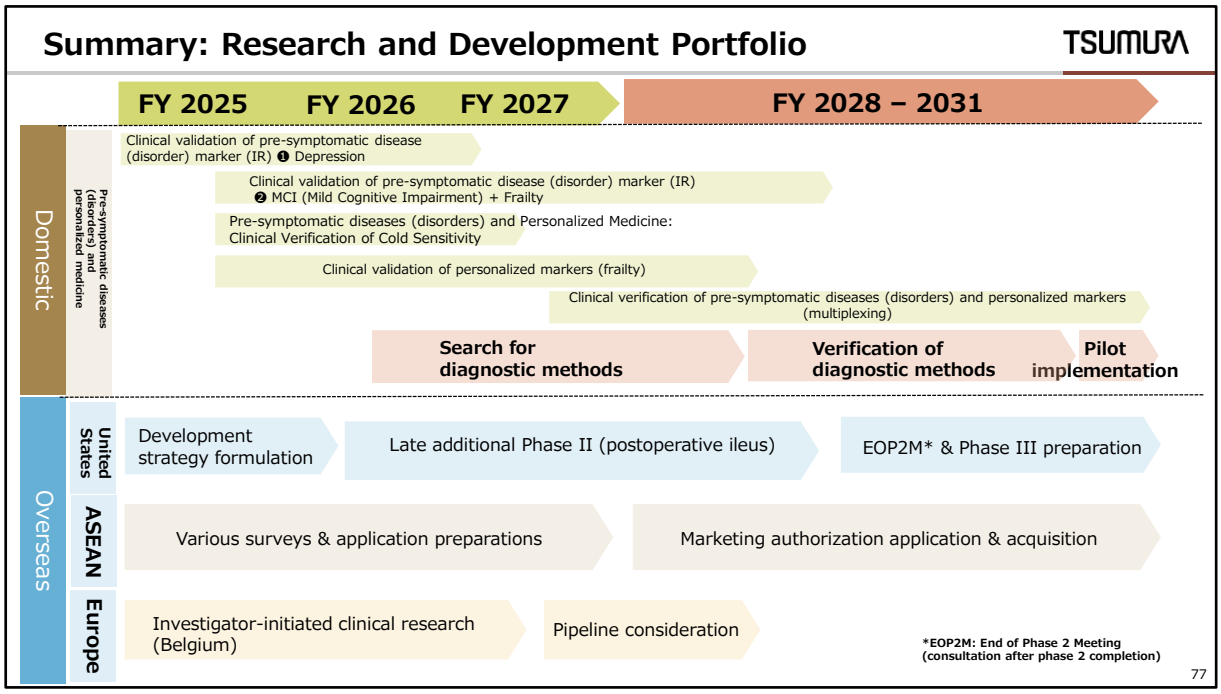
That concludes the explanation of the specific initiatives.
We strive to realize healthcare that leaves no one behind by improving global access to high-quality herbal preparations with scientific evidence.



Here is a summary of the research and development portfolio.

This is the research and development portfolio focusing on the standardization of Kampo treatment.
In addition to the research on Goreisan for the elderly field we explained today, we aim for further standardization of Kampo treatment in the fields of cancer and women's health, as you can see.



Next, the research and development portfolios related to pre-symptomatic diseases and disorders, personalized medicine, and international aspects in the US, ASEAN, and Europe are as shown.

We are challenging ourselves to realize "Tsumura Vision 'Cho-WA' 2031" by expanding the standardization of Kampo treatment, evolving toward personalized Kampo treatment, and scientifically elucidating the field of pre-symptomatic diseases and disorders.
Leveraging our accumulated expertise, we will accelerate the global expansion of Kampo product formulations, which are multi-component medicines.

That concludes our presentation. Thank you very much.

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