FY 2023
R&D Meeting

December 12, 2023
Nippon Shinyaku Co., Ltd.

NIPPON SHINYAKU CO., LTD.

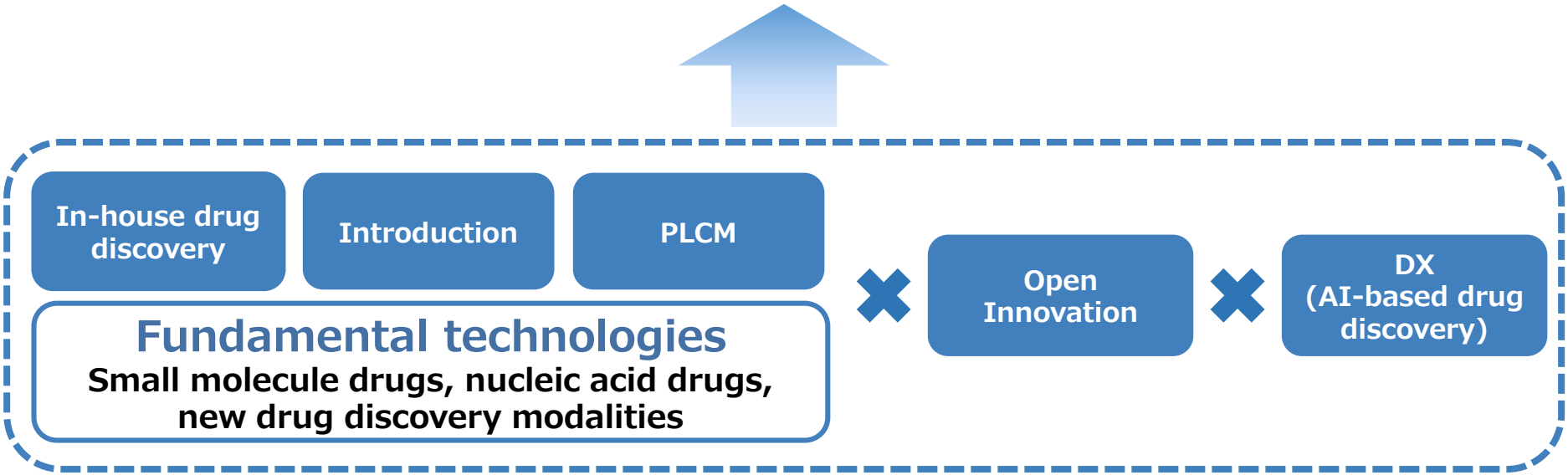
Introduction

NIPPON SHINYAKU CO., LTD.

R&D approach

Pursuing originality on a global scale

Providing the world with quality pharmaceuticals to address diseases with unmet treatment needs



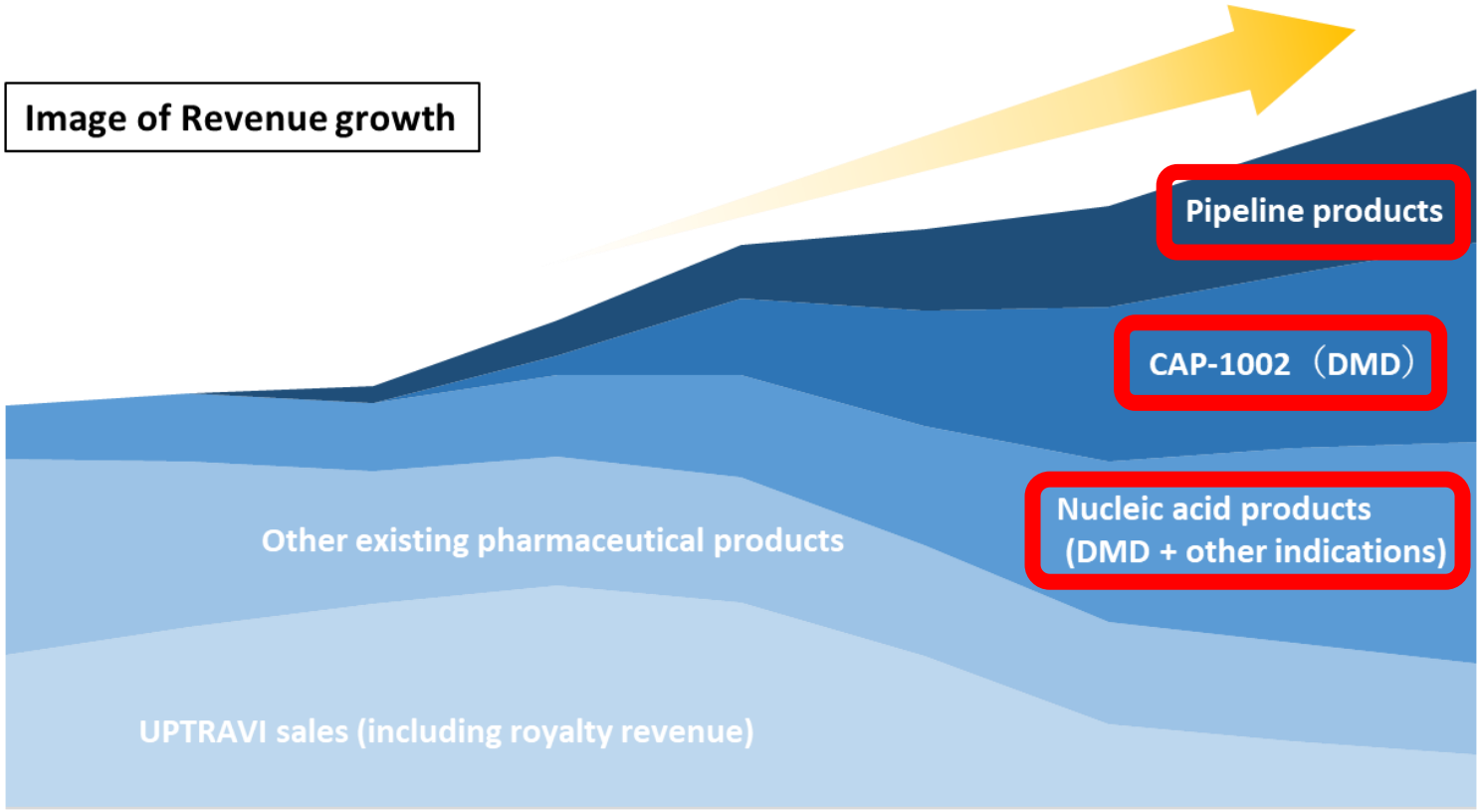
PLCM: Product life cycle management

<How to promote global expansion>

- Our own marketing: Disease areas where the number of patients is very small and the number of medical facilities to which we provide information is relatively limited
- Collaboration with partner companies: Disease areas where the estimated number of patients is above a certain level

Toward our sustainable growth

We will establish new growth drivers to overcome Uptravi's patent cliff and grow sustainably.



Other new products

- NS-87
- ZX008
- NS-018
- NS-580
- NS-229
- NS-401

etc.

In addition to nucleic acid drugs and a cell therapy for DMD, we believe that other new products will be driving force behind our sustainable growth.

R&D activities

NIPPON SHINYAKU CO., LTD.

Update of DMD pipelines

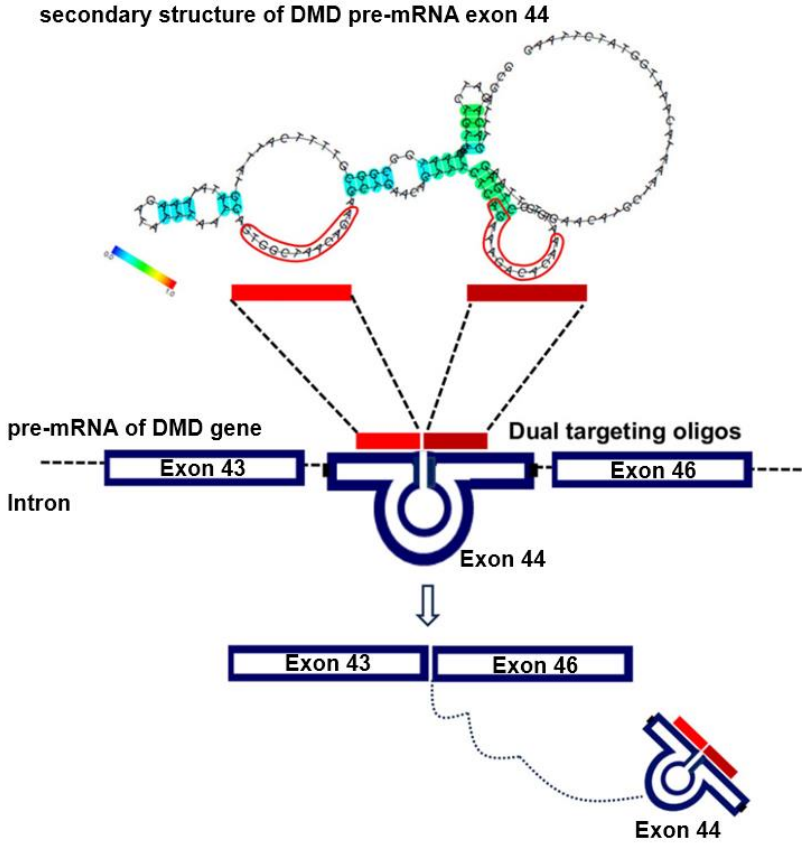
NIPPON SHINYAKU CO., LTD.

Progress of the DMD pipeline

Item	Target exon	Proportion of patients % of DMD	Schedule	Stage
				Research / Preclinical / Ph1 / Ph2 / Ph3 / Launch
NS-065/ NCNP-01	Exon 53	8%	Around the spring of FY2024 P3 data presentation	Global Ph3 / Launch (US, JP)
NS-089/ NCNP-02	Exon 44	6%	FPI: FY2023 LPO: FY2025	Preparation for Ph2 (US, JP)
NS-050/ NCNP-03	Exon 50	4%	FPI: FY2023 LPO: FY2026	Prep. for Ph1/2 (US, JP)
NS-051/ NCNP-04	Exon 51	13%	FPI: FY2023 LPO: TBD	
Exon 45 Skipping	Exon 45	8%	TBD	
Exon 55 Skipping	Exon 55	2%	TBD	
CAP-1002	-	-	Futility analysis End of 2023 Topline data End of 2024	
PPMO	TBD	TBD	TBD	
Gene therapy	-	-	TBD	

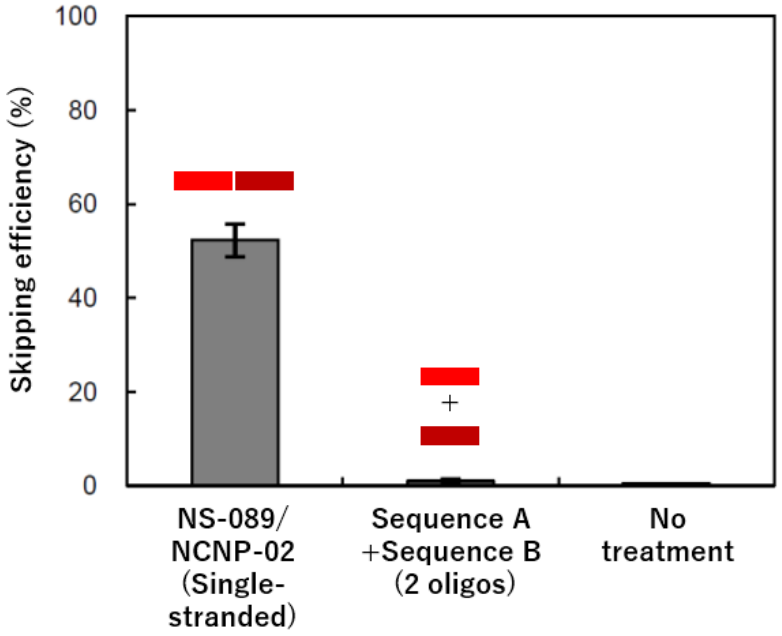
FPI: First Patient In, LPO: Last Patient Out

NS-089/NCNP-02 exon 44 skipping therapy



Schematic diagram of the mechanism of action of NS-089/NCNP-02

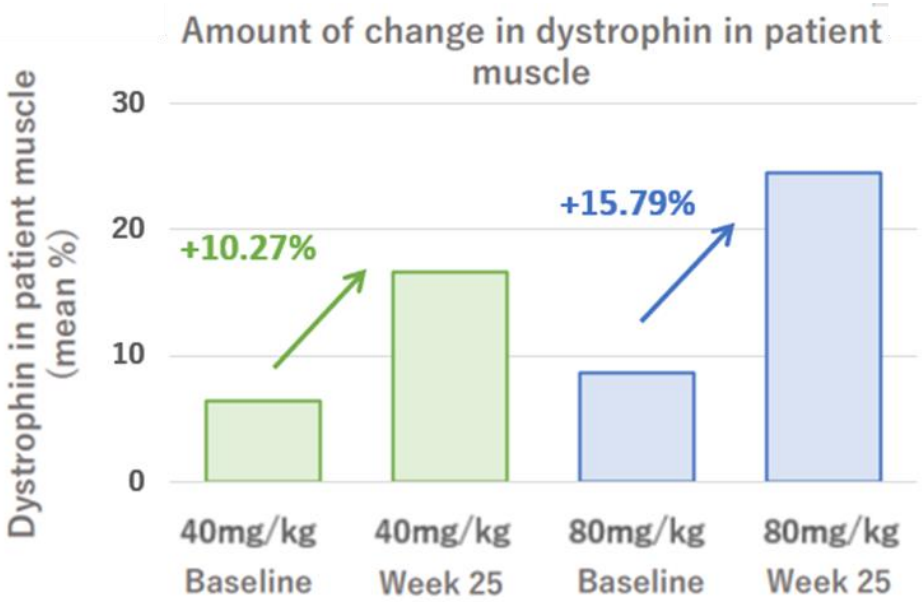
Induce exon 44 skips with NS-089/NCNP-02 in patients with DMD with exon 45 deletion and restore slightly shortened dystrophin expression



- **New highly active sequence search method that is a patent application technology**
- **World's first sequence-linked dual-targeting antisense nucleic acid drug targeting two distant nucleotide sequences**
- **Induction of dystrophin protein expression in muscle cells derived from DMD patients**

Paper Exon 44 skipping in Duchenne muscular dystrophy: NS-089/NCNP-02, a dual-targeting antisense oligonucleotide
Author Naoki Watanabe, Yuichiro Tone, Tetsuya Nagata, Satoru Masuda, Takashi Saito, Norio Motohashi, Kazuchika Takagaki, Yoshitsugu Aoki and Shin'ichi Takeda
Journal Molecular Therapy Nucleic Acids

Investigator-initiated trial of NS-089/NCNP-02
Dystrophin protein expression levels



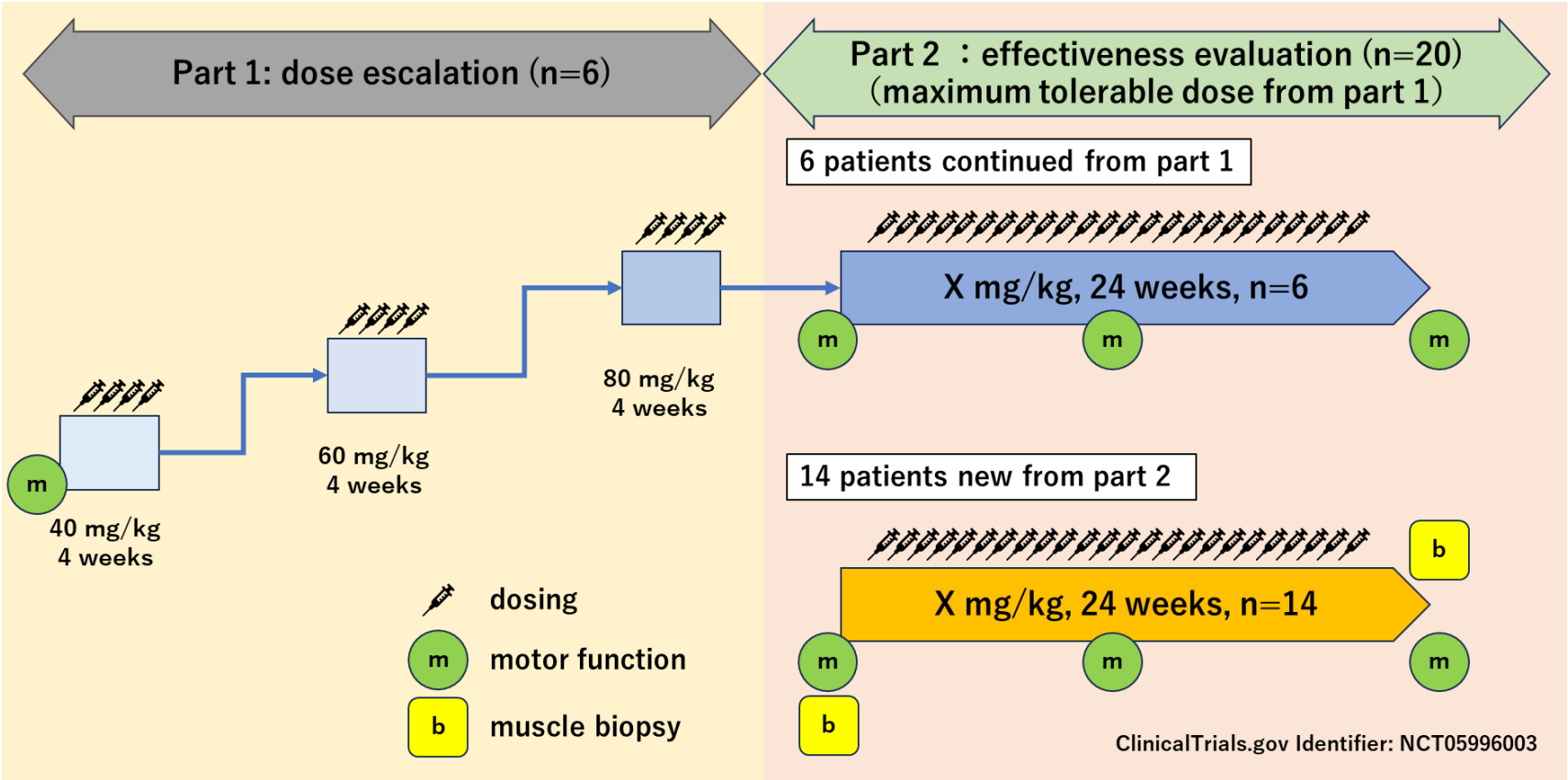
	Dystrophin protein % change (SD)
40mg/kg(n=3)	10.27 (1.88)
80mg/kg(n=3)	15.79 (6.44)
Mean (%)	13.03 (5.21)

ClinicalTrials.gov identifier NCT4129294

- In 6 patients treated (24 weeks), significant increases in exon skipping efficiency and dystrophin protein were observed. In addition, safety and tolerability were good.
- In Part 2 (dose-finding period), there was a tendency to maintain and improve motor function.
- Since this study had a small number of subjects (n=6) and did not include a placebo control group, the efficacy of this drug, including the maintenance of motor function, should be further investigated.

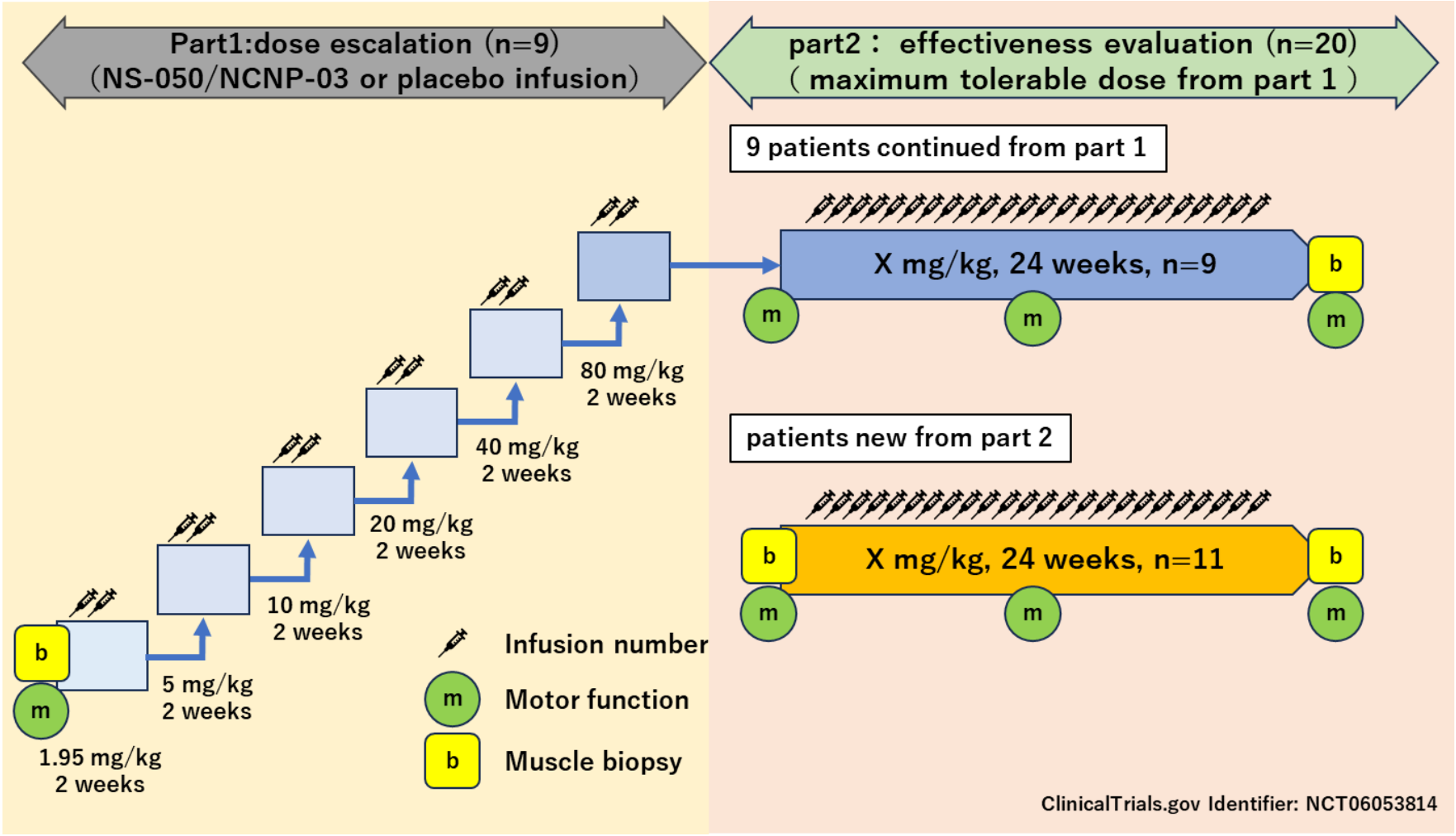
NS-089/NCNP-02 exon 44 skipping therapy

Orphan Drug, Rare Pediatric Disease, and Breakthrough Therapy designations from the U.S. FDA; currently preparing for global P2 study



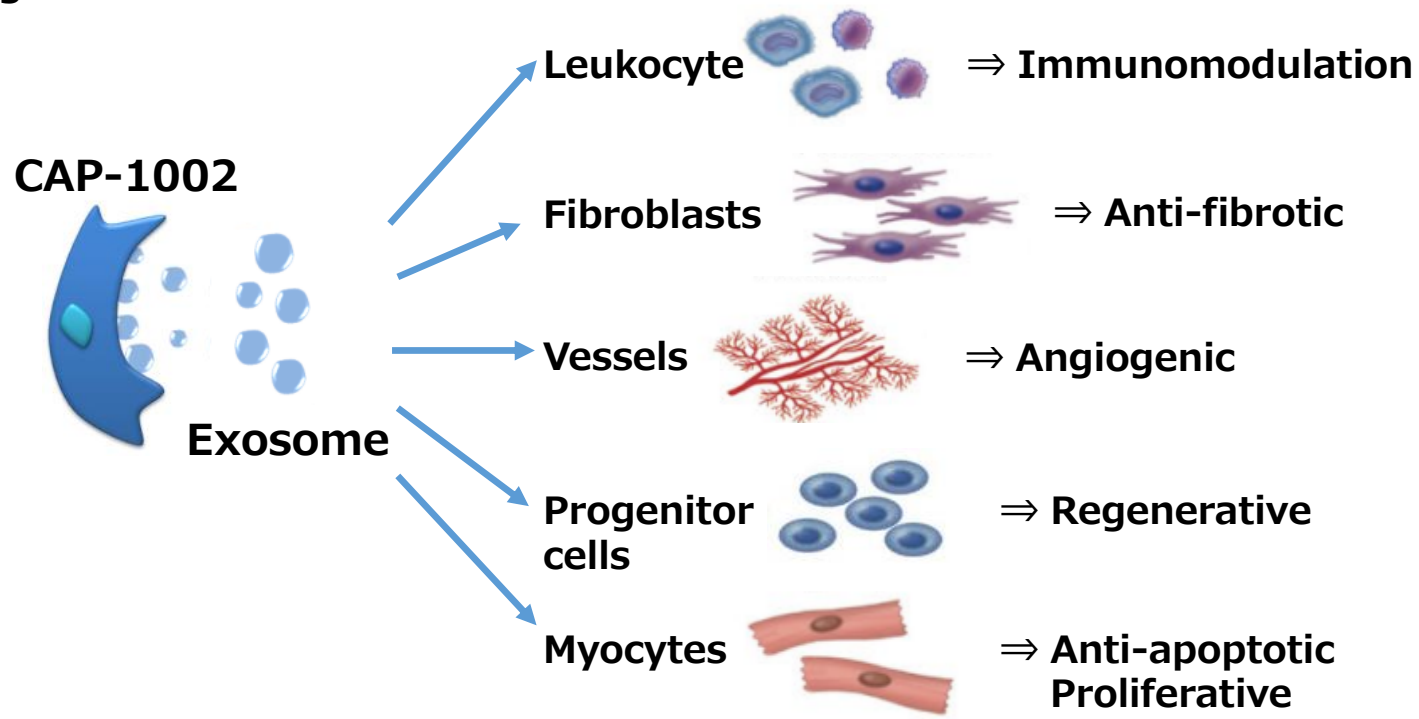
NS-050/NCNP-03 exon 50 skipping therapy

FDA and PMDA have agreed to the planned Phase Ⅰ/Ⅱ study of NS-050/NCNP-03. Global Phase 1/2 study is in preparation.

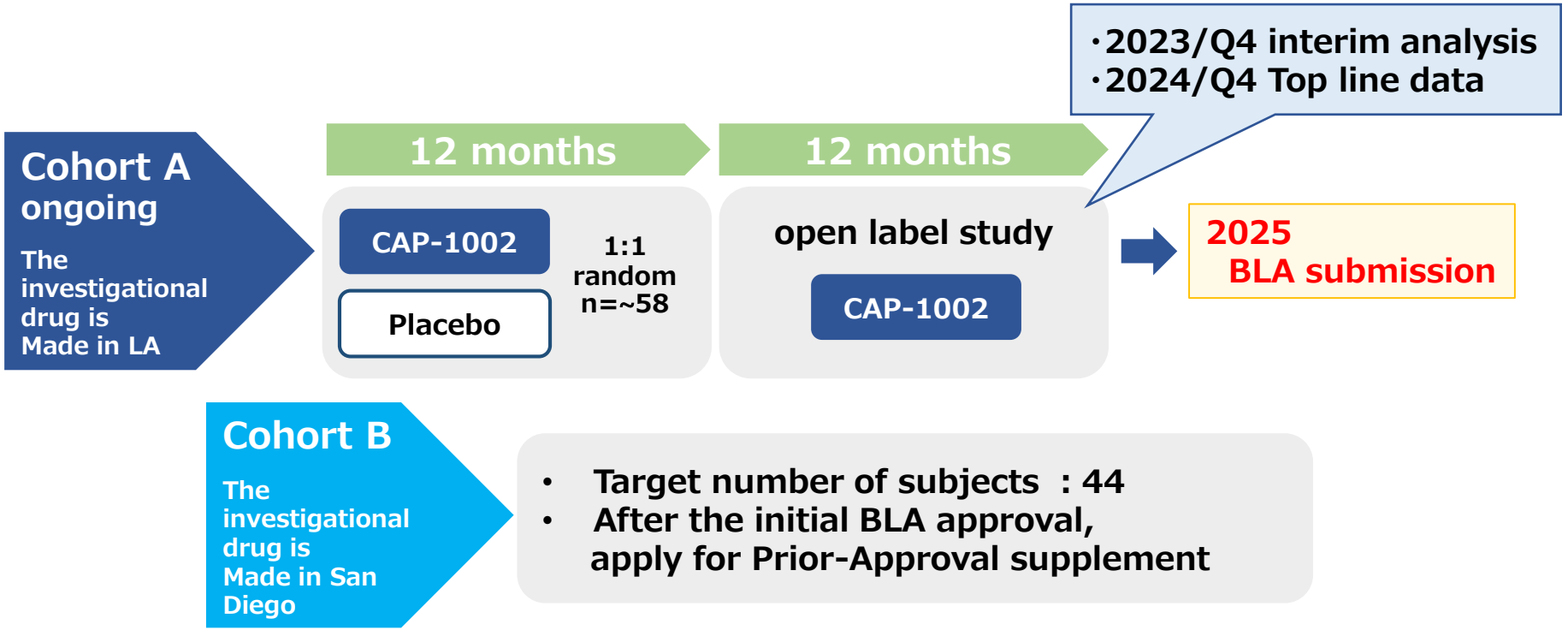


CAP-1002 Cell Therapy

- Cardiosphere-derived cell therapeutic.
- Exosomes (extracellular vesicles) released from this drug are expected to reduce oxidative stress, inflammation, fibrosis, and increase cellular energy and myocyte generation, resulting in slowing the decline of skeletal muscle and cardiac function in DMD.
- In the P2 study (HOPE-2 study), efficacy on upper limb function (PUL) and cardiac function was confirmed, and in the OLE study, it was confirmed that the effects lasted for a long time.
- Currently, the phase 3 trial (HOPE-3) is underway. Protocol amendment was submitted in August 2023.



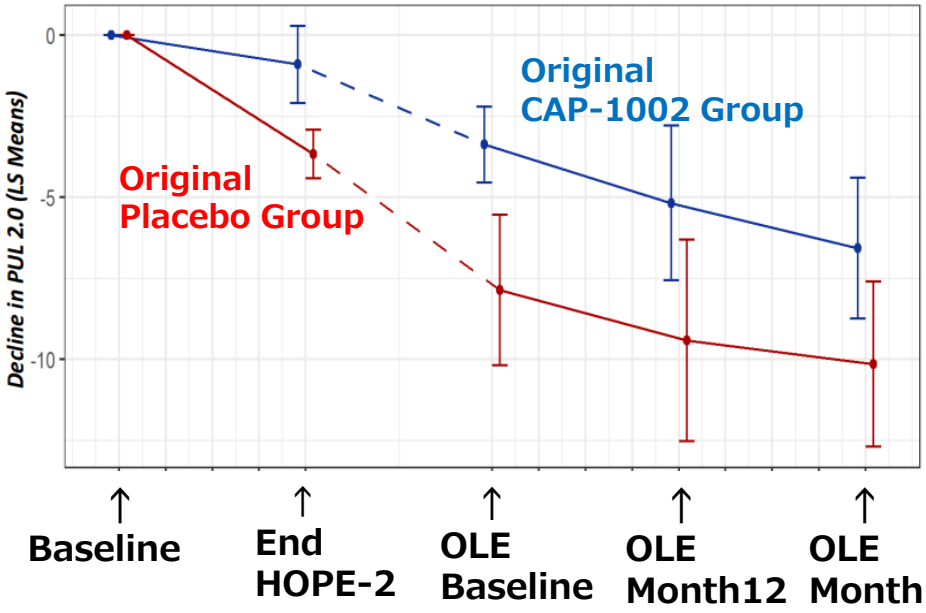
CAP-1002 Amendment of the protocol for the HOPE-3 trial

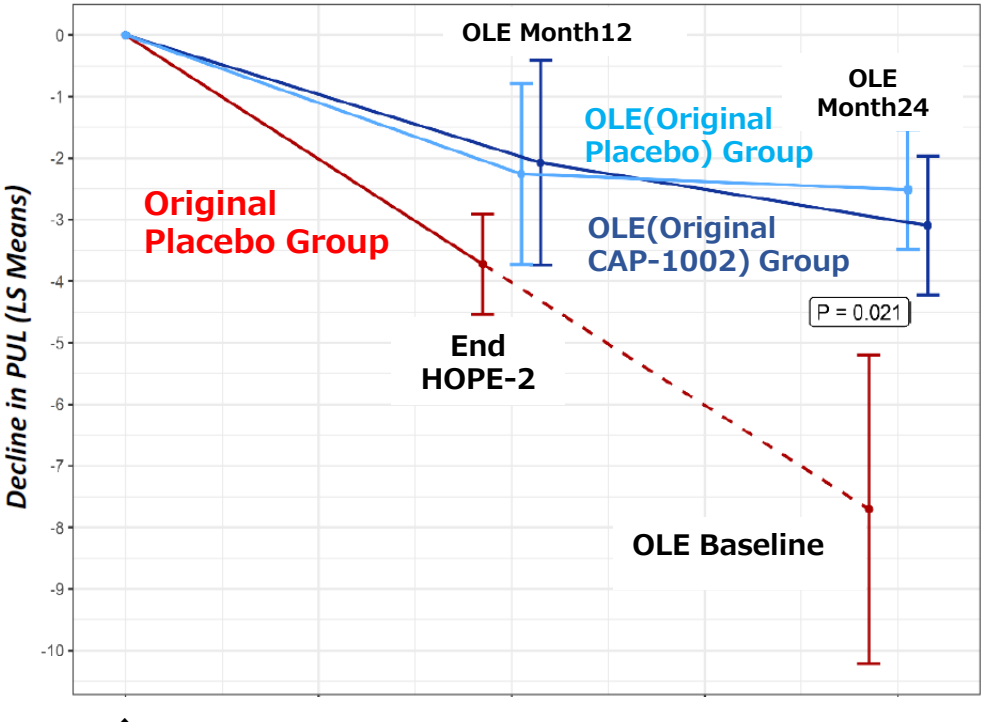


- The investigational product is being manufactured at a facility in Los Angeles, but in preparation for its commercial release, Capricor established an additional facility in San Diego.
- The HOPE-3 trial was divided into two cohorts: Cohort A (manufactured in Los Angeles) and Cohort B (manufactured in San Diego).
- The trial design and schedule until the Biological License Application (BLA) submission were agreed upon in a Type B meeting with the FDA.

CAP-1002 HOPE-2-OLE study

HOPE-2 study	Gap Phase	Open Label (OLE) Phase
CAP-1002 vs. Placebo	Off treatment	All patients received CAP-1002





Modified from WMS, October 2023

The linear mixed model uses all available data.

Administration period
- HOPE-2 study: CAP-1002 or placebo administered 4 times every 3 months
- Gap Phase : untreated period
- OLE Phase: CAP-1002 administered every 3 months for 2 years

- In the HOPE-2-OLE study, the average decrease in PUL 2.0 after 24 months of treatment with CAP-1002 was 2.8 points, while an average decrease of 7.7 points was observed in placebo group untreated for 24 months.
- Patients who received CAP-1002 treatment showed 64% reduction in disease progression.

CAP-1002 Press release for Interim Futility Analysis

December 11, 2023

Capricor Therapeutics™

Capricor Therapeutics Announces Continuation of Phase 3 HOPE-3 Trial of CAP-1002 in Duchenne Muscular Dystrophy Based on Completion of Interim Futility Analysis

--Favorable Interim Futility Analysis Results--

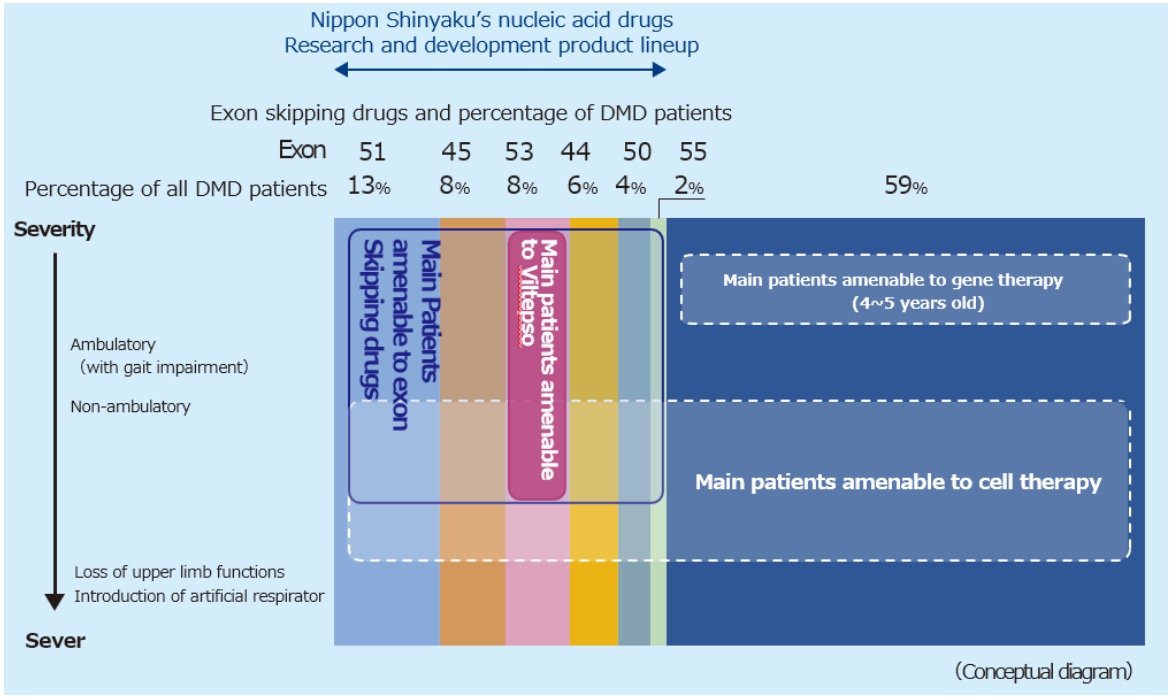
--Successful Completion Triggers First Milestone Payment Under U.S. Agreement with Nippon Shinyaku--

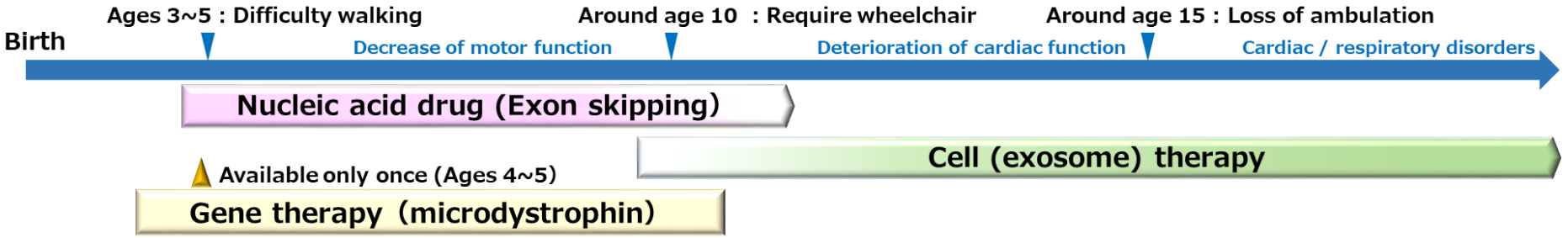
--HOPE-3 (Cohort A) Enrollment Complete; Topline Data Expected in the Fourth Quarter of 2024; Cohort B Enrollment Initiated--

--Company Plans to Request a Meeting with FDA in the First Quarter of 2024 to Further Discuss Opportunities for Expedited Approval Pathways--

excerpt from press release of Capricor Therapeutics, 11th Decemnber 2023

Positioning in the three DMD treatments





We are working to expand treatment options with various modalities to ensure that more patients receive the best treatment depending on the genetic background and stage of the disease.

Pipelines other than DMD

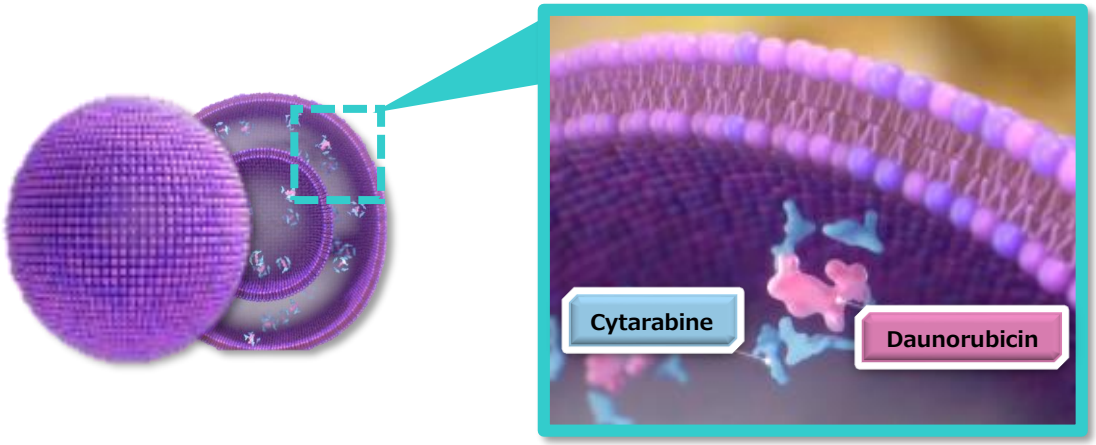
NIPPON SHINYAKU CO., LTD.

R&D pipeline (other than DMD)

Stage	Code No. (Generic name)	Therapeutic field	Indications	Origin	Development	Schedule
NDA filing	NS-87 (daunorubicin / cytarabine)	hematologic malignancies	high-risk acute myeloid leukemia	Licensed - in from Jazz Pharmaceuticals plc	Nippon Shinyaku	FY2023 application FY2023 expected to be approved
NDA filing	ZX008 (fenfluramine hydrochloride)	intractable disease・orphan disease	Lennox-Gastaut syndrome	Sales Alliance: UCB (Former Zogenix Corporation)	Distribution partnership: UCB S.A. (former : Zogenix, Inc.)	FY2023 application FY2023 expected to be approved
P III	ZX008 (fenfluramine hydrochloride)	intractable disease・orphan disease	CDKL5 deficiency disorder	Sales Alliance: UCB (Former Zogenix Corporation)	Distribution partnership: UCB S.A. (former : Zogenix, Inc.)	FY2025 Completion of the study
P III	GA101 (obinutuzumab)	intractable disease・orphan disease	lupus nephritis	Licensed - in from Chugai Pharmaceutical Co., Ltd.	Co - development: Chugai Pharmaceutical Co., Ltd.	Expansion of indications: from 2026 onward
P III	GA101 (obinutuzumab)	intractable disease・orphan disease	pediatric nephrotic syndrome	Licensed - in from Chugai Pharmaceutical Co., Ltd.	Co - development: Chugai Pharmaceutical Co., Ltd.	Expansion of indications: from 2026 onward
P III	GA101 (obinutuzumab)	intractable disease・orphan disease	extra renal lupus	Licensed - in from Chugai Pharmaceutical Co., Ltd.	Co - development: Chugai Pharmaceutical Co., Ltd.	Expansion of indications: from 2026 onward
P II	NS-018 (ilginatinib)	hematologic malignancies	myelofibrosis	Nippon Shinyaku	Nippon Shinyaku	LPO: FY2024 (TBD)
P II	NS-304 (selexipag)	cardiovascular	arteriosclerosis obliterans	Nippon Shinyaku	Nippon Shinyaku	FY2024 completion of the study
P II	NS-304 (selexipag)	intractable disease・orphan disease	pediatric pulmonary arterial hypertension	Nippon Shinyaku	Co - development: Janssen Pharmaceutical K.K.	FY2025 completion of the study
P II	NS-580	gynecology	endometriosis	Nippon Shinyaku	Nippon Shinyaku	FY2023 completion of the study
P II	NS-580	urological diseases	chronic prostatitis/chronic pelvic pain syndrome	Nippon Shinyaku	Nippon Shinyaku	FY2024 completion of the study
Preparation for P II	NS-229	intractable disease・orphan disease	Eosinophilic granulomatosis with polyangiitis	Nippon Shinyaku	Nippon Shinyaku	FY2025 completion of the study
P I / II	NS-401 (tagraxofusp)	hematologic malignancies	blastic plasmacytoid dendritic cell neoplasm	Licensed - in from The Menarini Group	Nippon Shinyaku	FY2026 completion of the study
P I	NS-917 (radgocitabine)	hematologic malignancies	relapsed/refractory acute myeloid leukemia	Licensed - in from Delta-Fly Pharma, Inc.	Nippon Shinyaku	FY2025 completion of the study
P I	NS-161	inflammatory diseases	inflammatory diseases	Nippon Shinyaku	Nippon Shinyaku	FY2023 completion of the study
P I	NS-025	urological diseases	urological diseases	Nippon Shinyaku	Nippon Shinyaku	FY2023 completion of the study
P I	NS-863	cardiovascular	cardiovascular diseases	Nippon Shinyaku	Nippon Shinyaku	FY2024 completion of the study

NS-87　high-risk Acute Myeloid Leukemia treatment

Planned trade name	VYXEOS
Active ingredient	Cytarabine and daunorubicin
Composition	• Containing cytarabine 100 mg and daunorubicin 44 mg in 1 vial (molar ratio of cytarabine to daunorubicin 5:1) • Encapsulated in nanoscale dual-structured liposomes of diametric 100nm
NDA submission	June 2023



JAZZ HP Mechanism of Delivery
https://vyxeospro.com/mechanism-of-delivery

High-risk Acute Myeloid Leukemia

●high-risk Acute Myeloid Leukemia

Defined as therapy-related acute myeloid leukemia (tAML) or AML with myelodysplasia-related changes (AML-MRC)

●Patient group

Approximately half of all AML patients* can be high-risk AML, among which 7+3 therapy (cytarabine, anthracycline combination) is currently used primarily in intensive chemotherapy-indicated patients. NS-87 may be used to treat this patient-group.

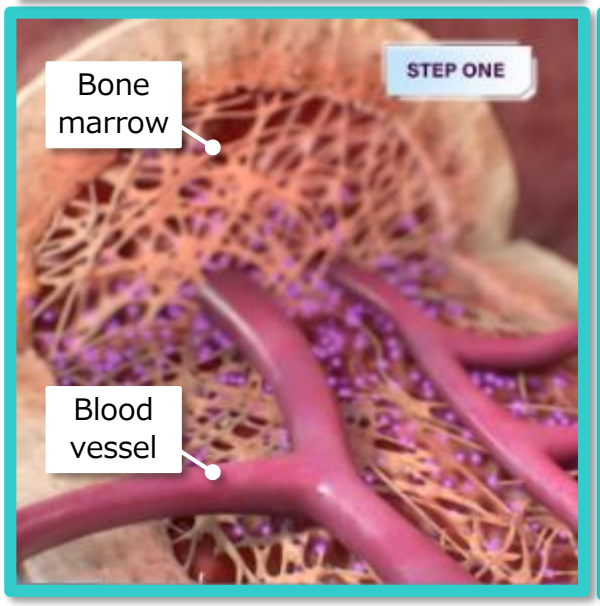
Overseas P3 study of NS-87 showed significant extension of overall survival compared with 7+3 therapy.

*There is no accurate statistics about the patients of AML. However, 14,000 people per year are diagnosed with leukemia. (Reference: Cancer Statistics)

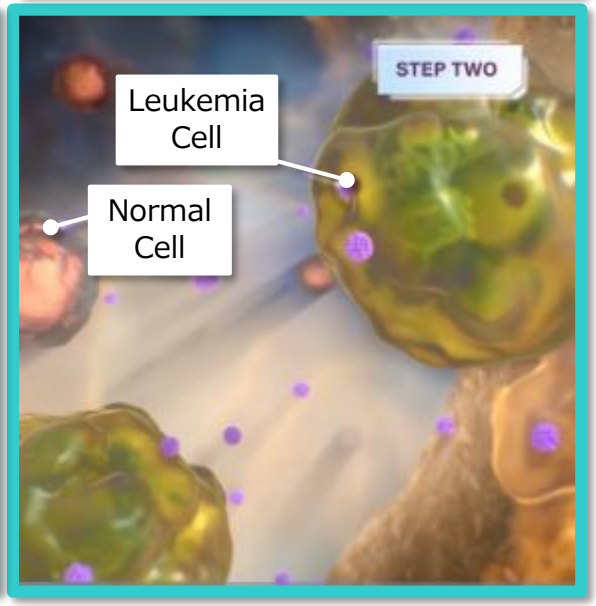
Characteristics of NS-87

- **Liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio**
- **It reaches the bone marrow as liposomes and remains for a long time.**
- **After the drug is taken up into leukemic cells in the bone-marrow, cytarabine and daunorubicin are released to exert their antitumor effects.**

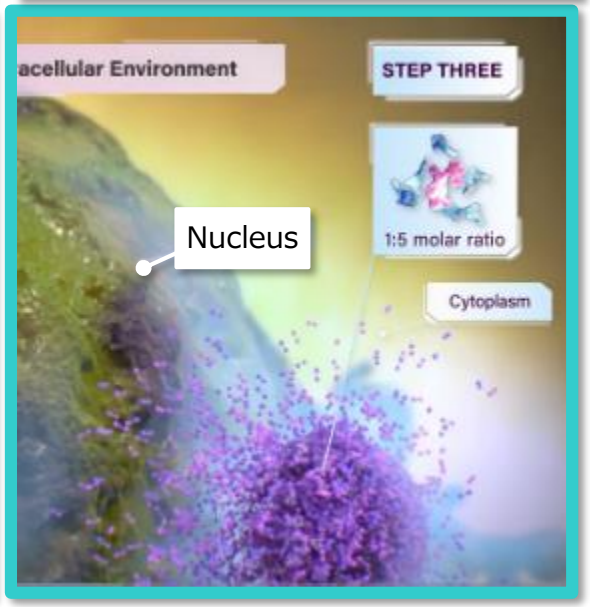
Reach and remain in the bone marrow



Uptake by leukemic cells

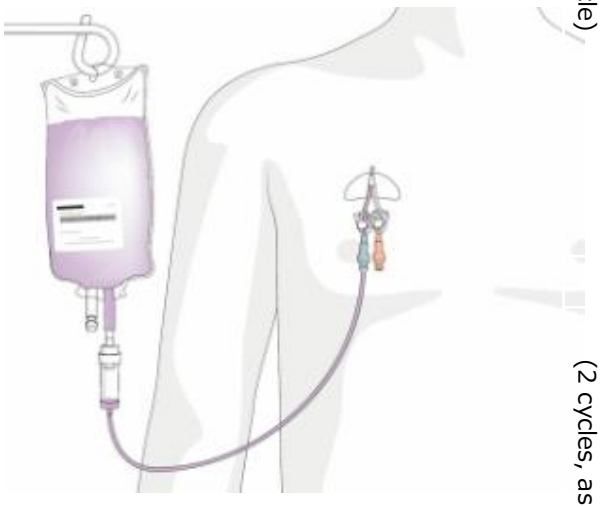


Release of active ingredients in cells



JAZZ-HP Mechanism of Delivery
https://vyxeospro.com/mechanism-of-delivery

Time and duration of NS-87



JAZZ-HP VYXEOS preparation and administration
https://vyxeospro.com/dosing-ordering/preparation

NS-87 vs 7+3 therapy (overseas P3 study)

	NS-87		7+3 therapy (5+2)		
Induction therapy (1 cycle)	DAY 1	Intravenous administration for 90 minutes	DAY 1	7-day continuous intravenous infusion	15-minute infusion
			DAY 2		15-minute infusion
	DAY 3	Intravenous administration for 90 minutes	DAY 3		15-minute infusion
			DAY 4		
	DAY 5	Intravenous administration for 90 minutes	DAY 5		
			DAY 6		
			DAY 7		
Induction therapy (2 cycles, as needed)	DAY 1	Intravenous administration for 90 minutes	DAY 1	5 days	15-minute infusion
			DAY 2		15-minute infusion
	DAY 3	Intravenous administration for 90 minutes	DAY 3		
			DAY 4		
			DAY 5		
Postremission therapy (1-2 cycles)	DAY 1	Intravenous administration for 90 minutes	DAY 1	5 days	15-minute infusion
			DAY 2		15-minute infusion
	DAY 3	Intravenous administration for 90 minutes	DAY 3		
			DAY 4		
			DAY 5		

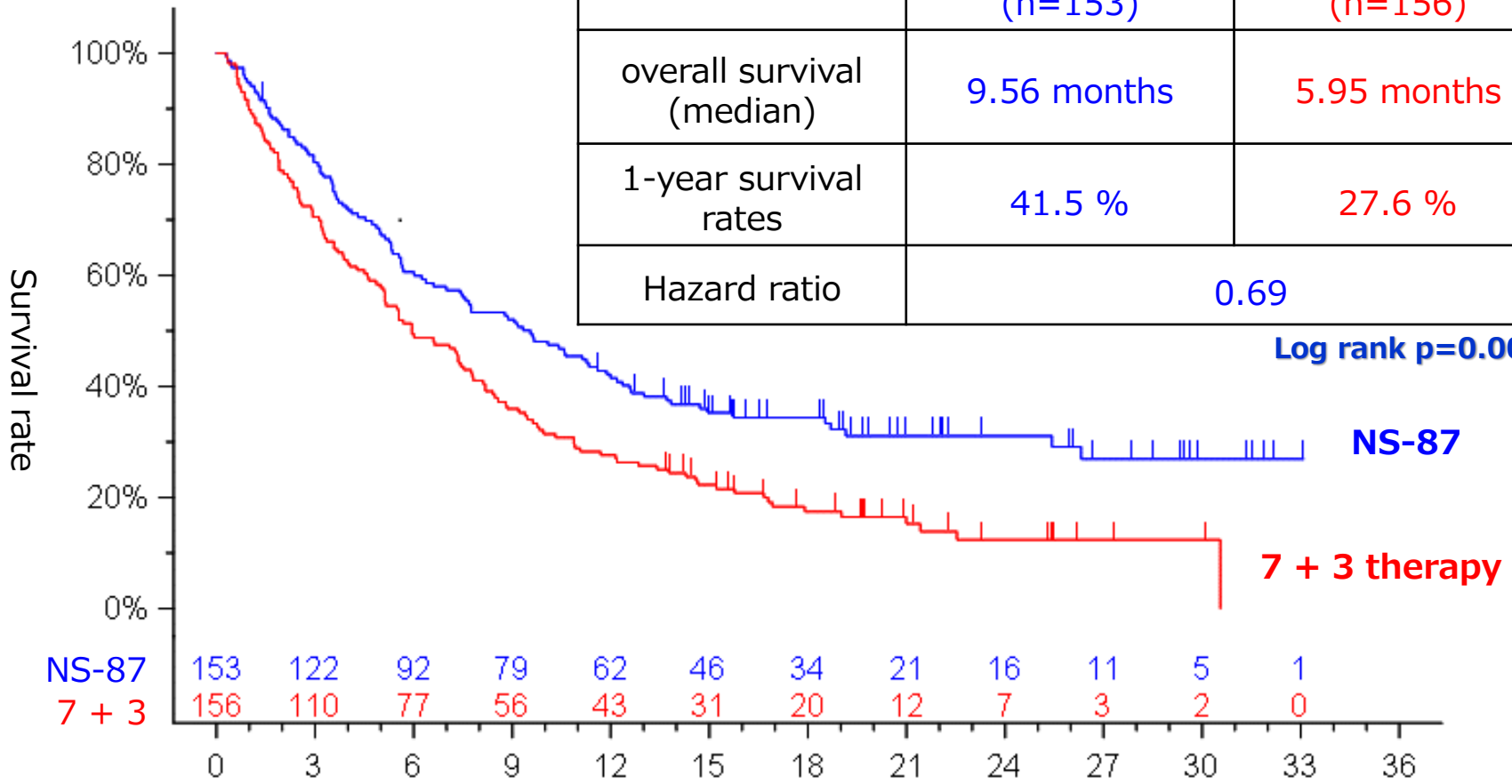
NS-87 Oversea P3 study

Subjects: Untreated high-risk AML 309 aged 60-75 years
Control group: 7 + 3 therapy (AraC 100 mg/m2 + DNR 60 mg/m^2)

[Primary: overall survival(OS)]

	NS-87 (n=153)	7+3 therapy (n=156)
overall survival (median)	9.56 months	5.95 months
1-year survival rates	41.5 %	27.6 %
Hazard ratio	0.69	

Log rank p=0.003



J Clin Oncol. 2018 Sep 10;36(26):2684-2692

NIPPON SHINYAKU CO., LTD.

NS-87 Summary of P1/2 studies

Design	Single-arm, open-label
Study Objectives	To investigate the pharmacokinetics, safety, and efficacy of NS-87 in patients with high-risk AML.
Study patient populations	High-risk AML
Period of registration	August 2019 - October 2021

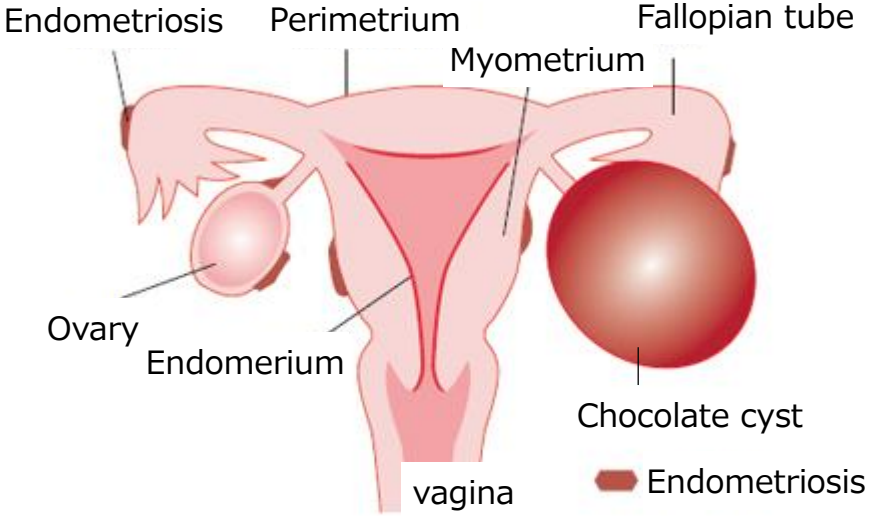
- **We conducted a phase 1/2 study in Japan. Based on the results of a phase 1/2 study and P3 studies, we applied for application for approval in June 2023.**
- **Orphan drug designation obtained.**

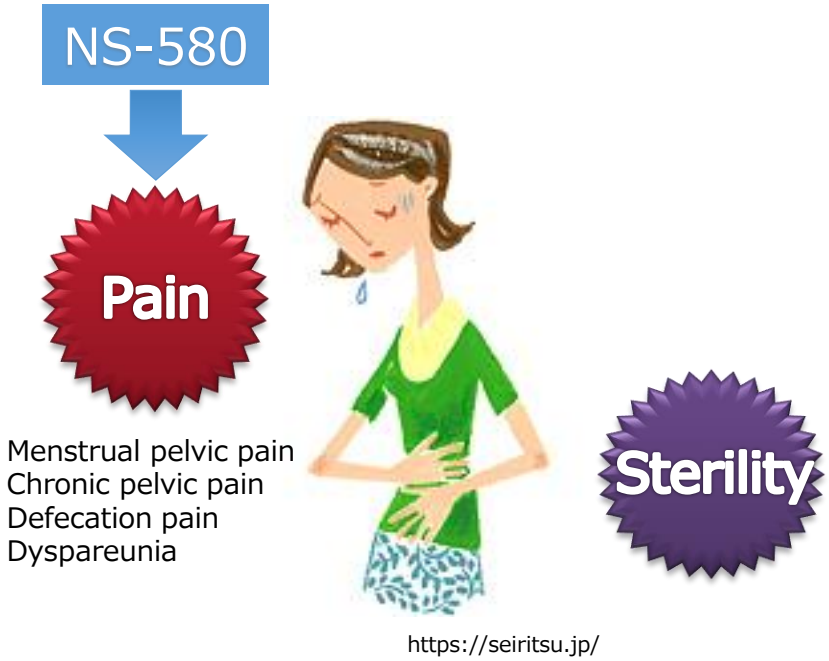
NS-580 Endometriosis Treatment

Stage	PIIb study
Development form	In-house development
Mechanism of action	microsomal prostaglandin E synthase-1 (mPGES-1) inhibition
Indications	Endometriosis
Dosage form	Oral drug
Characteristics	✓ Non-hormonal endometriosis treatment with analgesic effect and anti-proliferative effect ✓ Possible long-term use with few side effects

NS-580 Endometriosis

Chronic inflammatory disease in which endometrial tissue engrafts outside the uterus and proliferates and bleeds repeatedly according to menstruation





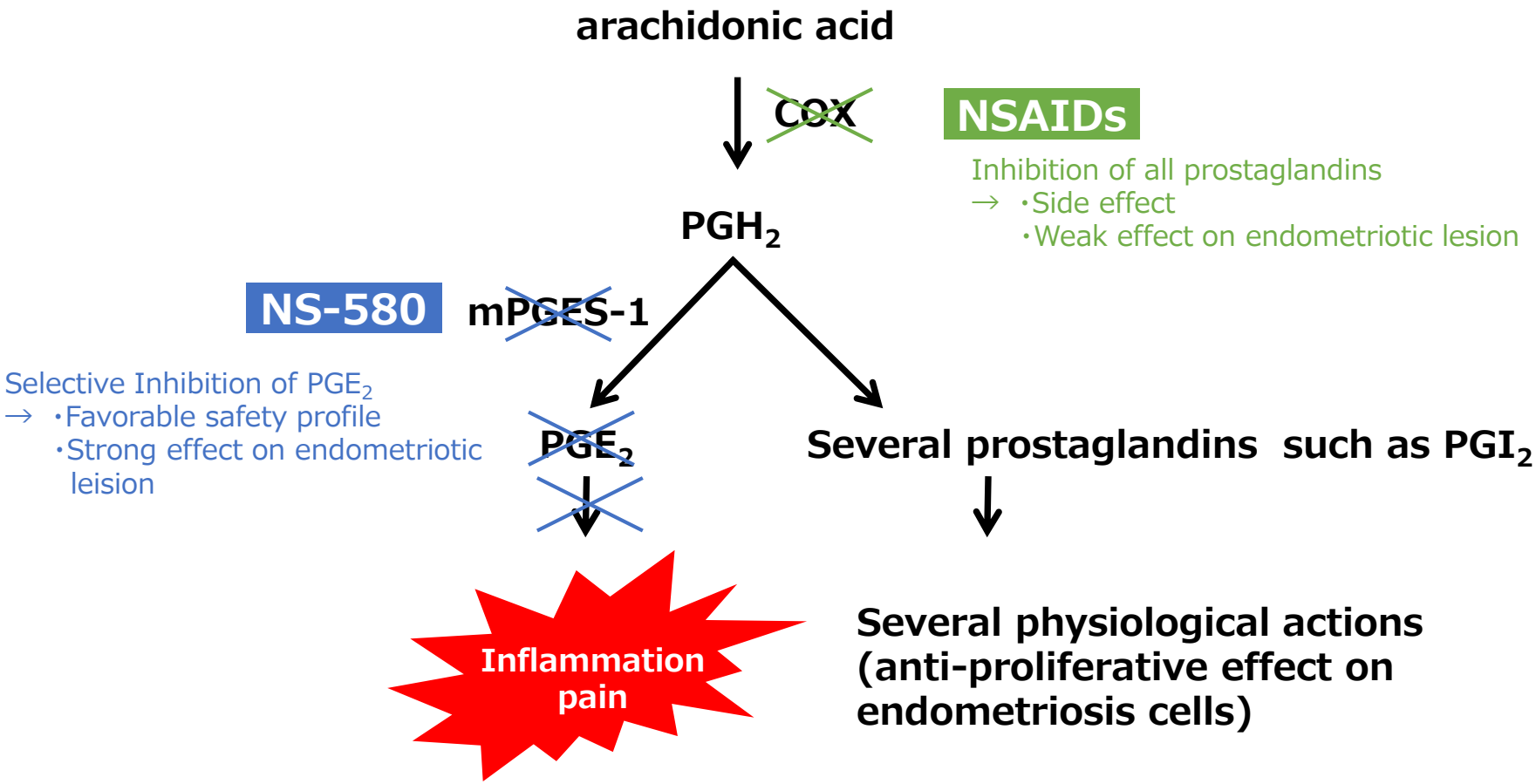
https://seiritsu.jp/

The figure published by the Japanese Obstetrics and Gynecology HP was partially modified

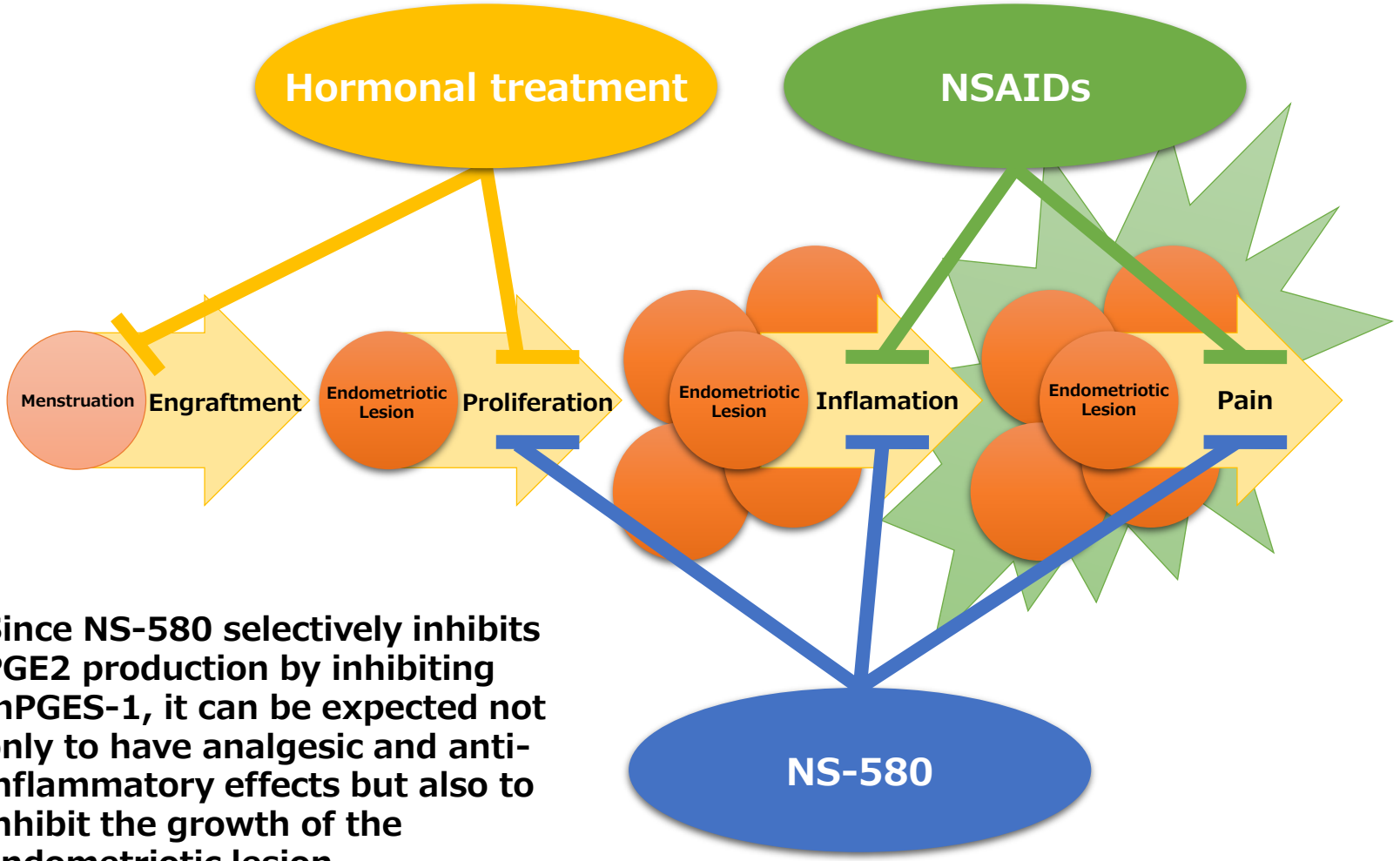
Endometriosis affects approximately 10% women of reproductive age and significantly reduces women's QOL.

NS-580 Mechanisms of Action

mPGES-1 inhibitor, NS-580 selectively inhibits PGE_2 production



Action point of each drug in Endometriosis



Since NS-580 selectively inhibits PGE2 production by inhibiting mPGES-1, it can be expected not only to have analgesic and anti-inflammatory effects but also to inhibit the growth of the endometriotic lesion.

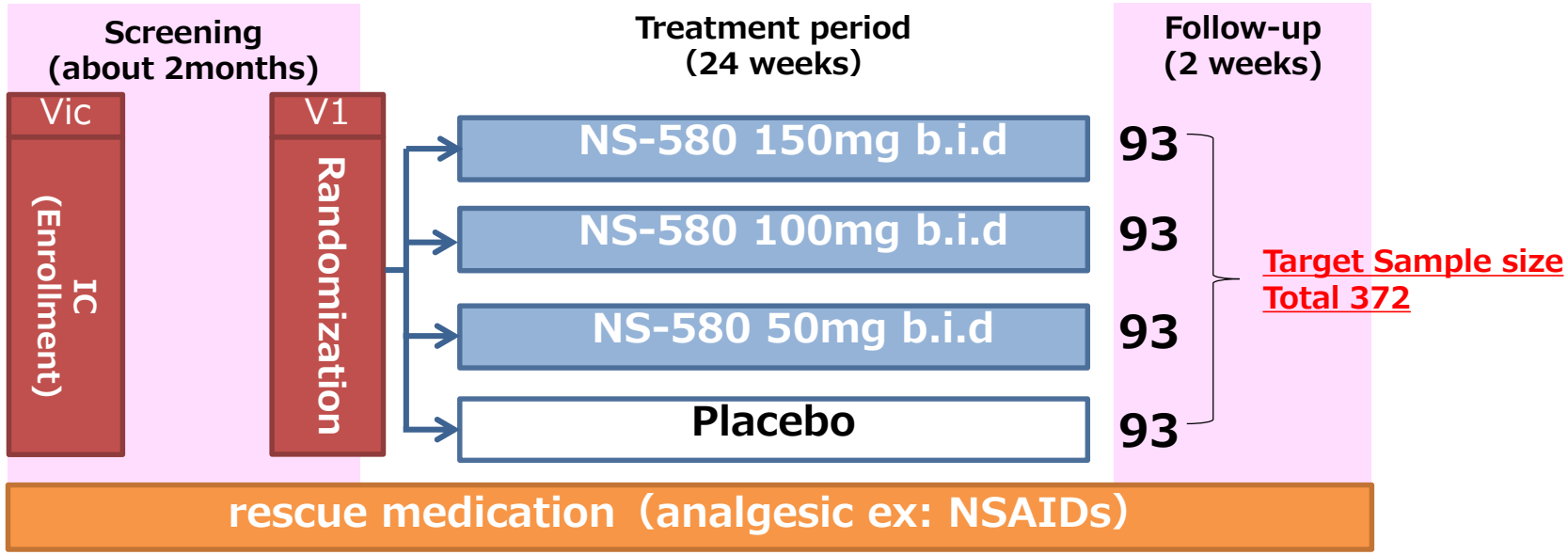
NS-580 P2a study (Endometriosis)

Study design	Randomized, double-blind, multicentre, placebo-controlled, parallel group comparison
Endpoint	Change in pain VAS (Visual analog scale)score
Dosage and Administration	Oral, once daily Dose: placebo, 100 mg, 300 mg/time
Target sample size	150 (100 mg : 300 mg : placebo = 2:2:1)

The analgesic effect of NS-580 was confirmed in Phase 2a study.

NS-580 P2b study (Endometriosis)

Study design	Randomized, double-blind, multicentre, placebo-controlled, parallel group comparison
Endpoint	Change in pain VAS score
Dosage and Administration	Oral, twice daily Dose: placebo, 50 mg, 100 mg, 150 mg/time
Target sample size	372 (50 mg : 100 mg : 150 mg : placebo=1:1:1:1)



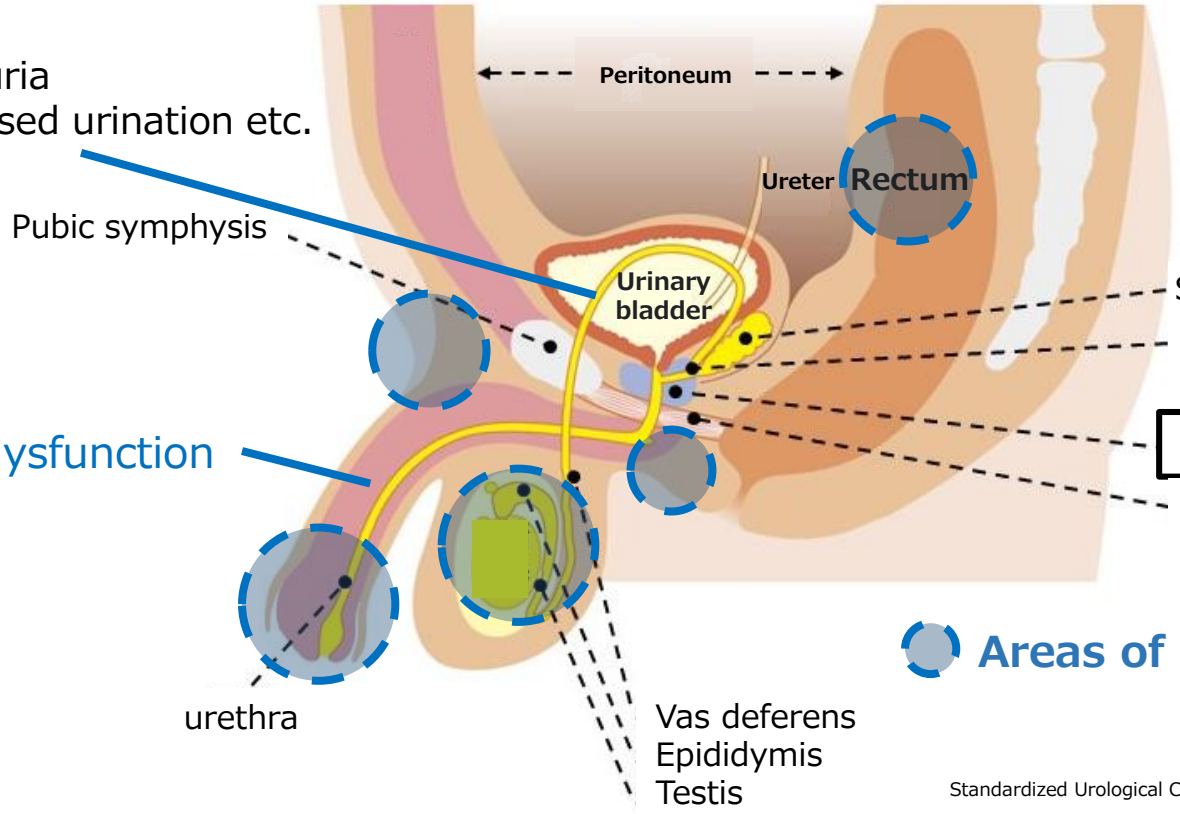
NS-580 Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Development stage	P2a study
Development form	In-house development
Mechanism of action	Membrane-bound prostaglandin E synthase-1 (mPGES-1) inhibition
Indications	Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)
Dosage form	Oral drug

CP/CPPS

Dysuria
・Pollakiuria
・Decreased urination etc.

Psychiatric symptoms
・Anxiety
・Stress
・QOL decreased



Sexual dysfunction

Inflammation

Areas of pain and discomfort

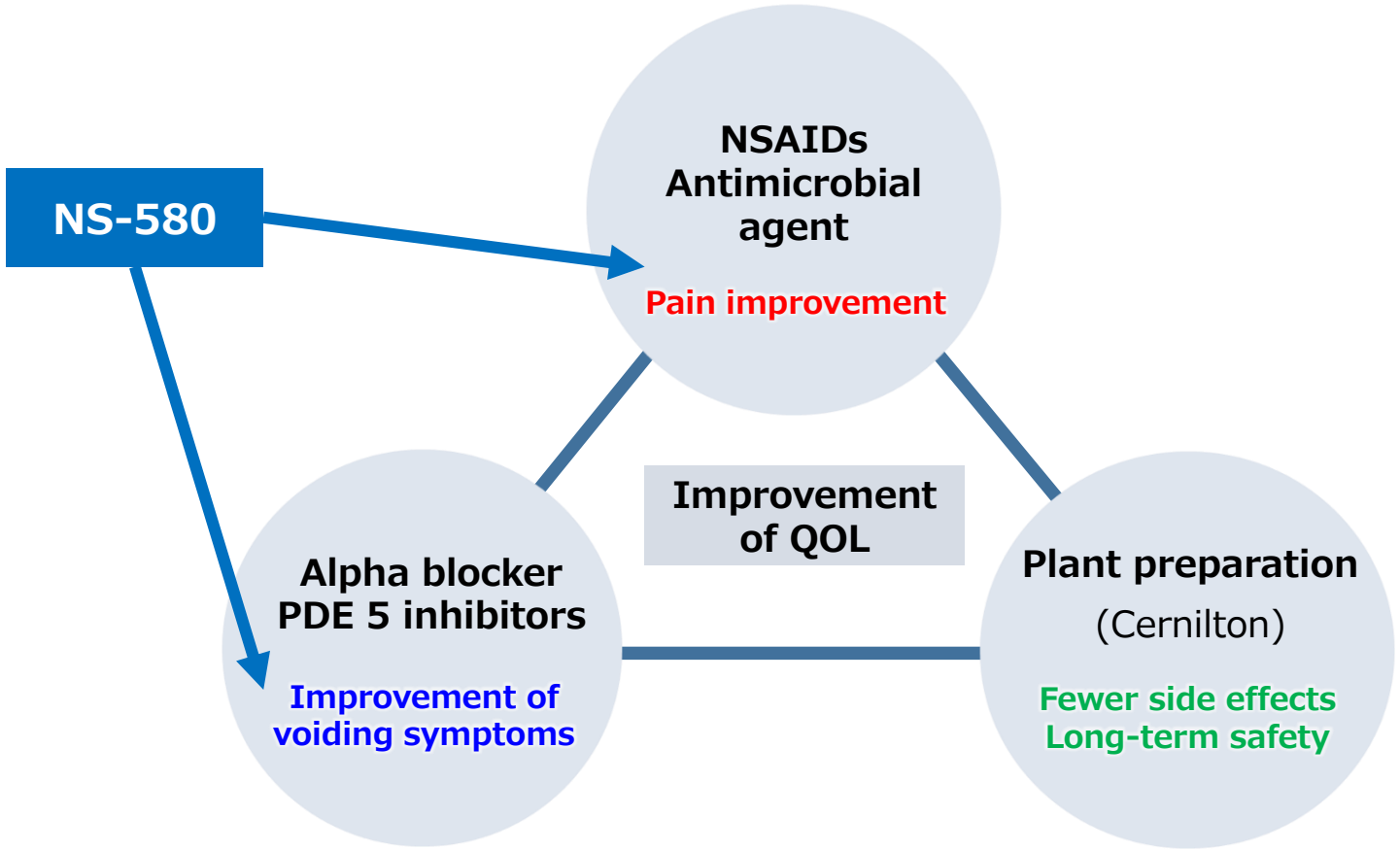
Standardized Urological Chemistry 8th Edition; Medical Shoin; P.18; 2010 Modified

Peripelvic and periurogenital pain persists **for 3 of 6 months**.
It is defined as the one with voiding and sexual dysfunction, and the etiology has not been clarified.

Number of patients

Japan: Approximately 2 million potential patients (5% of adult males)
Approximately 0.6 million patients were diagnosed
Overseas: About 4% of the male population

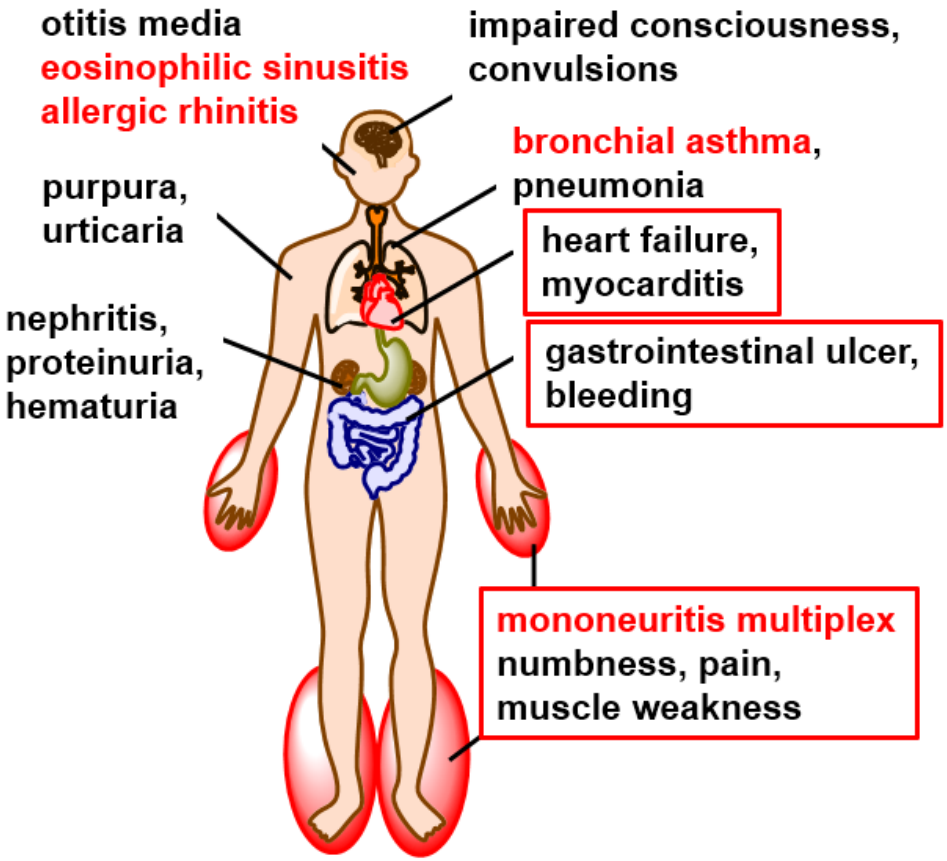
Treatment for CP/CPPS and Product-concept of NS-580



Product concept

Highly safe treatment for CP/CPPS that can be expected to control pain in the long term

NS-229 eosinophilic granulomatosis with polyangiitis

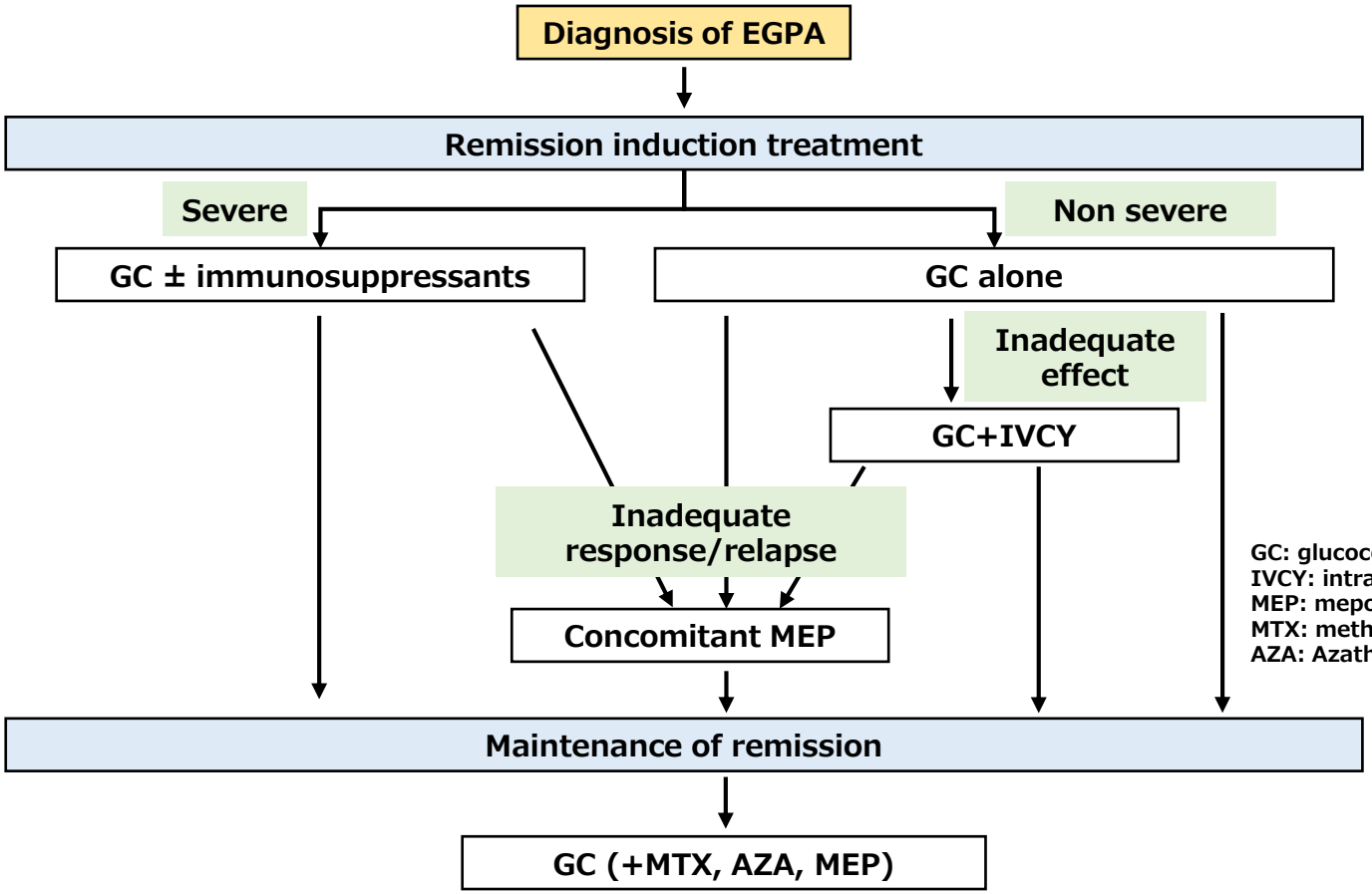


- **EGPA (eosinophilic granulomatosis with polyangiitis)**
  Rare and intractable diseases of unknown cause designated as intractable diseases in January 2015.

- **Characteristics of the clinical course:**
  Severe asthma with eosinophilia and allergic rhinitis (eosinophilic sinusitis) preceded by several years. Subsequently, a marked increase in peripheral blood eosinophils causes eosinophilic inflammation of various organs of the body and granulomatous necrotizing vasculitis of small to medium-sized vessels.

- **Number of specified medical expense beneficiary certificate holders (designated intractable diseases):**
  5,839 (as of the end of FY2021)
  *Refer to the number of specific medical expense beneficiary certificate holders at Japan Intractable Disease Information Center.

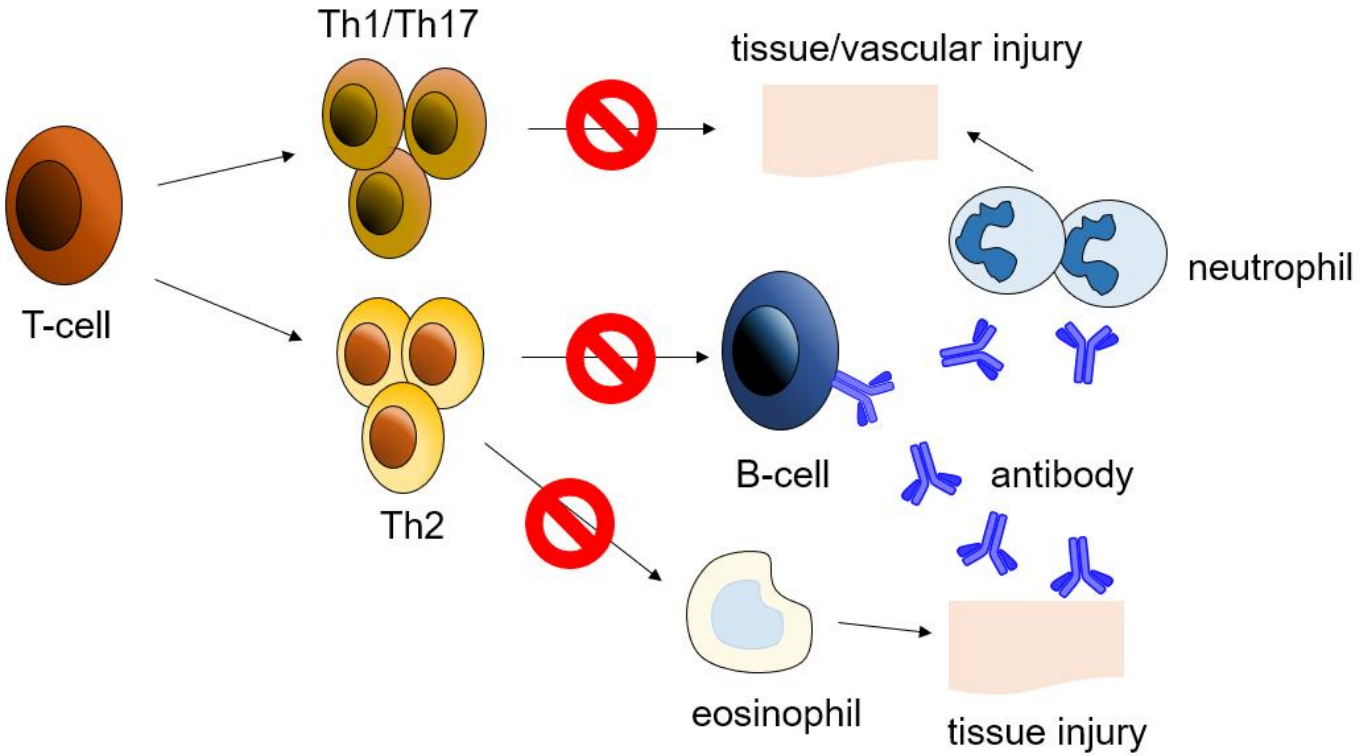
NS-229 eosinophilic granulomatosis with polyangiitis



Partially modified from ANCA-related vasculitis practice guideline 2023

- **In the treatment of EGPA, glucocorticoids are basically used to induce and maintain remission.**
- **NS-229 is assumed to be widely available in patients with EGPA, replacing glucocorticoids, by inhibiting symptom-related signaling of EGPA.**

NS-229 eosinophilic granulomatosis with polyangiitis

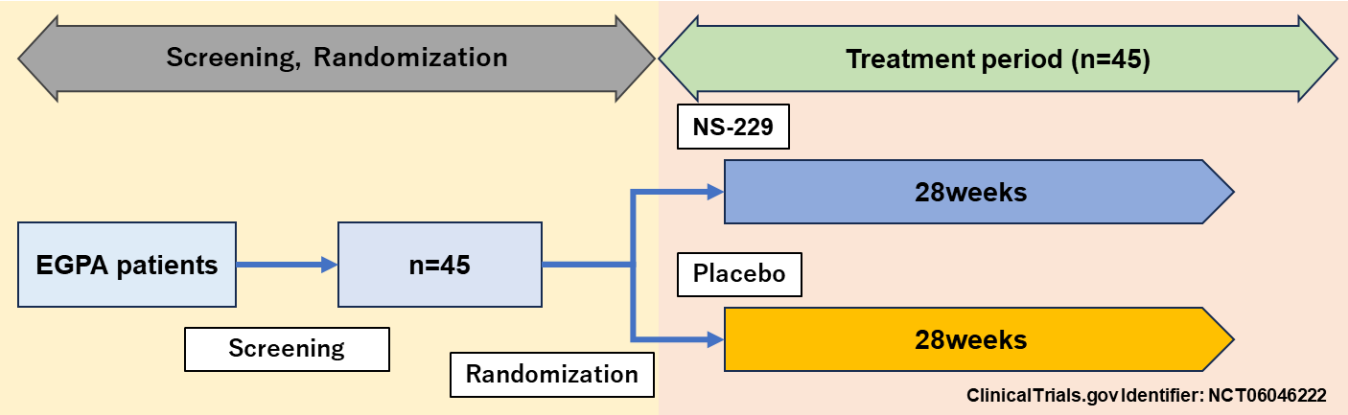


- **In EGPA, inflammatory cells, such as T cells, B cells, and eosinophils, are activated and lead to tissue damage.**
- **NS-229 has potent inhibitory effects on JAK1.**
- **Through inhibition of JAK1, it suppresses various cytokine signaling, suppresses activation of T cells, B cells, eosinophils, and other cells, and leads to improvement of disease status.**
- **NS-229 is a selective inhibitor of JAK1, and its selectivity reduces the effects of JAK2 inhibition on the hematopoietic system.**

NS-229 eosinophilic granulomatosis with polyangiitis

Study	A Double-Blind, Randomized, Placebo-Controlled Phase II Study to Evaluate the Efficacy and Safety of NS-229 in EGPA Patients
Design	NS-229 and placebo are compared. At baseline, approximately 45 subjects will be randomly assigned to receive NS-229 or placebo.
Primary efficacy endpoint	Percentage of subjects in remission (OGC 4.0)* at Week 28
Primary safety endpoint	Confirmation of adverse events and adverse drug reactions
Secondary efficacy endpoints	Percentage of subjects in remission (OGC 7.5)* at Week 28 Time to relapse/worsening
Number of subjects	Approximately 45 patients
Treatment period	28 weeks

***(OGC X): A score of 0 on the BVAS, which assesses vasculitis activity, and the amount of oral glucocorticoids administered is less than or equal to X mg/day.**



Accelerating drug discovery

～To exceed the target of launching more than one product per year～

NIPPON SHINYAKU CO., LTD.

Open Innovation: Innovation Research Partnering (IRP)

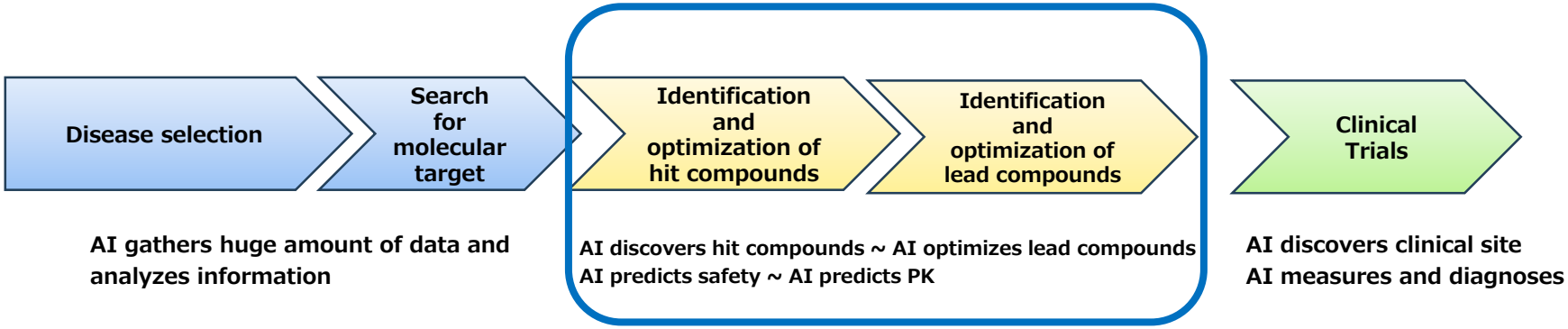
We established Innovation Research Partnering (IRP) in Boston area of the United States, where the heart of an ecosystem consisted by various players such as world-class universities, research institutions and bio-venture companies.

Building where IRP office is located

An event in IRP office

IRP will increase our access to the seeds of the world's most advanced drug discovery technologies and efficiently search for partner opportunities.
We believe that this will lead to accelerate and diversify in-house drug discovery research.

AI for drug discovery



- In particular, the use of AI for chemical synthesis, safety, and pharmacodynamicsis is increasing.
- AI is applied to existing R&D pipeline.

(Problem) In order to launch more than one product per year, refinement and high efficiency of drug discovery process and rapid development are required. Therefore, cooperation through IT adoption in view of the entire process is necessary.

We are developing an integrated system that collects and provides a huge amount of drug discovery information from research to clinical trials.

Safe Harbor Statement

- Materials and information provided during this presentation may contain so-called “forward-looking statements.” These statements are based on current expectations, forecasts and assumptions that are subject to risks and uncertainties which could cause actual outcomes and results to differ materially from these statements.
- Risks and uncertainties include general industry and market conditions, and general domestic and international economic conditions such as interest rate and currency exchange fluctuations. Risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, technological advances and patents attained by competitors; challenges inherent in new product development, including completion or failure of clinical trials; claims and concerns about product safety and efficacy; regulatory agency’s examination, obtaining regulatory approvals; domestic and foreign social security reforms; trends toward healthcare cost containment; and governmental laws and regulations affecting domestic and foreign operations.
- Also, for products that are approved, there are manufacturing and marketing risks and uncertainties, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials, and competition with others.
- The Company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.
- This English presentation was translated from the original Japanese version.
  In the event of any inconsistency between the statements in the two versions, the statements in the Japanese version shall prevail.

NIPPON SHINYAKU CO., LTD.

Nippon Shinyaku Co., Ltd.

R&D Meeting

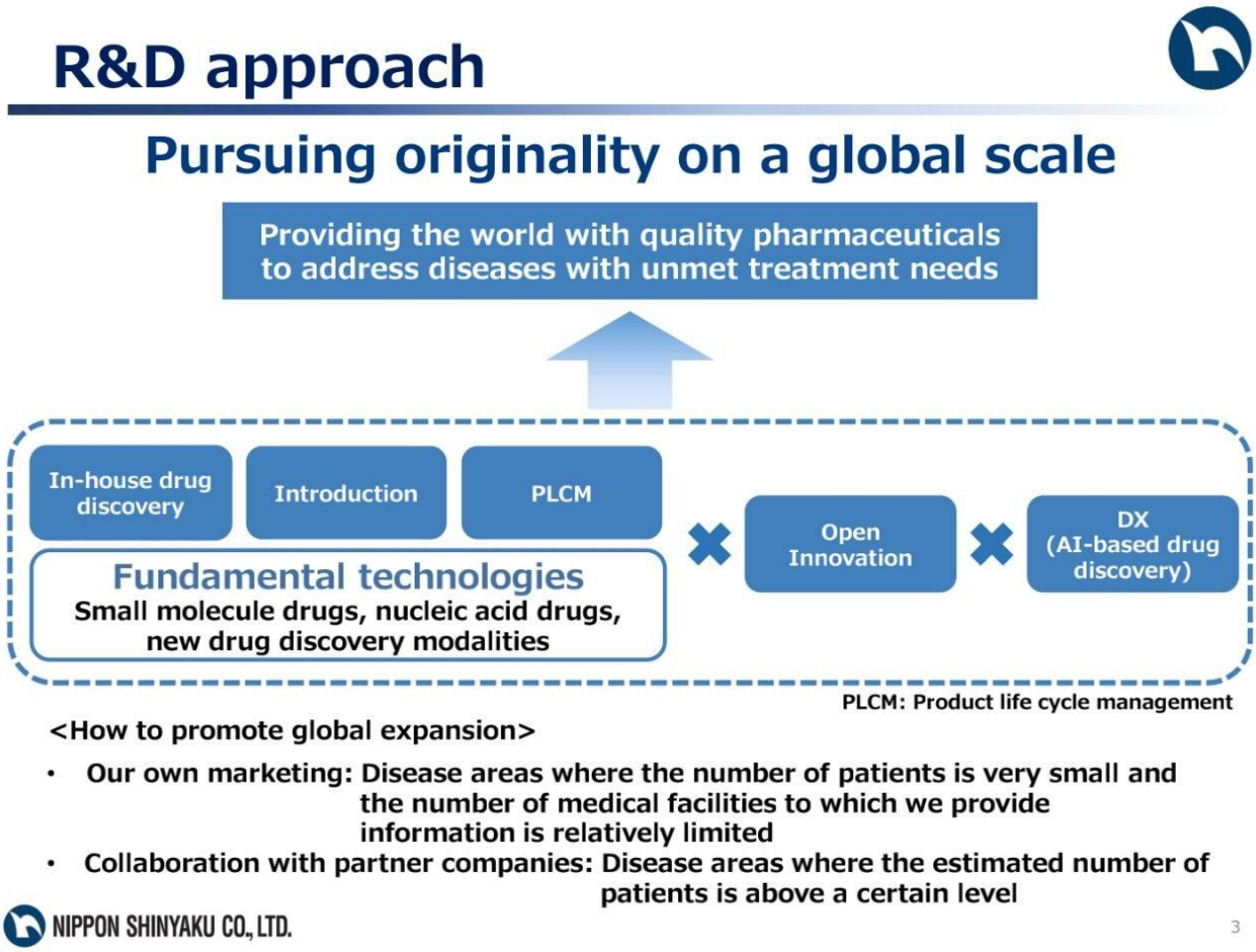
December 12, 2023

Presentation

Nakai: I am Nakai, President of Nippon Shinyaku Co., Ltd.

Thank you very much for joining our R&D meeting today.

Today, I would like to start from a brief introduction of the meeting. Then, Takagaki, Director of Research and Development Division, will explain R&D efforts into DMD and non-DMD pipelines and efforts to accelerate drug discovery.



First, I would like to explain Nippon Shinyaku's approach to R&D approach.

In the pharmaceutical business, we will provide valuable pharmaceuticals in areas and fields where treatment needs have yet to be met to realize our management philosophy of Helping People Lead Healthier, Happier Lives.

To this end, we need to enhance our development pipeline through the three pillars of in-house drug discovery, Introduction, and product lifecycle management or PLCM, using our own fundamental technologies.

We will further accelerate R&D by combining these three pillars with open innovation and DX.

In addition, since the number of patients with intractable and rare diseases, which is one of the areas we are focusing on, is relatively small, we believe that promoting global expansion will enable us to achieve sustainable growth.

We look not only at the domestic market but also at the global market to deliver needed drugs in an optimal way to patients around the world.

Regarding our global expansion concept, we are considering strategies with a view to in-house sales in the global market for disease areas where the number of patients is very small, and the number of medical facilities providing information is relatively limited.

On the other hand, if the disease area is above a certain level of the estimated number of patients, we will give priority to partnering with companies that have a broad sales network.

The patent for Uptravi, which is currently our driving force, is scheduled to expire in October 2026 in the US and in April 2027 in other regions including Japan.

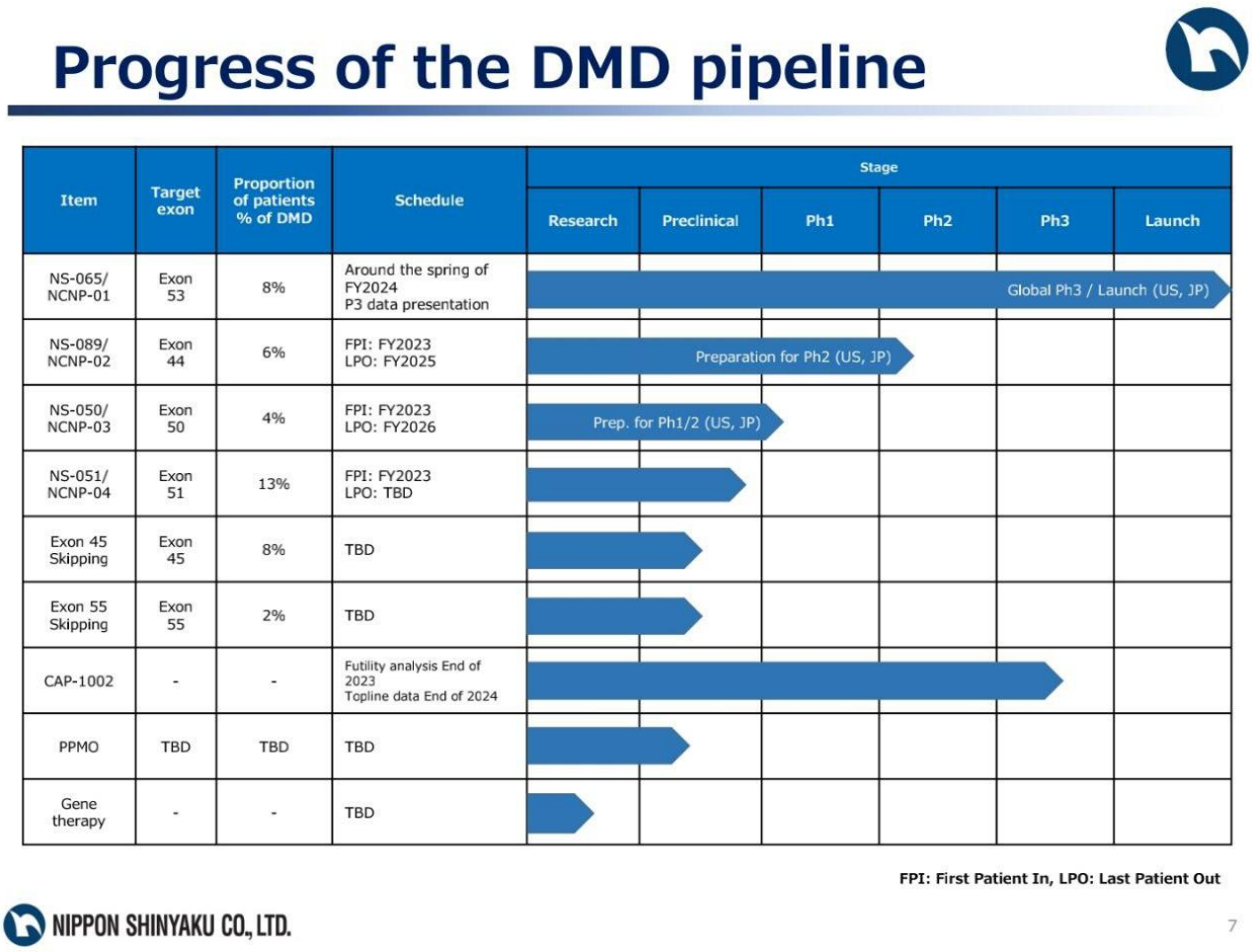
We need to actively promote R&D and establish new growth drivers in order to overcome this patent cliff and to achieve our sustainable growth.

In addition to the nucleic acid drugs such as NS-089, NS-050, and NS-051, and the cell therapy product CAP-1002, which are targeted for DMD, we are also expanding our non-DMD product lineup. We believe that these products will be the ones that drive our growth.

Next, Takagaki will explain the details about DMD and non-DMD pipeline as well as our efforts in acceleration of our drug discovery. Thank you.

Takagaki: I am Takagaki, Director, Research and Development Division.

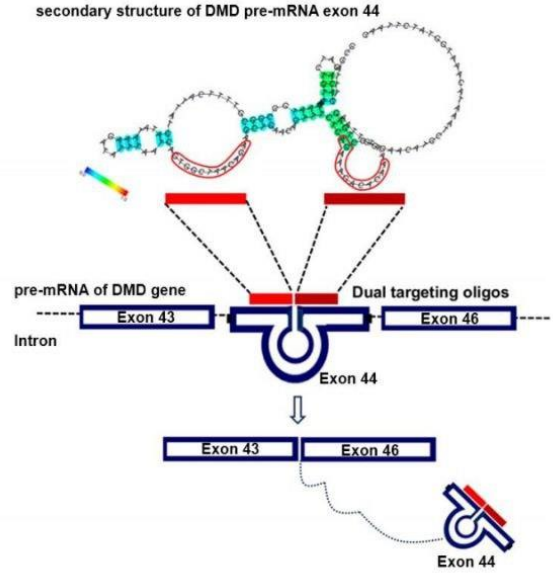
I would like to explain our R&D efforts.



First, I would like to talk about the DMD update.

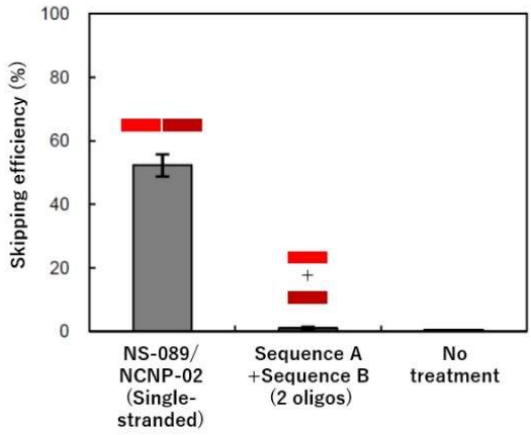
This table shows the progress of the DMD pipeline. The main progress made this fiscal year will be described on the slides that follow.

NS-089/NCNP-02 exon 44 skipping therapy



Schematic diagram of the mechanism of action of NS-089/NCNP-02

Induce exon 44 skips with NS-089/NCNP-02 in patients with DMD with exon 45 deletion and restore slightly shortened dystrophin expression



- **New highly active sequence search method that is a patent application technology**
- **World's first sequence-linked dual-targeting antisense nucleic acid drug targeting two distant nucleotide sequences**
- **Induction of dystrophin protein expression in muscle cells derived from DMD patients**

Paper Exon 44 skipping in Duchenne muscular dystrophy: NS-089/NCNP-02, a dual-targeting antisense oligonucleotide
Author Naoki Watanabe, Yuichiro Tone, Tetsuya Nagata, Satoru Masuda, Takashi Saito, Norio Motohashi, Kazuchika Takagaki, Yoshitsugu Aoki and Shin'ichi Takeda
Journal Molecular Therapy Nucleic Acids

NIPPON SHINYAKU CO., LTD.

8

First, I would like to introduce NS-089/NCNP-02, DMD's development items.

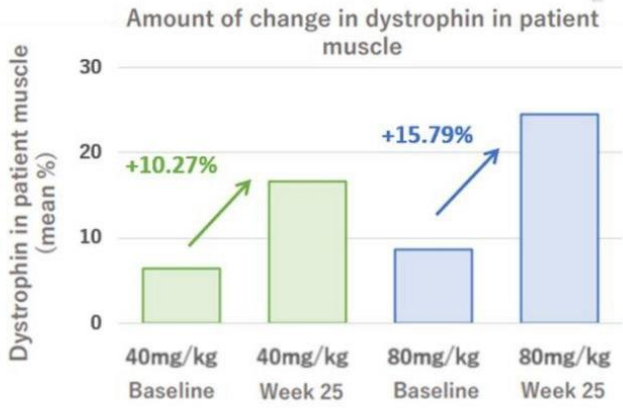
Like Viltepso, which is already approved, the mechanism of action of NS-089/NCNP-02 is to restore slightly shortened dystrophin expression by exon skipping.

The mechanism is the same, but unlike ordinary antisense nucleic acids that have sequences that bind to a single target, NS-089/NCNP-02 is a sequence-linked dual-targeting antisense nucleic acid that targets two distant nucleotide sequences.

Sequences that bind to each of the two targets in two locations are designed, linked, and created.

As shown in the graph on the right, mixing each of the two sequences has no activity, but by linking the two into a single sequence, strong activity is achieved.

Investigator-initiated trial of NS-089/NCNP-02
Dystrophin protein expression levels



	Dystrophin protein % change (SD)
40mg/kg(n=3)	10.27 (1.88)
80mg/kg(n=3)	15.79 (6.44)
Mean (%)	13.03 (5.21)

ClinicalTrials.gov identifier NCT4129294

- **In 6 patients treated (24 weeks), significant increases in exon skipping efficiency and dystrophin protein were observed. In addition, safety and tolerability were good.**
- **In Part 2 (dose-finding period), there was a tendency to maintain and improve motor function.**
- **Since this study had a small number of subjects (n=6) and did not include a placebo control group, the efficacy of this drug, including the maintenance of motor function, should be further investigated.**

I would like to explain the results of the investigator-initiated clinical trial for NS-089/NCNP-02.

The investigator-initiated clinical trial is divided into part one and part two. Safety and tolerability were confirmed at doses of 40 mg/kg and 80 mg/kg in part two while doses were titrated up in part one.

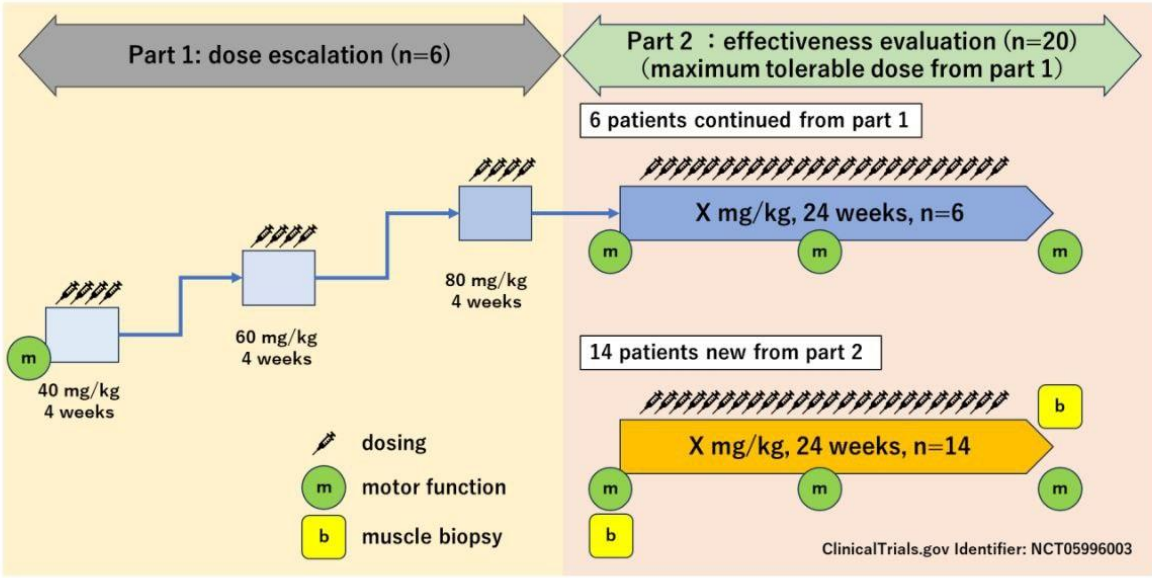
The upper left graph shows the results of the muscle biopsy after part two. As for the amount of change in dystrophin protein, the 40 mg/kg group showed an average of 10.27%, and the 80 mg/kg group showed an average of 15.79%, an increase in expression from baseline was observed.

The safety and tolerability of the drug during this administration period were good.

Since this study had only six subjects and did not include placebo control group, we believe that the efficacy of this drug should be further investigated.

NS-089/NCNP-02 exon 44 skipping therapy

Orphan Drug, Rare Pediatric Disease, and Breakthrough Therapy designations from the U.S. FDA; currently preparing for global P2 study



The last slide of NS-089/NCNP-02 is about the study design of the next phase of the Japan-US Phase II study.

The study design for NS-089/NCNP-02 is planned as shown in the figure based on the results of the investigator-initiated clinical trial in Japan.

The study design of the Japan-US Phase II consists of part one and part two.

In part one, the maximum tolerated dose will be obtained by gradually increasing the dose from 40 mg/kg, 60 mg/kg, and 80 mg/kg. In part two, efficacy will be confirmed by administering the maximum tolerated dose in part one once a week for 24 weeks.

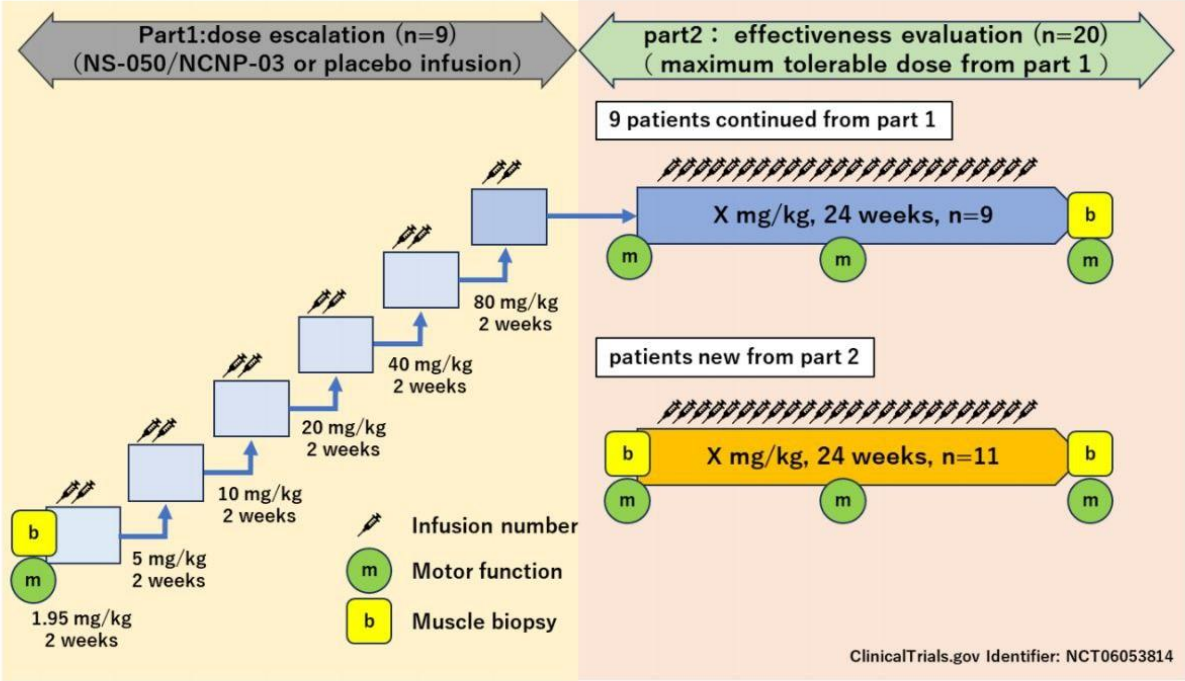
Based on the results of the investigator-initiated clinical trial, we are planning a Japan-US Phase II study for NS-089/NCNP-02. At the same time, in the US, we have filed various applications and received orphan drug designation, rare pediatric disease designation, and breakthrough therapy designation.

Breakthrough therapy designation is for drugs that have demonstrated meaningful preliminary clinical evidence compared to existing therapies for serious diseases. NS-089/NCNP-02 is the first in our DMD pipeline to be designated.

NS-089/NCNP-02 is currently preparing for Phase II study.

NS-050/NCNP-03 exon 50 skipping therapy

FDA and PMDA have agreed to the planned Phase Ⅰ/Ⅱ study of NS-050/NCNP-03. Global Phase 1/2 study is in preparation.



Next, I would like to explain about NS-050/NCNP-03.

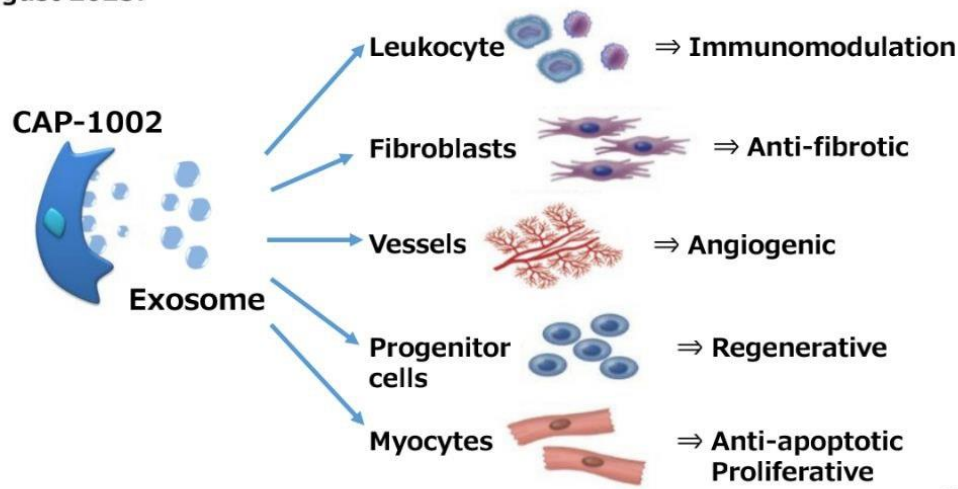
We are preparing for the global Phase I / II study, which will be a first-in-human study.

The design consists of part one and part two.

In part one, the dose is titrated in six steps from 1.95 mg/kg to 80 mg/kg to obtain the maximum tolerated dose. In part two, the dose is administered once a week for 24 weeks at the maximum tolerated dose in part one to confirm efficacy.

CAP-1002 Cell Therapy

- Cardiosphere-derived cell therapeutic.
- Exosomes (extracellular vesicles) released from this drug are expected to reduce oxidative stress, inflammation, fibrosis, and increase cellular energy and myocyte generation, resulting in slowing the decline of skeletal muscle and cardiac function in DMD.
- In the P2 study (HOPE-2 study), efficacy on upper limb function (PUL) and cardiac function was confirmed, and in the OLE study, it was confirmed that the effects lasted for a long time.
- Currently, the phase 3 trial (HOPE-3) is underway. Protocol amendment was submitted in August 2023.



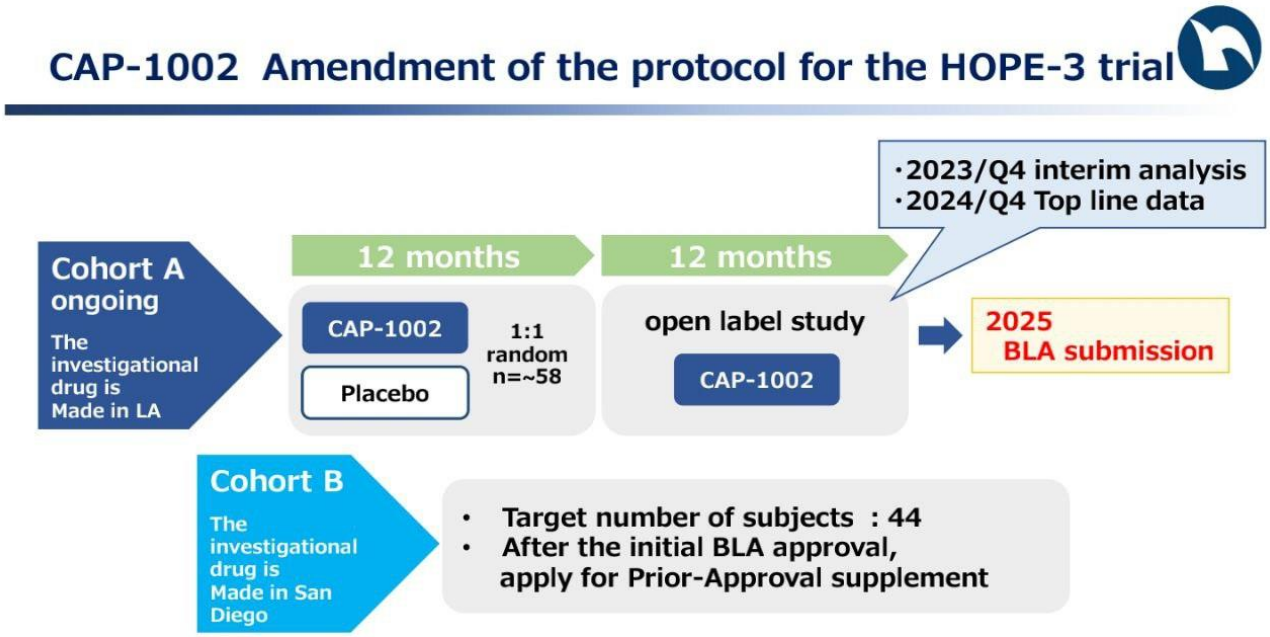
Next, I would like to explain about CAP-1002.

CAP-1002 is a cardiosphere-derived cell therapeutic.

Exosomes or extracellular vesicles released from CAP-1002 act on various cells to reduce oxidative stress, inflammation, fibrosis, and increase myocyte generation and angiogenesis, etc., resulting in slowing the decline of skeletal muscle and cardiac function.

In the Phase II study, HOPE-2, efficacy on upper limb function and cardiac function was confirmed. In the OLE study, it was confirmed that the effects lasted for a long time.

A Phase III study, HOPE-3, is currently underway, and Capricor has revised the protocol in August 2023.



- **The investigational product is being manufactured at a facility in Los Angeles, but in preparation for its commercial release, Capricor established an additional facility in San Diego.**
- **The HOPE-3 trial was divided into two cohorts: Cohort A (manufactured in Los Angeles) and Cohort B (manufactured in San Diego).**
- **The trial design and schedule until the Biological License Application (BLA) submission were agreed upon in a Type B meeting with the FDA.**

This is the content of the protocol amendment for the HOPE-3 trial.

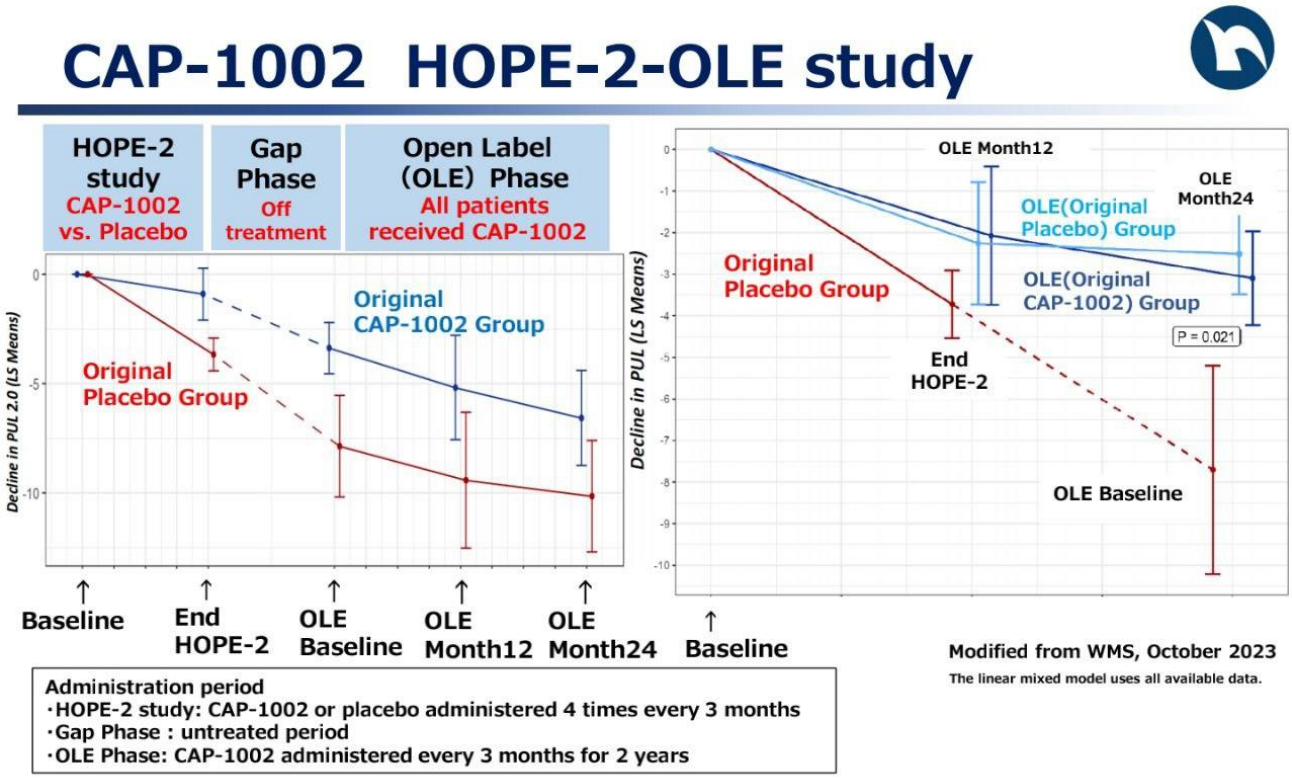
The investigational product is being manufactured at a facility in Los Angeles, but in preparation for its commercial release, Capricor established an additional facility in San Diego.

Since the investigational product made in San Diego also needs to be tested in humans, the HOPE-3 trial was divided into two cohorts, the study with the original investigational product manufactured in Los Angeles as Cohort A, and the study with the investigational product manufactured in San Diego as Cohort B.

For Cohort A, after a 12-month placebo-controlled randomized controlled trial will be followed by a 12-month open trial. An interim analysis will be performed in 2023/Q4, topline data will be obtained in 2024/Q4, and a BLA application will be filed in 2025. Later, I will explain about the results of the interim analysis, released last night in the US.

For Cohort B, Capricor plans to apply for Prior-Approval supplement after the completion of the study and obtain marketing approval for this formulation as well.

Regarding these study designs and timelines for BLA submissions, Capricor agreed with the FDA at a Type B meeting.



Results from the HOPE-2 trial and the two-year OLE study were presented by Capricor in a poster presentation at the World Muscle Society in October.

The figure on the left shows the upper limb function, PUL.

In the HOPE-2 study, CAP-1002 or placebo was administered for one year, followed by an untreated gap period, and then an open-label extension study allowed for two years of CAP-1002 administration took place. Regardless of treatment during the HOPE-2 study, the decline in upper limb function during the OLE period was similar with decrease by 2.8 points for two years.

The figure on the right indicates the change in upper limb function from baseline in the OLE study with blue and light blue lines, and the change in upper limb function from baseline to no treatment for two years in the HOPE-2 study with red lines. The decline in upper limb function after 24 months of treatment with CAP-1002 in HOPE-2-OLE was 2.8%, regardless of treatment during the HOPE-2 study.

In contrast, HOPE-2 placebo patients who did not receive treatment for 24 months experienced an average decrease by 7.7 points.

These results indicate that patients treated with CAP-1002 had a 64% reduction in disease progression.

CAP-1002 Press release for Interim Futility Analysis

December 11, 2023

Capricor Therapeutics

Capricor Therapeutics Announces Continuation of Phase 3 HOPE-3 Trial of CAP-1002 in Duchenne Muscular Dystrophy Based on Completion of Interim Futility Analysis

--Favorable Interim Futility Analysis Results--

--Successful Completion Triggers First Milestone Payment Under U.S. Agreement with Nippon Shinyaku--

--HOPE-3 (Cohort A) Enrollment Complete; Topline Data Expected in the Fourth Quarter of 2024; Cohort B Enrollment Initiated--

--Company Plans to Request a Meeting with FDA in the First Quarter of 2024 to Further Discuss Opportunities for Expedited Approval Pathways--

excerpt from press release of Capricor Therapeutics, 11th Decemnber 2023

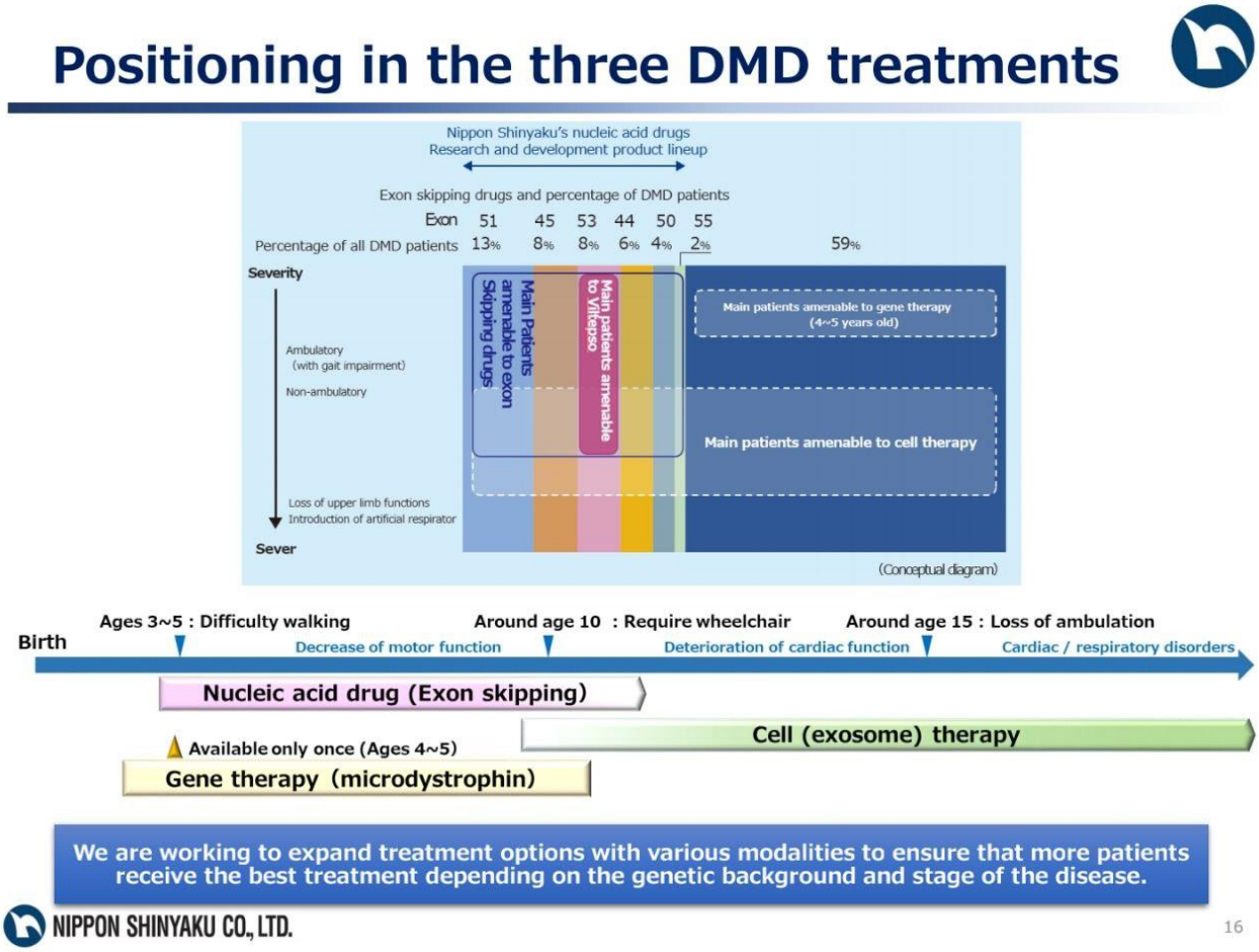
The interim analysis of CAP-1002 was released by Capricor on December 11, 2023.

The interim analysis results the continuation of Phase III HOPE-3 trial of CAP-1002. Based on the results, we will make a milestone payment to Capricor.

As I explained earlier, the enrollment has been completed for Cohort A, and topline data will be disclosed by December 2024.

For Cohort B, enrollment has begun.

Positioning in the three DMD treatments



I would like to explain about positioning in the DMD treatments.

Nucleic acid drug, cell therapy, and gene therapy have their own advantages and disadvantages. We believe that the best treatment can be achieved by combining them based on patient's genetic background, medical condition, and timing.

In the opinion of a US clinician specializing in muscle and a basic researcher of muscle, since muscle regeneration at an early age is active due to the abundance of stem cells in the patient's muscle and the expression of the DMD gene is high, patients eligible for exon skipping therapy are treated with nucleic acid drugs to produce a little short but functioning. It is desirable to express dystrophin protein to prevent muscle breakdown and maintain muscle mass.

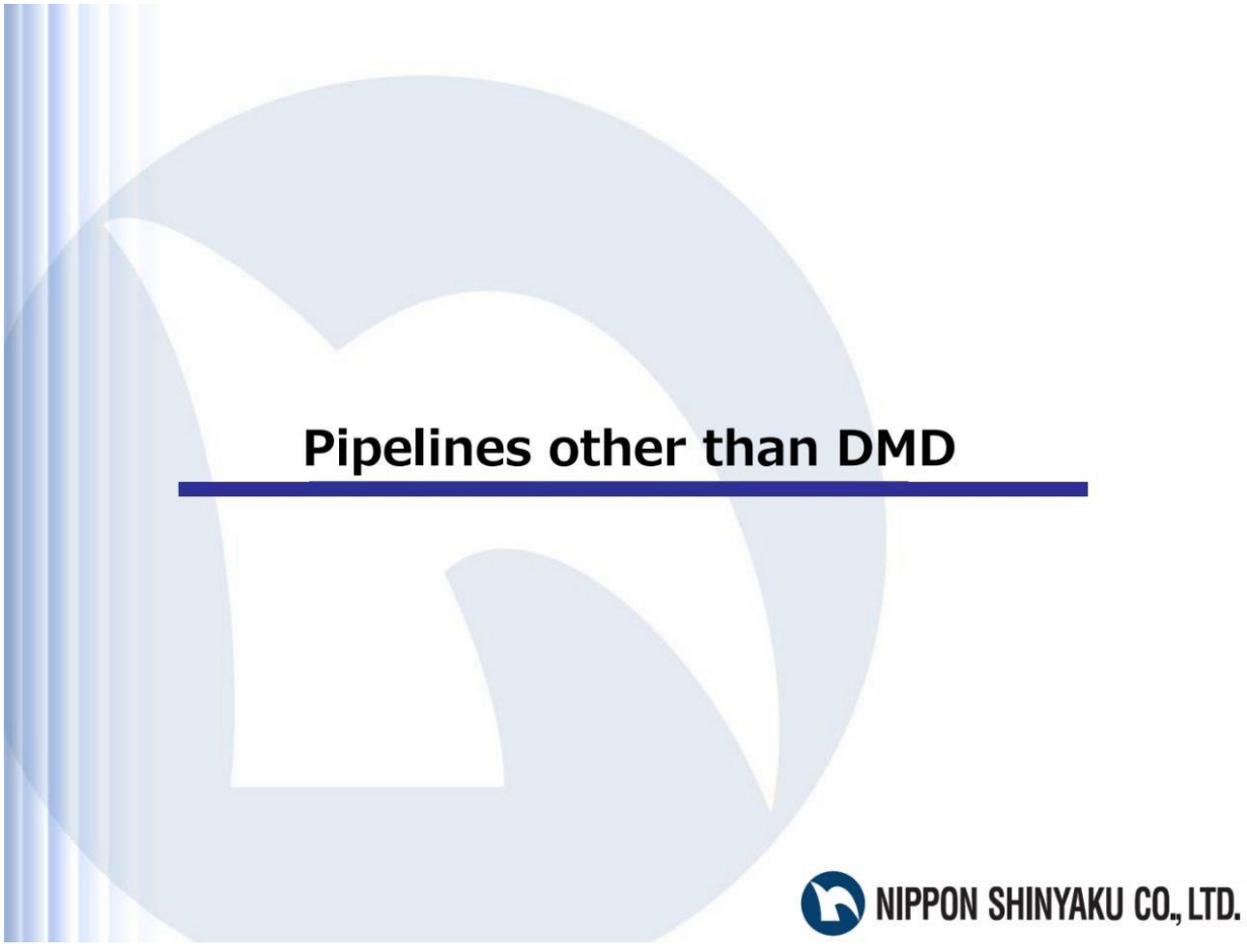
Gene therapy has been received accelerated approval in the US, and it is currently available for patients aged four to five years, and clinical trial results have not clearly demonstrated efficacy in patients aged six to seven years. Although there is a possibility that the subject may overlap with exon skipping therapy, effects of gene therapy are theoretically difficult to sustain over a long period of time. At this time, we believe that exon skipping drugs with long-term motor function data will be the preferred choice.

However, since exon skipping drugs need to be administered weekly, while gene therapy is administered only once, gene therapy may be chosen at the ages four to five for the convenience of treatment.

As I mentioned earlier, even if a patient undergoes gene therapy, the patient will return to exon skipping therapy when the effect of the therapy diminishes, or if the symptoms have progressed to the point of non-

ambulant, the patient will choose cell (exosome) therapy. Therefore, we believe that exon skipping drugs and gene therapy will coexist without competition.

As I explained earlier, as for cell therapy, clinical trials are underway for patients who have difficulty walking. Since evidence has been obtained so far that cell therapy contributes to upper limb motor function, we expect that cell therapy will be widely used for non-ambulant patients. The Company targets DMD by offering a range of therapeutic agents in multiple modalities. We will work to ensure that as many patients as possible receive optimal treatment according to their various genetic backgrounds and disease progression.



Next, I would like to discuss our pipeline for future growth other than DMD.

R&D pipeline (other than DMD)

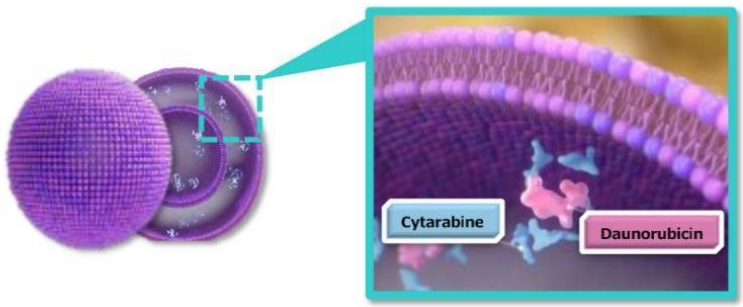
Stage	Code No. (Generic name)	Therapeutic field	Indications	Origin	Development	Schedule
NDA filing	NS-87 (daunorubicin / cytarabine)	hematologic malignancies	high-risk acute myeloid leukemia	Licensed - in from Jazz Pharmaceuticals plc	Nippon Shinyaku	FY2023 application FY2023 expected to be approved
NDA filing	ZX008 (fenfluramine hydrochloride)	intractable disease・orphan disease	Lennox-Gastaut syndrome	Sales Alliance: UCB (Former Zogenix Corporation)	Distribution partnership: UCB S.A. (former : Zogenix, Inc.)	FY2023 application FY2023 expected to be approved
P III	ZX008 (fenfluramine hydrochloride)	intractable disease・orphan disease	CDKL5 deficiency disorder	Sales Alliance: UCB (Former Zogenix Corporation)	Distribution partnership: UCB S.A. (former : Zogenix, Inc.)	FY2025 Completion of the study
P III	GA101 (obinutuzumab)	intractable disease・orphan disease	lupus nephritis	Licensed - in from Chugai Pharmaceutical Co., Ltd.	Co - development: Chugai Pharmaceutical Co., Ltd.	Expansion of indications: from 2026 onward
P III	GA101 (obinutuzumab)	intractable disease・orphan disease	pediatric nephrotic syndrome	Licensed - in from Chugai Pharmaceutical Co., Ltd.	Co - development: Chugai Pharmaceutical Co., Ltd.	Expansion of indications: from 2026 onward
P III	GA101 (obinutuzumab)	intractable disease・orphan disease	extra renal lupus	Licensed - in from Chugai Pharmaceutical Co., Ltd.	Co - development: Chugai Pharmaceutical Co., Ltd.	Expansion of indications: from 2026 onward
P II	NS-018 (ilginatinib)	hematologic malignancies	myelofibrosis	Nippon Shinyaku	Nippon Shinyaku	LPO: FY2024 (TBD)
P II	NS-304 (selexipag)	cardiovascular	arteriosclerosis obliterans	Nippon Shinyaku	Nippon Shinyaku	FY2024 completion of the study
P II	NS-304 (selexipag)	intractable disease・orphan disease	pediatric pulmonary arterial hypertension	Nippon Shinyaku	Co - development: Janssen Pharmaceutical K.K.	FY2025 completion of the study
P II	NS-580	gynecology	endometriosis	Nippon Shinyaku	Nippon Shinyaku	FY2023 completion of the study
P II	NS-580	urological diseases	chronic prostatitis/chronic pelvic pain syndrome	Nippon Shinyaku	Nippon Shinyaku	FY2024 completion of the study
Preparation for P II	NS-229	intractable disease・orphan disease	Eosinophilic granulomatosis with polyangiitis	Nippon Shinyaku	Nippon Shinyaku	FY2025 completion of the study
P I / II	NS-401 (tagraxofusp)	hematologic malignancies	blastic plasmacytoid dendritic cell neoplasm	Licensed - in from The Menarini Group	Nippon Shinyaku	FY2026 completion of the study
P I	NS-917 (radgocitabine)	hematologic malignancies	relapsed/refractory acute myeloid leukemia	Licensed - in from Delta-Fly Pharma, Inc.	Nippon Shinyaku	FY2025 completion of the study
P I	NS-161	inflammatory diseases	inflammatory diseases	Nippon Shinyaku	Nippon Shinyaku	FY2023 completion of the study
P I	NS-025	urological diseases	urological diseases	Nippon Shinyaku	Nippon Shinyaku	FY2023 completion of the study
P I	NS-863	cardiovascular	cardiovascular diseases	Nippon Shinyaku	Nippon Shinyaku	FY2024 completion of the study

Here is our R&D pipeline other than DMD.

I would like to introduce some of the development items in these pipelines indicated in red.

NS-87 high-risk Acute Myeloid Leukemia treatment

Planned trade name	VYXEOS
Active ingredient	Cytarabine and daunorubicin
Composition	• Containing cytarabine 100 mg and daunorubicin 44 mg in 1 vial (molar ratio of cytarabine to daunorubicin 5:1) • Encapsulated in nanoscale dual-structured liposomes of diametric 100nm
NDA submission	June 2023



JAZZ HP Mechanism of Delivery
https://vyxeospro.com/mechanism-of-delivery

First, let me explain about the NS-87.

NS-87, with the planned trade name VYXEOS, is a liposomal formulation containing cytarabine and daunorubicin, both of which are conventionally used in the treatment of leukemia.

The application was filed in June 2023.

High-risk Acute Myeloid Leukemia

●high-risk Acute Myeloid Leukemia

Defined as therapy-related acute myeloid leukemia (tAML) or AML with myelodysplasia-related changes (AML-MRC)

●Patient group

Approximately half of all AML patients* can be high-risk AML, among which 7+3 therapy (cytarabine, anthracycline combination) is currently used primarily in intensive chemotherapy-indicated patients. NS-87 may be used to treat this patient-group.

Overseas P3 study of NS-87 showed significant extension of overall survival compared with 7+3 therapy.

*There is no accurate statistics about the patients of AML. However, 14,000 people per year are diagnosed with leukemia. (Reference: Cancer Statistics)

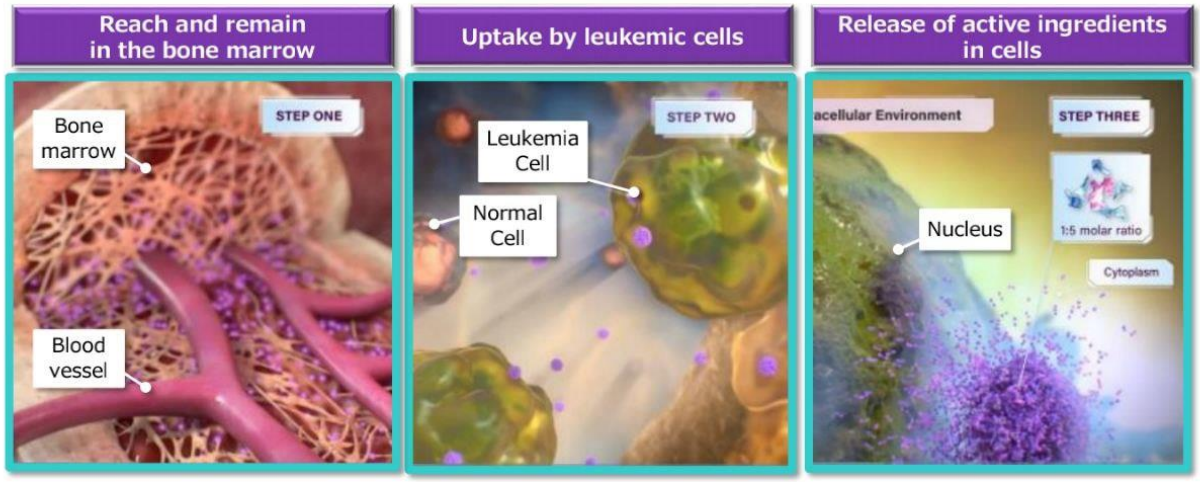
The planned indicaton for NS-87 are therapy-related acute myeloid leukemia or AML with myelodysplasia-related changes, which are considered to be poor prognosis among AML. These are referred to as high-risk AML.

Approximately half of all AML patients can be high-risk AML, and NS-87 is used in intensive chemotherapy-indicated patients.

Although 7+3 therapy is currently used primarily in this patient group, NS-87 showed significant extension of overall survival compared with 7+3 therapy in clinical trials.

Characteristics of NS-87

- **Liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio**
- **It reaches the bone marrow as liposomes and remains for a long time.**
- **After the drug is taken up into leukemic cells in the bone-marrow, cytarabine and daunorubicin are released to exert their antitumor effects.**



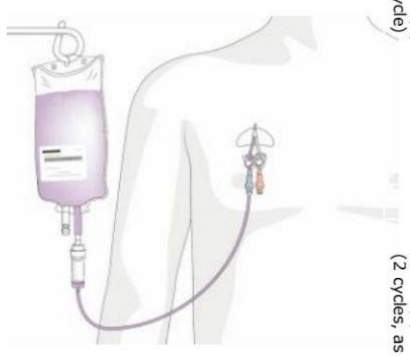
NIPPON SHINYAKU CO., LTD.

JAZZ-HP Mechanism of Delivery
https://vyxeospro.com/mechanism-of-delivery

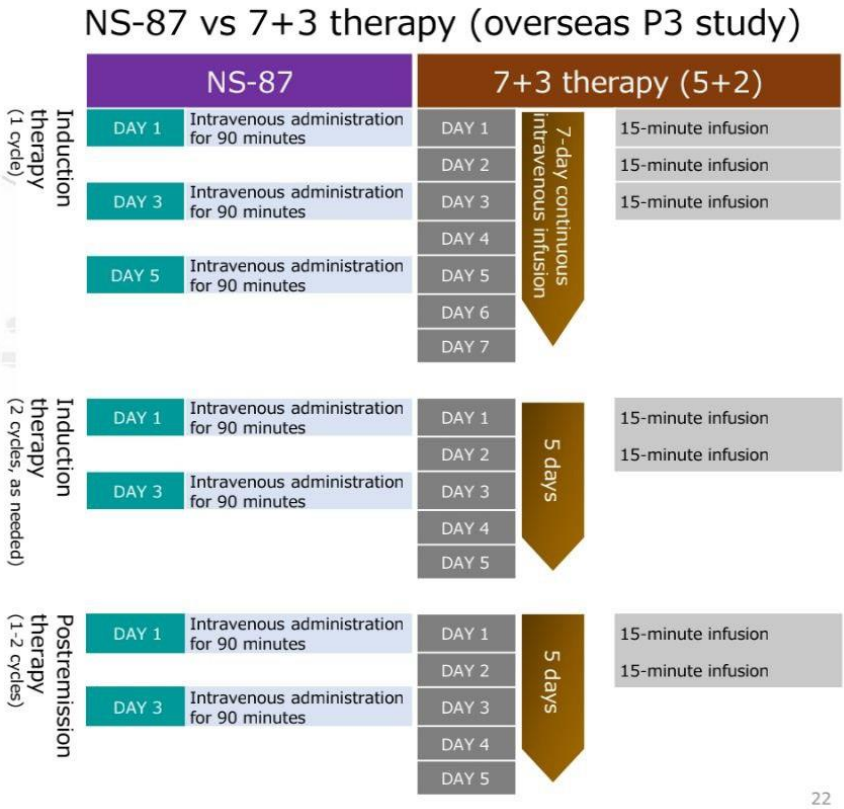
NS-87 is liposome formulation of cytarabine and daunorubicin in a 5:1 molar ratio with the highest antitumor efficacy. NS-87 is known to reach the bone marrow as liposome form and remain for a long time.

After the drug is taken up into leukemic cells in the bone-marrow, cytarabine and daunorubicin are released to exert their antitumor effects.

Time and duration of NS-87



JAZZ-HP VYXEOS preparation and administration
https://vyxeospro.com/dosing-ordering/preparation



NIPPON SHINYAKU CO., LTD.

7+3 therapy requires continuous intravenous infusion for five to seven days, whereas NS-87 is effective after 90 minutes of intravenous infusion over three or five days.

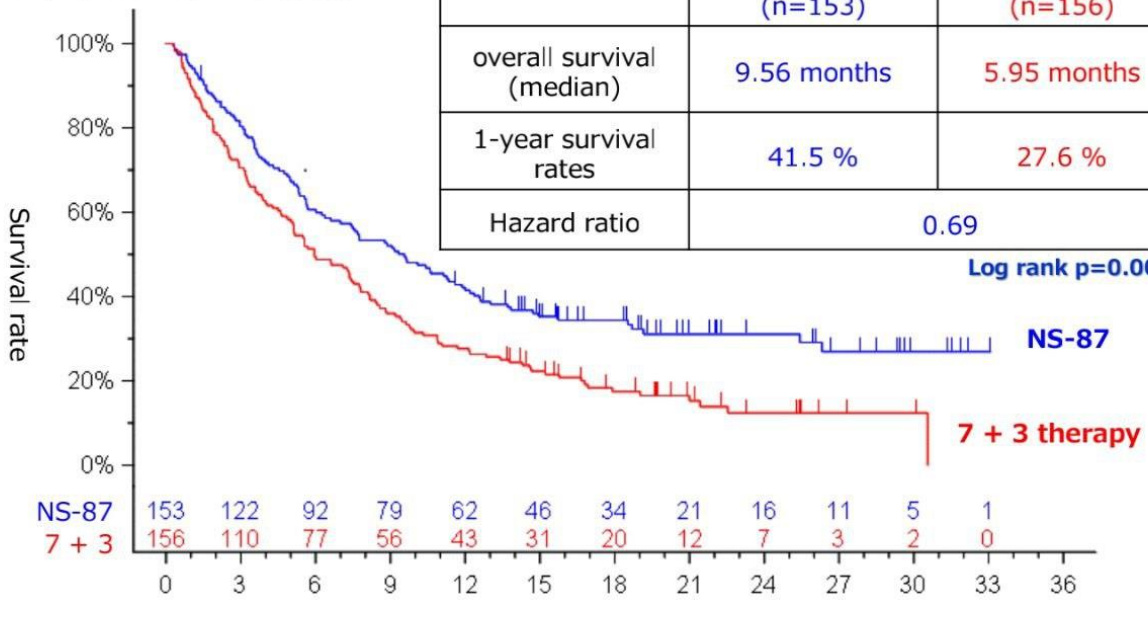
NS-87 enables to reduce the burden of treatment for both patients and healthcare professionals.

NS-87 Oversea P3 study

Subjects: Untreated high-risk AML 309 aged 60-75 years
Control group: 7 + 3 therapy (AraC 100 mg/m2 + DNR 60 mg/m^2)

[Primary: overall survival(OS)]

	NS-87 (n=153)	7+3 therapy (n=156)
overall survival (median)	9.56 months	5.95 months
1-year survival rates	41.5 %	27.6 %
Hazard ratio	0.69	



J Clin Oncol. 2018 Sep 10;36(26):2684-2692

NIPPON SHINYAKU CO., LTD.

23

The results of the overseas Phase III study are shown here.

The patients included 309 cases of untreated high-risk AML patients aged 60 to 75 years.

Overall survival with NS-87 was 9.56 months, compared to 5.95 months with 7+3 therapy, significantly prolonging overall survival.

NS-87 Summary of P1/2 studies

Design	Single-arm, open-label
Study Objectives	To investigate the pharmacokinetics, safety, and efficacy of NS-87 in patients with high-risk AML.
Study patient populations	High-risk AML
Period of registration	August 2019 - October 2021

- **We conducted a phase 1/2 study in Japan. Based on the results of a phase 1/2 study and P3 studies, we applied for application for approval in June 2023.**
- **Orphan drug designation obtained.**

A summary of the NS-87 domestic Phase I/ II study is shown here.

The design was a single-arm, open-label study, and the objective of the trial was to investigate the pharmacokinetics, safety, and efficacy of NS-87 in patients with high-risk AML.

Based on the results of the Phase I/II study in Japan and the overseas Phase III study conducted by Jazz Pharmaceuticals, we filed an application for manufacturing and marketing approval in June 2023.

The drug has already been designated as an Orphan Drug and is expected to be approved in March 2024, based on a review period of approximately 9 months.

NS-580 Endometriosis Treatment

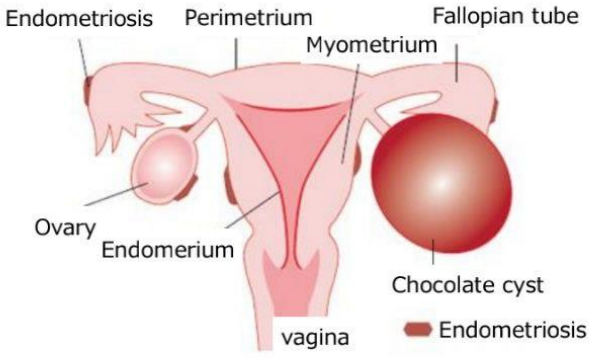
Stage	PIIb study
Development form	In-house development
Mechanism of action	microsomal prostaglandin E synthase-1 (mPGES-1) inhibition
Indications	Endometriosis
Dosage form	Oral drug
Characteristics	✓ Non-hormonal endometriosis treatment with analgesic effect and anti-proliferative effect ✓ Possible long-term use with few side effects

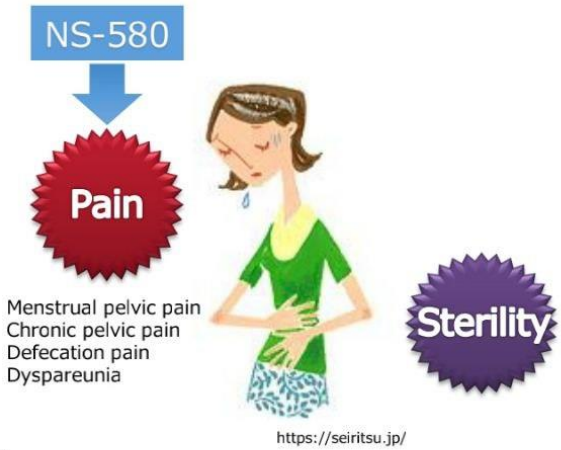
Next, I would like to introduce NS-580.

NS-580 is being developed for endometriosis and is currently undergoing a Phase IIb study in Japan. A microsomal prostaglandin E synthase-1 (mPGES-1) inhibitor is discovered and developed in-house.

NS-580 Endometriosis

Chronic inflammatory disease in which endometrial tissue engrafts outside the uterus and proliferates and bleeds repeatedly according to menstruation





https://seiritsu.jp/

The figure published by the Japanese Obstetrics and Gynecology HP was partially modified

Endometriosis affects approximately 10% women of reproductive age and significantly reduces women's QOL.

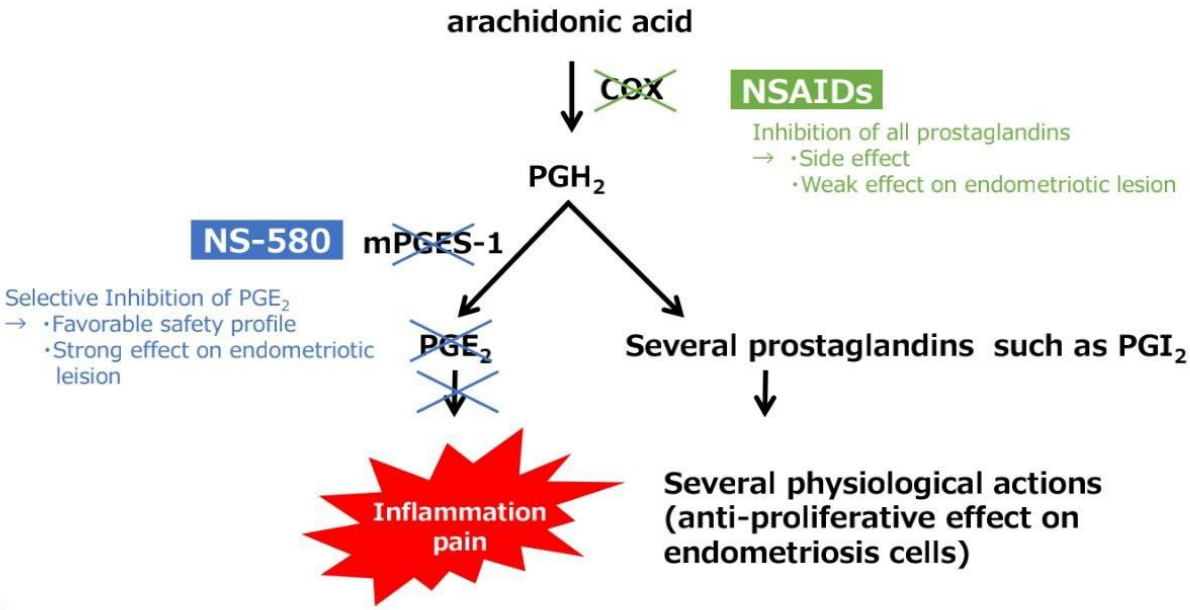
NIPPON SHINYAKU CO., LTD.

Endometriosis, for which NS-580 is indicated, is a chronic inflammatory disease in which endometrial tissue engrafts outside the uterus and continues to proliferate and bleed during the menstrual cycle.

Pain and sterility are the primary symptoms and significantly reduce women’s quality of life.

NS-580 Mechanisms of Action

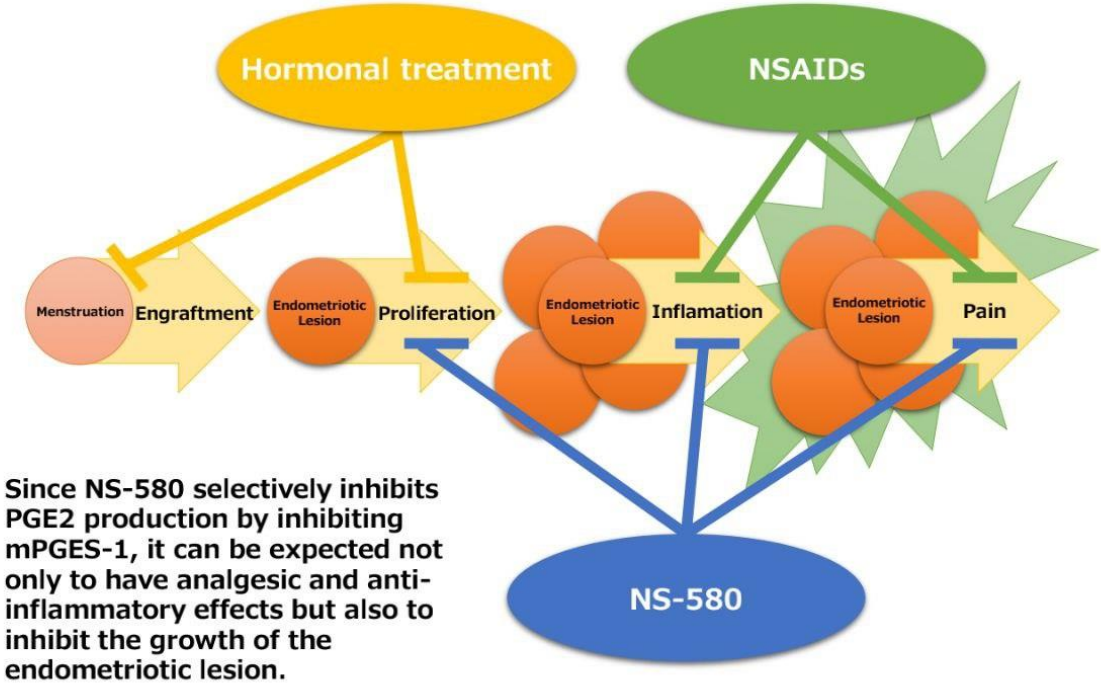
mPGES-1 inhibitor, NS-580 selectively inhibits PGE_2 production



NIPPON SHINYAKU CO., LTD.

NS-580 inhibits only the production of inflammation- and pain-inducing PGE_2 by blocking mPGES-1, the enzyme responsible for the final step in PGE_2 production. It does not inhibit other prostaglandins and is expected to be highly safe and effective for endometriosis lesions.

Action point of each drug in Endometriosis



Since NS-580 selectively inhibits PGE2 production by inhibiting mPGES-1, it can be expected not only to have analgesic and anti-inflammatory effects but also to inhibit the growth of the endometriotic lesion.

This slide shows the point of action of each drug on the pathogenesis of endometriosis. By selectively inhibiting PGE_2, NS-580 is expected to have analgesic and anti-inflammatory effects as well as inhibit the growth of the endometriotic lesion.

We expect it to act differently from existing hormonal treatment and NSAIDs.

NS-580 P2a study (Endometriosis)

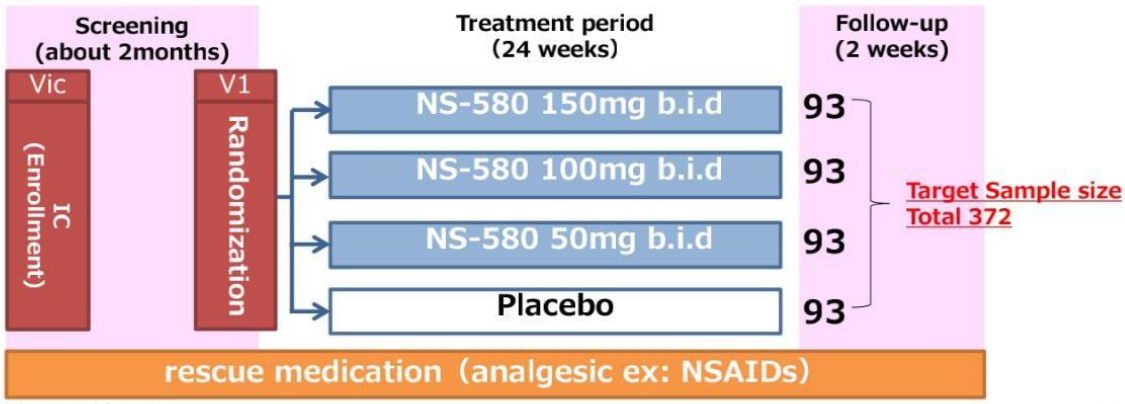
Study design	Randomized, double-blind, multicentre, placebo-controlled, parallel group comparison
Endpoint	Change in pain VAS (Visual analog scale)score
Dosage and Administration	Oral, once daily Dose: placebo, 100 mg, 300 mg/time
Target sample size	150 (100 mg : 300 mg : placebo = 2:2:1)

The analgesic effect of NS-580 was confirmed in Phase 2a study.

Phase IIa study was conducted in Japan. Pain associated with endometriosis was evaluated using VAS score. The target number of cases is 150, 60 cases in each of the two actual drug groups with different doses and 30 cases on placebo group. The results confirmed the analgesic effect of NS-580.

NS-580 P2b study (Endometriosis)

Study design	Randomized, double-blind, multicentre, placebo-controlled, parallel group comparison
Endpoint	Change in pain VAS score
Dosage and Administration	Oral, twice daily Dose: placebo, 50 mg, 100 mg, 150 mg/time
Target sample size	372 (50 mg : 100 mg : 150 mg : placebo=1:1:1:1)



NIPPON SHINYAKU CO., LTD.

30

Based on the results of the Phase IIa study, Phase IIb study is currently underway.

As in the Phase IIa study, pain associated with endometriosis is evaluated by VAS score.

NS-580 with three different doses and a placebo groups.

The target number of cases is 372, and case inclusion has already been completed.

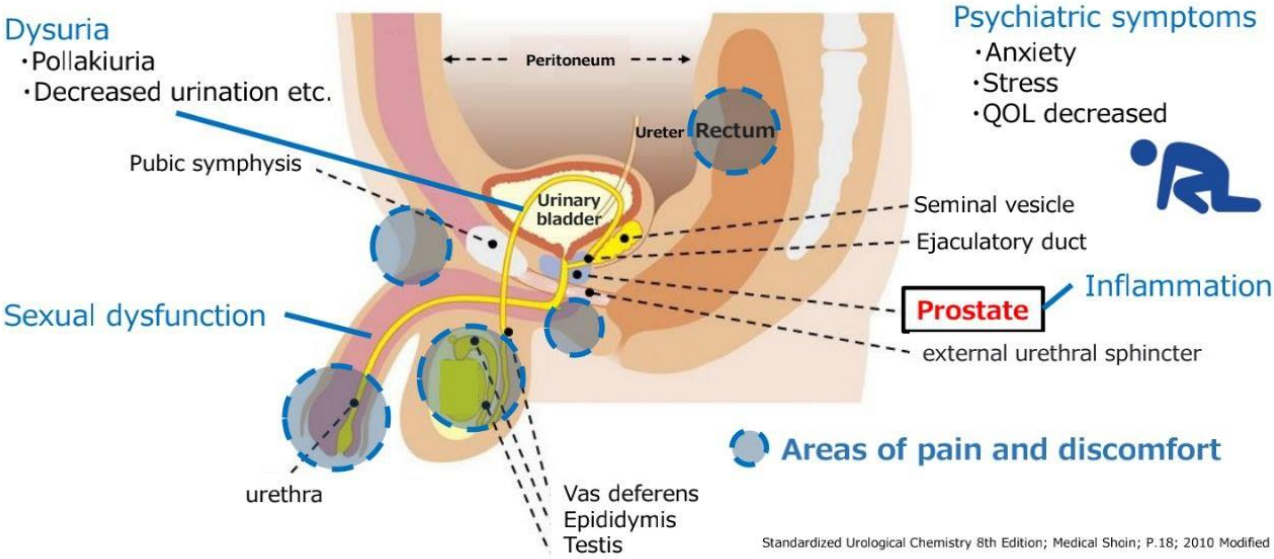
We expect NS-580 to answer the needs of endometriosis patients by acting differently from existing hormonal treatment and NSAIDs.

NS-580 Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Development stage	P2a study
Development form	In-house development
Mechanism of action	Membrane-bound prostaglandin E synthase-1 (mPGES-1) inhibition
Indications	Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)
Dosage form	Oral drug

NS-580 is also being developed for chronic prostatitis/chronic pelvic pain syndrome. The domestic Phase IIa study is currently underway.

CP/CPPS



Peripelvic and periurogenital pain persists **for 3 of 6 months**.
It is defined as the one with voiding and sexual dysfunction, and the etiology has not been clarified.

Number of patients

Japan: Approximately 2 million potential patients (5% of adult males)
Approximately 0.6 million patients were diagnosed
Overseas: About 4% of the male population

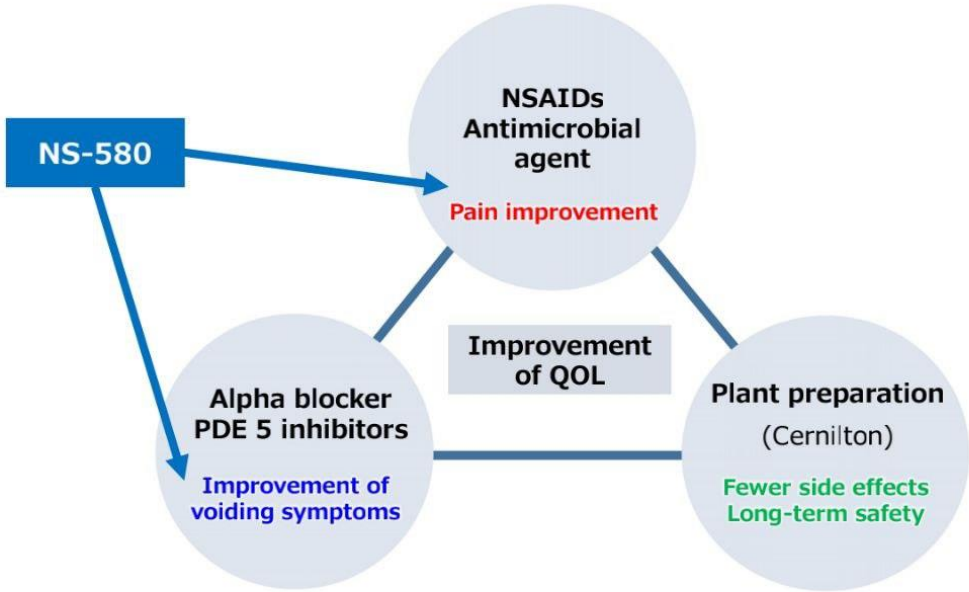
NIPPON SHINYAKU CO., LTD.

32

Chronic prostatitis/chronic pelvic pain syndrome is defined as peripelvic and periurogenital pain that persists for three out of six months. It is associated with urinary and sexual dysfunction, with no clear etiology.

The number of potential patients in Japan is approximately two million, and there are similar ratio of patients overseas.

Treatment for CP/CPPS and Product-concept of NS-580



Product concept

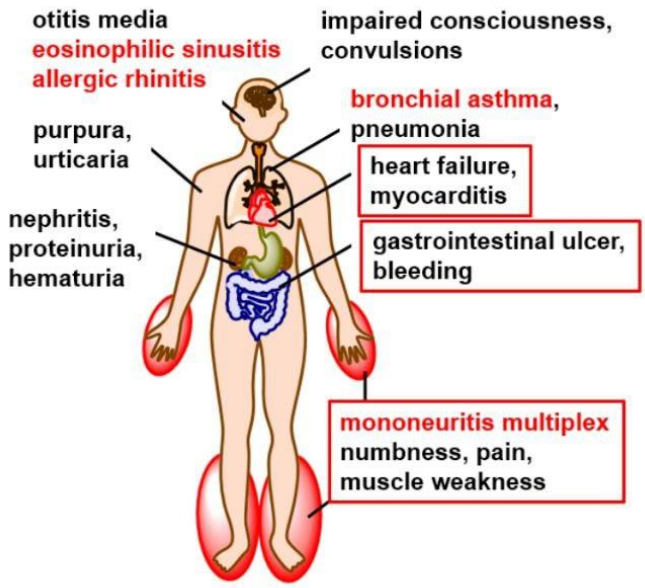
Highly safe treatment for CP/CPPS that can be expected to control pain in the long term

This slide shows the current status of CP/CPPS treatment and product concept of NS-580.

Currently, drugs are selected for each symptom, with NSAIDs and antibacterial agents used for pain relief and alpha blockers and PDE5 inhibitors for urinary symptoms. In addition, the only approved drug, Cernilton, is a safe drug, but new drugs are needed.

NS-580 is expected to become a new treatment option for CP/CPPS with a highly safe treatment and control pain in the long term.

NS-229 eosinophilic granulomatosis with polyangiitis



- **EGPA (eosinophilic granulomatosis with polyangiitis)**
  Rare and intractable diseases of unknown cause designated as intractable diseases in January 2015.
- **Characteristics of the clinical course:**
  Severe asthma with eosinophilia and allergic rhinitis (eosinophilic sinusitis) preceded by several years. Subsequently, a marked increase in peripheral blood eosinophils causes eosinophilic inflammation of various organs of the body and granulomatous necrotizing vasculitis of small to medium-sized vessels.
- **Number of specified medical expense beneficiary certificate holders (designated intractable diseases):**
  5,839 (as of the end of FY2021)
  *Refer to the number of specific medical expense beneficiary certificate holders at Japan Intractable Disease Information Center.

I would like to explain about NS-229.

NS-229 will be developed for a disease called eosinophilic granulomatosis with polyangiitis, EGPA.

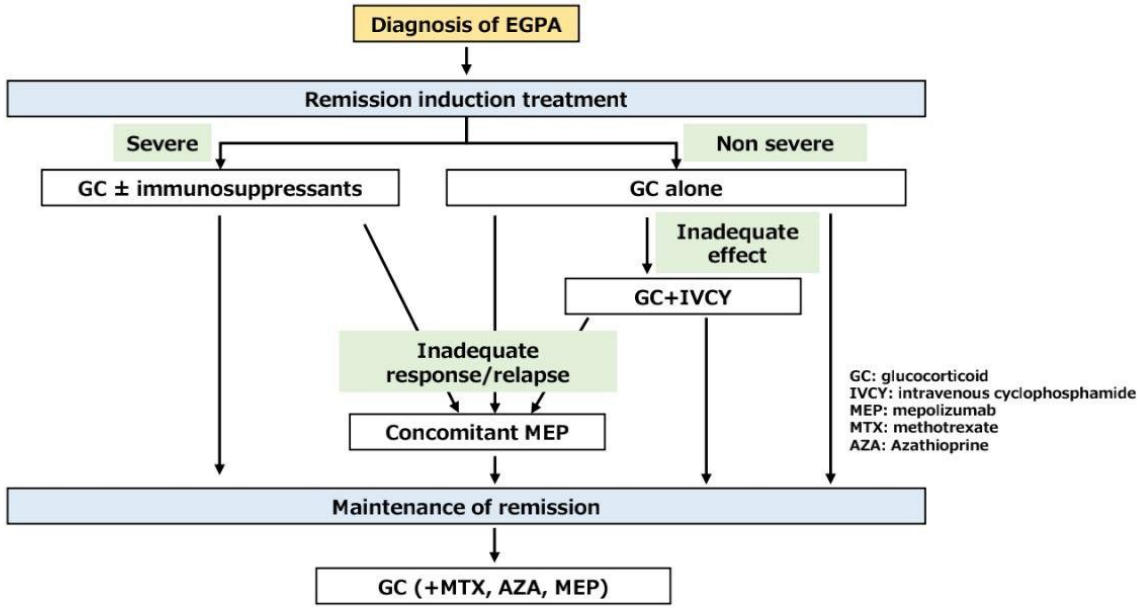
First, I will continue with a description of EGPA.

EGPA is a rare and intractable disease of unknown cause that was designated as an intractable disease in Japan in January 2015.

The figure on the left shows the symptoms that develop in EGPA patients. Symptoms of asthma and allergic rhinitis precede the onset of the disease, followed by systemic eosinophilic inflammation and vasculitis.

As of the end of FY2021, there were 5,839 EGPA patients receiving specific medical expenses in Japan. Considering that not all patients are receiving such expenses, we believe that there are probably more patients than this number in reality.

NS-229 eosinophilic granulomatosis with polyangiitis



Partially modified from ANCA-related vasculitis practice guideline 2023

- **In the treatment of EGPA, glucocorticoids are basically used to induce and maintain remission.**
- **NS-229 is assumed to be widely available in patients with EGPA, replacing glucocorticoids, by inhibiting symptom-related signaling of EGPA.**

NIPPON SHINYAKU CO., LTD. 35

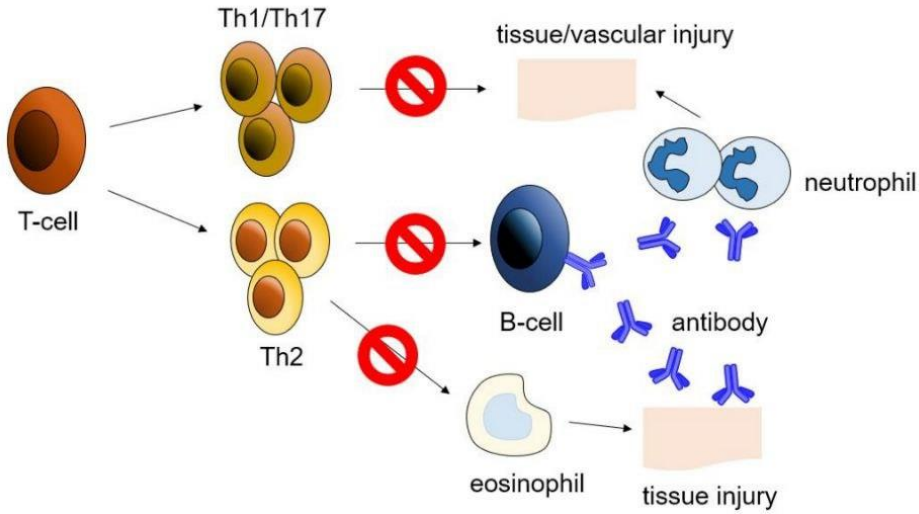
The ANCA-related vasculitis practice guideline was published in 2023 for the treatment of EGPA. The figure shown here is the basis for the treatment plan.

Treatment is divided into the remission induction phase and the remission maintenance phase. During remission induction, patients are treated with glucocorticoids alone or in combination with glucocorticoids and immunosuppressants or mepolizumab.

Once remission is achieved, glucocorticoid monotherapy is used to prolong and maintain the remission period. Alternatively, glucocorticoids are used in combination with methotrexate, azathioprine, or mepolizumab.

At this time, it is very important to keep glucocorticoid doses low in order to avoid the side effects caused by prolonged administration of glucocorticoids. NS-229 aims to be a drug that reduces glucocorticoid doses and controls disease activity while replacing its drug effects.

NS-229 eosinophilic granulomatosis with polyangiitis



- **In EGPA, inflammatory cells, such as T cells, B cells, and eosinophils, are activated and lead to tissue damage.**
- **NS-229 has potent inhibitory effects on JAK1.**
- **Through inhibition of JAK1, it suppresses various cytokine signaling, suppresses activation of T cells, B cells, eosinophils, and other cells, and leads to improvement of disease status.**
- **NS-229 is a selective inhibitor of JAK1, and its selectivity reduces the effects of JAK2 inhibition on the hematopoietic system.**

Next, I will discuss the mechanism of action of NS-229.

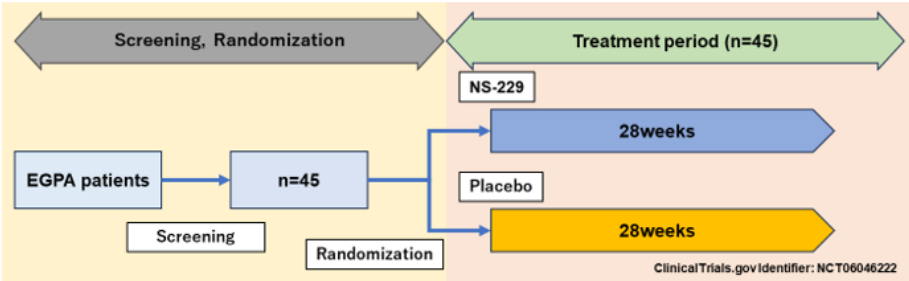
EGPA is an abbreviation for eosinophilic granulomatosis with polyangiitis, but its symptoms develop with the activation of not only eosinophils but also other inflammatory cells such as T cells and B cells, leading to various types of tissue injury.

NS-229 has potent JAK1 inhibitory activity and suppresses activation of eosinophils, T cells, and B cells by inhibiting various cytokine signaling through JAK1 inhibition, leading to improvement of disease conditions.

NS-229 eosinophilic granulomatosis with polyangiitis

Study	A Double-Blind, Randomized, Placebo-Controlled Phase II Study to Evaluate the Efficacy and Safety of NS-229 in EGPA Patients
Design	NS-229 and placebo are compared. At baseline, approximately 45 subjects will be randomly assigned to receive NS-229 or placebo.
Primary efficacy endpoint	Percentage of subjects in remission (OGC 4.0)* at Week 28
Primary safety endpoint	Confirmation of adverse events and adverse drug reactions
Secondary efficacy endpoints	Percentage of subjects in remission (OGC 7.5)* at Week 28 Time to relapse/worsening
Number of subjects	Approximately 45 patients
Treatment period	28 weeks

*(OGC X): A score of 0 on the BVAS, which assesses vasculitis activity, and the amount of oral glucocorticoids administered is less than or equal to X mg/day.



I will talk about the Phase II study for NS-229.

The Phase II study will be a double-blind, randomized, placebo-controlled trial. The 45 patients will be divided into the NS-229 group and placebo group.

This current study will confirm the safety of NS-229 while confirming that the patient is in remission with a reduced dose of glucocorticoids at the time of the last dose as efficacy.

This examination is currently under preparation.

Finally, I would like to introduce our efforts to expand our pipelines I have explained so far.

Currently, we have set a goal of launching an average of at least one new product per year. As President Nakai mentioned at the beginning of this presentation, we believe that we must exceed this goal in order to continue to grow in the future. To achieve this, it is necessary to expand our pipeline, shorten the R&D period, and accelerate drug discovery.

Open Innovation: Innovation Research Partnering (IRP)

We established Innovation Research Partnering (IRP) in Boston area of the United States, where the heart of an ecosystem consisted by various players such as world-class universities, research institutions and bio-venture companies.

Building where IRP office is located

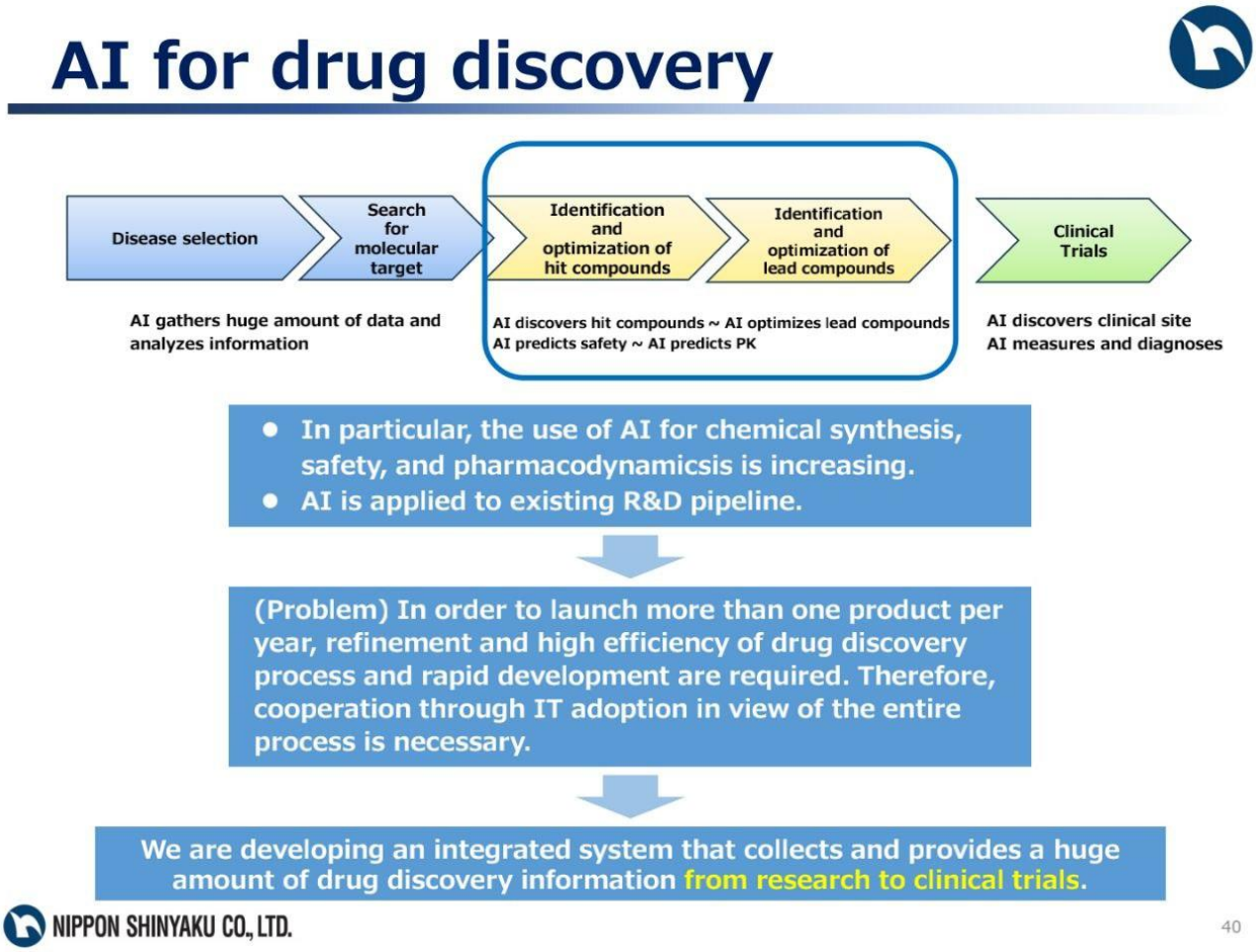
An event in IRP office

**IRP will increase our access to the seeds of the world's most advanced drug discovery technologies and efficiently search for partner opportunities.
We believe that this will lead to accelerate and diversify in-house drug discovery research.**

The nucleic acid drug Viltepso, which was launched in Japan and the US in 2020, is the fruit of more than 30 years of nucleic acid research at our company.

However, we cannot take so long to acquire new drug discovery modalities or to advance in-house drug discovery in the future. Therefore, we are considering shortening development time by acquiring superior external technologies.

Accordingly, we established Innovation Research Partnering in Boston area in January 2023. We aim to increase opportunities for co-creation with world-class scientists through open innovation, to build a diverse R&D portfolio, and to accelerate research.



Next, I would like to explain our use of AI in drug discovery.

The arrows at the top indicate the drug discovery process.

We are using AI in the identification and optimization of the framed compounds and in the prediction of their safety and pharmacokinetics, applying it to existing R&D items as well.

For example, when AI is used in the synthesis stage of a compound, AI predicts the steric structure of the target. The AI will be able to generate the structure of the compound to be bound to it, which is expected to shorten the period of time and discover more active compounds.

Currently, we are in the process of applying AI in each step of drug discovery. To further accelerate our R&D, we are developing an integrated system that collects and provides a huge amount of drug discovery information from research to clinical trials.

In the past, during the initial disease selection and molecular target search phase, researchers conducted literature searches to select targets, and at the same time, it was too time-consuming and difficult to investigate and consider the evaluation of the targets in clinical trials.

If there is an integrated system, AI will take over the labor of searching for such information, making it possible to draft new themes based on the search and clinical evaluation in a short period of time.

We will accelerate drug discovery through these efforts.

This is all. Thank you very much.

FY 2023 R&D Meeting Q&A (Summary)

Held on December 12, 2023

NO	Questions	Answers
1	I have a question about partnering and in-house development. In today's presentation, NS-580 and NS-229 are topics, and I think that you will collaborate with a partner company to promote the global expansion of NS-580. Other than that, will you promote products indicated for hematological and rare diseases with a partner company?	In basic terms, we are planning to collaborate with a partner company to expand NS-580 globally. The market size of NS-229 is not so large. If disease areas of each product are not same, different sales teams are required. However, we can leverage our sales basis such as market access, therefore, we are planning to promote the global expansion of NS-229 through our own marketing.
2	Are you planning to promote global expansion of NS-018 through your own marketing?	Since NS-018 targets relatively small market of myelofibrosis, we are considering our own marketing.
3	Please tell us when your gene therapy proceeds to pre-clinical.	Unlike small molecules, it is difficult to define the beginning of the preclinical stage in gene therapy. We consider preclinical to be the phase in which we initiate safety testing by establishing product specifications similar to those of commercial products, and we anticipate that this phase will take more than two years..
4	This is a question about the pipeline table on slide p.7. The blue arrow of PPMO is shorter than those of exon 45 skipping and exon 55 skipping, so it appears that the PPMO cannot be developed unless all the others are developed. However, considering a competitive situation, should PPMO of Viltepso, exon 45 skipping, and exon 51 skipping be developed faster despite some risks?	This table does not provide a direct indication of the timing of clinical trials, but it shows the current progress. We would like to develop PPMO as quickly as possible.
5	Regarding the development of PPMO, has the nucleic acid sequence been designed?	Yes, it has.
6	Is it possible to develop both conventional morpholino oligomer and PPMO at the same time?	We would like to simultaneously develop both of them as far as the budget allows. There are competitors, so we would like to strategically invest our management resources. We are still in the process of assessing a bold investment in PPMO. I will make a decision to proceed with the development of PPMO according to the situation.
7	Do you mean that you are still not in the position to intensively invest your management resources in the development of PPMO?	You are right.
8	According to the presentation material, NS-089 has been designated as a breakthrough therapy in the U.S. Has the information been released?	We have already issued the press release in July 2023.

9	Regarding the study design of NS-089, I understand that LPO will be in FY2025. Is there any plan to publish the results in part 1 earlier? If so, will it be published within 12 months?	Since muscle biopsy will not be done after part 1, the only result that will come out after part 1 is maximum tolerable dose. That is not enough to make a presentation, so we would like to confirm the dystrophin expression level with the last muscle biopsy after P2 study is completed. Then we will unveil the results.
10	Regarding slide page 9, the data of NS-089 that shows amount change in dystrophin in patient muscle, is there any concern that significant difference will not be observed due to the high baseline? The concept of this drug is to achieve 4 or 5% of dystrophin protein expression, which is the same level as the Becker type and a certain level of motor function can be maintained in such a case. I think that significant difference of motor function cannot be observed, if the baseline is high. I would like to hear your opinion about this.	The baseline of patients amenable to exon 53 skipping was originally close to zero. Therefore, we achieved 5% of dystrophin protein expression in the study for Viltepso. It is said that patients amenable to exon 44 skipping may not need medication because of the high baseline, but their symptoms progress slowly as they age. The patient organization in the U.S. has previously asked our U.S. subsidiary to develop exon 44 skipping therapy. The child of the representing of the patient organization that made the request is a patient amenable to exon 44 skipping, so it cannot be said that there is no need for exon 44 skipping therapy.
11	There was data in the article of NS-089 that nucleic acid might be distributed to cardiac muscle. However, the baseline of dystrophin protein expression of patients amenable to Exon 44 skipping is above a certain level. So I think that NS-089 would not be effective in animal experiments unless its dose was substantially increased. Does NS-089 with a new sequence design method have higher activity than Viltepso, though NS-089 is morpholino oligomer that do not basically affect cardiac muscle?	The permeability of morpholino oligomer into cardiac muscle is not different between NS-089 and Viltepso. However, NS-089 has higher activity than Viltepso, so it can be expected for NS-089 to be more effective. We do not know how much dystrophin expression in cardiac muscle is effective because the structure of skeletal and cardiac muscle are different. There are no data on the efficacy of dystrophin protein expression in cardiac muscle.
12	Can't you assume that dystrophin protein is expressed much longer if exon skipping is administered continuously because the cardiac muscle has no turnover?	I would like to expect such an effect, but now there is no evidence.
13	Regarding the HOPE-3 study of CAP-1002, is it correct that if the study is worth continuing is judged in interim futility analysis and how much CAP-1002 is effective was not observed?	Whether it is meaningless or acceptable to continue with this trial is judged in the futility analysis. The results indicate that there is no safety concern and regarding the efficacy, it is not a situation to suspend the study.
14	Will the milestone for the result of the interim futility analysis of HOPE-3 trial be recorded on P/L?	It will be recorded on BS this fiscal year.
15	Will the results of the HOPE-3 study of CAP-1002 be approved if the results at the same level as HOPE-2 study are confirmed?	The difference between HOPE-3 study and HOPE-2 study is the number of patients and that of HOPE-3 study is more than that of HOPE-2 study. We think that CAP-1002 can be approved if the results of HOPE-3 study are similar to that of HOPE-2 study. We know that Capricor Therapeutics has had frequent contact with FDA.
16	Do you have any information beyond the press release about the interim futility analysis of CAP-1002? Capricor Therapeutics is going to have a meeting with FDA in the first quarter of next year. Do they have confidence about expedited approval of CAP-1002?	We don't have further information than the press release. We have heard that they have requested a meeting with FDA to further discuss opportunities for accelerated approval pathways, but we have no information on the probability of expedited approval.

17	I have a question about CAP-1002. Is the equivalence of products manufactured in Los Angeles and San Diego evaluated in accordance with the specifications?	We understand that Los Angeles and San Diego sites can manufacture similar products. However, CAP-1002 is a biologic drug and the equivalence must be confirmed in clinical trials. Therefore, cohort B is underway in conjunction with cohort A.
18	One of the secondary endpoints of the HOPE-3 study of CAP-1002 is change in cardiac muscle function and structure. Although the primary endpoint is important for approval, it is likely that cardiac muscle function and structure are also commercially important. What is the commercial impact of secondary endpoints?	Because of the cardiosphere-derived exosomes, we expect an effect on cardiac muscle. If the change in cardiac muscle function and structure in the secondary endpoints can be proved, it is expected to have a positive effect on the factors that determine the lifespan of DMD patients because DMD patients tend to die due to the decline in cardiac function.
19	In the Q&A section of IR meeting for the 2Q, we heard that one of the payers has a policy of reimbursement for Viltepso after using gene therapy. Have you confirmed the example of reimbursement after the IR meeting in November?	We have told our U.S. subsidiaries to pay close attention, but we have not yet confirmed the actual examples.
20	Although I don't know whether it is related to NS-580, you have recently published a patent stating that prostaglandins are effective in combining tumor immunity. How committed are you to developing this?	Chemotherapy other than hematologic cancer is not our target areas. We would like to develop it if we can collaborate effectively with other companies.
21	What level of efficacy and safety was achieved in the P2a study of NS-580 for endometriosis? Based on the mechanism, I think that the short-term effect is weak, but the long-term effect becomes gradually stronger because it inhibits the growth of the endometriotic lesion. Although it is not a comparative study with other drugs, what sort of positioning is likely to be expected from the efficacy and safety data? Why is the number of administrations changed to twice-daily in the P2b study?	It is hard to explain the details, but the analgesic effect of NS-580 was confirmed in P2a study. We will determine the potential of NS-580 by the twice-daily administration based on the results of the P2a study. There are patients who hesitate to use hormonal treatments due to the side effects and some people in Japan who are reluctant to use hormonal treatments themselves. Therefore, regarding to the position of NS-580, it is assumed that NS-580 will be used by those kind of patients. We would like to carefully review the positioning according to the results.
22	Is NS-580 mechanistically available in combination with hormone therapy or NSAIDs?	We assume that NS-580 will be used separately from them basically.
23	Is NS-229 similar to Avacopan? In addition, are the target patient group and the positioning of NS-229 similar to those of Avacopan?	Since the mechanism of action of NS-229 is different from that of Avacopan, we expect different effects. Avacopan is not indicated for EGPA but other ANCA-related diseases, so they are not in competition.