

# R&D Meeting

Dainippon Sumitomo Pharma Co., Ltd.

14th March 2006



# R&D Decision Process

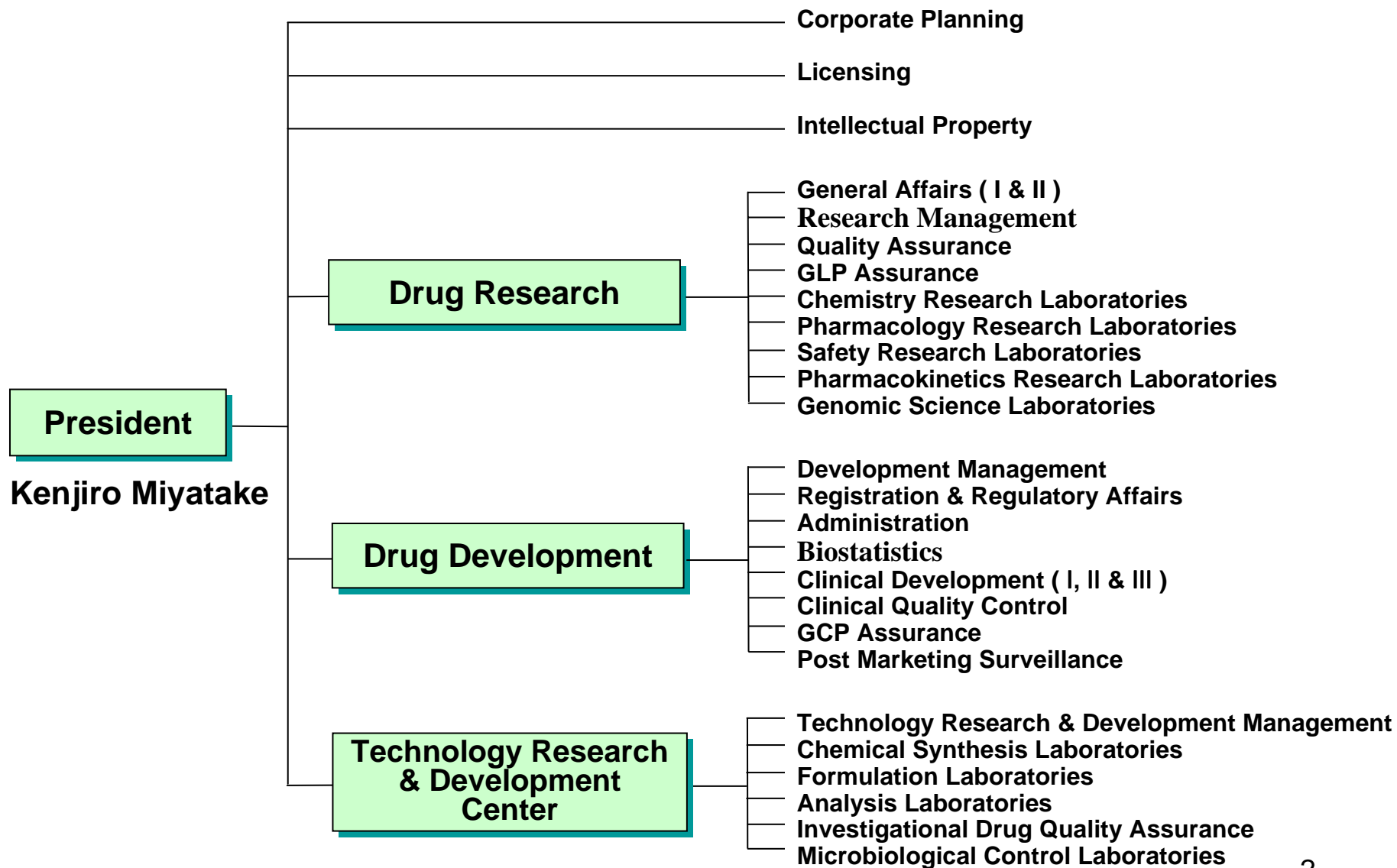
Dainippon Sumitomo Pharma Co., Ltd.

Director, Corporate Planning  
Tetsuya Oida



14<sup>th</sup> March 2006

# Drug Research & Development



# The DSP Project System

**- Total Portfolio Efficiency -  
Maximization of Corporate Value**

**- Efficient Use of Resources -  
Project Prioritization**

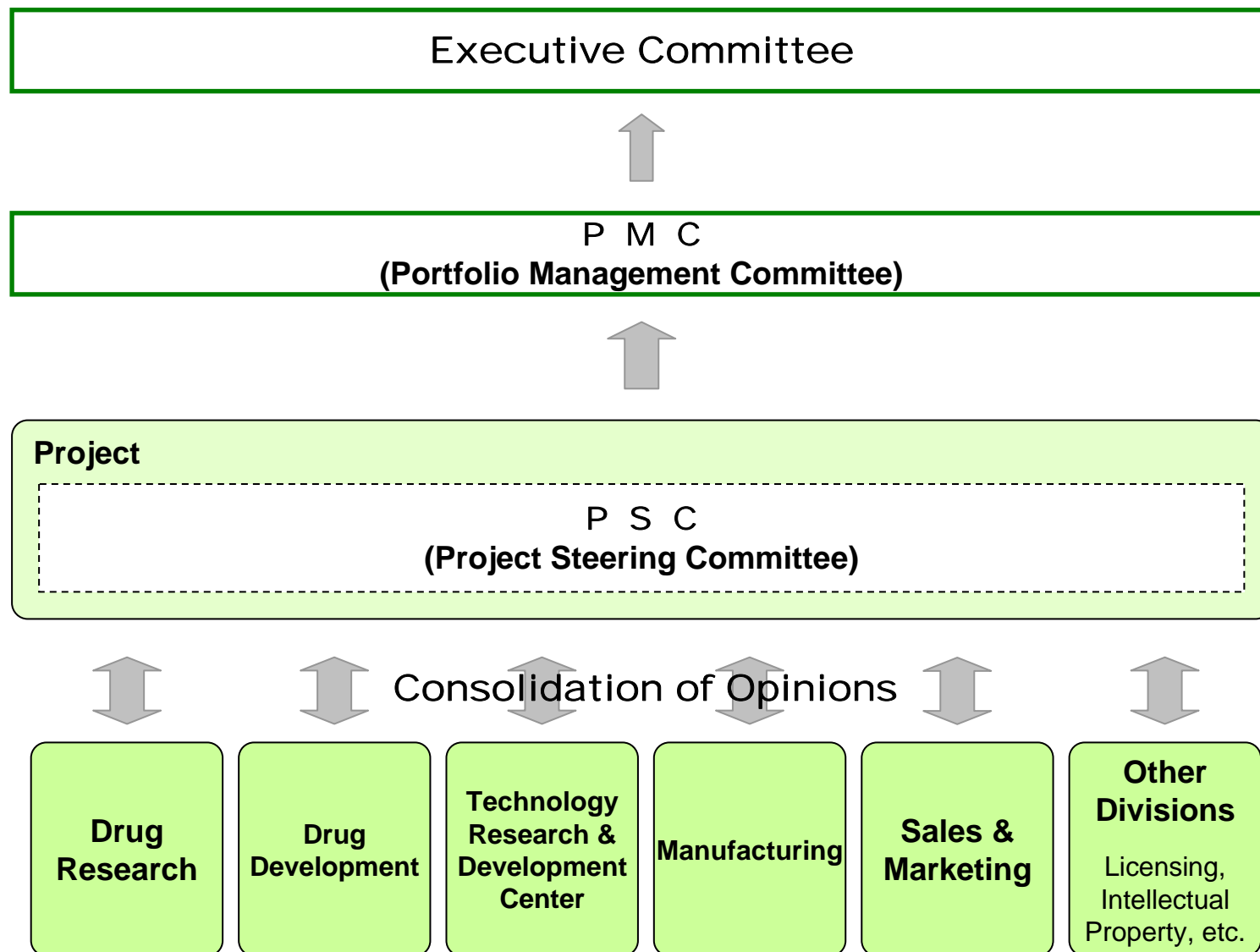
## **Project System**

Designed to promote seamless activities across internal company boundaries

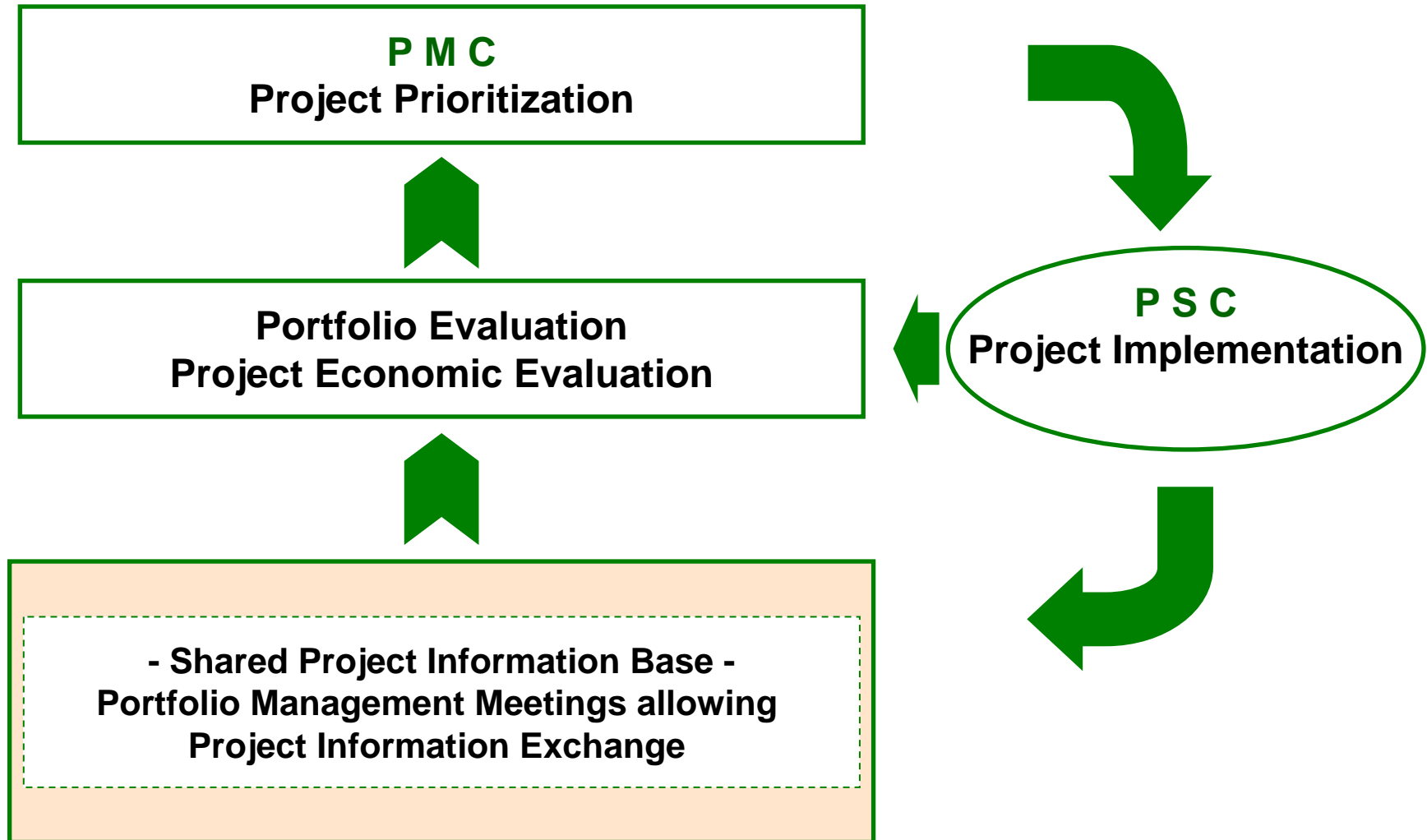
- ▶ **Rapid promotion of projects by strengthening collaboration channels**
- ▶ **Greater shared knowledge base**
- ▶ **Develop & up-skill human resources**

Project Scope: A compound in the preclinical or clinical stages, or a product currently marketed

# Decision Process for Projects



# Project Portfolio Management



# Drug Research Overview

Dainippon Sumitomo Pharma Co., Ltd.

Executive Director, Drug Research  
Yuichi Yokoyama, Ph.D.



14<sup>th</sup> March 2006

# **1. Drug Research Organization**

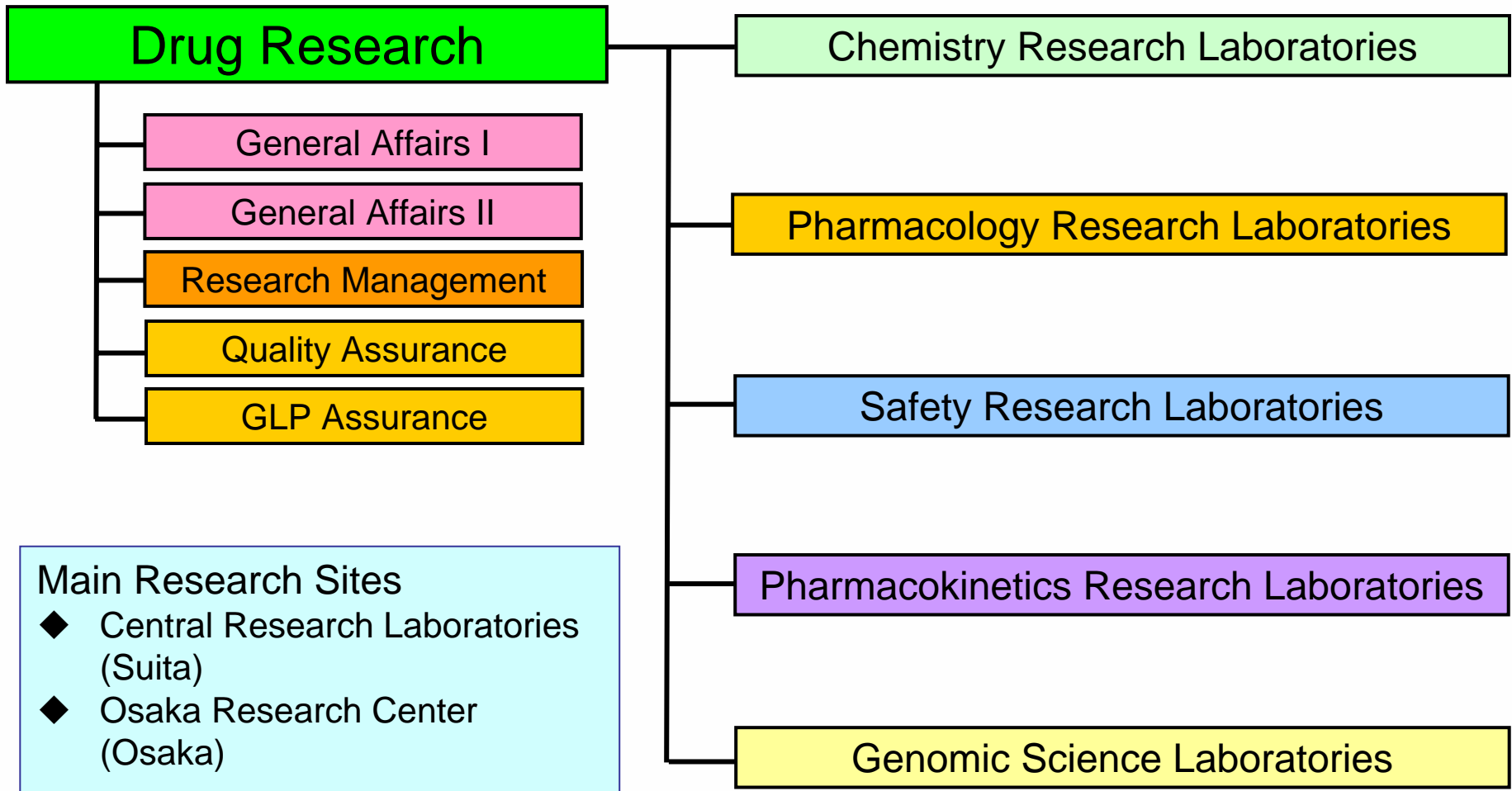
## **2. Main Research Areas**

### **3. Technology Development**

- Target Identification and Validation
- Improvement in Speed and Success Rate



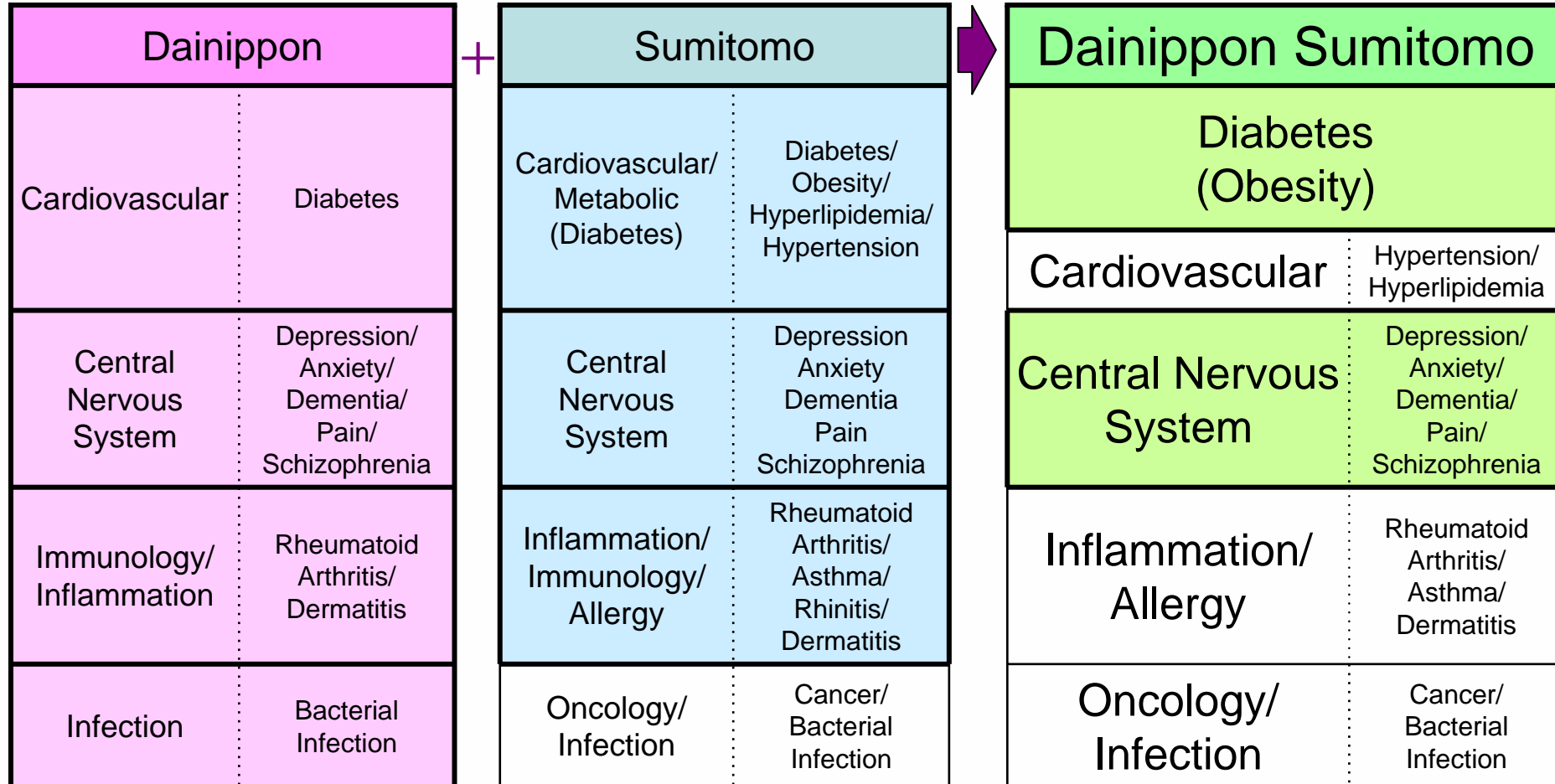
# Drug Research Organization



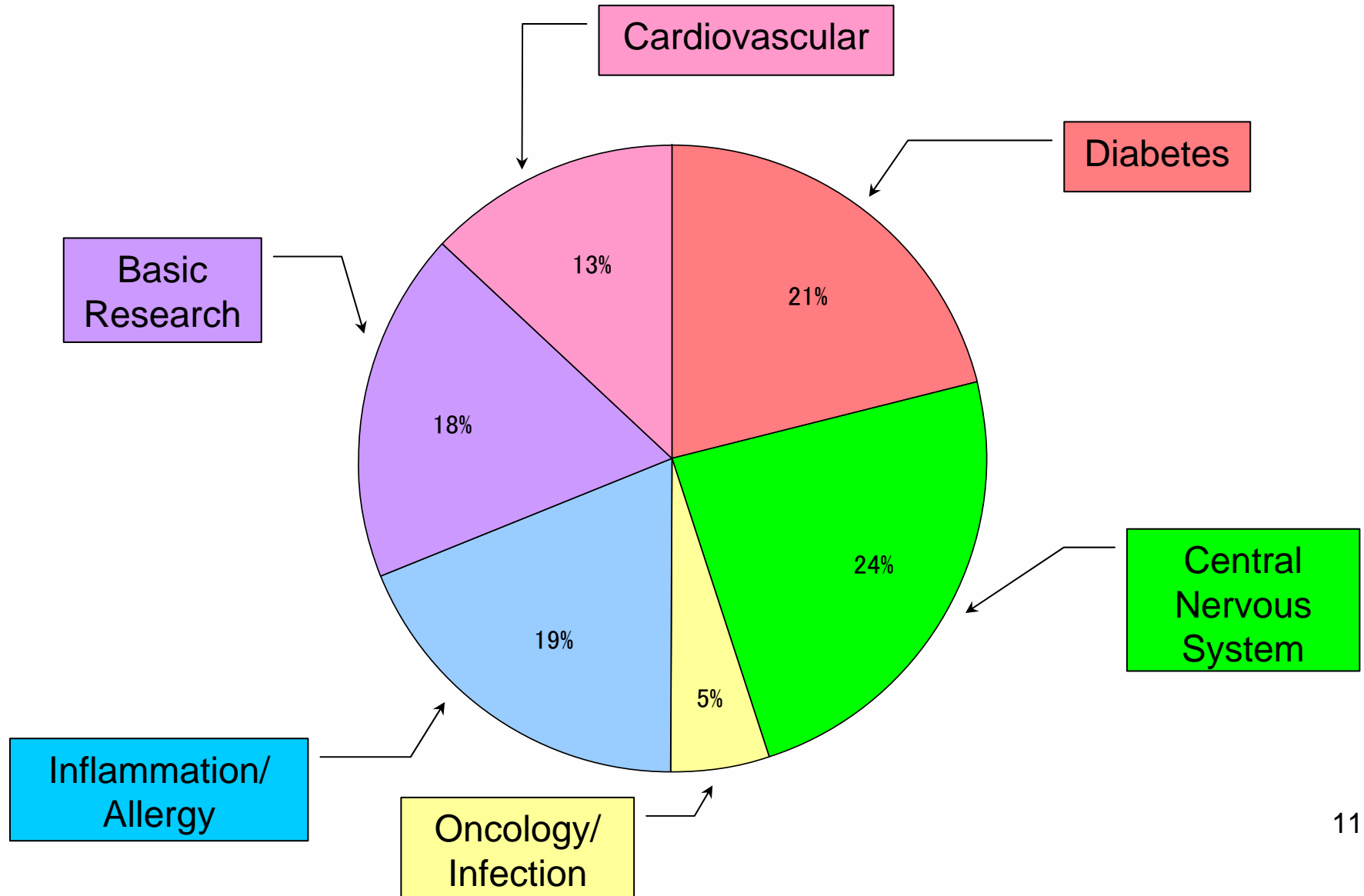
# Research Sites and Functions

	Central Research Laboratories	Osaka Research Center
Chemistry Research Laboratories	All functions at both sites	
Pharmacology Research Laboratories	Central Nervous System	Diabetes & Cardiovascular Inflammation & Allergy Oncology & Infection
Safety Research Laboratories	Non-GLP Studies	GLP Studies
Pharmacokinetics Research Laboratories	Discovery Pharmacokinetics Studies	Development Pharmacokinetics Studies
Genomic Science Laboratories	Protein Structure Analysis	Protein Structure Analysis Genomics and Proteomics Studies

# Main Drug Research Areas



# Focusing on Diabetes and CNS



# Oral Antidiabetics

## Main Mechanism and Target

### Biguanide

*Hepatic Gluconeogenesis Inhibition*

- **Metformin (Melbin)**
- (SMP-862: under development)

### Glitazone

*Muscular Glucose Uptake Accelerator*

### Aldose Reductase Inhibitor

(Complication Therapy)

*Neural Sorbitol Accumulation Inhibition*

- Epalrestat
- Fidarestat
- **AS-3201** (under development)

### $\alpha$ -Glucosidase Inhibitor

*Glucose Absorption Inhibition in Gut*

- Voglibose
- Acarbose
- **Miglitol (Seibule)**

### Sulfonylurea

*Insulin Secretagogue*

- Glimepiride
- **Gliclazide (Glimicron)**
- Glibenclamide

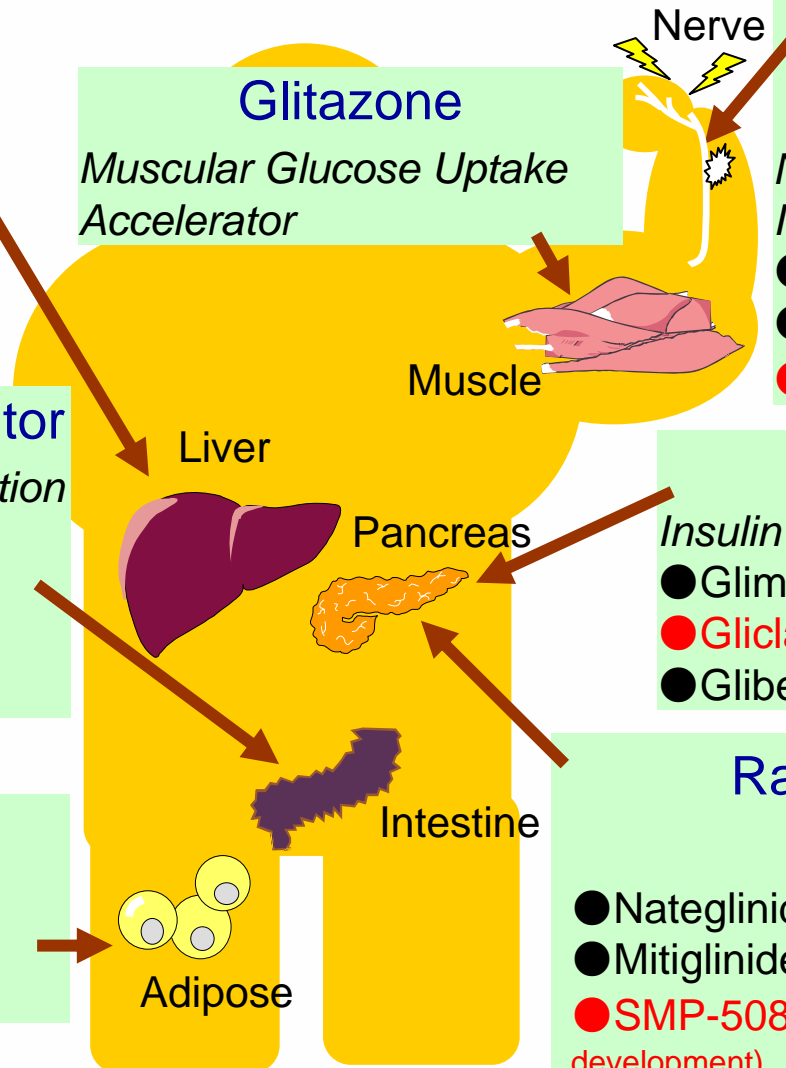
### Glitazone

*Adipose Glucose Uptake Accelerator*

- Pioglitazone

### Rapid-acting Insulin Secretagogue

- Nateglinide
- Mitiglinide
- **SMP-508 (Repaglinide)** (under development)



# Focusing on Diabetes

		Main Indication/ Mechanism of Action	Marketed Products	Development Compounds	Research Phase	
Metabolic syndrome-related diseases	Diabetes	Insulin Secretagogue	Sulfonylurea	Glimicron		
			Rapid-acting Insulin Secretagogue		Repaglinide	○
		Insulin Sensitizer		Melbin	Metformin	○
		Glucose Absorption Inhibitor		Seibule		○
		Complication therapy			Ranirestat	○
		Antiobesity				○
	CV	Hypertension		Amlodin Cetapril Almarl		○
		Hyperlipidemia		Lipoclin	SMP-797	○

# Focusing on CNS

Main Indication		Products	Development	Research
Functional	Schizophrenia	Lullan Serenace Halomonth	Blonanserin Lurasidone	
	Depression	Noritren Abilit		○
	Anxiety	Sediel Erispan	AC-5216	
Organic	Parkinson's disease	Dops Akineton	Zonisamide	
	Dementia		AC-3933	○
	Epilepsy	Excegran Mystan		
Pain		Morphine		○

Accelerated development through collaboration with Merck

Accelerated development through collaboration with Novartis

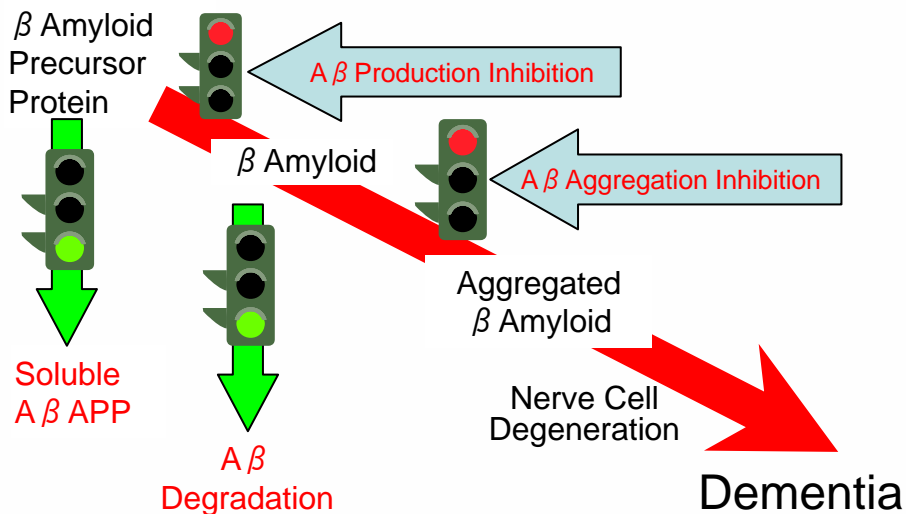
Strengthened research through KASPAC collaboration

# KASPAC Project (2000.8-)

**KASPAC:** Karolinska Institute + Dainippon Sumitomo  
(Karolinska Institute Sumitomo Pharmaceuticals Alzheimer Center)  
• Exploration of Discovery Targets for Alzheimer's disease

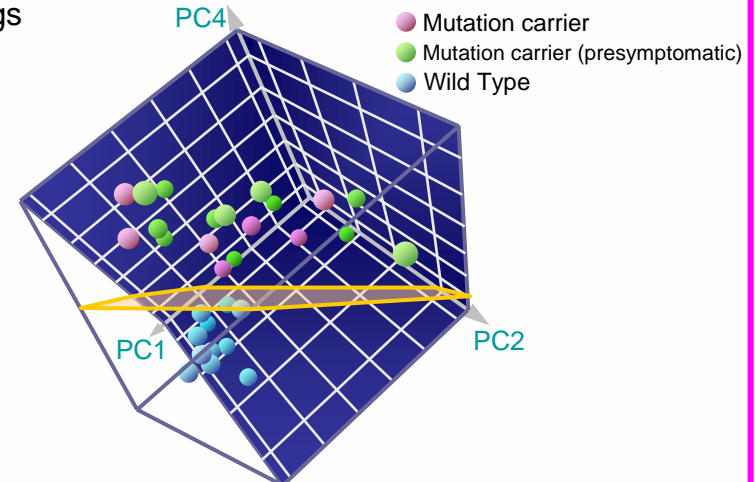


## Drug Discovery based on Amyloid Hypothesis



## Exploratory Research of Alzheimer-related Genes

A unique gene expression signature discriminates familial Alzheimer's disease mutation carriers from their wild-type siblings





# Technology Development

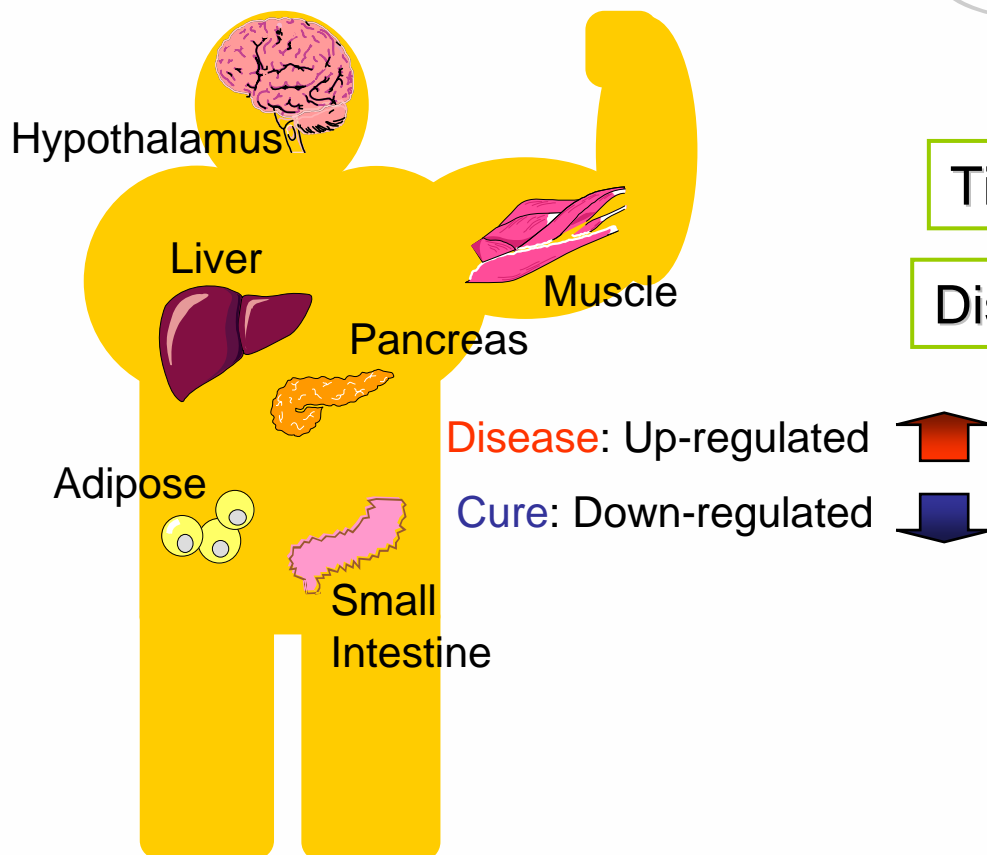
- ◆ Target Identification and Validation
  - Genomic Science Laboratories
  - Collaborations and Alliances
- ◆ Improvement in Speed and Success Rate
  - Discovery Pharmacokinetics Studies
  - Discovery Toxicology Studies

# Genomic Science Laboratories

(Target Identification & Validation)

## ★ Metabolic Syndromes

Obesity  
Insulin Resistance/Diabetes  
Hyperlipidemia/Arteriosclerosis, etc



## Gene-expression Profile



Tissue-specific Gene Expression

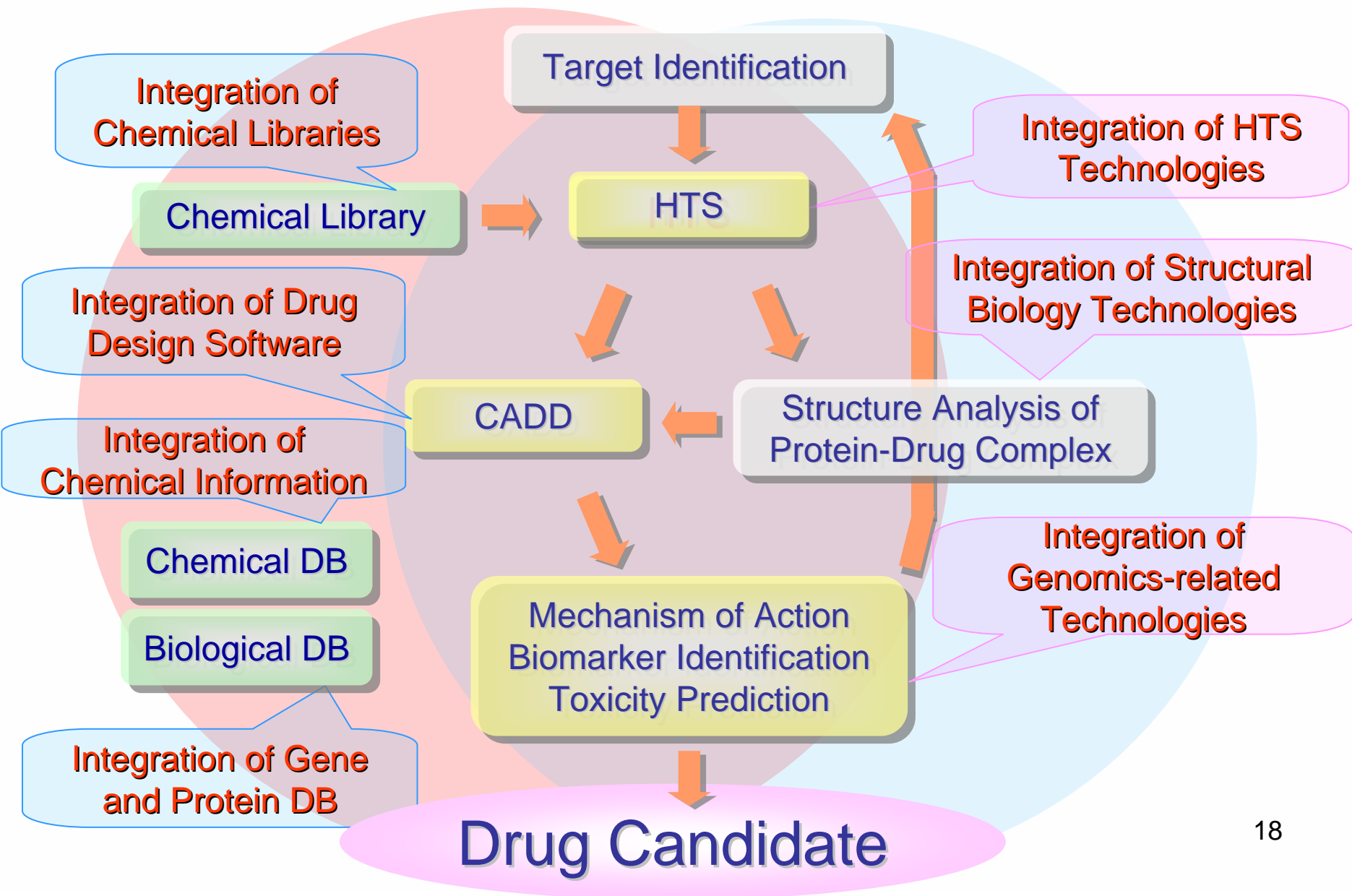
Disease-specific Gene Expression

Target Candidate

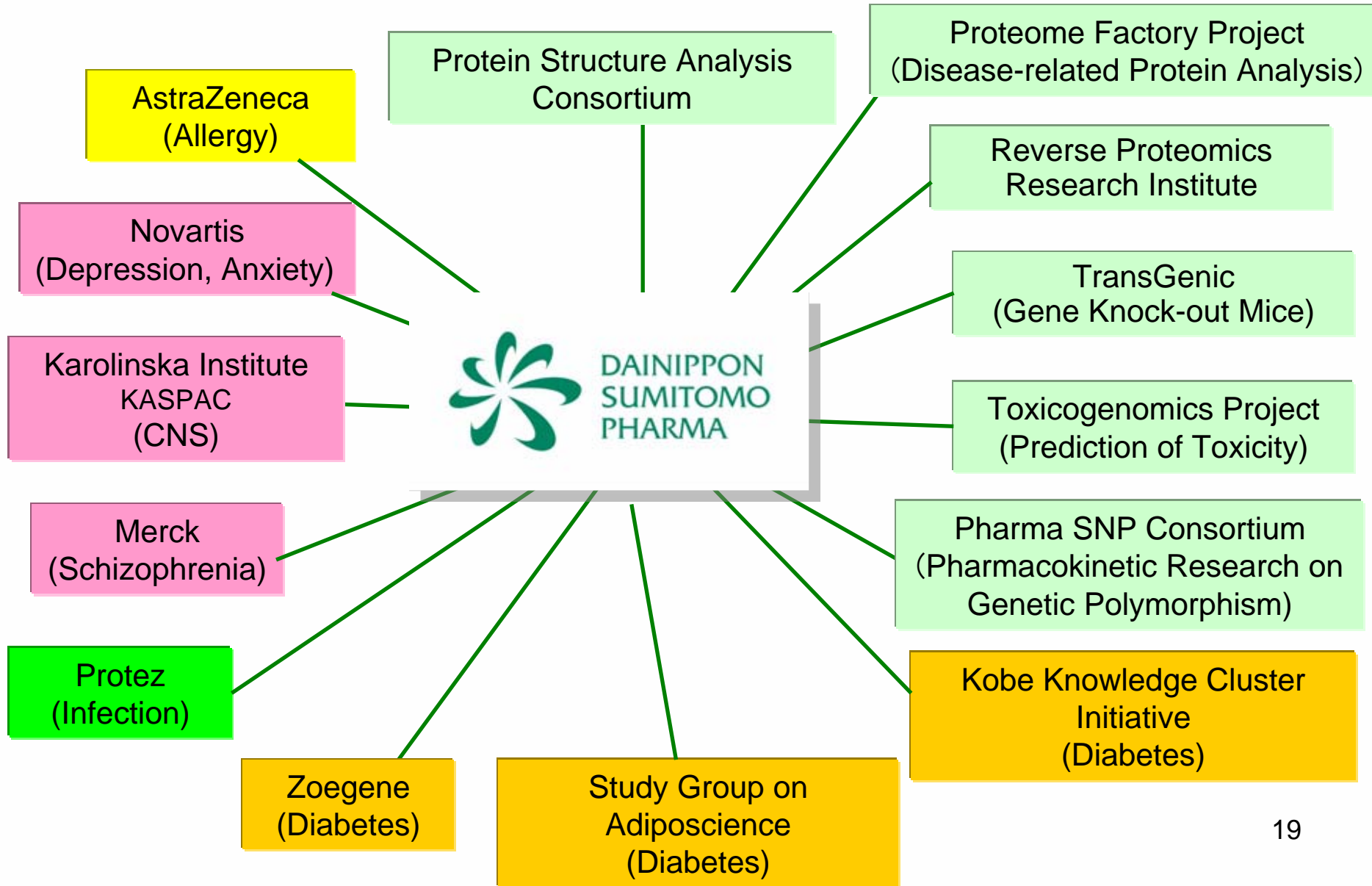


Hit Compound

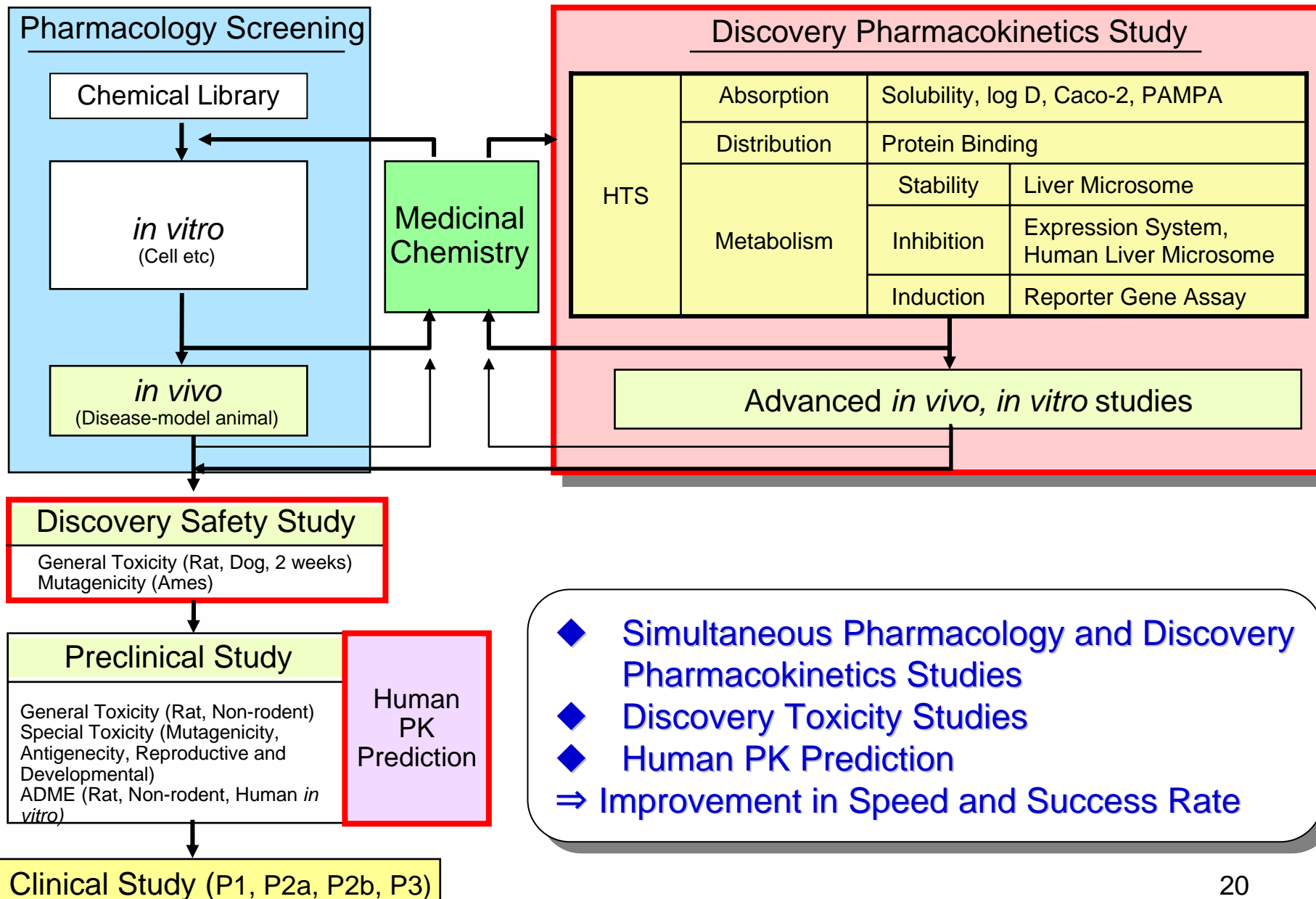
# Promoting Technology Integration



# Collaborations and Alliances



# Discovery Pharmacokinetics & Toxicology



# Drug Development Overview

Dainippon Sumitomo Pharma Co., Ltd.

Executive Director, Drug Development  
Keiichi Ono, Ph.D.



14<sup>th</sup> March 2006

- 1. Mission of Drug Development**
- 2. Organizational Structure of Drug Development**
- 3. Status of Drug Development**

# Mission of Drug Development Division

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- Development of Medicinal Products that Meet Therapeutic Needs
- Creation of Medicinal Products with Competitive Superiority in the Market
- Earliest Possible Provision of New Drugs to Health Care Professionals



Drug Development  
Division




- Development Management
- Registration & Regulatory Affairs
- Administration
- Biostatistics
- Clinical Development I
- Clinical Development II
- Clinical Development III
- Clinical Quality Control
- GCP Assurance
- Post Marketing Surveillance

Clinical Development in the US and EU





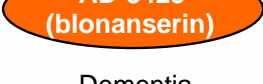
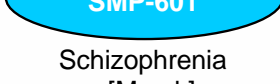


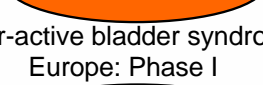
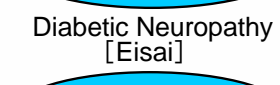
- London
- New Jersey

# R&D Pipeline

Pre-registration	Phase III	Phase II		Phase I
Fabry's disease <b>SMP-536</b>		Diabetic neuropathy <b>AS-3201 (ranirestat)</b>	Diabetes <b>SMP-508 (repaglinide)</b>	Dementia <b>AC-3933</b>
Systemic fungal infection <b>SM-26000</b>		Hepatocellular carcinoma <b>SM-11355 (miriplatin)</b>	Diabetes <b>SMP-862 (metformin)</b>	Hypercholesterolemia <b>SMP-797</b>
Schizophrenia <b>AD-5423 (blonanserin)</b>	(Compensated cirrhosis and Chronic hepatitis C) <b>SUMIFERON</b>	Schizophrenia <b>SM-13496 (lurasidone)</b>	Anxiety & Depression <b>AC-5216</b>	
(Parkinson's disease) <b>zonisamide</b>	(Febrile neutropenia) <b>MEROPEN</b>	Rheumatoid arthritis <b>SMP-114</b>	(Cervical spondylosis) <b>PRORENAL</b>	
(Non-Hodgkin's lymphoma) <b>CALSED</b>	(Under preparation for Phase III) Diabetic neuropathy US/Canada <b>AS-3201 (ranirestat)</b>	(Post-gastrectomy syndrome) <b>GASMOTIN</b>	Dementia US <b>AC-3933</b>	Over-active bladder syndrome Europe <b>SMP-986</b>
(Intravenous injection) <b>EPHEDRINE NAGAI</b>		Europe, US <b>AD-5423 (blonanserin)</b>	Hypercholesterolemia Europe <b>SMP-797</b>	
		Rheumatoid arthritis Europe <b>SMP-114</b>		

 Development in Japan (New Chemical Entity)
  Development in Japan for new indication (new indication etc.)
  Overseas development

# Overseas Clinical Development

Clinical Studies (Dainippon Sumitomo Pharma)	Clinical Studies (Out-Licensed)
Diabetic neuropathy US/Canada: Phase III	Anxiety/Depression [Novartis]
	
Rheumatoid arthritis Europe: Late Phase II	Cancer [Sunesis]
	
Schizophrenia Europe, US: Phase II	Life-threatening infection [Protez]
	
Dementia US: Early Phase II	Schizophrenia [Merck]
	
Hypercholesterolemia Europe: Early Phase II	Cancer [Conforma]
	
Over-active bladder syndrome Europe: Phase I	Diabetic Neuropathy [Eisai]

# Pre-registration

Product code	Generic name	Target disease	Formulation
SMP-536	Agalsidase alfa	Fabry's disease	Injection
SM-26000	Amphotericin B liposome	Systemic fungal infection	Injection
AD-5423	Blonanserin	Schizophrenia	Tablet Powder
AD-810N	Zonisamide	Parkinson's disease (New indication)	Tablet
CALSED	Amrubicin hydrochloride	Non-Hodgkin's lymphoma (New indication)	Injection
Ephedrine	Ephedrine hydrochloride	Hypotension under anesthesia (New administration route)	Injection

# Summary of SMP-536 (agalsidase alfa)

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Target disease:	Fabry's disease (Orphan drug)
Mode of action:	$\alpha$ -galactosidase A (recombinant) enzyme replacement therapy
Formulation:	Injection (Infusion)
In-house/Licensed:	Licensed from Shire
Stage:	Pre-registration

# Profile of SMP-536 (agalsidase alfa)

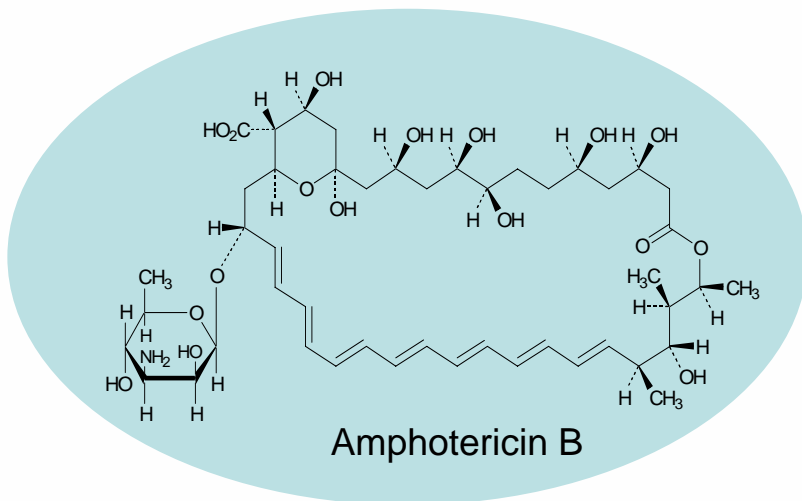
	<b>SMP-536</b>	<b>Fabrazyme</b>
Dose	0.2 mg/kg	1.0 mg/kg
Dosing duration	Longer than 40 minutes	Longer than 2-4 hours*
Dosing frequency	Once every 2 weeks	Once every 2 weeks
Dosing route	Intravenous infusion	Intravenous infusion
Therapeutic effects	Decrease in CTH (GL-3) Improvement of Pain/QOL	Decrease in CTH (GL-3)
Number of countries where approved	34 countries	35 countries

\*: An infusion rate of 0.25-0.5 mg/minute was used to calculate the duration for infusion to a patient with body weight of 60 kg.

## Summary of SM-26000 (amphotericin B liposome)

Target disease:	Systemic fungal infection
Mode of action:	Amphotericin B liposome
Formulation:	Freeze-dried powder for intravenous injection
In-house/Licensed:	Licensed from Gilead Sciences
Stage:	Pre-registration

# Profile of SM-26000

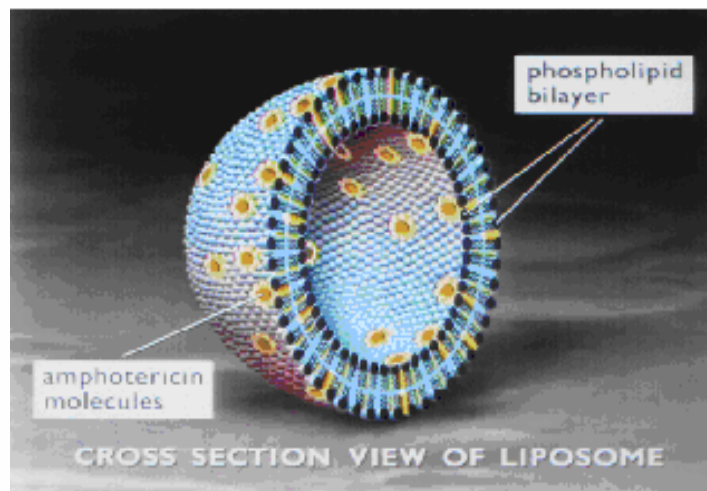


## Profile of amphotericin B

- Wide anti-fungal spectrum
- Fungicidal effect
- Safety issues
- Renal damage: Limited dose levels

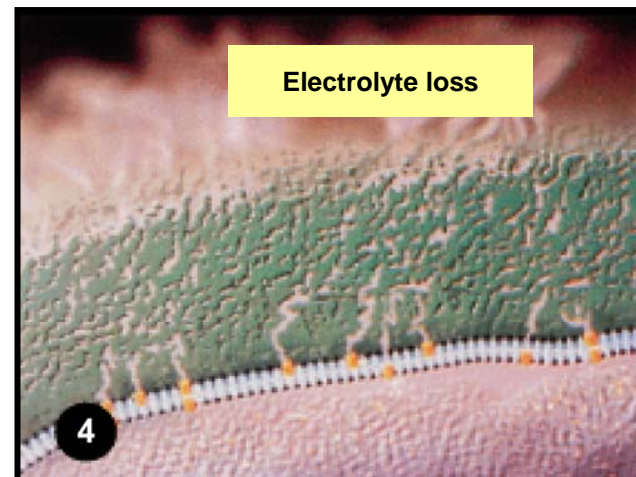
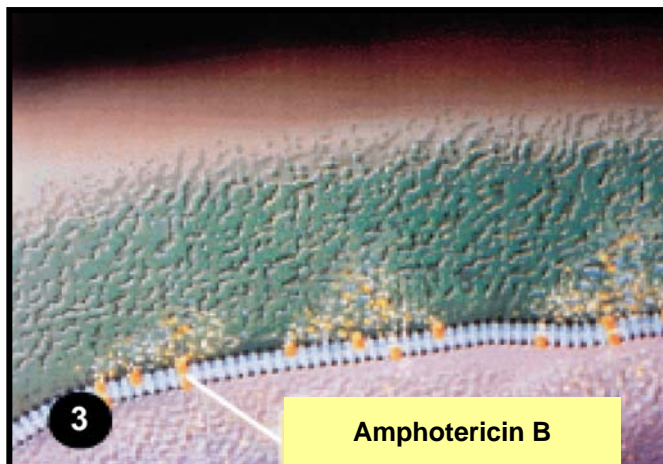
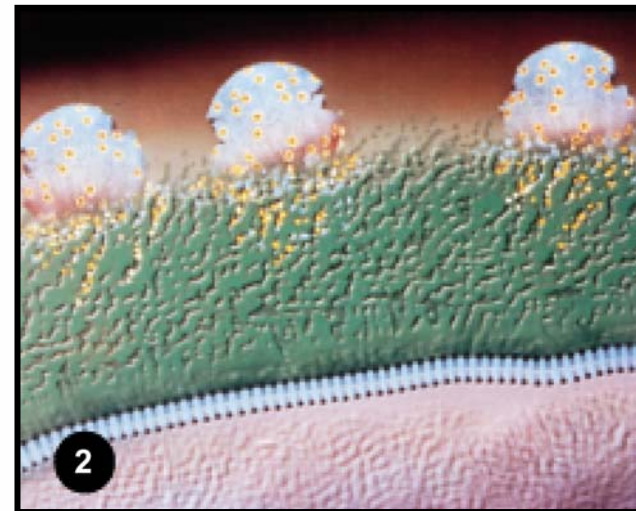
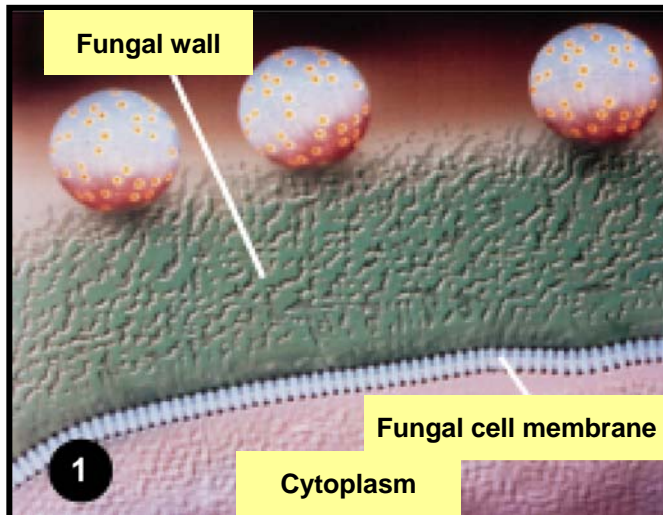
## Profile of SM-26000

- Liposome formulation of amphotericin B
- Anti-fungal activity not less than amphotericin B suspension (Fungizone)
- Reduction in adverse effects





# Mode of action: SM-26000

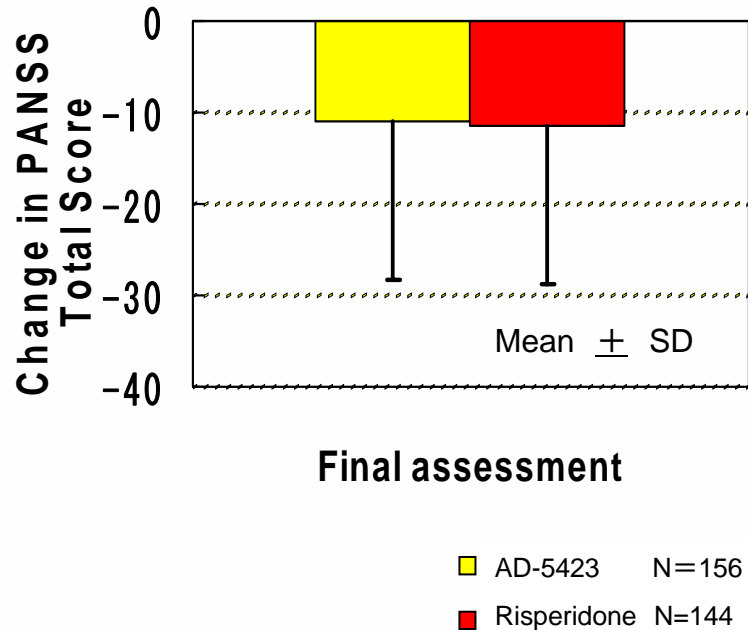


# Summary of AD-5423 (blonanserin)

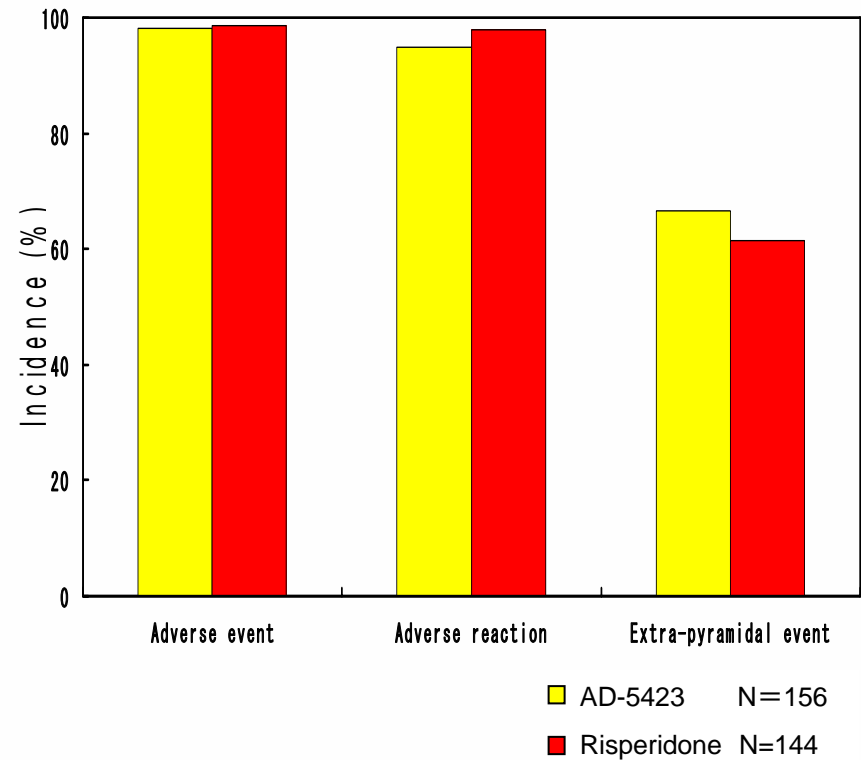
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Target disease:	Schizophrenia
Mode of action:	Selectively blocking Dopamine-D <sub>2</sub> , Serotonin 5-HT <sub>2</sub> receptors; Low affinity for Histamine H <sub>1</sub> , Muscarine M <sub>1</sub> , adrenaline $\alpha_1$ receptors
Formulation:	Tablet, Powder
In-house/Licensed:	In-house
Stage:	Pre-registration

## Change in PANSS Total Score



## Incidence of adverse events, adverse reaction, extra-pyramidal adverse event



# Expected profile of AD-5423 (blonanserin)

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- Wide-spectrum effect: Effective not only on positive symptoms but also on negative symptoms of schizophrenia
- Less incidence of extra-pyramidal adverse events than the typical neuroleptic agent (haloperidol)
- Less risk of clinically significant weight-gain caused by an atypical neuroleptic

# Summary of AD-810N (zonisamide)

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Target disease:	Parkinson's disease
Mode of action:	Increase in dopamine level in the CNS (caused by MAO-B inhibitory effect or something else)
Formulation:	Tablet
In-house/Licensed:	In-house
Stage:	Pre-registration

# Expected profile of AD-810N (zonisamide)

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- In addition to a MAO-B inhibitory effect, a new mechanism of action unknown to conventional anti-Parkinson's disease agents (the molecular level mechanism has yet to be clarified): Expected to solve tachyphylaxis of L-DOPA and wearing-off of symptoms
- Expected to be effective on patients with insufficient treatment on medication of L-DOPA and other anti-Parkinson's disease agents: Addition of a clinically significant choice to treat Parkinson's disease

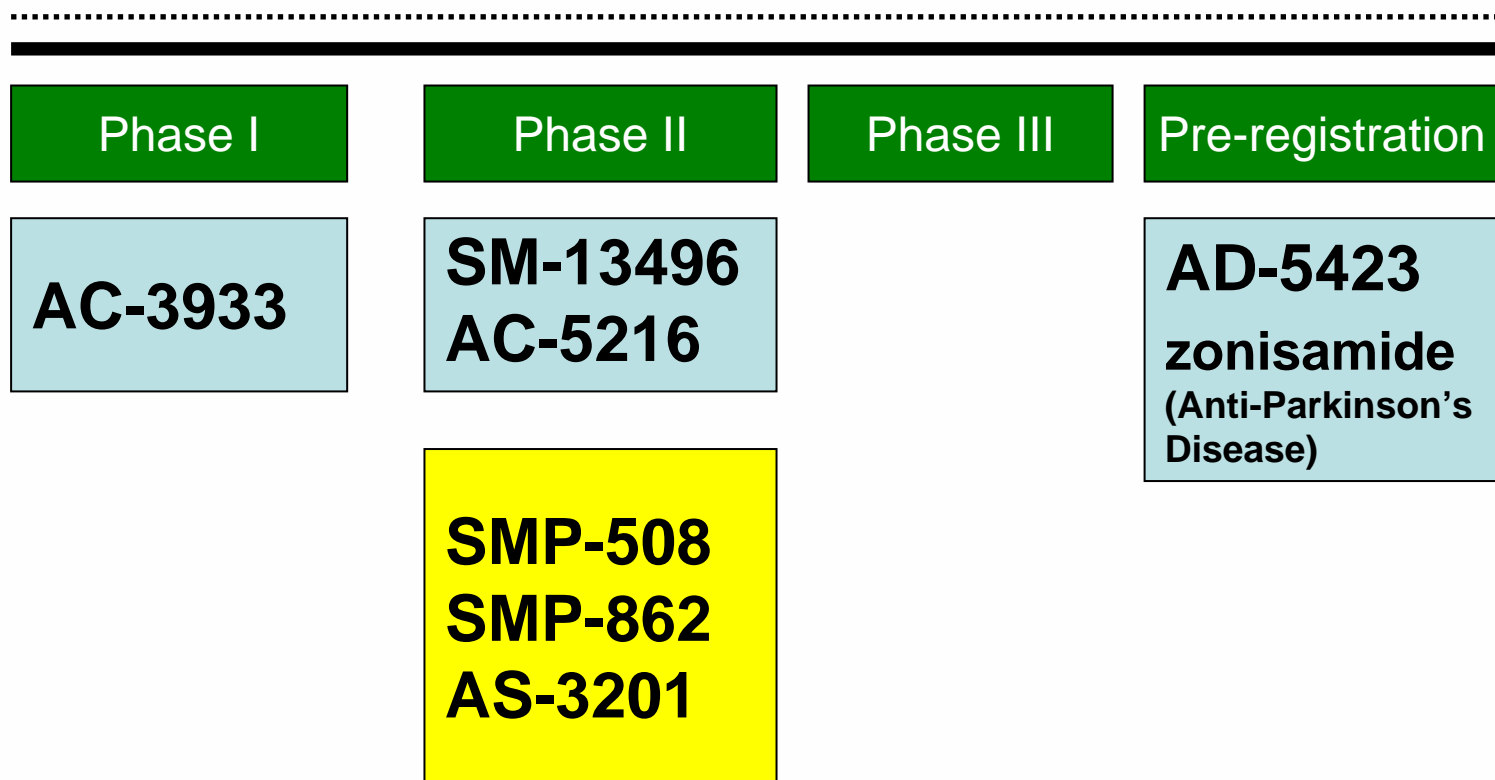
# Therapeutic Areas for Strategic Development

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- ★ Strategic Therapeutic Areas
  - ☆ Area I: CNS disease
  - ☆ Area II: Diabetes

# Pipeline in strategic therapeutic areas (CNS, Diabetes)

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# Various approaches to CNS diseases

CNS diseases	Under development	Currently marketed
Schizophrenia	AD-5423 SM-13496	Lullan Serenace Halomonth
Depression		Noritren Abilit
Anxiety	AC-5216	Sediel Erispan
Parkinson's disease	Zonisamide	Dops Akineton
Dementia	AC-3933	
Epilepsy		Excegran Mystan
Insomnia		Erimin

# Summary of SM-13496 (Iurasidone)

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Target Disease: Schizophrenia

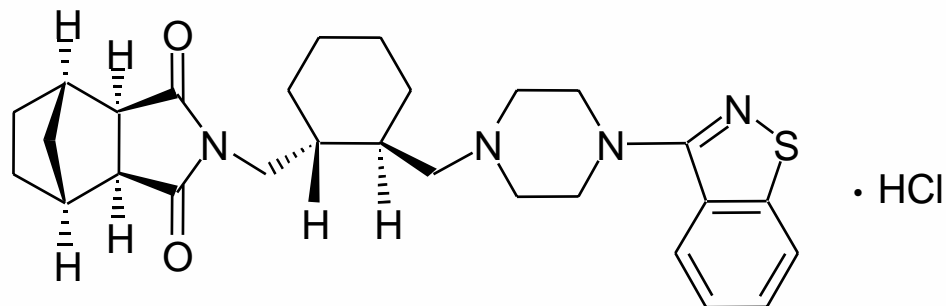
Mode of action: High affinity to receptors of  
Dopamine D<sub>2</sub>, Serotonin 5-HT<sub>2</sub>, 5-HT<sub>7</sub>,  
5-HT<sub>1A</sub>, etc.

Formulation: Tablet

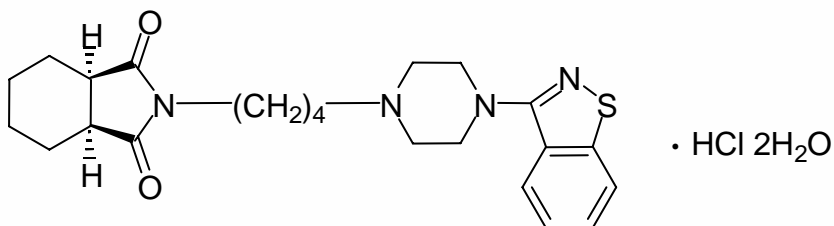
In-house/Licensed: In-house

Stage: Late Phase II (in Japan)  
Preparation for Phase III (by Merck  
outside Japan)

SM-13496 (lurasidone)

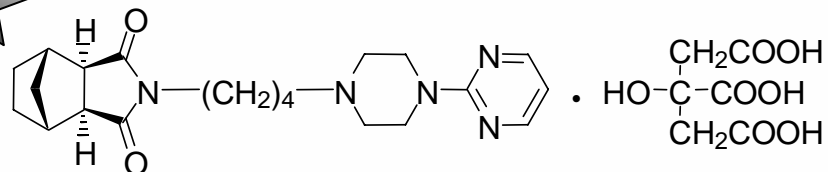


Lurasidone, D2/5-HT7, 5-HT1A, 5-HT2



Lullan<sup>®</sup>, D2/5-HT2 antagonist

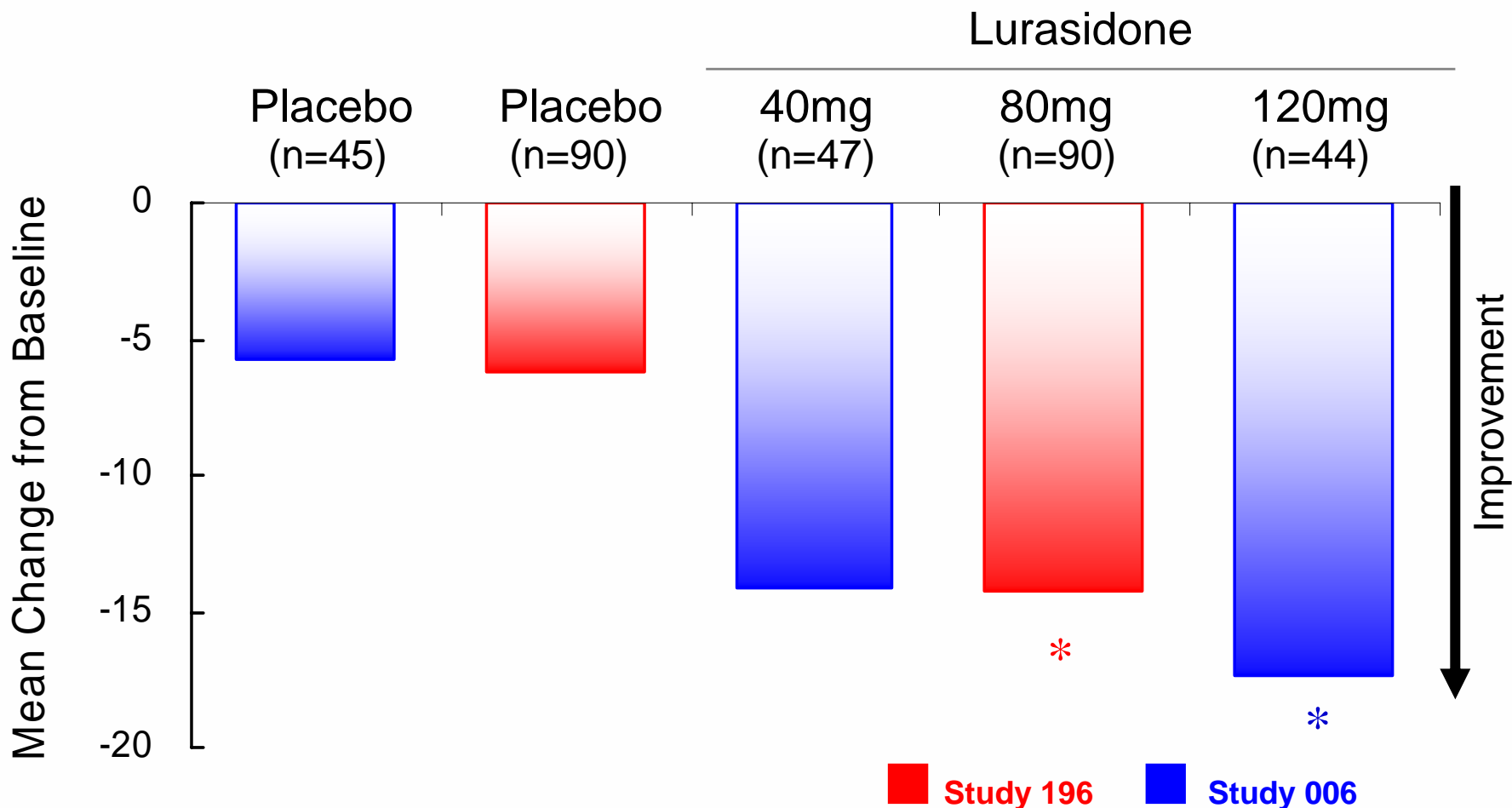
Lullan



Sediel<sup>®</sup>, 5-HT1A agonist (Anti-anxiety)

Sediel

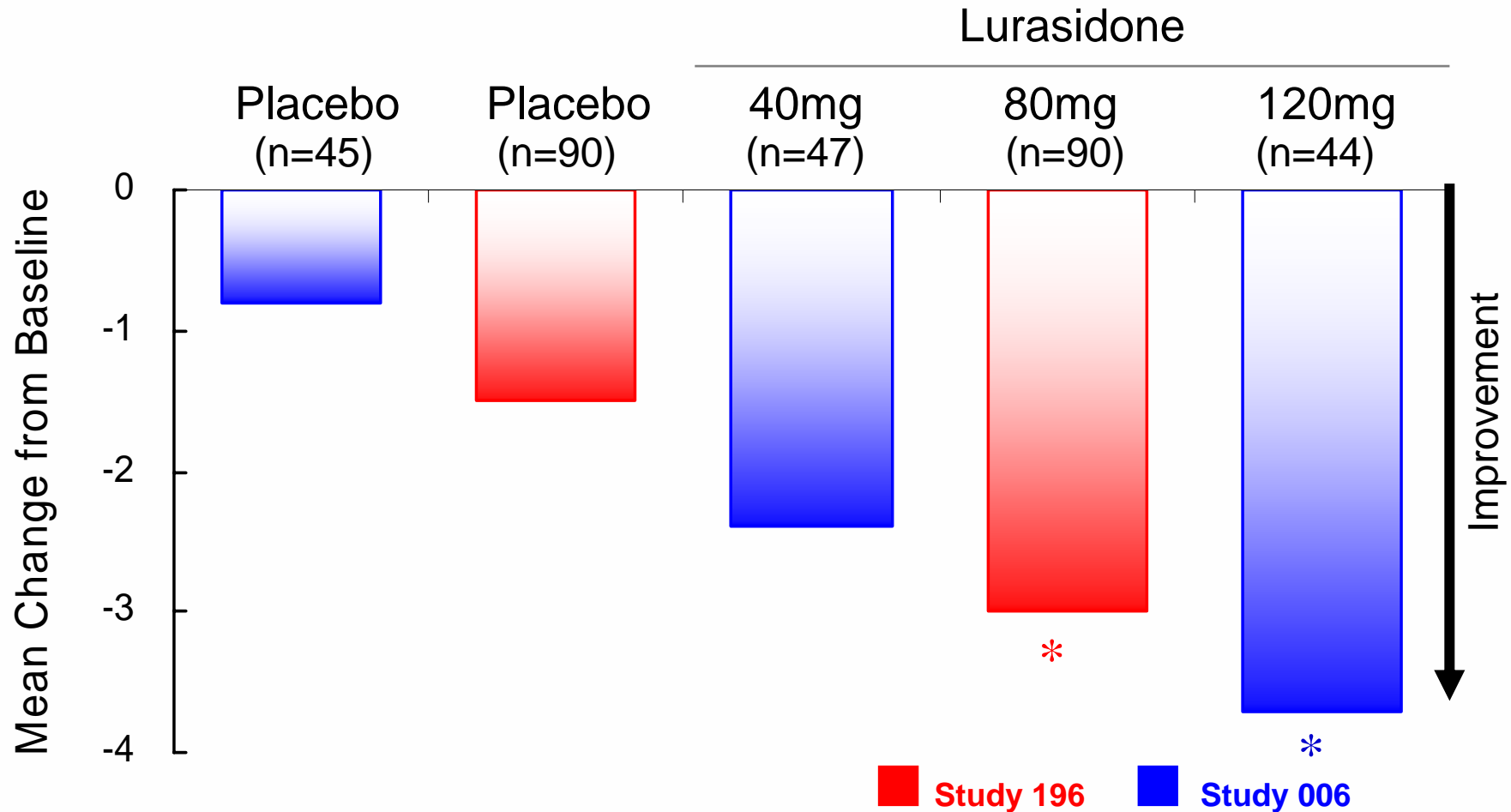
# PANSS total score



Mean change from baseline at end point (LOCF analysis)

\*:  $p < 0.05$  vs corresponding placebo group

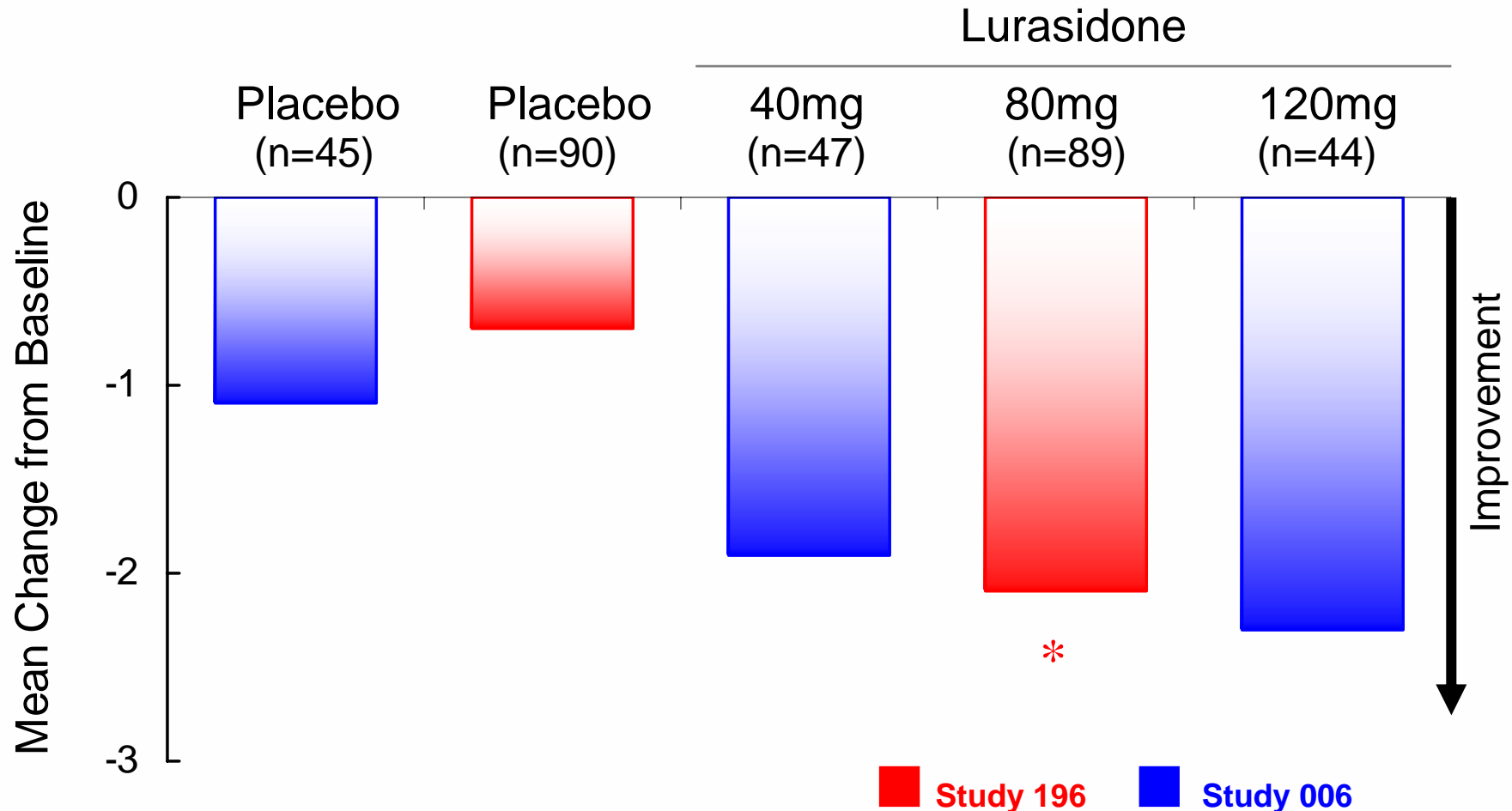
# PANSS - Negative Subscale



Mean change from baseline at end point (LOCF analysis)

\*: p < 0.05 vs corresponding placebo group

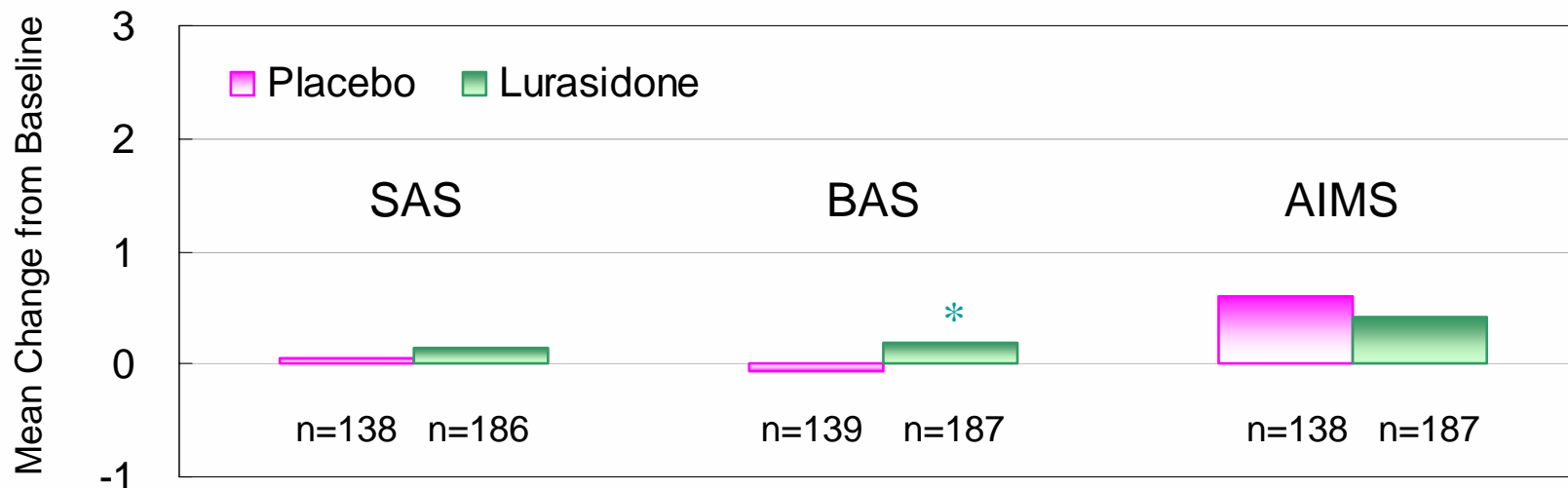
# PANSS - Cognitive Subscale



Mean change from baseline at end point (LOCF analysis)

\*:  $p < 0.05$  vs corresponding placebo group

# EPS Scales



SAS: Simpson-Angus Rating Scale

BAS: Barnes Akathisia Scale

AIMS: Abnormal Involuntary Movement Scale

Mean change from baseline at end points (LOCF analysis) in two pooled studies.

\*:  $p < 0.05$  vs placebo group

BAS score  $> 2$  is considered clinically significant.

# Summary of AC-5216

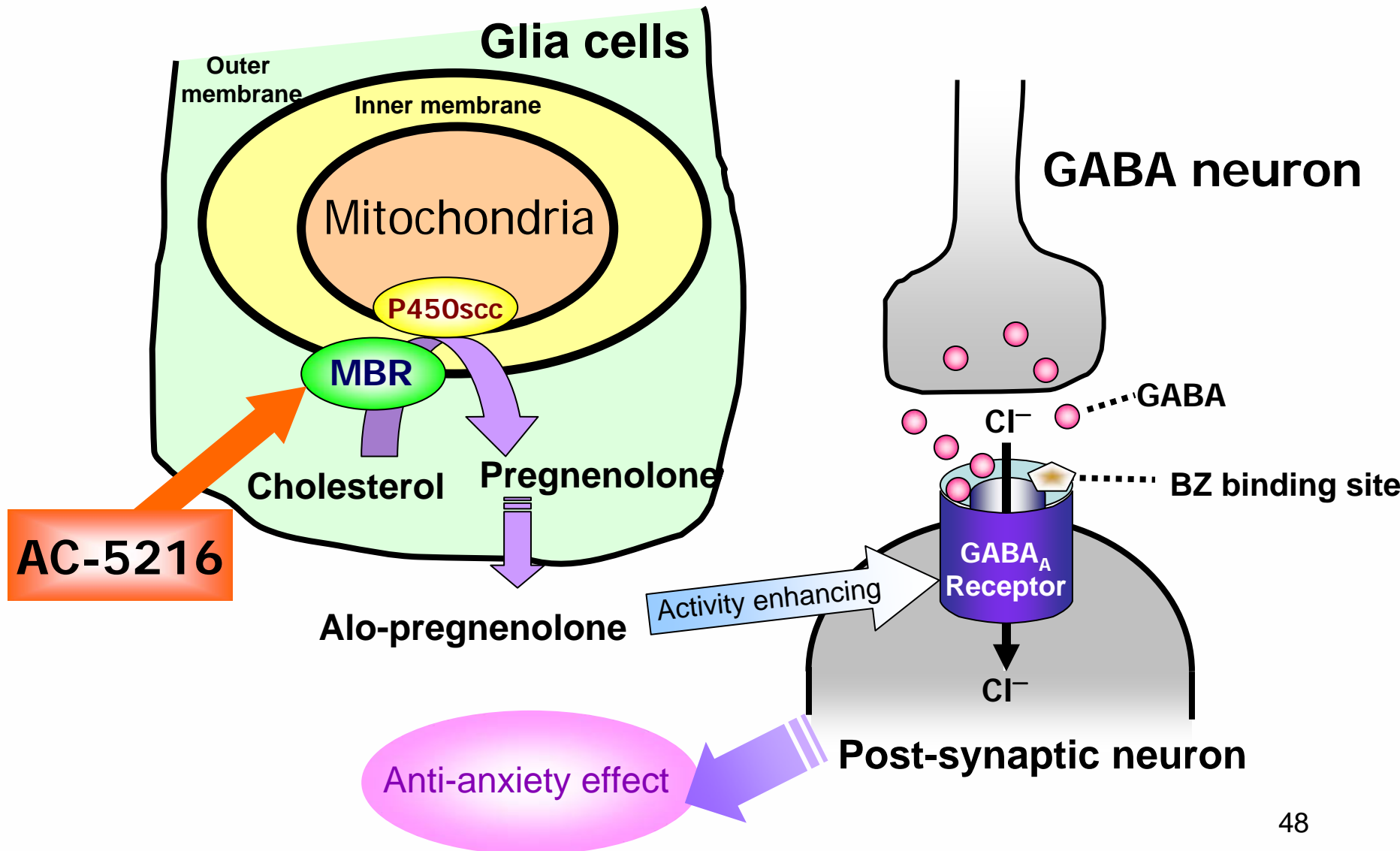
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Target disease:	Anxiety/depression
Mode of action:	Ligand for mitochondria-type benzodiazepine receptor
Formulation:	Tablet
In-house/Licensed:	In-house
Stage:	Early Phase II in Japan Early Phase II outside Japan (by Novartis)



# Anti-anxiety mechanism of AC-5216

- Mitochondria-type benzodiazepine ligand (MBR) -



# Expected profile of AC-5216

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- Novel pharmacological profile for an anti-anxiety and anti-depression agent
- Binding to mitochondria-type benzodiazepine receptor, resulting in generation of neuro-steroids to effect anti-anxiety
- Fewer adverse drug effects, such as the muscle relaxation and memory impairment found with the use of benzodiazepines

# Summary of AC-3933

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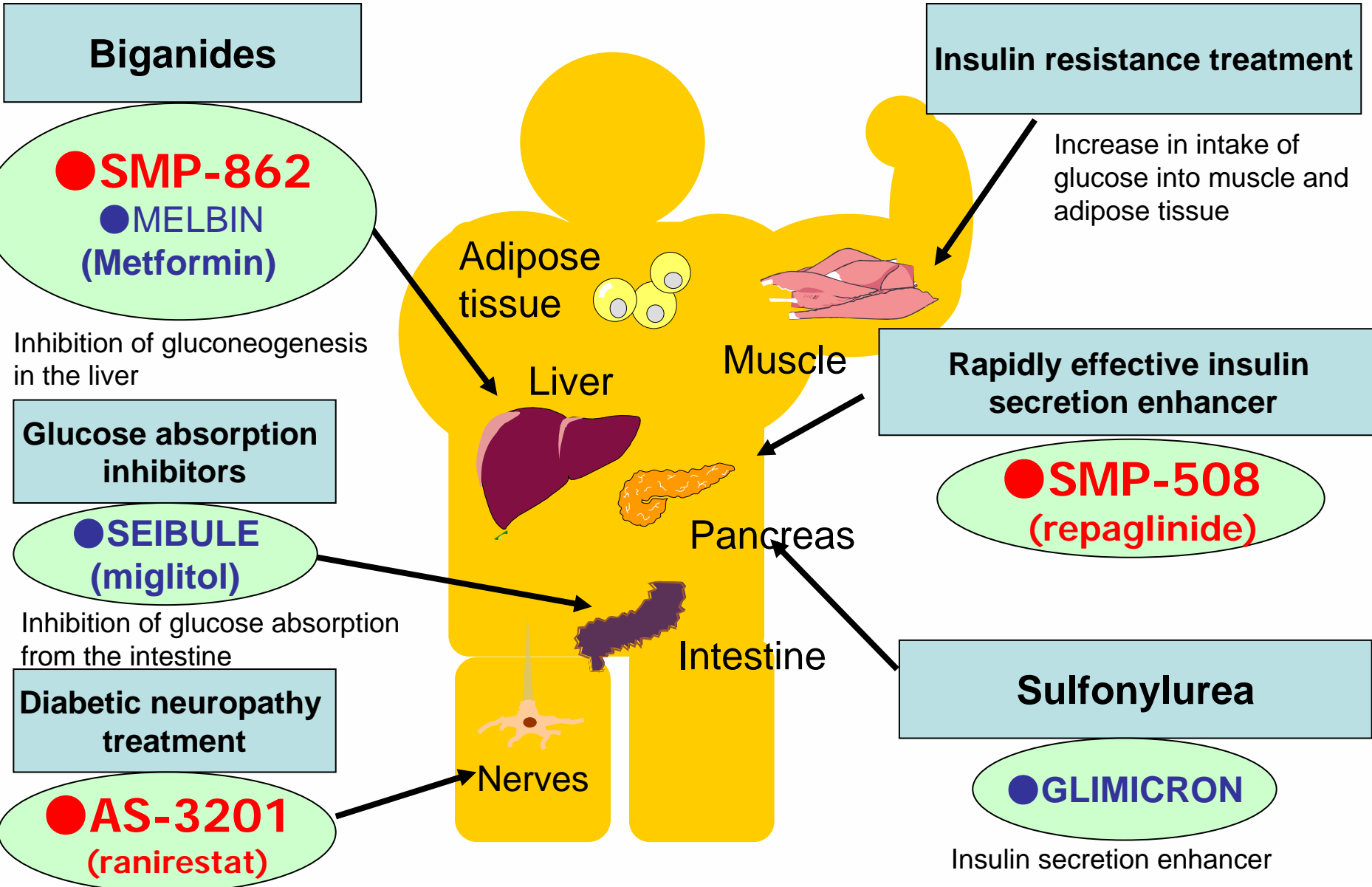
Target disease:	Dementia
Mode of action:	Benzodiazepine receptor partial inverse-agonist
Formulation:	Tablet
In-house/Licensed:	In-house
Stage:	Phase I in Japan Early Phase II overseas

# Expected profile of AC-3933

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- Benzodiazepine receptor partial inverse agonist
- New mechanism different from existing anti-dementia drugs: AC-3933 suppresses the GABA neurons that inhibitory regulate the cholinergic neurons, resulting in the activation of cholinergic neurons
- Activation of glutamate neurons as well
- Superior therapeutic effects than existing anti-dementia drugs on memory impairment—a core symptom in dementia—due to the dual activation of cholinergic neurons and glutamate neurons

# Various approaches to diabetes treatment

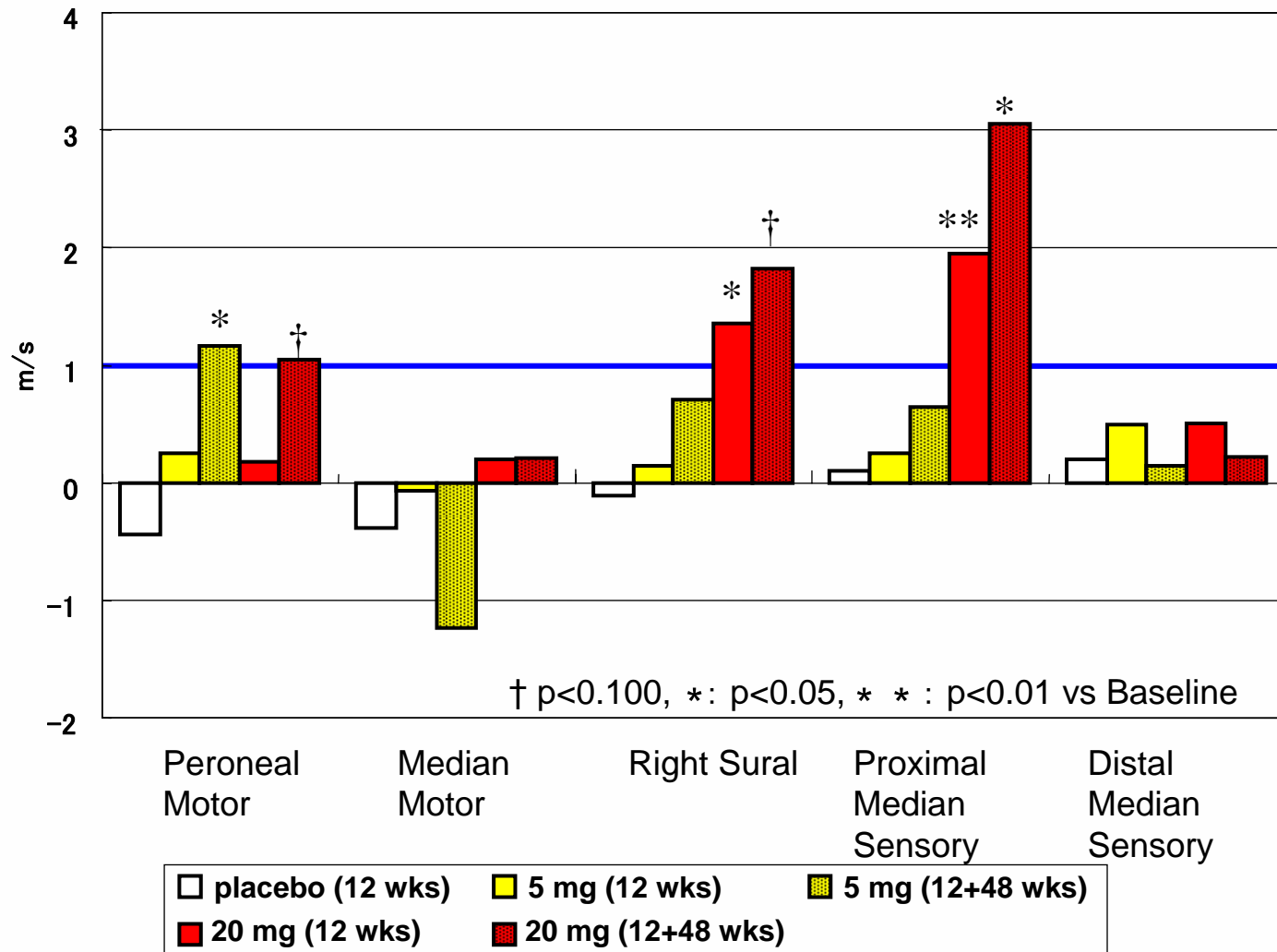


# Summary of AS-3201 (ranirestat)

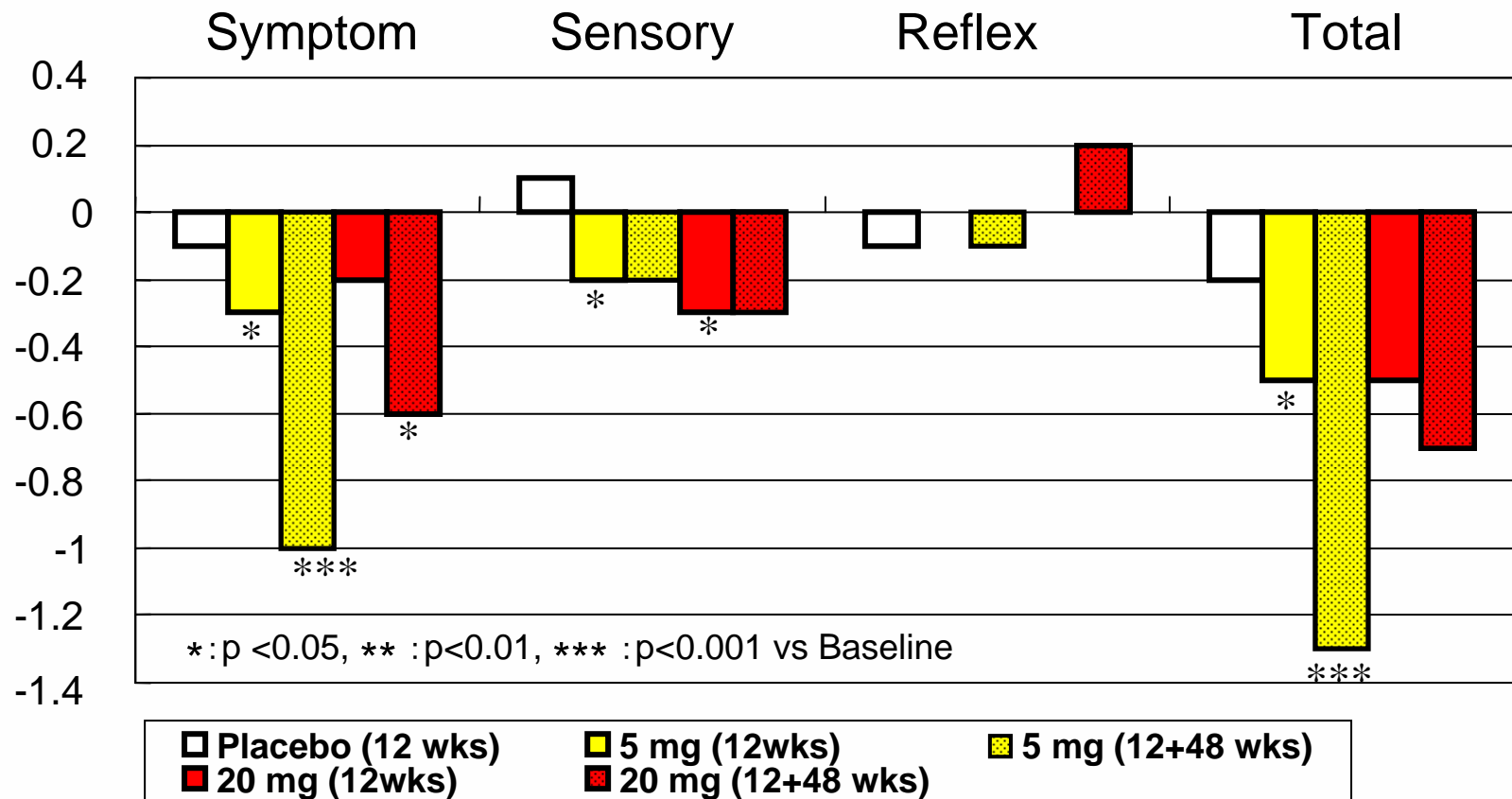
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Target disease:	Diabetic neuropathy
Mode of action:	Prophylaxis and treatment of diabetic neuropathy by inhibiting aldose reductase
Formulation:	Tablet
In-house/Licensed:	In-house (Licensed to Eisai for overseas development)
Stage:	Early Phase II in Japan; co-development with Kyorin Phase III in North America

# Mean change in Nerve Conduction Velocity (NCV) for the 12 week biopsy and 48 week extension studies of ranirestat



# Mean change in Toronto Clinical Neuropathy Score (TCNS) for the 12 week biopsy and 48 week extension studies of ranirestat





## Expected profile of AS-3201 (ranirestat)

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- AS-3201 inhibits the aldose reductase that metabolizes glucose to sorbitol, thereby controlling the sorbitol accumulation in nerve cells that causes abnormal cellular function. AS-3201's ability to inhibit sorbitol accumulation is expected to have both a prophylactic and improving effect on diabetic neuropathy.
- AS-3201 has high affinity for aldose reductase, resulting in potent inhibition of sorbitol accumulation
- AS-3201 shows good distribution to nerve tissues, the target organs for treatment in diabetic neuropathy, with sustained efficacy

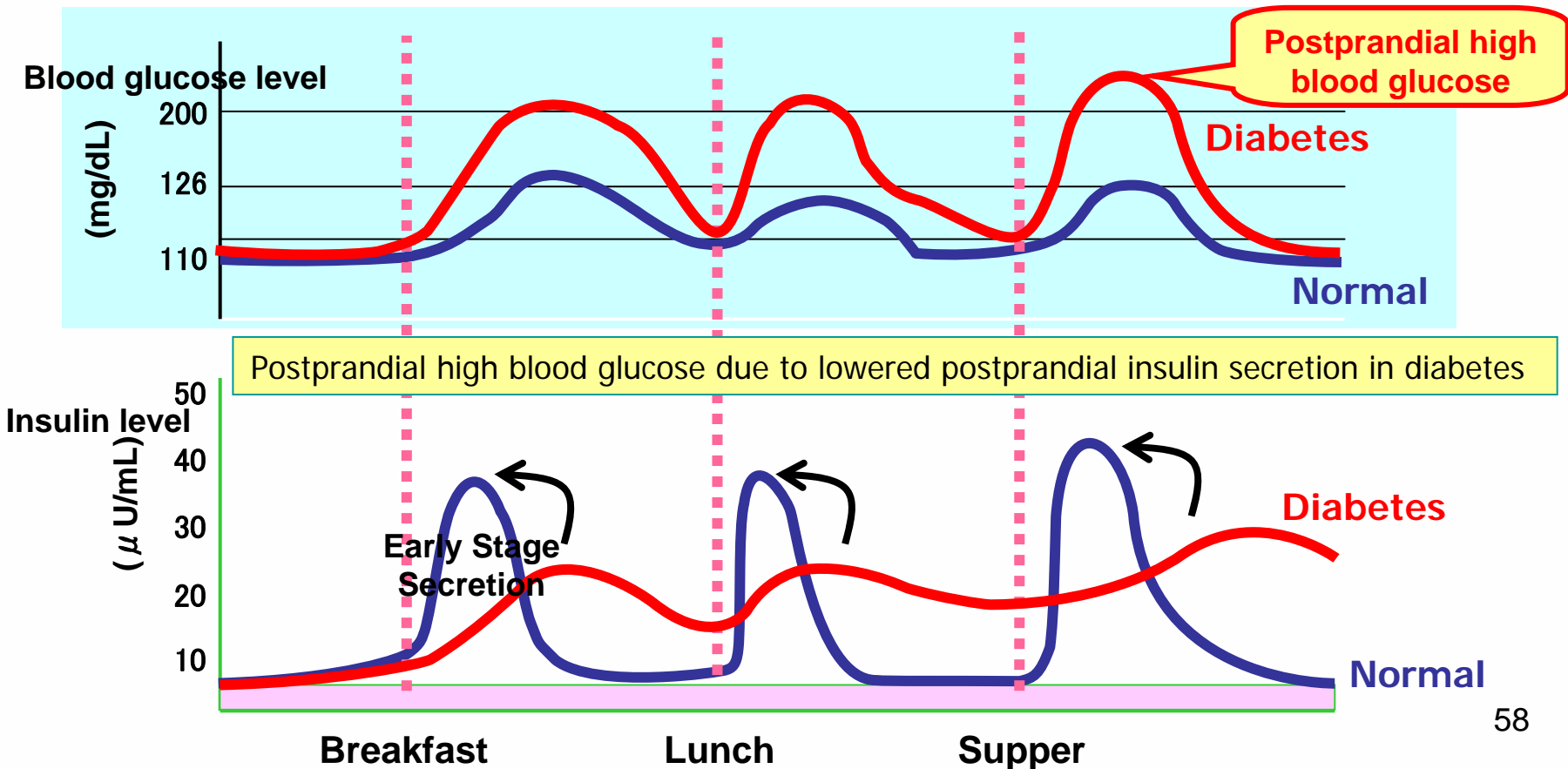
# Summary of SMP-508 (repaglinide)

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Target disease:	Type II diabetes
Mode of action:	Rapid absorption and rapid metabolism: Rapid effects on insulin secretion
Formulation:	Tablet
In-house/Licensed:	Licensed (from Novo Nordisk)
Stage:	Late Phase II

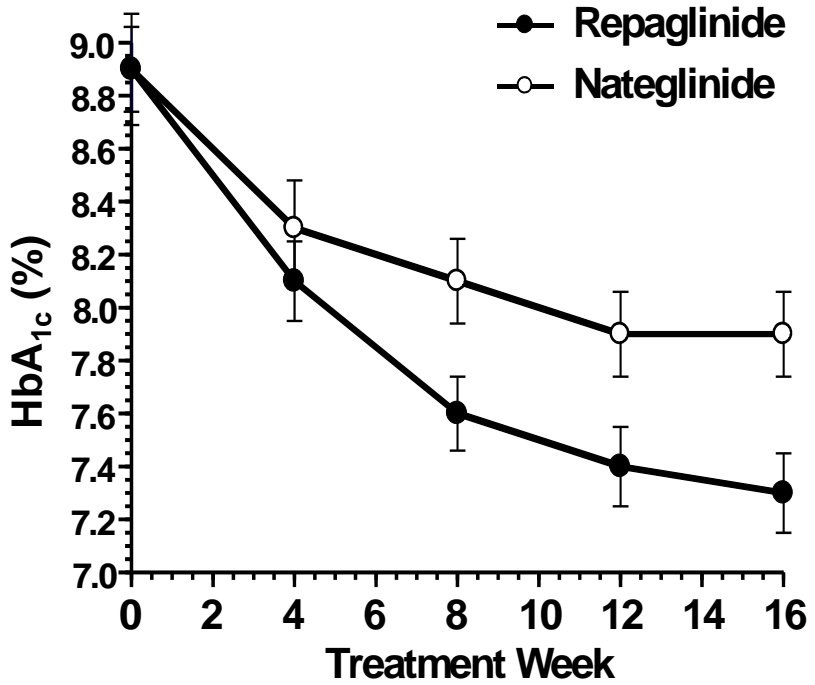
# Suppression of postprandial high blood glucose by rapidly effective insulin secretion enhancer

Rapidly enhances postprandial insulin secretion at early stage, resulting in normalized insulin level and suppression of postprandial high blood glucose

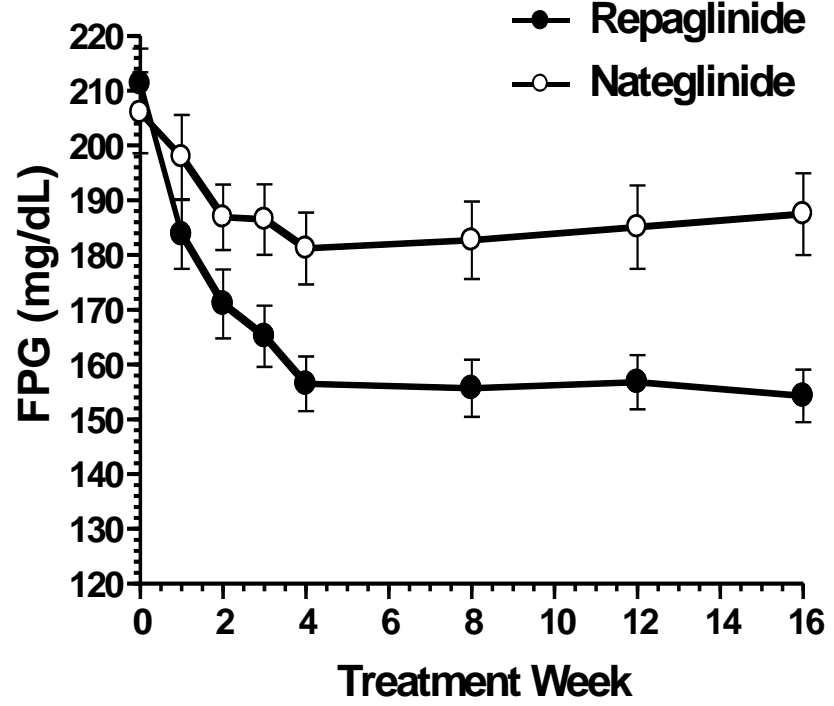


# Comparison of Repaglinide with Nateglinide in the clinical studies conducted overseas

HbA<sub>1c</sub>



Blood glucose in fasting state



	Single Dose (mg)	Δ Postprandial blood glucose AUC (mg/dL·min)	Δ HbA <sub>1c</sub> (%)	Δ blood glucose in fasting state (mg/dL)
<b>Repaglinide</b>	0.5-4	-6261.5	<b>-1.57</b>	<b>-57.1</b>
<b>Nateglinide</b>	60-120	-5888.3	-1.04	-18.4

# Summary of SMP-862 (metformin)

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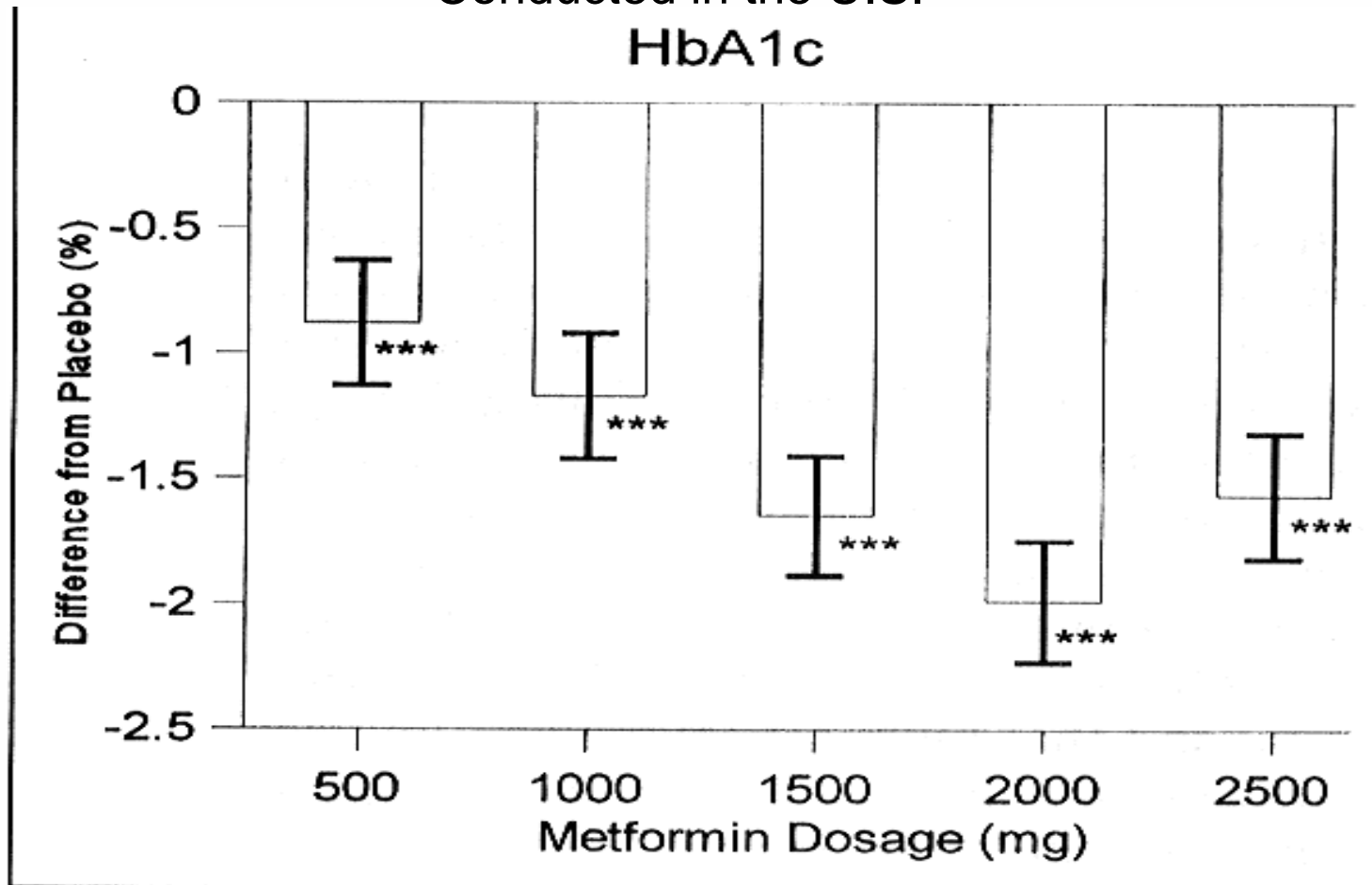
Target disease:	Type II diabetes
Mode of action:	Inhibition of gluconeogenesis in the liver Enhancement of insulin sensitivity in the muscle and liver, resulting in improvement of insulin resistance
Formulation:	Tablet
In-house/Licensed:	Licensed from Merck Sante
Stage:	Late phase II

## Expected profile of SMP-862 (metformin)

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- Revision of the current restrictions for diabetes type II patients with additional new indications and dosage regimens
  - The current indication/dosage regimen—
  - Indicated patients: patients failing to receive sufficient efficacy with SU-type anti-diabetes drugs or unable to increase dose level due to experiencing adverse drug reactions
  - Dosage regimen: Upper limit of 750 mg/day
- Expected to become a first line therapy for type II diabetes as a blood glucose lowering agent without enhancing insulin secretion
- Expected to become an add-on therapy in combination with other anti-diabetes drugs

# Glucophage (Metformin) Dose-response Study Conducted in the U.S.



Glucophage (metformin) or placebo was administered for 14 weeks to type-II diabetic patients who started diet therapy with insufficient effects or to those who had taken sulfonylureas with 3-week wash-out period before starting the study.

# Pipeline in other therapeutic areas

(cardiovascular, metabolic disease, inflammation/allergy, infection)

Phase I	Phase II	Phase III	Pre-registration
SMP-797  SMP-986	SM-11355  SMP-114  GASMOTIN (New indication)  Prorenal (New indication)	SUMIFERON (New indication)  MEROPEN (New indication) (Under preparation for Phase III)	SMP-536  SM-26000  CALSED (New indication)



# Summary of SM-11355 (miriplatin)

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Target disease:	Hepatocellular carcinoma
Mode of action:	DNA bridging
Formulation:	Freeze-dried powder for injection (injection to artery in the liver)
In-house/License:	In-house
Stage:	Phase II

## Expected profile of SM-11355 (miriplatin)

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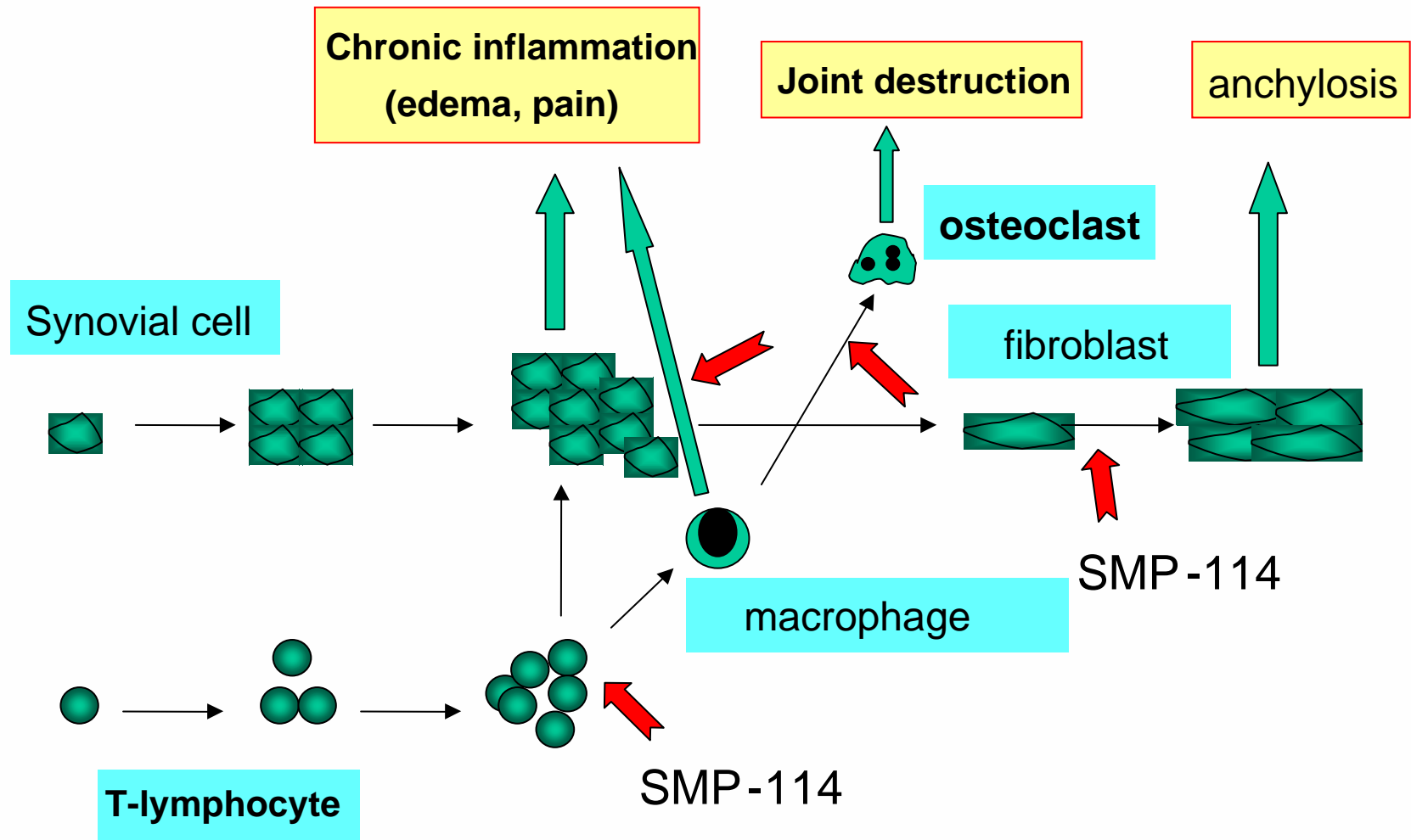
- Easy suspension in Lipiodol and sustained release from Lipiodol are expected to be useful for TAE (trans-arterial embolization)
- Locally sustained release is expected to provide an efficient anti-tumor effect while avoiding systemic adverse reactions.
- Repeated administration of the drug possible for hepatic cancer, which is known to be recurrent, through avoidance of blood vessel lesions at the site of administration.

# Summary of SMP-114

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Target disease:	Rheumatoid arthritis
Mode of action:	Oral DMARD with a new pharmacological mechanism, improving rheumatism symptoms, as well as suppressing worsening of joint damage malformation of the joint
Formulation:	Tablet
In-house/Licensed:	In-house
Stage:	Early Phase II in Japan Late Phase II outside Japan

# Pharmacological mechanism of SMP-114

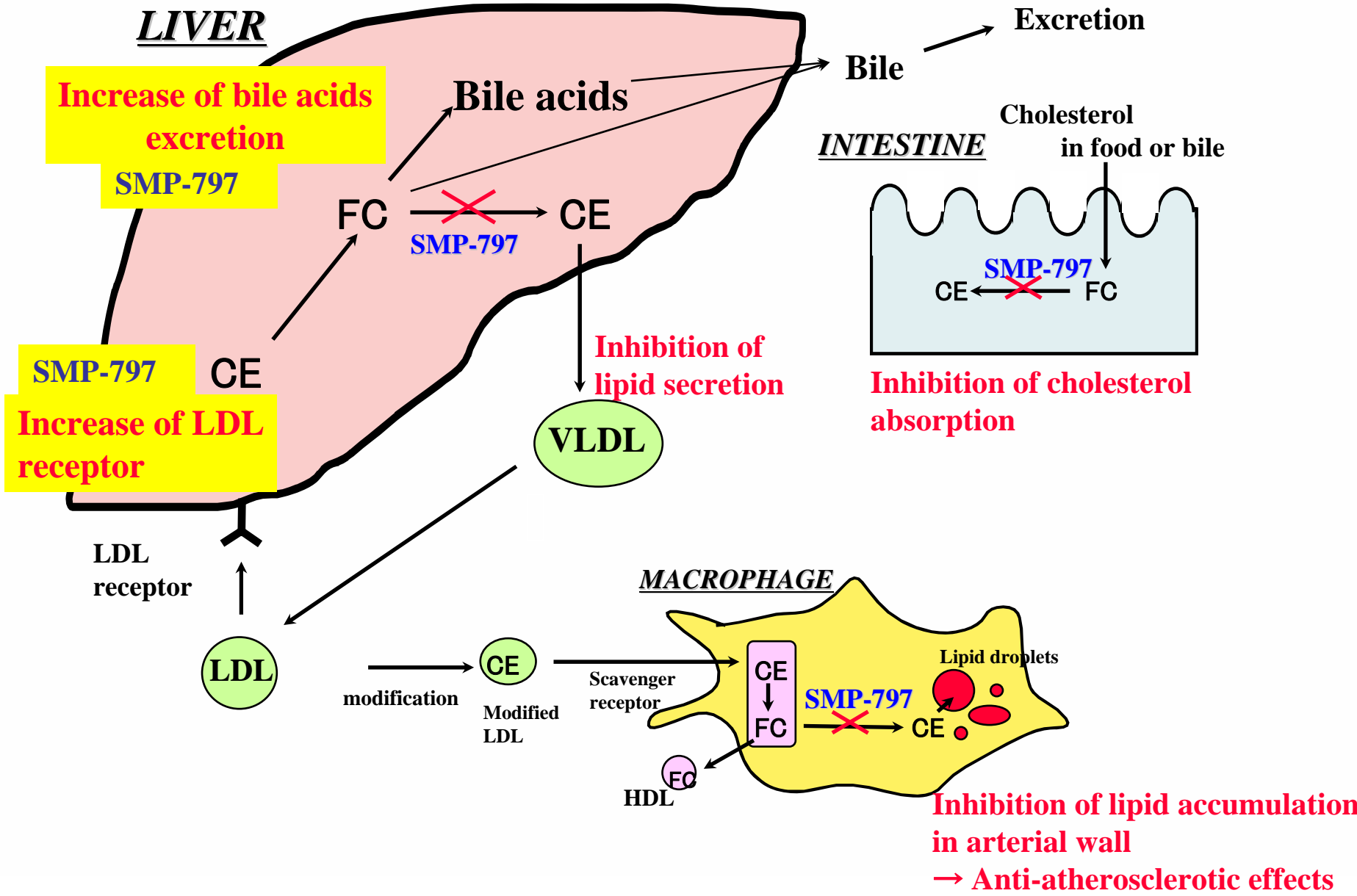


# Summary of SMP-797

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Target disease:	cholesteremia
Mode of action:	A lowering of plasma cholesterol by ACAT inhibition and enhancing LDL receptor activity leads to the direct inhibition of the progress of arteriosclerosis by ACAT inhibition
Formulation:	Tablet
In-house/Licensed:	In-house
Stage:	Phase I in Japan Early Phase II outside Japan

# Effects of SMP-797



# Summary of SMP-986

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Target disease:	Frequent urination, nocturnal frequent urination, incontinence, urgency of urination caused by over-active bladder syndrome
Mode of action:	Anti-muscarine action and suppression of abnormal nerve transmission to the CNS
Formulation:	Tablet
In-house/Licensed:	In-house
Stage:	Phase I outside Japan

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