R&D Decision Process

Dainippon Sumitomo Pharma Co., Ltd.

Director, Corporate Planning
Tetsuya Oida

14th March 2006
Drugs Research & Development

President
Kenjiro Miyatake

Drug Research & Development Center

Corporate Planning
Licensing
Intellectual Property

Drug Research

General Affairs (I & II)
Research Management
Quality Assurance
GLP Assurance
Chemistry Research Laboratories
Pharmacology Research Laboratories
Safety Research Laboratories
Pharmacokinetics Research Laboratories
Genomic Science Laboratories

Drug Development

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

Technology Research & Development Management
Chemical Synthesis Laboratories
Formulation Laboratories
Analysis Laboratories
Investigational Drug Quality Assurance
Microbiological Control Laboratories
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
Project Portfolio Management

- Shared Project Information Base
- Portfolio Management Meetings allowing Project Information Exchange

P M C
Project Prioritization

Portfolio Evaluation
Project Economic Evaluation

P S C
Project Implementation
Drug Research Overview

Dainippon Sumitomo Pharma Co., Ltd.

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

14th 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

Main Research Sites
- Central Research Laboratories (Suita)
- Osaka Research Center (Osaka)

Drug Research
- General Affairs I
- General Affairs II
- Research Management
- Quality Assurance
- GLP Assurance

Chemistry Research Laboratories

Pharmacology Research Laboratories

Safety Research Laboratories

Pharmacokinetics Research Laboratories

Genomic Science Laboratories
## Research Sites and Functions

<table>
<thead>
<tr>
<th>Central Research Laboratories</th>
<th>Osaka Research Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemistry Research Laboratories</strong></td>
<td>All functions at both sites</td>
</tr>
<tr>
<td><strong>Pharmacology Research Laboratories</strong></td>
<td>Central Nervous System</td>
</tr>
<tr>
<td><strong>Safety Research Laboratories</strong></td>
<td>Non-GLP Studies</td>
</tr>
<tr>
<td><strong>Pharmacokinetics Research Laboratories</strong></td>
<td>Discovery Pharmacokinetics Studies</td>
</tr>
<tr>
<td><strong>Genomic Science Laboratories</strong></td>
<td>Protein Structure Analysis</td>
</tr>
</tbody>
</table>
Focusing on Diabetes and CNS

- Cardiovascular: 21%
- Diabetes: 24%
- Central Nervous System: 19%
- Inflammation/Allergy: 18%
- Basic Research: 13%
- Oncology/Infection: 5%
Oral Antidiabetics
Main Mechanism and Target

**Biguanide**
- Hepatic Gluconeogenesis Inhibition
  - Metformin (Melbin)
    (SMP-862: under development)

**α-Glucosidase Inhibitor**
- Glucose Absorption Inhibition in Gut
  - Voglibose
  - Acarbose
  - Miglitol (Seibule)

**Glitazone**
- Adipose Glucose Uptake Accelerator
  - Pioglitazone

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

**Adipose Glucose Uptake Accelerator**
- Pioglitazone

**Aldose Reductase Inhibitor**
- (Complication Therapy)
  - Epalrestat
  - Fidarestat
  - AS-3201 (under development)

**Muscular Glucose Uptake Accelerator**
- Pioglitazone

**Liver**

**Sulfonylurea**
- Insulin Secretagogue
  - Glimepiride
  - Gliclazide (Glimicron)
  - Glibenclamide

**Muscle**

**Intestine**

**Glucose Absorption Inhibition in Gut**
- Voglibose
- Acarbose
- Miglitol (Seibule)

**Rapid-acting Insulin Secretagogue**
- Nateglinide
- Mitiglinide
- SMP-508 (Repaglinide) (under development)
## Main Indication / Mechanism of Action

<table>
<thead>
<tr>
<th>Metabolic syndrome-related diseases</th>
<th>Main Indication / Mechanism of Action</th>
<th>Marketed Products</th>
<th>Development Compounds</th>
<th>Research Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Insulin Secretagogue</td>
<td>Glimicron</td>
<td>Repaglinide</td>
<td>○</td>
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<tr>
<td></td>
<td>Sulfonylurea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid-acting Insulin Secretagogue</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Insulin Sensitizer</td>
<td>Melbin</td>
<td>Metformin</td>
<td>○</td>
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<tr>
<td></td>
<td>Glucose Absorption Inhibitor</td>
<td>Seibule</td>
<td></td>
<td>○</td>
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<tr>
<td></td>
<td>Complication therapy</td>
<td></td>
<td>Ranirestat</td>
<td>○</td>
</tr>
<tr>
<td></td>
<td>Antiobesity</td>
<td></td>
<td></td>
<td>○</td>
</tr>
<tr>
<td>CV</td>
<td>Hypertension</td>
<td>Amlodin, Cetapril, Almarl</td>
<td></td>
<td>○</td>
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<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>Lipoclin</td>
<td>SMP-797</td>
<td>○</td>
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</tbody>
</table>
### Focusing on CNS

<table>
<thead>
<tr>
<th>Main Indication</th>
<th>Products</th>
<th>Development</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Lullan, Serenate, Halomonth</td>
<td>Blonanserin, Lurasidone</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Noritren, Abilit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>Sediel, Erispan</td>
<td>AC-5216</td>
<td></td>
</tr>
<tr>
<td><strong>Organic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Dops, Akineton</td>
<td>Zonisamide</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td>AC-3933</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Excegran, Mystan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Morphine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Accelerated development through collaboration with Merck**
- **Accelerated development through collaboration with Novartis**
- **Strengthened research through KASPAC collaboration**
Exploratory Research of Alzheimer-related Genes
A unique gene expression signature discriminates familial Alzheimer’s disease mutation carriers from their wild-type siblings.

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
- Aβ Production Inhibition
- Aβ Aggregation Inhibition
- Aggregated β Amyloid Degradation
- Soluble Aβ APP Degradation
- β Amyloid Precursor Protein Degradation
- Dementia

Exploratory Research on Alzheimer-related Genes
- A unique gene expression signature discriminates familial Alzheimer’s disease mutation carriers from their wild-type siblings.

PC1
PC2
PC4
- Mutation carrier
- Mutation carrier (presymptomatic)
- Wild Type
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

- GeneChip Expression Analysis
- GeneLogic DB (Human data)
- Disease-model animal
- GeneChip Expression Analysis

Tissue-specific Gene Expression

Disease-specific Gene Expression

Target Candidate

HTS

Hit Compound
Promoting Technology Integration

- Integration of Chemical Libraries
  - Chemical Library
- Integration of Drug Design Software
- Integration of Chemical Information
  - Chemical DB
  - Biological DB
- Integration of Gene and Protein DB
- Target Identification
  - HTS
  - CADD
  - Structure Analysis of Protein-Drug Complex
  - Mechanism of Action
    - Biomarker Identification
    - Toxicity Prediction
  - Drug Candidate

Integration of HTS Technologies
Integration of Structural Biology Technologies
Integration of Genomics-related Technologies
Discovery Pharmacokinetics & Toxicology

**Pharmacology Screening**
- Chemical Library
  - *in vitro* (Cell etc)
  - *in vivo* (Disease-model animal)

**Medicinal Chemistry**

**Discovery Pharmacokinetics Study**
- Absorption
  - Solubility, log D, Caco-2, PAMPA
- Distribution
  - Protein Binding
- Metabolism
  - Stability
  - Liver Microsome
  - Inhibition
  - Expression System, Human Liver Microsome
  - Induction
  - Reporter Gene Assay

**Advanced *in vivo, in vitro* studies**

**Discovery Safety Study**
- General Toxicity (Rat, Dog, 2 weeks)
- Mutagenicity (Ames)

**Preclinical Study**
- General Toxicity (Rat, Non-rodent)
- Special Toxicity (Mutagenicity, Antigenecity, Reproductive and Developmental)
- ADME (Rat, Non-rodent, Human *in vitro*)

**Human PK Prediction**

**Clinical Study (P1, P2a, P2b, P3)**

- **Simultaneous Pharmacology and Discovery Pharmacokinetics Studies**
- **Discovery Toxicity Studies**
- **Human PK Prediction**

⇒ Improvement in Speed and Success Rate
1. Mission of Drug Development

2. Organizational Structure of Drug Development

3. Status of Drug Development
Mission of Drug Development Division

• 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
Organizational Structure of Drug Development

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

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

- **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)
- **Diabetic neuropathy**
  - US/Canada: Phase III
  - **AS-3201** *(ranirestat)*
- **Rheumatoid arthritis**
  - Europe: Late Phase II
  - **SMP-114**
- **Schizophrenia**
  - Europe, US: Phase II
  - **AD-5423** *(blonanserin)*
- **Dementia**
  - US: Early Phase II
  - **AC-3933**
- **Hypercholesterolemia**
  - Europe: Early Phase II
  - **SMP-797**
- **Over-active bladder syndrome**
  - Europe: Phase I
  - **SMP-986**

#### Clinical Studies (Out-Licensed)
- **Anxiety/Depression**
  - [Novartis]
  - **AC-5216**
- **Cancer**
  - [Sunesis]
  - **AG-7352**
- **Life-threatening infection**
  - [Protez]
  - **SMP-601**
- **Schizophrenia**
  - [Merck]
  - **SM-13496** *(lurasidone)*
- **Cancer**
  - [Conforma]
  - **CALSED**
- **Diabetic Neuropathy**
  - [Eisai]
  - **AS-3201** *(ranirestat)*
## Pre-registration

<table>
<thead>
<tr>
<th>Product code</th>
<th>Generic name</th>
<th>Target disease</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMP-536</td>
<td>Agalsidase alfa</td>
<td>Fabry’s disease</td>
<td>Injection</td>
</tr>
<tr>
<td>SM-26000</td>
<td>Amphotericin B liposome</td>
<td>Systemic fungal infection</td>
<td>Injection</td>
</tr>
<tr>
<td>AD-5423</td>
<td>Blonanserin</td>
<td>Schizophrenia</td>
<td>Tablet Powder</td>
</tr>
<tr>
<td>AD-810N</td>
<td>Zonisamide</td>
<td>Parkinson’s disease (New indication)</td>
<td>Tablet</td>
</tr>
<tr>
<td>CALSED</td>
<td>Amrubicin hydrochloride</td>
<td>Non-Hodgkin’s lymphoma (New indication)</td>
<td>Injection</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Ephedrine hydrochloride</td>
<td>Hypotension under anesthesia (New administration route)</td>
<td>Injection</td>
</tr>
<tr>
<td><strong>Summary of SMP-536 (agalsidase alfa)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Target disease:</strong></td>
<td>Fabry’s disease (Orphan drug)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mode of action:</strong></td>
<td>$\alpha$-galactosidase A (recombinant) enzyme replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Formulation:</strong></td>
<td>Injection (Infusion)</td>
<td></td>
<td></td>
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<tr>
<td><strong>In-house/Licensed:</strong></td>
<td>Licensed from Shire</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage:</strong></td>
<td>Pre-registration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Profile of SMP-536 (agalsidase alfa)

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

*: 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

1. Fungal wall
2. Fungal cell membrane
3. Cytoplasm
4. Amphotericin B
5. Electrolyte loss
Summary of AD-5423 (blonanserin)

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 α<sub>1</sub> receptors

Formulation: Tablet, Powder

In-house/Licensed: In-house

Stage: Pre-registration
Change in PANSS Total Score

Change in PANSS Total Score

Final assessment

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

Incidence (%)

AD-5423 N=156
Risperidone N=144

Adverse event
Adverse reaction
Extra-pyramidal event
Expected profile of AD-5423 (blonanserin)

- 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
<table>
<thead>
<tr>
<th><strong>Summary of AD-810N (zonisamide)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target disease:</strong> Parkinson’s disease</td>
</tr>
<tr>
<td><strong>Mode of action:</strong> Increase in dopamine level in the CNS (caused by MAO-B inhibitory effect or something else)</td>
</tr>
<tr>
<td><strong>Formulation:</strong> Tablet</td>
</tr>
<tr>
<td><strong>In-house/Licensed:</strong> In-house</td>
</tr>
<tr>
<td><strong>Stage:</strong> Pre-registration</td>
</tr>
</tbody>
</table>
Expected profile of AD-810N (zonisamide)

- 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

★ Strategic Therapeutic Areas
★ Area I: CNS disease
★ Area II: Diabetes
Pipeline in strategic therapeutic areas (CNS, Diabetes)

Phase I
- AC-3933

Phase II
- SM-13496
- AC-5216

Phase III
- SMP-508
- SMP-862
- AS-3201

Pre-registration
- AD-5423
  zonisamide (Anti-Parkinson’s Disease)
### Various approaches to CNS diseases

<table>
<thead>
<tr>
<th>CNS diseases</th>
<th>Under development</th>
<th>Currently marketed</th>
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</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>AD-5423 SM-13496</td>
<td>Lullan Serenace Halomonth</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td>Noritren Abilit</td>
</tr>
<tr>
<td>Anxiety</td>
<td>AC-5216</td>
<td>Sediel Erispan</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Zonisamide</td>
<td>Dops Akineton</td>
</tr>
<tr>
<td>Dementia</td>
<td>AC-3933</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td></td>
<td>Excegran Mystan</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td>Erimin</td>
</tr>
</tbody>
</table>
### Summary of SM-13496 (lurasidone)

<table>
<thead>
<tr>
<th>Target Disease:</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action:</td>
<td>High affinity to receptors of Dopamine D₂, Serotonin 5-HT₂, 5-HT₇, 5-HT₁A, etc.</td>
</tr>
<tr>
<td>Formulation:</td>
<td>Tablet</td>
</tr>
<tr>
<td>In-house/Licensed:</td>
<td>In-house</td>
</tr>
<tr>
<td>Stage:</td>
<td>Late Phase II (in Japan) Preparation for Phase III (by Merck outside Japan)</td>
</tr>
</tbody>
</table>
Lurasidone, D2/5-HT7, 5-HT1A, 5-HT2

Lullan®, D2/5-HT2 antagonist

Lullan

Sediel®, 5-HT1A agonist (Anti-anxiety)

Sediel

SM-13496 (lurasidone)
PANSS total score

Mean change from baseline at end point (LOCF analysis)

* p<0.05 vs corresponding placebo group
Mean change from baseline at end point (LOCF analysis)

*: p<0.05 vs corresponding placebo group
Mean change from baseline at end point (LOCF analysis)

*: p<0.05 vs corresponding placebo group
Mean change from baseline at end points (LOCF analysis) in two pooled studies.

EPS Scales

BAS score >2 is considered clinically significant.

SAS: Simpson-Angus Rating Scale
BAS: Barnes Akathisia Scale
AIMS: Abnormal Involuntary Movement Scale
## Summary of AC-5216

<table>
<thead>
<tr>
<th>Target disease:</th>
<th>Anxiety/depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action:</td>
<td>Ligand for mitochondria-type benzodiazepine receptor</td>
</tr>
<tr>
<td>Formulation:</td>
<td>Tablet</td>
</tr>
<tr>
<td>In-house/Licensed:</td>
<td>In-house</td>
</tr>
<tr>
<td>Stage:</td>
<td>Early Phase II in Japan</td>
</tr>
<tr>
<td></td>
<td>Early Phase II outside Japan (by Novartis)</td>
</tr>
</tbody>
</table>
Anti-anxiety mechanism of AC-5216 - Mitochondria-type benzodiazepine ligand (MBR) -

- **GABA neuron**
- **Post-synaptic neuron**
- **Cholesterol**
- **Pregnenolone**
- **Alo-pregnenolone**
- **MBR**
- **AC-5216**
- **Glia cells**
- **Mitochondria**
- **P450scc**
- **GABA**
- **BZ binding site**
- **GABA\textsubscript{A} Receptor**
- **Activity enhancing**
- **Anti-anxiety effect**

The diagram illustrates the flow of cholesterol to pregnenolone, which is converted by P450scc to Alo-pregnenolone. This compound then binds to the MBR, leading to an anti-anxiety effect by enhancing the activity of the GABA\textsubscript{A} Receptor in the post-synaptic neuron.
Expected profile of AC-5216

- 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

<table>
<thead>
<tr>
<th>Target disease:</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action:</td>
<td>Benzodiazepine receptor partial inverse-agonist</td>
</tr>
<tr>
<td>Formulation:</td>
<td>Tablet</td>
</tr>
<tr>
<td>In-house/Licensed:</td>
<td>In-house</td>
</tr>
<tr>
<td>Stage:</td>
<td>Phase I in Japan</td>
</tr>
<tr>
<td></td>
<td>Early Phase II overseas</td>
</tr>
</tbody>
</table>
Expected profile of AC-3933

- 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

Biganides

- **SMP-862**
- **MELBIN** (Metformin)

Glucose absorption inhibitors

- **SEIBULE** (miglitol)

Diabetic neuropathy treatment

- **AS-3201** (ranirestat)

Insulin resistance treatment

- Increase in intake of glucose into muscle and adipose tissue

Rapidly effective insulin secretion enhancer

- **SMP-508** (repaglinide)

Sulfonylurea

- **GLIMICRON**

Insulin secretion enhancer
Summary of AS-3201 (ranirestat)

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

† p<0.100, *: p<0.05, **: p<0.01 vs Baseline
Mean change in Toronto Clinical Neuropathy Score (TCNS) for the 12 week biopsy and 48 week extension studies of ranirestat

-1.4  -1.2  -1.0  -0.8  -0.6  -0.4  -0.2  0  0.2  0.4
Symptom  Sensory  Reflex  Total

* p < 0.05, ** p < 0.01, *** p < 0.001 vs Baseline
Expected profile of AS-3201 (ranirestat)

- 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)

<table>
<thead>
<tr>
<th>Target disease:</th>
<th>Type II diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action:</td>
<td>Rapid absorption and rapid metabolism: Rapid effects on insulin secretion</td>
</tr>
<tr>
<td>Formulation:</td>
<td>Tablet</td>
</tr>
<tr>
<td>In-house/Licensed:</td>
<td>Licensed (from Novo Nordisk)</td>
</tr>
<tr>
<td>Stage:</td>
<td>Late Phase II</td>
</tr>
</tbody>
</table>
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.

- Postprandial high blood glucose due to lowered postprandial insulin secretion in diabetes.

Graph showing:
- Blood glucose level (mg/dL) with two lines: one for Normal and another for Diabetes.
- Insulin level (μU/mL) with two lines: one for Normal and another for Diabetes.
- Breakfast, Lunch, Supper time points with insulin secretion peaks.

Insulin secretion is enhanced early on in the graph, leading to normal insulin levels and suppression of postprandial high blood glucose in the diabetic condition.
Comparison of Repaglinide with Nateglinide in the clinical studies conducted overseas

HbA$_{1C}$

Blood glucose in fasting state

---

<table>
<thead>
<tr>
<th></th>
<th>Single Dose (mg)</th>
<th>Δ Postprandial blood glucose AUC (mg/dL・min)</th>
<th>Δ HbA1c (%)</th>
<th>Δ blood glucose in fasting state (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td>0.5-4</td>
<td>−6261.5</td>
<td>−1.57</td>
<td>−57.1</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60-120</td>
<td>−5888.3</td>
<td>−1.04</td>
<td>−18.4</td>
</tr>
</tbody>
</table>

Diabetes Care, Vol. 27, No.6, 1265-1270: Repaglinide versus Nateglinide monotherapy, Julio Rosenstock et al
Summary of SMP-862 (metformin)

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)

- 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) 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)

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Pre-registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMP-797</td>
<td>SM-11355</td>
<td>SUMIFERON (New indication)</td>
<td>SMP-536</td>
</tr>
<tr>
<td>SMP-986</td>
<td>SMP-114</td>
<td>MEROPEN (New indication)</td>
<td>SM-26000</td>
</tr>
<tr>
<td></td>
<td>GASMOTIN (New indication)</td>
<td>(Under preparation for Phase III)</td>
<td>CALSED (New indication)</td>
</tr>
</tbody>
</table>
Summary of SM-11355 (miriplatin)

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)

- 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.
<table>
<thead>
<tr>
<th><strong>Summary of SMP-114</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target disease:</strong></td>
</tr>
<tr>
<td><strong>Mode of action:</strong></td>
</tr>
<tr>
<td><strong>Formulation:</strong></td>
</tr>
<tr>
<td><strong>In-house/Licensed:</strong></td>
</tr>
</tbody>
</table>
| **Stage:**             | Early Phase II in Japan  
                        | Late Phase II outside Japan |
Pharmacological mechanism of SMP-114

Chronic inflammation (edema, pain)
Joint destruction
anchylosis

Synovial cell
T-lymphocyte
macrophage
fibroblast
osteoclast
SMP-114
## Summary of SMP-797

<table>
<thead>
<tr>
<th>Target disease:</th>
<th>cholesteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action:</td>
<td>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</td>
</tr>
<tr>
<td>Formulation:</td>
<td>Tablet</td>
</tr>
<tr>
<td>In-house/Licensed:</td>
<td>In-house</td>
</tr>
</tbody>
</table>
| Stage:          | Phase I in Japan  
                  Early Phase II outside Japan  |
**Effects of SMP-797**

**LIVER**
- Increase of bile acids excretion
- Increase of LDL receptor

**Bile acids**
- FC → CE
- SMP-797

**INTESTINE**
- Cholesterol in food or bile
- Inhibition of cholesterol absorption

**MACROPHAGE**
- Inhibition of lipid accumulation in arterial wall
- Anti-atherosclerotic effects

**INTESTINE**
- VLDL
- LDL modification

**Excretion**
- Bile

**HDL**
- Scavenger receptor
- Lipid droplets
<table>
<thead>
<tr>
<th>Summary of SMP-986</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target disease:</strong></td>
</tr>
<tr>
<td><strong>Mode of action:</strong></td>
</tr>
<tr>
<td><strong>Formulation:</strong></td>
</tr>
<tr>
<td><strong>In-house/Licensed:</strong></td>
</tr>
<tr>
<td><strong>Stage:</strong></td>
</tr>
</tbody>
</table>
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