Research and Development at Shionogi

March 22, 2007  13:00-15:00
At Tokyo Branch Office
Speakers

Overview: Isao Teshirogi, Ph.D.
Director of the Board; Senior Executive Officer
Executive General Manager
Pharmaceutical Research & Development Division

Research: Hirosato Kondo, Ph.D.
Corporate Officer
General Manager, Discovery Research Laboratories

Development: Takuko Sawada
General Manager
Strategic Development Department
Realization of the 2nd Medium-Term Business Plan and sustainable growth

Achieving growth by continuously launching new products

Shionogi’s R&D is committed to

- Securing the continuous discovery of drug seeds
- Enhancing R&D productivity in stages from Drug Candidate Selection (DCS) to Proof of Concept (POC)
- Accelerating clinical development in Japan, the USA and EU
Progress toward the goals of the 2nd Medium-Term Business Plan (1)

- Enrich the product line for infectious diseases and add pain and metabolic syndrome to new target areas
  - Infectious diseases: Expanded scope to include antiviral agents, etc. while concentrating on antibacterial infectious diseases
  - Pain: Made progress in the development of novel pain treatment
  - Metabolic syndrome: Developed S-2367 as a global strategic product
  - Frontier areas: Progressed steadily in selected R&D programs

- Advance at least 5 new chemicals entities to Phase II or more advanced stages by the end of FY 2009 to introduce blockbuster to succeed Crestor®
  - S-2367 (Anti-obesity: in Phase II)
  - S-364735 (Anti-HIV: in Phase II)
  - S-777469 (Antipruritic treatment: in Phase I)

Promote continuous global development for multiple products
Progress toward the goals of the 2nd Medium-Term Business Plan (2)

- **Establish the pipeline stream through active licensing activities**
  Adapalene (Acne vulgaris), Peramivir (Anti-Influenza): In-licensing

- **Increase R&D efficiency and success probability by forming active alliances with outside resources**
  Enriched R&D pipeline (Purdue Pharma L.P. in the USA, Hokkaido University)
  To be out-licensed a product in an unfocused research area through an optional agreement (S-0373)
  Out-licensed phospholipase A2 program (Anthera Pharmaceuticals, Inc. in the USA)
  Joint development agreement with Eli Lilly Japan K.K. (Duloxetine; Diabetic neuropathic pain)

- **Maximize product potential through life-cycle management from early development stage**
  Addition of new formulations: OxiNorm, Finibax® kit product, Claritin® dry syrup, Cetrotide® sustained release formulation (NS75B)
  Expansion of indications: Duloxetine, NS75B, Finibax®
  Clinical trials for evidence: Crestor®, Finibax®, Imunace®
Achieving the goals set for FY2006 (1)

- Further advancement in R&D activities
  
  **Visualized R&D activities**
  
  Promoted information sharing through open-frame monitoring system for R&D progress
  
  Established TA conference to maximize product value through MPDR (Marketing, Production, Development, Research)

- Research
  
  **Advance 3 out of 4 compounds from DCS to FTIH**
  
  Advanced S-777469 (Antipruritic treatment) to FTIH
  
  Evaluating back-up compounds of broad-spectrum cephem antibiotic, pain treatment and alleviator of opioid-induced adverse effects

  **Advance 4 or more compounds from late discovery stage to DCS**
  
  Advanced 3 out of 4 compounds from DCS to FTIH: Prostaglandin D2 antagonist (backup for S-5751), Molecular-targeted anti-cancer drug, Small molecule TPO mimetic

FTIH: First trial in human
Achieving the goals set for FY2006 (2)

- Development
  - Launch 4 products
    - Launched: Cetrotide®, OxiNorm, Finibax® kit product
    - To be approved in FY2007: Claritin® dry syrup
  - File NDAs for 2 products
    - Filed: Irbesartan, Pirfenidone
  - Move Phase II products to the next clinical stage
    - S-2367 (Anti-obesity): Demonstrated POC in the USA; Phase IIb clinical study is in progress
    - S-013420 (Novel macrolide antibiotic): Advanced clinical phase: Phase IIb is in progress
    - Duloxetine (Diabetic peripheral neuropathic pain): Advanced clinical phase; preparing for Phase IIb/III
    - S-5751 (Prostagrandin D2 receptor antagonist): Discontinued development Back-up compound is in progress
  - Other products
    - S-364735 (Anti-HIV): Completed phase I; Phase II is in progress
    - NS75B (Benign prostatic hypertrophy): Completed Phase I/II; Phase IIb is in progress
New challenges based on past achievement

- **Enrich pipeline in the targeted therapeutic areas**
- **Advance stages from DCS to FTIH in timely and solid manner**
- **Develop human resources for global development**
Main targets for the period from FY2007 to FY2009

- Secure continuous source for drug seeds through alliances
- Rapidly set up simultaneous development system in Japan, the USA and EU for accelerated new drug development
- Concentrate resources on the targeted therapeutic areas and achieve the highest R&D productivity in the pharmaceutical industry while accelerating the speed of development for in-house drug candidates from DCS to POC

Challenge the objectives in a flexible, systematic and efficient manner, develop world-class human resources; and generate high R&D productivity
Secure drug seeds continuously

Develop in-house drug candidates globally

**R&D Organization (Effective April 1, 2007)**

**Pharmaceutical Research Division**
- Discovery Research Laboratories
- Developmental Research Laboratories
- Intellectual Property

**Pharmaceutical Development Division**
- Strategic Development
- Clinical Research
- Biostatistics
**Desired R&D image for the end of FY2009**

**Aggressive R&D approach with spirit of venture companies**
- mobility, planning & commitment -

**Research**

**Continuously discover globally competitive drugs**
Ensure FTIH for 2 or more new in-house drug candidates each year

**Development**

**Simultaneously develop multiple in-house products in Japan, the USA and EU**
Secure either one to two Phase IIb and one Phase III products or three Phase IIb products
**Targeted milestones for FY2007**

**Research**
- Advance 2 compounds currently in DCS to FTIH
- Advance 4 or more compounds in late discovery stage to DCS
- Strengthen the discovery research for drug “seeds”
  - Hold ‘Pharma-Innovation Discovery Competition Shionogi’ to collect ideas from the public
  - Build a collaborative research facility in Hokkaido University campus
- Promote global research alliances on the targeted 3 research areas

**Development**
- Launch Claritin® dry syrup
- File an NDA for Duloxetine (Depression)
- Respond properly to NDA review for Irbesartan and Pirfenidone
- Promote global development for compounds in late development stage
  - S-2367 → Conduct interim analysis for Phase IIb study
  - S-777469 → Initiate POC study simultaneously both in Japan and the USA (Pruritus resulting from atopic dermatitis)
  - S-013420 → Make a ‘go/no-go’ decision to enter Phase III study (Domestic)
### Development status and launch schedule for new drugs (As of March 2007)

**Three targeted R&D areas**

**Infectious Diseases**
- Doripenem (Bacterial infection)
- Finibax® kit product (FY2006)

**Pain**
- Final review stage for in-licensing (Non-cancer pain treatment)
- OxiNorm (FY2006)

**MS**
- Final review stage for in-licensing (Insulin sensitizer)
- (FY2008)

**Frontier areas**

**Allergy**
- Claritin® (New formulation)
- (FY2007)

**Others**
- S-0139 (Cerebrovascular diseases)
- Pirfenidone (Idiopathic pulmonary fibrosis)
- (FY2008)

- NS75A (Uterine myoma)
- Adapalene (Acne vulgaris)
- (FY2009)

- S-013420 (Bacterial infection)
- S-364735 (HIV infection)
- S-2367 (Anti-obesity)
- S-777469 (Pruritus resulting from AD)
- S-777469 (Cerebrovascular diseases)
- NS75B (Benign Prostatic Hypertrophy)
- Duloxetine (Depression)

- Duloxetine (DNP)
- S-2367 (Anti-obesity)
- S-777469 (Pruritus resulting from AD)
- S-0139 (Cerebrovascular diseases)
- NS75B (Benign Prostatic Hypertrophy)
- Duloxetine (Depression)

- Doripenem (Bacterial infection)
- Finibax® kit product (FY2006)

- OxiNorm (FY2006)
- (FY2008)

- Claritin® (New formulation)
- (FY2007)

- Pirfenidone (Idiopathic pulmonary fibrosis)
- (FY2008)

- Adapalene (Acne vulgaris)
- (FY2009)

- Cetrotide®
- FY2006

**DNP:** Diabetic Neuropathic Pain, **AD:** Atopic Dermatitis
Research Division
Research goals for the 2\textsuperscript{nd} Medium-term Business Plan

Three Targeted Areas

- Infectious Diseases
- Metabolic Syndrome
- Pain

Frontier Area (Allergy and respiratory diseases, etc.)

1. Enrich product line for infectious diseases and add pain and metabolic syndrome to new target areas
2. Move at least 5 new chemical entities to Phase II or more advanced stages by the end of FY2009
3. Establish an unbroken pipeline stream through strategic development of licensing activity
4. Increase the R&D efficiency and success rate by forming active alliances with outside resources
5. Maximize product potential through life cycle management from an early development stage
Desired R&D image for the end of FY2009

Continuously discover globally competitive drugs
Ensure FTIH for 2 or more in-house new drug candidates each year

Achieve the highest R&D productivity in the pharmaceutical industry

→ through agile footwork
→ by developing outstanding drug discovery technologies
To realize the desired R&D image

Research framework at Shionogi

- Plan cross-divisional strategy by MPDR and provide feedback to each division
- Develop and in-license frontier key technologies
- Discover novel and original drug “seeds”
- Enrich back-up/contingency plan
- Utilize strategic alliances

Keep framework functioning efficiently = Realize high productivity
For the efficiency of the framework, organize mechanisms to harmonize each function and promote drug discovery
Mechanisms to promote drug discovery

- Portfolio Management of Research Program
  - Promote program selection and focusing to enhance success probability
  - Keep a balance BIC with FIC while producing novel drugs continuously as well as innovative drugs

- Resource allocation
  - Optimize resources timely and flexibly including optimization for strategic outsourcing

- Develop human resources
  - Develop future leaders by promoting young researchers
  - Develop world-class human resources

FIC: First in class, BIC: Best in class
Achievement in FY2006

- Advanced 1 out of 4 compounds from DCS to FTIH
  - Advanced S-777469 (Antipruritic treatment) to FTIH
  - For the remaining 3 DCS compounds in infection and pain areas, evaluations of back-up compounds are under way

- Selected 3 new compounds to DCS
  - Prostaglandin D2 inhibitor (back-up of S-5751)
  - Molecular targeted anti-cancer drug
  - Small molecule TPO mimetic

- Agreed to establish collaborative research institute with Hokkaido University
Milestone targets and measures for FY2007

- Ensure FTIH for 2 compounds and DCS for 4 compounds
  - Promote further program selection and focusing
  - Expand capabilities to predict compound risk accurately at earlier stage

- Strengthen the discovery research for drug “seeds”
  - Hold ‘Pharma-Innovation Discovery Competition Shionogi’ to collect ideas from the public
  - Build a collaborative research facility in Hokkaido University campus

- Promote global research alliances on the targeted 3 research areas
Topics in Research Division during FY2006

- Profile of drug candidates
- Other topics
Infectious Diseases area: New generation of HIV integrase inhibitors next to S-364735

Efficacy against highly resistant viruses for the preceding competitor

Reduction of anti-virus activity by mutations

Resistant mutations

- New generation compound
- Preceding competitor

SHIONOGI & CO., LTD.
Infectious Diseases area: Strengthen drug discovery research for influenza virus

**Focus on anti-influenza and anti-HIV research as two main pillars**

- **In-licensing of Peramivir**
  - Neuraminidase inhibitor
  - Shows strong efficacy against pathogenic H5N1 virus (including avian flu) as well as seasonal influenza virus (both type A and type B)
  - Applicable not only against community acquired influenza infection but also against serious influenza infection requiring hospitalization

- **Initiated drug discovery research for new generation compound**
Pain area: Novel anti-neuropathic pain compound with alleviated side effect profile

Analgesic effect and motor dysfunction in neuropathic pain model

**Compound X**
- No observation of motor dysfunction with wide dosage range

**Gabapentine**
- **First-line therapy:** Observation of motor dysfunction in the effective dosage range

---

**Graph**
- **X-axis:** Dosage (mg/kg p.o.)
- **Y-axis:** Analgesic effect and Motor dysfunction
- **Legend:** Normal, Dysfunctional

---

SHIONOGI & CO., LTD.
Pain area: Alleviator of opioid-induced adverse effects

CTZ: Chemoreceptor trigger zone

- Cerebrum, Spinal Cord → Analgesic effect
- 4th ventricle
- CTZ
- opioid

Side effect
- Emesis
- Constipation

Back-up compound
- Exhibits both anti-emesis and anti-constipation effects in the same dosage range
- More potent than the preceding compound by 10 to 100 times
- Good PK/PD profile

CTZ: Chemoreceptor trigger zone
**MS area: Post Crestor® Strategy**

**Pipeline for prevention/treatment of cardiovascular events**

- **Diabetic**
  - **Products**
    - Dimelin®
  - Research program/In-licensing under review
    - Insulin sensitizer

- **Hypertension**
  - **Products**
    - Fluitran®, Longes®, Landel®
  - Under development
    - Irbesartan

- **Obesity**
  - Under development
    - S-2367
  - Research program
    - S-2367 follow up

- **Lipid disorder**
  - Shionogi products
    - Crestor®
  - Research program/In-licensing under review
    - Drugs for HDL-C elevation
    - Drugs for LDL-C reduction

**Arteriosclerosis Diseases**

**Diabetic Complication**

**Metabolic Syndrome**
**MS area: Drug discovery for novel anti-diabetic compound with weight-reducing potency**

**Inhibitory effect on body weight increase**

- **Body weight change (g)**
  - Vehicle
  - Compound X

- **Days after drug administration**
  - 0
  - 7
  - 14
  - 21

**Mesenteric adipose mass**

- **Fat weight (g/100g Body weight)**
  - Normal value

**Fasting glucose & insulin level**

- **Fasting glucose (mg/ml)**
  - Normal value

- **Fasting insulin (ng/ml)**
  - Normal value
Frontier area: Pharmacological effects of S-777469 (1)

Orally active anti-pruritic drug with anti-inflammatory action via new mechanism of action

Anti-pruritic effect

<table>
<thead>
<tr>
<th>Substance P</th>
<th>Compound 48/80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cont Veh 10 30 (mg/kg)</td>
<td>Cont Veh 10 30 (mg/kg)</td>
</tr>
</tbody>
</table>

Histamine

No. of scratching (30min.)

| Cont Veh 0.3 1 3 10 1 3 10 30 (mg/kg) |

Fexofenadine

SHIONOGI & CO., LTD.
**Frontier area: Pharmacological effects of S-777469 (2)**

**Anti-inflammatory effect**

- **Dermatitis score:** Sum of severity in each item
- **Erythema/hemorrhage:** 0: n.d., 1: mild, 2: moderate, 3: severe
- **Scarring/dryness:**
- **Edema:**
- **Excoriation/erosion:**
  
  n.d.: not detectable

---

**Atopic dermatitis model induced by mite antigen**

- **Dermatitis score:**
  - Sum of severity in each item
  - Erythema/hemorrhage
  - Scarring/dryness
  - Edema
  - Excoriation/erosion

- **Vehicle**
- **S-777469 10 mg/kg**
- **Fexofenadine 30 mg/kg**

---

**Graph:**
- X-axis: Days after drug administration
- Y-axis: Dermatitis score
- Data points for different treatments shown with error bars.
**Frontier area: Molecular-targeted anti-cancer drug**

**Life prolongation effect in human tumor-bearing mouse**

- Human cancer cells were implanted in the immuno-deficient mouse
- Drugs were orally administrated once daily (35 days ~)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Average survival days</th>
<th>Increased survival time [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle control</td>
<td>76</td>
<td>-</td>
</tr>
<tr>
<td>Reference compound (100 mg/kg)</td>
<td>87</td>
<td>14</td>
</tr>
<tr>
<td>DCS (40 mg/kg)</td>
<td>115*</td>
<td>52</td>
</tr>
</tbody>
</table>

* P<0.05 vs reference compound, Logrank test

DCS potently prolonged survival time at the lower dose compared with reference compound
Frontier Area: Small molecule TPO mimetic

**CFU-MK assay using human bone marrow-derived CD 34 positive cell**

- Effective at 0.3mg/kg and more in *in-vivo* animal model

- DCS compound induced differentiation/proliferation of hematopoietic stem cell into megakaryocyte similar to hTPO

- After culture for 12 days in the presence of drugs, megakaryocyte was stained with CD41 antibody

**Platelet increasing ratio**

<table>
<thead>
<tr>
<th>DCS compound</th>
<th>0.3 (mg/kg)</th>
<th>1</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1.1</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>DCS compound</td>
<td>1.5</td>
<td><strong>2.1</strong></td>
<td><strong>2.7</strong></td>
</tr>
</tbody>
</table>

*SHIONOGI & CO., LTD.*

*CFU-MK: Colony-forming units megakaryocyte*
Establish “Shionogi Innovation Center for Drug Discovery”

- The first research institute of a private company built in the Japanese national university campus
- Accelerate drug discovery through the extensive alliance with Hokkaido University

- **Research plan**
  - Drug discovery research for biomedicine based on glycoengineering
  - Discovery research for novel drug “seeds”
  - Development of key technologies

- **Action Plan**
  - FY2007
    - Construction of facility
    - Start collaboration
  - FY2008
    - Start full-scale research

Rendering of Research Facility
Milestones of Research Division for FY2007

- Ensure FTIH for 2 compounds and DCS for 4 compounds
- Strengthen the discovery research for drug “seeds”
- Promote globally collaborative research on the targeted 3 research areas
Clinical Development

- Realization of the 2\textsuperscript{nd} medium-term business plan
  - Targeted Development Division goals for the 2\textsuperscript{nd} medium-term business plan
  - Desired image at the end of FY2009
  - Achievement of FY2006 goals
  - Main targets for the period from FY2007 to FY2009
  - Targeted milestones and measures for FY2007
Targeted Development Division goals for the 2nd Medium-term Business Plan

Three Targeted Areas

1. Enrich product line for infectious diseases and add pain and metabolic syndrome to new target areas
2. Move at least 5 new chemical entities to Phase II or more advanced stages by the end of FY2009
3. Establish an unbroken pipeline stream through strategic development of licensing activity
4. Increase the R&D efficiency and success rate by forming active alliances with outside resources
5. Maximize product potential through life cycle management from an early development stage
**Desired image for the end of FY2009**

**Simultaneously develop multiple in-house products in Japan, the USA and EU**

Secure either one to two Phase IIb and one Phase III products or three Phase IIb products

- In a position to establish the development base and start operation in EU in addition to the USA
- In a position to enable to file NDAs both in the USA and EU by ourselves or through alliances with business partner
Achievement of FY2006 goals (1)

Achievement:

1. Launched 3 products which were under NDA review (Cetrotide®, Finibax® kit product, OxiNorm)
2. Filed NDAs for Irbesartan and Pirfenidone
3. Made a ‘go/no-go’ decision for 4 products in Phase II (S-013420, Duloxetine; Diabetic peripheral neuropathic pain, S-2367, S-5751)

*Claritin® dry syrup: pending the progress of NDA review by authority*
**Achievement of FY2006 goals (2)**

**Since April 2006**

- **Finibax® kit product**  NDA filed → Launched
- **OxiNorm**  NDA filed → Launched
- **Cetrotide®**  NDA filed → Launched → Post-marketing clinical study is in progress
- **Irbesartan**  Phase III → NDA filed
- **Pirfenidone**  Phase III → NDA filed
- **Duloxetine**  Phase IIa → In preparation for Phase IIb/III
  (Diabetic peripheral neuropathic pain)
- **S-013420**  Phase IIa → Phase IIb
- **S-2367**  Phase IIa → Phase IIb
- **NS75B**  Phase I/II → Phase IIb
- **S-364735** *  Phase I → Phase II
- **S-777469**  Pre-clinical → Phase I

*Shionogi-GSK (JV) Product

**Advanced almost all the products to next phases**
Achievement of FY2006 goals (3)

- Promoted further selection on development compounds and positively out-licensed compounds in unfocused areas
  - S-5920 (Acute chest syndrome in sickle cell disease)
  - S-3013 (Arteriosclerosis)
  - S-0373 (Spinocerebellar ataxia, Parkinson's disease)
  - S-0139 (Cerebrovascular diseases)

- In-licensed targeted area products
  - Peramivir (Influenza)
  - LDL-C reducer
  - Insulin sensitizer treatment
  - Non-cancer pain treatment
Achievement of FY2006 goals (4)

- Development of new formulations for approved products
  Finibax® kit product, OxiNorm, Claritin® dry syrup,
  Cetrotide® sustained release formulation (NS75B)

- Post-Marketing clinical studies: Studies are in progress
  Crestor® - Prevention of plaque extension in coronary arteries (IVUS study)
  Finibax® - Establish 3 times/day administration based on PK/PD theory
  Imunace® - Pharmacogenomics test with renal cell carcinoma

- Additional indications:
  Duloxetine - Diabetic neuropathic pain (In preparation for Phase III)
  NS75B (Cetrorelix pamoate) - Benign Prostatic Hypertrophy (Phase IIb is in progress)
  Finibax® - Pediatric use (Planning Protocol)
Main targets for the period from FY2007 to FY2009

Accumulate experience in overseas development and accelerate the speed of globalization

1. Development of global strategic products
   Promote overseas activities with S-2367, S-364735 and S-777469
   Continuously discover compounds competitive in global market to follow the above 3 products

2. Construct a functional organization and intensify investment in R&D
   Streamline strategic core organization to promote simultaneous development in Japan/the USA/EU and develop human resources
   Continuously increase investment in development

3. Positively seek business opportunities
   Accelerate global development through strategic alliances
Targeted milestones and measures for FY2007

Set challenging goals and accomplish them steadily

- **NDA ~ Launch**
  - Launch of Claritin® dry syrup
  - Complete phase III and NDA filing for Duloxetine (Depression)

- **Go/No-Go Decisions**
  - S-2367 Conduct interim analysis for Phase IIb study
  - S-364735 Make a go/no-go decision
  - S-777469 Advance to Phase II and initiate development simultaneously in Japan and the USA
  - S-013420 Make a go/no-go decision to enter Phase III study

- **FTIH**
  - 3 products (2 in-house products and Peramivir)

- **Life Cycle Management**
  - Finibax® Complete post-marketing clinical study and initiate clinical study for pediatric use
**Targeted milestones and measures for FY2007**

Optimize operating efficiency to enhance development capability

---

1. **Resources**
   - Positively utilize outside resources in Japan and abroad
   - Promote recruitment for mid-carrier specialists
   - Enhance function of Shionogi USA, Inc.

2. **Process and Infrastructure**
   - Reform and streamline the development processes to operate on a global basis
   - Increase the number of products to be controlled under EDC (Electronic Data Capture) system
   - Establish and operate clinical data base on a global basis
   - Start electronic filing for NDA (eIND, eCTD)
Core Development Products

- Product characteristics
- Indications
- Pre-clinical and clinical study data, etc.
**S-2367: Profile**

- **Anti-obesity (Oral)**
- **Neuropeptide Y (NPY) Y5 receptor antagonist**

**Key findings from pre-clinical studies**
- Increased energy consumption
- Suppressed visceral fat accumulation and improved blood glucose and serum lipid levels
- Expected product profile without rebound
- Confirmed excellent safety

**Key findings from clinical studies to date**
- Once-daily administration (T ½ : about 20 hours)
- No serious adverse events observed
- Achieved positive Phase IIa proof-of-concept achieved in US study

*Phase IIb studies are under way in the USA*
S-2367: Outline of Phase 2b Study

- Two Phase IIb Studies are under way.
  - Study 1
    - RCD (Reduced calorie diet)-lead in followed by RCD with S-2367 or placebo treatment
    - Number of patients: 750
    - Maximum dose: 1600 mg
  - Study 2
    - LCD (Low calorie diet)-lead in followed by RCD with S-2367 or placebo treatment
    - Number of patients: 750
    - Maximum dose: 1600 mg
- Year-long studies based on FDA Draft Guidance for “Developing Products for Weight Management”
- Interim analyses are planned 6 month later after study initiation
S-2367: Future Development

● Phase IIb studies:
  ● Studies 1 and 2:
    – Initiated patient enrollment in March for completion within 2007
    – Scheduled to conduct interim analysis within FY2007 (i.e. by March 2008)

● Other clinical studies:
  ● Drug-drug interaction study
    – Successfully completed
  ● MTD study (Maximum Tolerance Dose Study):
    – Smoothly ongoing and to be completed in 2Q 2007

USA NDA scheduled for within FY2010
**S-364735: Profile**

- Developed by Shionogi-GlaxoSmithKline Pharmaceuticals, LLC
- Integrase inhibitor (Oral)
  (Novel anti-HIV drug with a different mechanism of action from existing drugs)
- Strong anti-HIV activity in inhibiting virus replication (at 1nM level) *in vitro*
- Resistant mutation slow to emerge
- Good pharmacokinetics profile
- Low risk of drug-drug interactions
- Confirmed no severe clinical adverse events in the studies

Phase II study is under way in the USA

SHIONOGI & CO., LTD.
**S-364735: Summary of Phase I and Outline of Phase II Study**

- **Summary of Phase I study**
  - Pharmacokinetics:
    - Plasma concentration exceeded the targeted treatment trough value
    - No drug inhibition/induction against metabolic enzyme
    - Food effect was observed for plasma concentration
  - Safety:
    - Confirmed safety, good tolerability and no severe adverse events

- **Outline of Phase II study**
  - Design of study:
    - Assess efficacy, safety, tolerability and pharmacokinetics by monotherapy for 10 days
**S-364735: PK data of multiple dose study (Median)**

Target trough plasma concentration (Cmin), 62 ng/mL, for S-364735 was calculated from *in vitro* anti-HIV activity to achieve enough anti-viral activity in humans.

Exceeded target trough value by administration of over 50mg BID.
**S-777469: Profile**

- Target Indication: Atopic dermatitis
- Orally active drugs with anti-pruritic anti-inflammatory efficacy based on novel mechanism of action
- Inhibits scratching behavior induced by various pruritogenic agents in mouse model
- Demonstrated anti-inflammatory efficacy in chronic mouse model
- Good safety profile in GLP tox studies
- Phase I multiple dose study to be initiated simultaneously in Japan and the USA in 2Q FY2007
- POC study to be initiated in Japan and the USA by the end of 2007
- Phase I single dose study is under way
**S-777469: Latest update on Japanese Phase I single dose study**

- Good tolerability
- Rapid elevation of blood concentration level
- Dose-dependent elevation of exposure up to 800 mg
Pirfenidone: Profile

- Licensed from MARNAC, INC. (USA) and KDL, Inc. (Japan)
- Idiopathic pulmonary fibrosis
- Anti-fibrosis (Oral)
- Designated as an orphan drug by Pharmaceuticals and Medical Devices Agency (PMDA)
- Completed Phase III clinical studies in November 2006
- With VC (vital capacity) change, significantly inhibited worsening of the condition compared with a placebo.

NDA filed in March 2007
Pirfenidone: Design of Phase III clinical study

- **Design of the clinical trial:** Double-blind placebo-controlled study
  - Study to compare efficacy of pirfenidone 1800mg versus placebo
  - Evaluated Risk/Benefit when the dose is reduced:
    - Set Pirfenidone 1200mg (low dose) Group
  - Target sample size: 250 patients (1800mg–100 patients: 1200mg-50 patients: placebo-100 patients)
  - FAS (Full analysis set):
    - 267 patients (1800mg-108 patients: 1200mg-55 patients: placebo-104 patients)
  - Significance level: 0.10 (Power 80%)

- **Endpoints**
  - Primary Endpoint: Change in Vital Capacity (VC)
  - Secondary Endpoint:
    - Distribution of progression-free survival
      (definition of disease progression: death or more than 10% decrease in VC)
      - Change for lowest SpO₂ (arterial oxygen saturation) from beginning to 52nd week of administration
## Pirfenidone: Results of Phase III clinical study (Efficacy: FAS)

### Analysis of covariance for VC (Vital Capacity): 52 weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Adjusted mean (L)</th>
<th>Difference with Group P(L)</th>
<th>2-sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group H</td>
<td>104</td>
<td>- 0.09</td>
<td>0.07</td>
<td>0.0416</td>
</tr>
<tr>
<td>Group L</td>
<td>54</td>
<td>- 0.08</td>
<td>0.09</td>
<td>0.0394</td>
</tr>
<tr>
<td>Group P</td>
<td>103</td>
<td>- 0.16</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**Pirfenidone: Results of Phase III clinical study**

### Analysis of covariance for lowest SpO₂: 52 weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Adjusted mean (%)</th>
<th>Difference with Group P (%)</th>
<th>2-sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group H</td>
<td>99</td>
<td>- 1.70</td>
<td>- 0.17</td>
<td>0.7393</td>
</tr>
<tr>
<td>Group L</td>
<td>53</td>
<td>- 0.84</td>
<td>0.69</td>
<td>0.2485</td>
</tr>
<tr>
<td>Group P</td>
<td>100</td>
<td>- 1.53</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Pirfenidone: Results of Phase III clinical study

- Distribution of progression-free survival (52 weeks)

Definition of disease progression: death or more than 10% decrease in VC

Survival rate

Log-rank test p-value

- H vs P: 0.0280
- L vs P: 0.0655
- H vs L: 0.9106

SHIONOGI & CO., LTD.
**Peramivir: Profile**

- Licensed from BioCryst Pharmaceuticals, Inc. (the USA)
- Anti-influenza virus drug (neuraminidase inhibitor)
- Highly active against influenza A and B viruses
  → Stronger activity against influenza B virus than Tamiflu
- Strong activity against the highly pathogenic avian influenza virus (H5N1)
- Strong binding power with neuraminidase and difficult to dissociate
  → Possibly effective even with only one administration
- Possibly effective even if administered more than 48 hours after infection (Delay Administration)
- Broad indications from ordinary seasonal influenza to serious influenza that requires hospital care
- The U.S. Department of Health and Human Services (DHHS) awarded US$102.6 million to BioCryst for advanced development of Peramivir to treat seasonal and life-threatening influenza
- Phase II study is ongoing in USA (intramuscular injection)
  
  **Phase I in preparation (Japan)** SHIONOGI & CO., LTD.
**Peramivir: Anti-virus activities against influenza viruses**

<table>
<thead>
<tr>
<th>Virus type/subtype</th>
<th>No. of Isolates</th>
<th>IC$_{50}$[nM]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Peramivir</td>
<td>Oseltamivir carboxylate</td>
</tr>
<tr>
<td>A/H1N1</td>
<td>5</td>
<td>0.34 (0.26-0.43)</td>
<td>0.45 (0.45-0.60)</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>6</td>
<td>0.60 (0.47-0.87)</td>
<td>0.37 (0.27-0.45)</td>
</tr>
<tr>
<td>B</td>
<td>8</td>
<td>1.36 (1.08-1.95)</td>
<td>8.50 (5.33-18.3)</td>
</tr>
</tbody>
</table>

Peramivir: Efficacy in a model (ferret) infected with highly pathogenic avian influenza A/Vietnam/1203/04(H5N1)

S-013420: Profile

- Licensed from Enanta Pharmaceuticals (the USA)
- Novel macrolide antibiotic (Oral)
  (Novel characteristic of bridged structure)
- Broad spectrum enough to cover major causing bacteria causing respiratory infections
- Strong antibacterial activity against *S. pneumoniae* (including penicillin or macrolide resistant stains)
- Good PK profile
- Suitable for pediatric usage because of no bitterness

Phase IIb study in progress

SHIONOGI & CO., LTD.
Summary of Phase IIa Study

Efficacy:
- Confirmed high efficacy (clinical efficacy and bacteriological response) in a short dosing period (3 days)

Safety:
- No serious adverse event; safe and well-tolerated
- Transaminase elevation and digestive symptoms were major adverse events (similar to those of analog drugs)

Outline of Phase IIb Study

Targeted disease
- Pneumonia caused by bacteria or atypical pathogen

Study design
- Randomized double blinded dose finding study

Accumulate study cases to initiate Phase III study in the next winter season
S-013420: Change of parameters for efficacy

【Body Temperature】

![Graph showing body temperature changes over time for different treatment durations: pre-dosing, 3 days after beginning of treatment, 5 days after beginning of treatment, 7 days after completion of treatment.]

【CRP】

![Graph showing CRP levels over time for different treatment durations: pre-dosing, 3 days after beginning of treatment, 5 days after beginning of treatment, 7 days after completion of treatment.]

【Severity of chest radiography】

![Graph showing severity of chest radiography over time for different treatment durations: pre-dosing, 3 days after beginning of treatment, 5 days after beginning of treatment, 7 days after completion of treatment.]

【WBC】

![Graph showing WBC levels over time for different treatment durations: pre-dosing, 3 days after beginning of treatment, 5 days after beginning of treatment, 7 days after completion of treatment.]

© SHIONOGI & CO., LTD.
Irbesartan: Profile

- Licensed from Sanofi-Aventis (France)
- Currently co-developed by Dainippon Sumitomo Pharma Co., Ltd.
- Hypertension treatment
- Angiotensin II receptor antagonist (Oral)
- Approved for diabetic nephropathy (the USA & EU)
- Conducting Phase III study for heart failure (the USA & EU)
- Not pro-drug

Proved non-inferiority to another angiotensin II receptor antagonist through double-blind study

NDA filed in December 2006
Duloxetine: Profile

- Licensed from Eli Lilly and Company (the USA), Shionogi and Eli Lilly Japan K.K. will co-market Duloxetine
- Anti-depressant (Oral)
- SNRI: Serotonin & Norepinephrine Reuptake Inhibitor
- Side effects on autonomic nervous system induced by anticholinergic effects of Duloxetine are less than those of tricyclic antidepressants

Conducting additional clinical trials with higher dosages to maximize the efficacy of Duloxetine, taking into account the dosage levels used abroad.

NDA filing is scheduled during FY 2007
**Duloxetine:**

*Additional Indication - Diabetic peripheral neuropathic pain (DPNP)*

- Treatment of diabetic peripheral neuropathic pain (Oral)
- Shionogi and **Eli Lilly Japan K.K.** will co-develop and co-market Duloxetine for the indication
- First-line drug for DPNP; no approved drug with high efficacy is available in Japan.
- DPNP is a diabetes complication; Duloxetine will contribute to expanding and strengthening the pipeline in MS area and pain area
- Life Cycle Management after approval for depression

**Eli Lilly obtained an indication for DPNP in the USA in September 2004**

SHIONOGI & CO., LTD.
Duloxetine (Diabetic peripheral neuropathic pain): Phase IIa study

● **Dose-response study**
  - Dosing period: 13 weeks
  - Target sample size: 200 patients
  - Study schedule:
    - FPI: November 2005
    - LPO: December 2006
    - Key Open: March 9, 2007

Go on to Phase IIb/III study

● **Continuation study following dose-response study**
  - Dosing period: 52 weeks
  - Target sample size: Patients proceeded from dose-response study
  - Study schedule:
    - FPI: March 2006
    - LPO: December 2007 (Planned)

FPI: First patient in, LPO: Last patient out
**NS75B: Profile**

- Sustained-release formulation of Cetrotide®, Licensed from Zentaris AG (Germany)
- Generic name: Cetrorelix pamoate
- GnRH (Gonadotropin releasing hormone) antagonist (IM)
- Treatment for Benign Prostatic Hypertrophy (BPH)
- Good characteristics of both $\alpha_1$ blocker and antiandrogenic agent
- Minor and temporary suppression of sexual function and that of markers for prostatic cancer
- Surgical treatment may be avoided
**NS75B: Current status of development**

- **Phase I/II study completed**
  - Confirmed good sustained release curve from PK data
  - Suppression of testosterone is dose dependent
  - Confirmed suppression of markers for prostatic cancer (PSA)
  - Confirmed no serious adverse event, tolerability was comfortable

- **Phase IIb study started**
  - Primary Endpoint: Improvement of International Prostate Symptom Score (IPSS)
  - Number of patients: 300
  - Duration: 8 months
  - FPI: December 21, 2006
  - Key Open: April, 2008 (Planned)
  - Introduced Electronic Data Capture (EDC)

- **Co-development with Nippon Kayaku Co., Ltd. was discontinued**
  - Both companies focus on the areas where they have advantages
  - Shionogi expects synergy because it has products (antibiotics etc.) in urologic market
  - Shionogi expects acceleration of development due to centralization
**NS75B: PK in Phase I/II single dose study**

- Cmax and AUC were dose dependent
- Tmax was about 48 hrs and T1/2 was over 10 days. Confirmed good sustained release curve
**NS75B: Testosterone concentration change in Phase I/II single dose study**

- Suppression term and degree of testosterone was dose dependent
- The obtained results were similar to those in EU study; improvement of BPH can be expected
NS75B: Suppression of PSA in Phase I/II single dose study

- Confirmed no suppression of markers for prostatic cancer (PSA)
Targeted milestones for FY2007

Set challenging goals and accomplish them steadily

- **NDA ~ Launch**
  - Launch Claritin® dry syrup
  - Complete Phase III and NDA filing for Duloxetine (Depression)

- **Go/no-Go Decisions**
  - S-2367  Conduct interim analysis for Phase IIb study
  - S-364735  Make a go/no-go decision
  - S-777469  Initiate POC study simultaneously in Japan and the USA
  - S-013420  Make a go/no-go decision to enter Phase III study

- **FTIH**
  - 3 products (2 in-house products and Peramivir)

- **Life Cycle Management**
  - Finibax®  Complete post-marketing clinical study and initiate clinical study for pediatrics
These presentation materials contain forward-looking statements regarding the Company’s plans, outlook, strategies and results for the future. All forward-looking statements are based on judgements derived from the information available to the Company at the time of publication.

Certain risks and uncertainties could cause the Company’s actual results to differ materially from any projections presented in these presentation materials.