# Overview of Product Pipeline

November 4, 2004

Yamanouchi Pharmaceutical Co., Ltd.

Shinji Usuda, Ph. D.

Corporate Vice President

Director of Drug Development Division

**Cautionary statement regarding forward-looking information**

This material includes forward-looking statements based on assumptions and beliefs in light of the information currently available to management and subject to significant risks and uncertainties. Actual financial results may differ materially depending on a number of factors including adverse economic conditions, currency exchange rate fluctuations, adverse legislative and regulatory developments, delays in of new product launch, pricing and product initiatives of competitors, the inability of the company to market existing and new products effectively, interruptions in production, infringements of the company's intellectual property rights and the adverse outcome of material litigation.

# Product pipeline in Japan (Approved/Filed)

| Code No. | Therapeutic target/ indication | Class of compound | Dosage form |
|---|---|---|---|
| **Approved** | | | |
| Harnal D (tamsulosin) | Functional symptoms with BPH | $\alpha_1$ receptor antagonist (without water tablet/ WOWTAB) | Oral |
| Advaferon (interferon alphacon-1) | Chronic hepatitis C virus infection | Consensus interferon (New Formulation of 9MIU) | Injection |
| **Filed** | | | |
| YM152 (finasteride) | Benign prostate hyperplasia (BPH) | 5$\alpha$-reductase inhibitor | Oral |
| YM670 (multiporous gelatine particles) | Arterio-embolization (liver) | Transcatheter arterial embolization (TAE) | Particle |
| YM177 (cerecoxib) | Rheumatoid arthritis, osteoarthritis, low back pain, etc. | Cyclooxygenase II inhibitor | Oral |
| YM905 (solifenacin) | Urinary frequency, urinary incontinence or urgency associated with overacitve bladder | Muscarinic receptor antagonist | Oral |

# Product pipeline in Japan (P-II or P-III)

| Code No. | Therapeutic target/ indication | Class of compound | Dosage form |
|---|---|---|---|
| **P-III** | | | |
| YM529 (minodronate) | Osteoporosis | Bisphosphonate | Oral |
| **P-II** | | | |
| YM974 (valdecoxib) | Rheumatoid arthritis, osteoarthritis, low back pain, etc. | Cyclooxygenase II inhibitor | Oral |
| YM978 (parecoxib) | Acute pain | Cyclooxygenase II inhibitor | Injection |

# Product pipeline in Japan (new indications/new formulations)

| Code No. | Therapeutic target/ indication | Class of compound | Dosage form |
|---|---|---|---|
| **P-III** | | | |
| YM617 (tamsulosin) | Lower urinary tract syndrome | $\alpha_1$ receptor antagonist | Oral |
| YM086 (telmisartan) | Diabetic nephropathy | Angiotensin II receptor antagonist | Oral |
| YM643 (interferon alphacon-1) | Chronic hepatitis C virus infection<br>Combination with ribavirin | Antivirus | Injection/oral<br>combination therapy |
| YM060 (ramosetron) | Irritable bowel syndrome (IBS) | 5-$HT_3$ receptor antagonist | Oral |
| YM026 (nateglinide) | Type II diabetes<br>Concomitant treatment with Biganides | Rapid onset insulin secretion enhancer | Oral |
| YM177 (cerecoxib) | Post surgical pain, post traumatic pain, tooth extract pain | Cyclooxygenase II inhibitor | Oral |

# Product pipeline in EU/US (Launched, NDA/MAA filing or approval)

| Code No. | Regions | Therapeutic target/indication | Class of compound | Dosage form |
|---|---|---|---|---|
| **Launched** | | | | |
| Vesicare (solifenacin) | EU* | Urinary frequency, urinary incontinence or urgency associated with overacitve bladder | Muscarinic receptor antagonist | Oral |
| *Launched ;The Netherlands, U.K., Germany, France, Denmark, Ireland, Norway To be launched; 10 other European countries | | | | |
| **Approved** | | | | |
| Omnic-OCAS (tamsulosin) | EU* | Functional symptoms with BPH | $\alpha_1$ receptor antagonist | Oral (TOCAS** ) |
| *Approved ;The Netherlands **tamsulosin oral controlled absorption system | | | | |
| **Filed** | | | | |
| YM905 (solifenacin) | US | Urinary frequency, urinary incontinence or urgency associated with overacitve bladder | Muscarinic receptor antagonist | Oral |
| YM087 (conivaptan) | US | Euvolemic or hypervolemic hyponatremia | Vasopressin receptor antagonist | Injection |

# Product pipeline in EU/US
# P-II or additional formulations

| Code No. | Regions | Therapeutic target/indication | Class of compound | Dosage form |
|---|---|---|---|---|
| **P-II** | | | | |
| YM087 (conivaptan) | EU US | Acutely decompensated chronic heart failure | Vasopressin receptor antagonist | Injection |
| YM178 | EU | Overacitve bladder | $\beta_3$ receptor agonist | Oral |
| YM443 | US | Functional dyspepsia | Acetylcholine level enhancer | Oral |
| YM150 | EU | Prevention of deep vein thrombosis, prevention of thromboembolism in atrial fibrillation | Factor Xa inhibitor | Oral |
| YM060 (ramosetron) | | Irritable bowel syndrome (IBS) | 5-$HT_3$ receptor antagonist | Oral |
| **P-II <New Formulation>** | | | | |
| YM617 (tamsulosin) | EU | Functional symptoms with BPH | $\alpha_1$ receptor antagonist (without water tablet/WOWTAB) | Oral |

# Projects in the P-I or pre-clinical stage

| Therapeutic areas | Number of projects |
|---|---|
| Urinary system | 3 |
| Cardiovascular | 2 |
| Locomotorium | 2 |
| Endocrine system | 3 |
| CNS | 1 |
| Others | 3 |
| Total | 14 |

# Termination of development

| Code No. | Development stage/ indications | Reasons: |
|---|---|---|
| **JPN** | | |
| YM294 (oprelvekin) | Filed: Chemotherapy-induced thrombocytopenia | Differences remained between the regulatory authorities' views and Yamanouchi's even after repeated discussions on the benefit of IL-11 in the treatment of acute myeloid leukemia, and Yamanouchi concluded that it's study results would not lead to obtaining the approval. |
| YM454 (perflutren) | P-II: Echocardiography | Development for cardiovascular echo imaging was discontinued as a result of prior termination of relevant development for liver echo imaging. |

Vasopressin receptor antagonist

# YM087

（Generic name: conivaptan）

# Summary of YM087

Stage
- NDA submission in the US (January 2004)

Indication
- Hyponatremia

Mechanism of action
- Vasopressin $V_{1a}/V_2$ dual antagonist

Dosage form
- Injection (intravenous dosing)

P-III data publication
- Heart Failure Society of America (September, 2004)
- America Society of Nephrology (October, 2004)

# Hyponatremia – Incidence & Symptoms -

## Incidence of hyponatremia

- Hyponatremia is a decrease in plasma sodium concentration below 135 mEq/L caused by an excess of water relative to solute.
- Hyponatremia is the most common electrolyte disorder, occurring in 1 - 6% of all patients admitted to the hospital.
- Hyponatremia has been reported in over 50% of hospitalized patients with AIDS.

## Symptoms and signs

- Manifestations of hyponatremia can be subtle and consistent mainly of changes in mental status, including altered personality, lethargy, and confusion.
- As the plasma $Na^+$ falls below 115 mEq/L, stupor, neuromuscular hyperexcitability, convulsions, prolonged coma and death can result.

The Merck Manual of Diagnosis and Therapy 17th Edition Section 2, Chapter 12
Exp Clin Endocrinol Diabetes 1999, 107, 157-165

# Hyponatremia - cause & treatment -

Hyponatremia reflects an excess of total body water (TBW) relative to total body $Na^+$ content. Since total body $Na^+$ content is reflected by extracellular fluid (ECF) volume status, it is useful to classify the causes of hyponatremia with volume status, namely, hypervolemia, euvolemia (normal), and hypovolemia.

| Hyponatremia | Causes/Disorders | Medical treatment |
|---|---|---|
| Hypervolemia | Heart failure, Hepatic cirrhosis, Renal disorders | Restriction of $Na^+$ and water intake (diuretics) |
| Euvolemia | SIADH, Diuretics, Psychogenic polydipsia | Restriction of water intake |
| Hypovolemia | $Na^+$ losses by vomiting or diarrhea | Replacement of $Na^+$ and water (saline) |

SIADH: syndrome of inappropriate antidiuretic hormone secretion, TBW: total body water.

New Engl J Med 2000, 342, 1581-1589; Merk Mannual 17th Ed 1999, 126-131

# P-III Pivotal Study Synopsis

## Objectives:

- To determine the efficacy of YM087 (conivaptan) on serum sodium in patients with euvolemic or hypervolemic hyponatremia
- To assess safety

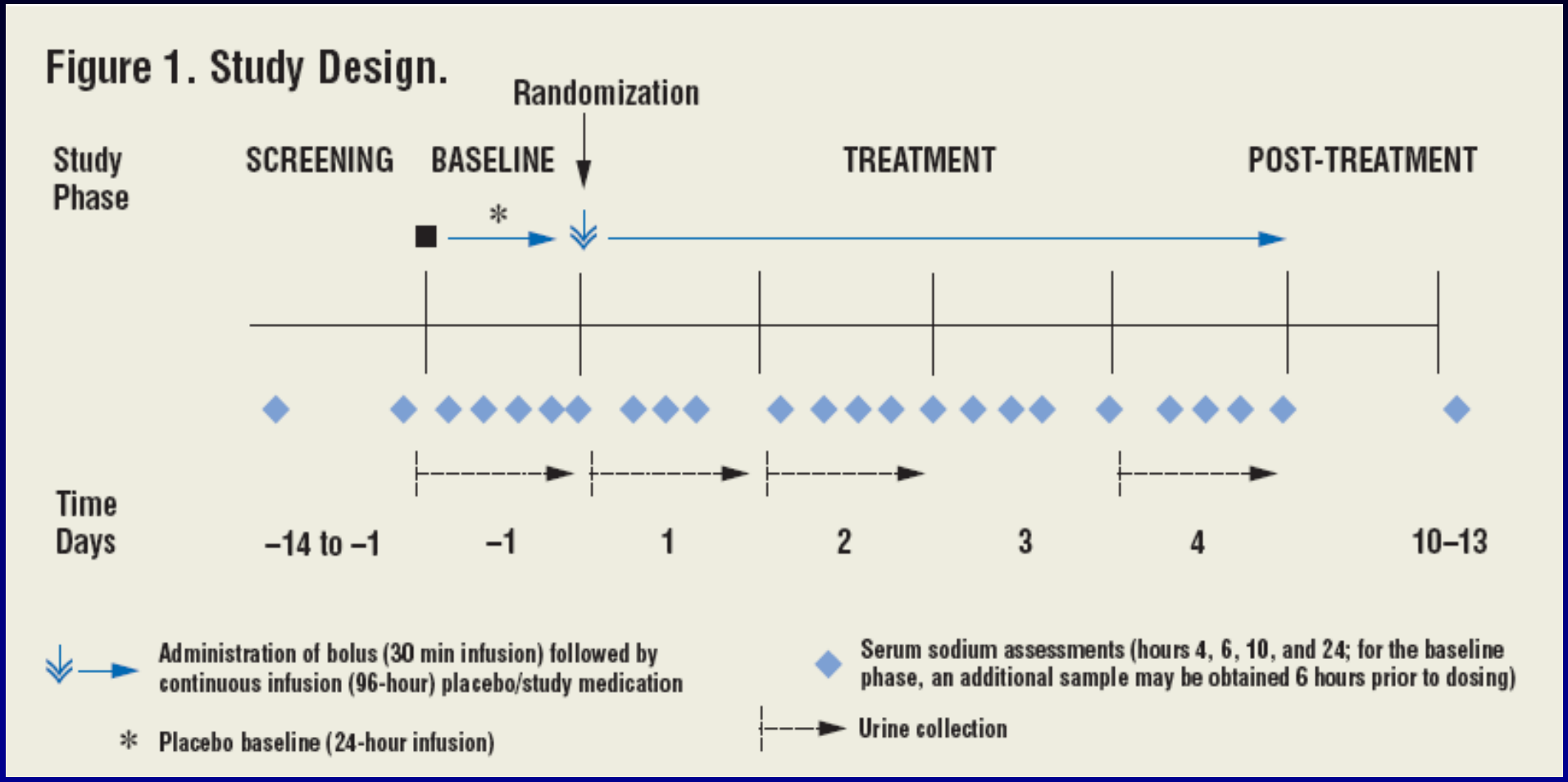
## Study populations:

- Patients with euvolemic or hypervolemic hyponatremia
  (Serum sodium concentration: higher than 115 mEq/L and less than 130 mEq/L)
- Number of patients: 84 received treatment, and 66 completed treatment.

## Primary efficacy parameter:

- Change from the baseline in serum sodium over treatment as the area under the serum sodium effect curve (AUC)

# Study Design



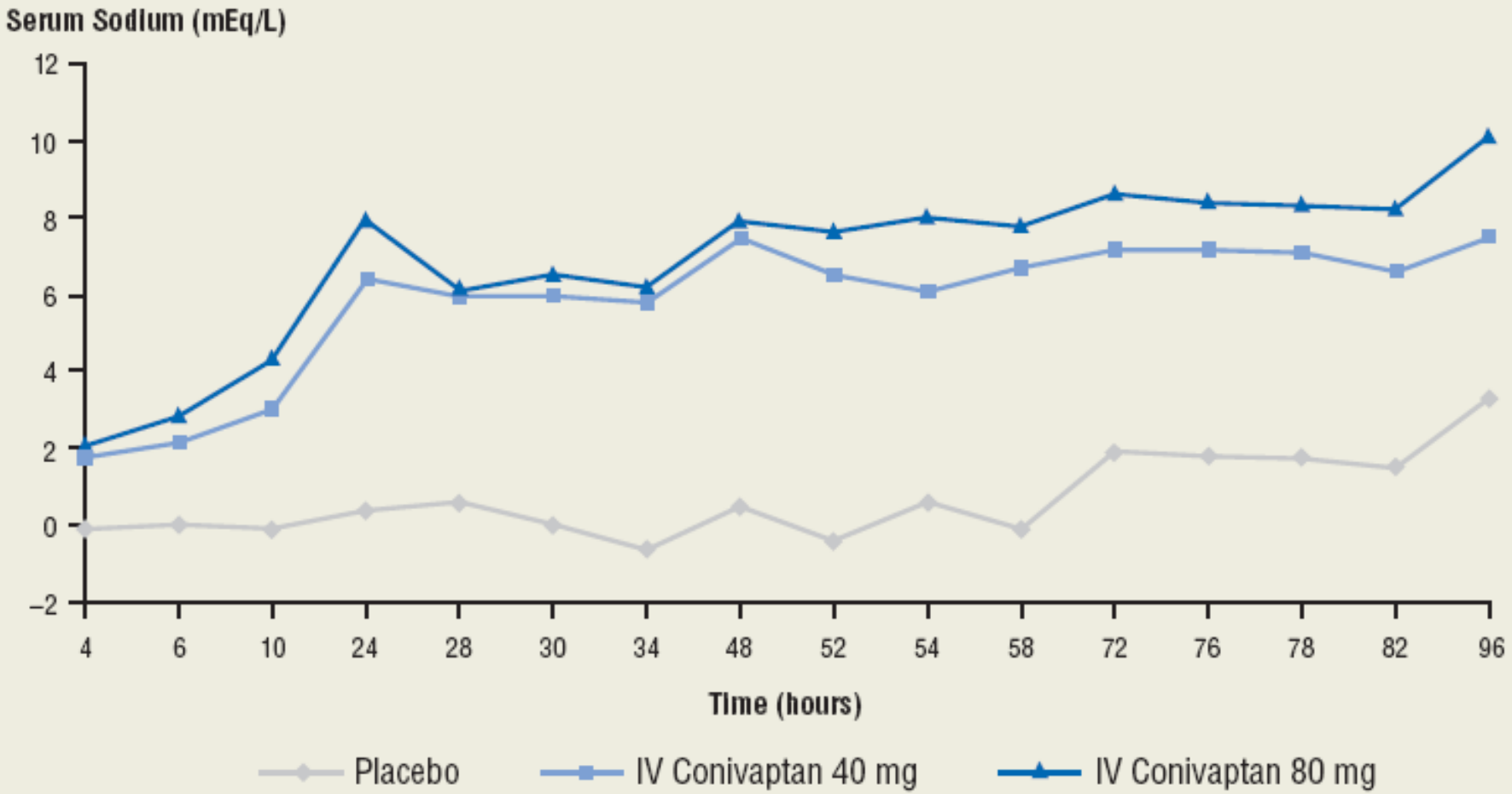

*The 8th Annual Scientific Meeting of the Heart Failure Society of America*

Patients were randomly assigned in a 1:1:1 ratio to

- 20 mg bolus followed by 40 mg/day infusion for 4 days (180 mg in total)
- 20 mg bolus followed by 80 mg/day infusion for 4 days (360 mg in total)
- Placebo (diluted solution only)

# Study Results
## - Efficacy: serum $Na^+$ concentration -

Figure 3. Mean change from baseline serum [$Na^+$] over the duration of treatment.




*The 8th Annual Scientific Meeting of the Heart Failure Society of America*

# Conclusion

- Conivaptan increased the serum $Na^+$ AUC significantly during the 4-day treatment phase.
- Conivaptan significantly increased the serum Na AUC, in the subgroup of patients with hyponatremia with hypervolemica and euvolemia.
- Conivaptan showed significant improvement effects in all secondary parameters(*).
- Conivaptan was well tolerated.
- The study results suggest that conivaptan can be an efficacious treatment drug for hyponatremia with sufficient tolerability.

*Secondary endpoints: Time (hr) from the first dose of conivaptan to ≥4 mEq/L increase from the baseline serum [$Na^+$],
Total time (hr) which patients have a ≥4 mEq/L increase from the baseline in serum [$Na^+$],
Changes in serum [$Na^+$] from the baseline to the end of the treatment phase,
Number of patients with ≥6 mEq/L increase in serum $Na^+$ or normal [$Na^+$] concentrations (≥135 mEq/L)