# **Development Forum**

### **Presentation to Analysts**

November 21, 2013

Tokyo, Japan

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# **Forward-looking statements**

This document contains certain forward-looking statements relating to such items as the company's (including its domestic and overseas subsidiaries) forecasts, targets and plans. These forward-looking statements are based upon information available to the company at the present time and upon reasonable assumptions made by the company in making its forecasts, but actual results in practice may differ substantially due to uncertain factors.

These uncertain factors include, but are not limited to, potential risks associated with the pharmaceutical industry's domestic and international operating environment, intellectual property risks, the risk of adverse reactions to pharmaceutical products, legal risks, risks arising from product manufacturing deficiencies, risks due to fluctuations in the market prices of raw materials, fuel and products, as well as exchange rate and financial market volatility.

This document contains information on pharmaceutical products (including products under development), but its contents should not be construed as promotion, advertising or as a medical recommendation

# Agenda

# Session 1

One Drug Development Organization – The Future

### **Session 2**

Current US FDA stance on characterization of risk and benefit, and use of global data

### **Striving to Become a Global Specialty Pharma**



## **Striving to Become a Global Specialty Pharma**



### Formation of ODDO\* Striving to Become a Global Specialty Pharma



# ODDO One Drug Development Organization

### Mission

 ODDO will design and conduct efficient, effective and compliant drug development in Europe and the US to build KHK Global Specialty Pharmaceutical businesses, bringing new medicines to patients

### Major goals

- Form one drug development organization in Europe and US with growth driven by KHK's innovative pipeline
- File KW-0761, KW-6002 and KRN23 for approvals
- Support and build the business in Europe and the US

### ODDO KHK Drug Development in Europe and the US



: Staffed by KKP (US) and PSK (EU) personnel

Staffed by KKP (US) personnel only

# **Innovative Pipeline for Europe and US**

| Compound                | MOAª   | Therapeutic<br>Area | Stage   | Remark                    |
|-------------------------|--|---------------------|---------|---------------------------|
| KW-0761<br>(Poteligeo®) | Anti-CCR4 Humanized<br>Mab                           | Oncology            | Ph III  | ATL, CTCL, PTCL           |
| KW-6002<br>(Nouriast®)  | Adenosine A <sub>2A</sub><br>Receptor Antagonist     | Neurology           | Ph III  | Parkinson's Disease       |
| KRN23 <sup>b</sup>      | Anti-FGF23<br>Fully Human Mab                        | Others              | Ph II   | X-Linked Hypophosphatemia |
| KW-2478                 | Hsp90 inhibitor                                      | Oncology            | Ph II   | Multiple Myeloma          |
| BIW-8962                | Anti-GM2 Humanized<br>Mab                            | Oncology            | Ph I/II | SCLC                      |
| КНК4083                 | Immunomodulator                                      | Immunology          | Ph I    | Autoimmune disease        |
| КНК2804 <sup>ь</sup>    | Anti-tumor specific<br>glycoprotein<br>humanized Mab | Oncology            | Ph I    | Solid Tumors              |

<sup>a</sup> Mechanism of Action

<sup>b</sup> KRN23 is partnered with Ultragenyx; KHK2804 is partnered with Teva Pharmaceutical Industries Ltd.

# **Innovative Pipeline for Europe and US**



\* Research and Preclinical candidates not yet disclosed 10 KYOWA HAKKO KIRIN PHARMA, INC. \*\* KRN23 is partnered with Ultragenyx; KHK2804 is partnered with Teva Pharmaceutical Industries Ltd.

# Making the Leap to Global Specialty Pharma

#### **KW-0761**

- Defucosylated, humanized monoclonal antibody to C-C Chemokine Receptor 4 (CCR4)
- Approved in Japan as Poteligeo<sup>®</sup> for relapsed or refractory CCR4-positive Acute T-cell Leukemia-lymphoma (ATL)

#### **KW-6002**

- Small-molecule inhibitor of adenosine A2A receptor
- Approved in Japan as Nouriast<sup>®</sup> for Parkinson's disease

#### KRN23

Fully human monoclonal antibody to Fibroblast Growth Factor 23 (FGF23)

### **KW-0761** Defucosylated, Humanized Monoclonal Antibody to CCR4

Approved as Poteligeo<sup>®</sup> in Japan for relapsed or refractory CCR4-positive Adult T-cell Leukemia-lymphoma (ATL)



Shinkawa et al, J Biol Chem 2003;278:3466 Ishii et al, Clin Cancer Res 2010;16:1520

Jones et al., Blood 2000; 96:685

Imai et al., Int. Immunol 1999, 11:81

# **KW-0761: Global Development**

| Region | Indication                              | Development Phase                                 |                                  |                       |                     |
|--------|---|---|----------------------------------|-----------------------|---------------------|
|        |   | Pilot<br>(P1/2a)                                  | Pivotal<br>(P2b/3)               | BLA/MAA<br>submission | BLA/MAA<br>approval |
| Japan  | <b>ATL</b><br>(relapsed)                | 0761-0501<br>(NCT00355472)                        | 0761-002<br>(NCT00920790)        | April 2011            | March 2012          |
|        | <b>ATL</b><br>(1 <sup>st</sup> -line)   | in combination<br>with mLSG15                     | 0761-003<br>(NCT01173887)        | July 2013             |                     |
|        | <b>T/NK cell lymphoma</b><br>(relapsed) |   | <b>0761-004</b><br>(NCT01192984) | July 2013             |                     |
| Global | <b>ATL</b><br>(relapsed/refractory)     |   | <b>0761-009</b><br>(NCT01626664) | USA, Europe           |                     |
|        | <b>CTCL</b><br>(relapsed/refractory)    | KW-0761-001/002<br>(NCT00888927)<br>(NCT01226472) | <b>0761-010</b><br>(NCT01728805) | USA, Europe           |                     |
|        | <b>PTCL</b><br>(relapsed/refractory)    | <b>0761-007</b><br>(NCT01611142)                  | Europe                           |                       |                     |

ATL: Adult T-cell Leukemia-Lymphoma, CTCL: cutaneous T-cell Lymphomas, PTCL: Peripheral T-Cell Lymphoma, BLA: Biologics License Applications, MAA: Marketing authorization application

### KW-0761-009 Phase II Trial for ATL

#### **Population:**

Subjects with Adult T-cell Leukemia-Lymphoma (ATL) who are relapsed or refractory after at least one prior systemic therapy regimen

#### **Study Design:**

Open-label, 2:1 randomized, global Phase II trial to evaluate safety and efficacy of KW-0761 or chemotherapy (investigator's choice of pralatrexate, GemOx or DHAP)

#### **Primary Endpoint:**

**Overall Response Rate** 



### KW-0761-010 Phase III Trial for Cutaneous T Cell Lymphoma

#### **Population:**

Subjects with mycosis fungoides (MF) or Sézary syndrome (SS) who have progressed following at least one prior course of systemic therapy

#### **Study Design:**

Open-label, randomized, global phase III trial to evaluate safety and efficacy of KW-0761 versus vorinostat

#### **Primary Endpoint:**

Progression free survival



- KW-0761 has been approved in Japan as Poteligeo<sup>®</sup> and is currently in development in Europe and the US for PTCL, ATL and CTCL
- KW-0761 may have uses in other tumors due to effects on the immune system

### KW-6002 Small-molecule inhibitor of adenosine A2A receptor

Approved in Japan as Nouriast<sup>®</sup> for Parkinson's disease

First in Class Parkinson's Disease treatment

- Reduces average "OFF" time in Parkinson's patients receiving treatment with L-DOPA who are experiencing wearing off phenomenon
- 40mg daily dose improves motor capacity\* during "ON" time
- **End-of-dose wearing off, Peak-dose dyskinesia, and ON-OFF phenomena:**



### KW-6002-014: Phase III Trial for Parkinson's disease

#### **Population:**

Moderate to severe Parkinson's disease patients with motor fluctuations and dyskinesia on levodopa combination therapy

#### **Study Design:**

12-week, double-blind, placebo-controlled, randomized, multicenter study to evaluate efficacy and safety of istradefylline 20 and 40 mg/d versus placebo

#### **Primary Endpoint:**

Change from Baseline in total hours per day spent in the OFF state.



#### ClinicalTrials.gov Identifier: NCT01968031

### Careful Attention to Data Quality; Efforts to Reduce Placebo Effect

#### Ensuring Quality of Site and Investigator

- All Sites and Staff must have 2 years of experience in Parkinson's research
- "ON/OFF" time scores entered by the site will be monitored during the trial and indicate the need for any additional site training

#### Ensuring Quality of Patient-reported Data

- During screening, patients will be trained on how to score "ON/OFF" time and must complete an "ON/OFF" self-rating (Hauser diary)
- During screening, scores recorded by the site staff and the patient must agree
- An electronic pen will record the time a score is entered by patients. Scoring times will be monitored during the trial and indicate the need for additional patient training.

#### Reducing Placebo Effect

- Site personnel will be trained in tactics to minimize the placebo effect
- Site personnel will be trained and certified on how to score "ON/OFF" time
- One-third of patients will be randomized to placebo alone

- FDA agreed that the design and planned analysis of the study adequately address the objectives necessary to support a regulatory submission
- Dosing of first patient expected November 2013

- KW-6002 has been approved in Japan as Nouriast<sup>®</sup> and is currently in development in the US for Parkinson's disease with motor fluctuations and dyskinesia on levodopa combination therapy
- The phase III trial is a multinational study and being conducted with special efforts to ensure data quality and reduce the placebo effect
- The trial is being conducted under a SPA agreement with FDA

### KRN23 Fully Human Monoclonal Antibody to FGF23

KHK is collaborating with Ultragenyx to develop and commercialize KRN23 Aiming to launch clinical trials for pediatric XLH\* in 2014

**Ultragenyx Pharmaceutical Inc.** 

Established in 2010, specializing in therapeutic drug development for rare metabolism-related hereditary diseases CEO and President: Emil D. Kakkis, M.D., Ph.D.



#### **Details of collaboration**

- Parties to collaborate on development and commercialization in USA, Canada, and EU
  - Ultragenyx to lead development efforts in the XLH indication.
  - Parties to share development costs
- Parties to share commercial responsibilities and profits in USA and Canada
- Kyowa Hakko Kirin responsible for commercialization in the EU
- Ultragenyx responsible for development and commercialization in Mexico, Central & South America

\* X-linked hypophosphatemia (XLH) - a syndrome due to excessive concentrations of FGF23 in the blood associated with excessive loss of phosphate in the urine leading to hypophosphatemia and resulting in a rare disease characterized by poor bone growth and mineralization.

### KRN23-US-02 Phase I trial for Adult XLH

#### **Population:**

Adults with X-Linked Hypophosphatemia

#### Study Design:

Multicenter, phase I, **double-blind**, **randomized**, **placebo-controlled**, single-dose (Intravenous and Subcutaneous), dose-escalation study of KRN23 versus Placebo

#### **Endpoints:**

Safety, tolerability, pharmacokinetics, and pharmacodynamics (TmP/GFR\*, serum phosphorus, 1,25(OH)<sub>2</sub>D\*\*)

# Abstract of main results<sup>1</sup> awarded "The Most Distinguished Clinical Research Abstract" by American Society for Bone and Mineral Research (ASBMR) at 2013 meeting

<sup>1</sup>Carpenter, et al ; A First-In-Human, Randomized, Double-blind, Placebo-Controlled, Single Dose Study of a Humanized Monoclonal Anti-FGF23 Antibody (KRN23) in X-linked Hypophosphatemia.

\* TmP/GFR: renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate.

TmP/GFR is an indication of the ability of the kidney to retain phosphate.

\*\* 1,25(OH)<sub>2</sub>D: 1,25 dihydroxy vitamin D

## **Safety Data**

#### Treatment Emergent Adverse Events

- KRN23 (24/29) > placebo (4/9)
- Most common were:
  - Intravenous administration: nausea (24%); headache (18%)
  - Subcutaneous administration: elevated serum amylase and back pain (17%)
  - Most were mild
- No Serious Adverse Events, Deaths, or Adverse Events leading to withdrawal
- No significant changes in vital signs, renal u/s, ECGs, or biochemical values
- No hypersensitivity/infusion reactions

#### Maximum tolerated single dose not reached

#### No anti-KRN23 antibody detected

- KRN23 is partnered with Ultragenyx for development in pediatric and adult X-Linked Hypophosphatemia
- Single-dose phase I trial showed dose-dependent increases in serum phosphorus and 1,25 dihydroxy Vitamin D
- Results from multiple dose trials will be presented at a scientific forum in the future

# **Session 1 Summary**

- ODDO represents a rapid integration of KHK assets to enhance infrastructure and expertise for drug development in US and Europe
- KHK has an innovative pipeline based on rigorous science
- KW-0761, KW-6002 and KRN23 are enabling KHK's leap to Global Specialty Pharmaceutical Company

# Agenda

# Session 1 One Drug Development Organization – The Future

### Session 2

Current US FDA stance on characterization of risk and benefit, and use of global data

### Ensure that drugs approved for marketing are safe and effective for intended use

### FDA decisions are based on assessment of Benefit and Risk

- Decisions are patient-focused
- Decisions must be consistent with applicable guidelines and policies

# FDA's Benefit-Risk Framework\*

| Decision Factor                 | Evidence and Uncertainties | Conclusions and Reasons |  |  |
|---------------------------------|----------------------------|-------------------------|--|--|
| Analysis of Condition           |                            |                         |  |  |
| Current Treatment Options       |                            |                         |  |  |
| Benefit                         |                            |                         |  |  |
| Risk                            |                            |                         |  |  |
| Risk Management                 |                            |                         |  |  |
| Benefit-Risk Summary Assessment |                            |                         |  |  |

\*FDA Publication: Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making; Draft PDUFA V Implementation Plan - February 2013

• http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

# **Decision Factors**



# For Each Decision Factor, FDA considers...

#### Evidence

Trial data

#### Uncertainties

- Identify sources of uncertainty, such as lack of data, conflicting outcomes, and marginal results
- Define assumptions about how uncertainties may impact outcome for patients in the post-marketing setting
  - Given the uncertainties, will results apply to patients who will receive the drug after approval?

#### Conclusions

 Conclusions are based on interpretation of evidence, opinions, uncertainties and assumptions

#### Reasons

Basis for conclusions

# **Summary of Benefit-Risk Assessment**

Explains rationale for the final regulatory decision, including important judgments that contributed to the decision

- States key evidence and uncertainties
- Accounts for current understanding of disease condition and alternative therapies, against which benefit-risk is weighed
- Explains rationale for labeling, risk management requirements, and other postmarketing requirements
- Notes differences of opinion in scientific and clinical judgment and explains how differences were resolved or taken into account in the final decision
- Experts and companies may disagree with FDA's decision because of differences of opinion or interpretation of data

# FDA's Benefit-Risk Framework

#### Staged implementation

- **2014** 
  - FDA will publish available Benefit-Risk Assessments
  - FDA will use new format for all initial NDA/BLAs for new drugs
- **2016** 
  - FDA will use new format for supplemental NDA/BLAs

# This enhanced transparency may make future FDA approval decisions more predictable

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# **Global Clinical Trials to Support New Drug Applications**

# **Global Clinical Trials**

#### FDA Concern - More data are coming from countries outside the US

- FDA inspections have not found significant differences between US and non-US sites in the quality of trial conduct
- However, there are many potential differences in populations and medical practice

#### FDA allows a marketing application based on non-US data if:

- The trials are adequate and well-controlled
- Conducted by investigators of recognized competence
- Conducted in compliance with Good Clinical Practices
- Submission includes all documentation expected for a US trial
- Data are applicable to US population and US medical practice
  - Subset analyses by region

Khin NA, Yang P, Hung HM, et. al.. Regulatory and scientific issues regarding use of foreign data in support of new drug applications in the United States: an FDA perspective. Clin Pharmacol Ther. 2013 Aug;94(2):230-42.

# **Global Clinical Trials**

#### Global Trials allow exploratory comparisons of subset data from different regions

- Differences between regions in observed response inevitably occur as a result of chance differences among patient subsets
- It is rarely possible to determine whether observed differences are real unless they are large, but even fairly large differences may occur by chance

# **Planning Global Trials for Quality**

#### Identify activities important to final quality

 Activities that, if done incorrectly, would decrease trial's ability to reach reliable conclusions or reduce subject safety

#### Identify critical risks to those activities

#### Manage these critical risks

For example,

- Use precise definitions, similar treatment standards, similar concomitant medications, similar treatment assessments
- Power global trial conservatively

 Carefully select investigators with qualifications, training and resources necessary for the trial

#### Monitor Early

- Consider supplemental central monitoring
- Identify errors early to allow early corrective and preventive actions
- Identify missing data, variations in protocol implementation early
- Pay attention to prevent errors previously identified as critical

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# Orphan Drug versus Breakthrough Therapy

## **FDA Designations**

### **Orphan Drug**

#### Requirement

 Drug intended to treat a rare disease or condition (i.e., affecting fewer than 200,000 people in the US)

#### Incentives

- Tax credits up to 50% of trial costs
- Waiver of PDUFA User Fees (~\$2M)
- 7-year marketing exclusivity
- Assistance from Office of Orphan Product Development and opportunity for special grants

### **Breakthrough Therapy**

#### Requirement

- Drug intended to treat a serious condition
- Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies

#### Incentives

- Same benefits of fast track designation
  - Frequent interactions with review team
  - Possible early submission of certain elements of NDA
  - Eligible for priority review
- Also: intensive guidance on an efficient drug development program, including involvement of FDA senior managers

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# **Thank You Very Much**

# END

# **Breakthrough Therapy**

|                              | Fast Track   | Breakthrough   | Accelerated   | Priority Review   |
|------------------------------|--|--|---|---|
| Reference                    | FD&C Act, § 506(b)   | FD&C Act, § 506(a)   | 21CFR314, sub H<br>21CFR601, sub E<br>FD&C Act, § 506(c)  | PDUFA 1992  |
| Qualifying<br>Criteria       | <ul> <li>Treat serious condition</li> <li>Unmet medical need</li> </ul>                  | <ul> <li>Treat serious condition</li> <li>Substantial improvement<br/>of clinically significant<br/>endpoint over available<br/>therapy</li> </ul> | <ul> <li>Treat serious condition</li> <li>Advantage over<br/>available therapies</li> <li>Effect on surrogate<br/>endpoint</li> </ul>             | <ul> <li>Treat serious condition</li> <li>Provide significant<br/>improvement in safety or<br/>effectiveness</li> </ul> |
| When to<br>Submit            | •With/after IND<br>•Before pre-BLA<br>meeting  | •With/after IND<br>•Before EOP2 meeting  | Discuss with review division  | With BLA, NDA or efficacy supplement  |
| Timeline for<br>Response     | Within 60 calendar days  | Within 60 calendar days  | Within 60 calendar days   | Within 60 calendar days   |
| Features                     | <ul> <li>Actions to expedite<br/>development + review</li> <li>Rolling review</li> </ul> | <ul> <li>Fast track features</li> <li>Guidance</li> <li>FDA Sr. Mgrs involved</li> </ul>   | Approval based on surrogate endpoint  | Shorter clock for review<br>(6 months)  |
| Additional<br>Considerations | •Can be withdrawn if criteria no longer met  | Can be withdrawn if<br>criteria no longer met  | <ul> <li>Early submission of<br/>Promotional Material</li> <li>Post approval studies to<br/>confirm approval</li> <li>Can be withdrawn</li> </ul> | Assigned at time of BLA,<br>NDA or efficacy<br>supplement   |