Kyowa Kirin R&D Meeting 2023

December 11, 2023

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Yoshifumi Torii, Ph.D.  Executive Officer, Vice President, Head of R&D Division
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These uncertain factors include, but are not limited to, potential risks of the business activities in the pharmaceutical industry in Japan and overseas, intellectual property risks, risk of side effects, regulatory risks, product defect risks, risks of changes to the prices for raw materials, risks of changes to market prices, as well as risks of changes to foreign exchange rates and financial markets.

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Our Vision toward 2030

Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile, as a Japan-based Global Specialty Pharmaceutical company built on the diverse team of experts with shared passion for innovation.

Provide pharmaceuticals for unmet medical needs

We are focused on developing medicines for diseases where there is a clear patient need for new options. We make full use of multiple therapeutic modalities, including biotechnology such as antibody technology, and beyond, building on our Kyowa Kirin established strengths.

Address patient-centric healthcare needs

We will meet the needs of patients and society by providing value across the entire patient care pathway, delivering cutting-edge science and technology, grounded in our in-depth pharmaceutical knowledge and expertise.

Retain the trust of society

We pursue world-class product quality and operational excellence to grow our business in ways which build long-term trust with our stakeholders.

* Make patients smile through dramatic improvements in quality of life by identifying the unmet medical needs of people battling with medical conditions and by creating and supplying new drugs or services that help them overcome those challenges.
The Kyowa Kirin Group is aiming to build a competitive technology platform by enhancing and combining its drug discovery technologies and its drug discovery modalities. By matching that technology platform with disease-oriented science and by harnessing open innovation with partners that have specific strengths, we aim to develop completely new technologies or select efficient drug discovery targets to create life-changing value.

**Technology**

We will continue to evolve our antibody technology, while also pursuing the possibilities of other modalities and building a platform that leads to innovative new therapies.

**Disease Biology**

Continue to provide “Only-one value drug” for UMN, while utilizing the disease science* cultivated to date within KKC

* Nephrology, Oncology, Immunology & allergy, CNS

**Open Innovation (OI)**

Continue to work on collaborative research activities* with academia, startups and other partners, combine this with rapid access to start up information gained from investment in VC funds and CVC funds, and tap into external innovation through advanced OI activities

* Reenergize the San Diego research base

Create Life-changing value with clear competitive advantages
The key drivers of our future growth

<table>
<thead>
<tr>
<th>Global Strategic Products</th>
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</thead>
<tbody>
<tr>
<td>rocatinlimab (atopic dermatitis)</td>
</tr>
<tr>
<td>rocatinlimab (asthma)</td>
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<tr>
<td>KHK4951 nAMD</td>
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<tr>
<td>KHK4951 DME</td>
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<tr>
<td>Ph2 start schedule under consideration</td>
</tr>
<tr>
<td>Scheduled to start within 2023</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Development Pipelines (Ph2 or later)</th>
</tr>
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<tbody>
<tr>
<td>KK4277</td>
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<tr>
<td>KK2260</td>
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<tr>
<td>KK2269</td>
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<tr>
<td>Other biologics</td>
</tr>
<tr>
<td>Scheduled to start in 2024Q1</td>
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<table>
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<tr>
<th>Early-Stage Pipelines (Ph1 or earlier)</th>
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<tbody>
<tr>
<td>Note: Orchard Therapeutics plc’s Pipelines</td>
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<table>
<thead>
<tr>
<th>Other biologics</th>
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<tbody>
<tr>
<td>OTL-200 (EU: Libmeldy®)</td>
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<tr>
<td>OTL-203</td>
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<td>OTL-201</td>
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</table>
Today’s agenda

- Development Pipeline using REGULGENT™ - Our bispecific antibody technology
  - About REGULGENT™
  - KK2260
  - KK2269

- Toward the Successful Creation and Delivery of Life-changing Value
  - KHK4951 (Ph1 study results and Ph2 studies overview)
  - Orchard Therapeutics plc (HSC-GT)
Development Pipeline using REGULGENT™
Our bispecific antibody technology

- **About REGULGENT™**
- KK2260
- KK2269
About REGULGENT™

General characteristics of bispecific antibodies

- Able to perform actions that IgG cannot by acting on two types of antigens*
- Composed of a combination of non-common L-chain antibodies or by utilizing antibody-like molecules

Characteristics of REGULGENT™

Simple structure, minimized immunogenicity

- Use of common L-chain (*), only natural IgG sequence
- Uniformity with no combination of different molecules
- Physical properties and pharmacokinetics equivalent to IgG

Bivalent-bivalent binding, N&C-terminal type

- Can be expanded to a variety of mechanisms of action

Stable production process, easy handling

- High productivity equivalent to IgG
- Can be adapted to the conventional antibody manufacturing process

Proprietary bispecific antibody technology created from our antibody R&D experience
Development Pipeline using REGULGENT™
Our bispecific antibody technology

- About REGULGENT™
- KK2260
- KK2269
Relationship between cells and iron

Iron is an important element for cell growth and survival

- DNA synthesis
  Ribonucleotide reductase - requires iron ions in the active center

- Energy generation
  Iron ion is required for ATP production via TCA cycle\(^2\) in mitochondria

TfR1 contributes to cellular uptake of iron

- Iron ions bind to transferrin, which binds to TfR1 and is taken up into the cell
- TfR1 is recycled after intracellular iron supply and is again involved in iron uptake

1. Transferrin receptor 1; 2. Tricarboxylic acid cycle = Citric acid cycle

Relationship between cancers and iron

- Many cancer types have an association with iron

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small-cell lung cancer</td>
<td>Cell culture, animal models and epidemiological</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Cell culture, animal models, human tissue studies and epidemiological</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Cell culture and animal models</td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
<td>Cell culture, animal models and epidemiological</td>
</tr>
<tr>
<td>Oesophageal, stomach, aerodigestive and gastric cancer</td>
<td>Human tissue studies, animal models and epidemiological</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Cell culture, human tissue studies, animal models and epidemiological</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Cell culture and epidemiological</td>
</tr>
<tr>
<td>Haematological cancers (leukaemias, lymphomas and myeloma)</td>
<td>Cell culture, animal models, epidemiological and clinical case study</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Cell culture and animal model</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Cell culture, animal models and clinical trial</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Cell culture</td>
</tr>
</tbody>
</table>

Torti, S. V. et al., Nat Rev Cancer, 2013

- High expression of TfR1 in many cancer types which affects cancer growth and prognosis

TfR1 expression of ESCC patient: Chan et al., ONCOLOGY REPORTS, 2014


TfR1 = CD71: Transferrin receptor 1, Ki-67: One of the cell growth marker protein, ESCC: Esophageal squamous cell carcinoma
Anticancer effects and systemic side effects of iron depletion

- Efficacy of Deferoxamine, an Iron Chelator, in Hepatocellular Carcinoma

Anticancer effect observed by iron depletion in cancer cells

- However, systemic iron depletion raises a safety concern (e.g. severe anemia) because iron plays an important function in all cells

Need to find a way to suppress systemic side effects and exert only anticancer effects

KK2260: EGFR-TfR1 bispecific antibody

To avoid systemic side effects = selective iron depletion in cancer cells

- No neutralizing activity when bound to TfR1 only or EGFR only
- Cross-links TfR1 and EGFR to induce TfR1 degradation in lysosomes
KK2260: Drug Efficacy and Safety in Nonclinical Studies

**Efficacy:** ESCC¹ PDX² model (EGFR+/TfR1+)

![Graph showing tumor volume over time for different treatments: Vehicle, Cisplatin, and KK2260.]

- High efficacy was shown in all three models evaluated.

**Safety**

- 200 mg/kg of KK2260 was administered to cynomolgus monkeys once a week x 4 times.
  → No serious toxicity, including skin toxicity³, was observed. Mild and transient anemia was observed.

In nonclinical studies, we found that KK2260 was able to exert its effects while suppressing systemic side effects.

Development for EGFR-high expressing cancers are planned.

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1. Esophageal squamous cell carcinoma.
2. Patient-derived xenograft. ESCC PDX tumors were obtained from In-Vivo Science Inc.
3. Known as the side effect of EGFR neutralization
Development Pipeline using REGULGENT™
Our bispecific antibody technology

- About REGULGENT™
- KK2260
- **KK2269**
About CD40 agonistic antibody

**Expectations**
To cure cancer by inducing de novo anti-tumor immunity in patients that are not sufficiently aquaired anti-tumor immunity and/or that are refractory to existing immunotherapy

**Issues**
Over-activation of the systemic immune system, resulting in a narrow therapeutic window

**Cancer Immunity Cycle**

1. Release of tumor antigens
2. Tumor antigen uptake by dendritic cells
3. Antigen presentation in lymph nodes and priming of anti-tumor T cells
4. T-cell migration and infiltration
5. Tumor Recognition by Cytotoxic T Cells and cytotoxicity

PD-1 pathway inhibition

*Modified from: Immunity, Volume 39, Issue 1, 2013, 1–10*
KK2269: CD40-EpCAM* bispecific antibody

- Targets CD40 and EpCAM simultaneously, exerting CD40 agonist activity against dendritic cells in close proximity to the tumor
- Successfully separated the induction of anti-tumor immunity from its side effects (systemic immune hyperactivation)

*EpCAM: Epithelial Cell Adhesion Molecule, marker molecules for epithelial tumors

Examples of EpCAM-high expressing tumors

https://www.cbioportal.org/cBioPortal

Underline: Cancer types to be evaluated in Ph1
KK2269: CD40-EpCAM* bispecific antibody

Function as a CD40 agonist only for dendritic cells in close proximity to the cancer

Examples of EpCAM-high expressing tumors

- Colon ca.
- Stomach ca.
- Thyroid ca.
- Lung ca.
- Ovarian ca.
- Pancreatic ca.
- Prostate ca.

Underline: Cancer types to be evaluated in Ph1

https://www.cbioportal.org/cBioPortal

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KK2269: Efficacy and safety confirmed in non-clinical studies

**Efficacy**
- KK2269 showed remarkable synergy with certain chemotherapy
- Characteristic delayed tumor regression suggesting the induction of de novo anti-tumor immunity (see below).

**Safety**
- High safety profile observed in cynomolgus monkeys up to 200 mg/kg (the highest dose in the GLP study)

### Survival rate

- **Efficacy**
  - Human CD40-expressing Tg mice
  - PD1-resistant tumor model
  - DTX: Docetaxel

- **Safety**
  - KK2269 (i.v.)

### Tumor volume by individual

- **Non-clinical studies demonstrated the concept:** anti-tumor efficacy with high safety

- At euthanasia due to criteria or at the study endpoint
Full value of KK2269 in chemo combination

1. Chemo
2. Tumor disruption (ICD*)
   • Release of tumor antigens and immunostimulants
3. Accumulation of dendritic cells in tumors
   • Activation
   • Tumor antigen uptake
4. Acceleration of the action of KK2269 (tumor-dendritic cell cross-linking)

Evaluation of activation of dendritic cells in tumor

- IL-12
- CD80/86
- Cross presentation Th1/CTL activation
- Vital co-stimulatory factors for T cell priming

Synergy of Chemo+KK2269 was confirmed.
POC to be obtained in clinical trials

*: Immunogenic cell death
Toward the Successful Creation and Delivery of Life-changing Value

- **KHK4951** (Ph1 study results and Ph2 studies overview)
- **HSC-GT** (Orchard Therapeutics plc)
Active ingredient - tivozanib: A small molecule VEGFR inhibitor discovered by Kyowa Kirin with high selectivity and potent activity
Completed Ph1 study in patients with exudative neovascular age-related macular degeneration (nAMD)

- Abnormal angiogenesis results in macular damage and significant vision impairment
- Caused by VEGF*1 production from retinal pigment epithelial cells
- Drug-treated patient number
  - Japan: approx. 200,000
  - Global: approx. 1.6 million

*1: Vascular endothelial Growth Factor

Standard of Care: Intravitreal injection of anti-VEGF drugs
Due to invasive administration route and treatment burden (e.g. hospital visit) of the SOC, there is clear medical needs for non-invasive treatment option.
Nano-crystallized formulation for delivery of active ingredients to the posterior ocular tissues

The nano-crystallized formulation we developed enabled efficient delivery of the active ingredients to the posterior ocular tissues.
## Ph1 study

### Cohort 1
- **Single dose HVs**
  - **Tivozanib eye drops**
  - **Placebo eye drops**
  - **Randomization (R): 1:1**
  - **Follow-up period:**
    - Day 1
    - Day 23

### Cohort 2
- **Multiple doses HVs**
  - **Tivozanib eye drops, tid, 21 days**
  - **Placebo eye drops, tid, 21 days**
  - **Randomization (R): 1:1**
  - **Follow-up period:**
    - Day 1
    - Day 23

### Cohort 3
- **Multiple doses nAMD patients**
  - **Tivozanib eye drops, tid, 21 days**
  - **Placebo eye drops, tid, 21 days**
  - **Follow-up period:**
    - Day 1
    - Day 23

### Primary objective
- **Safety and tolerability (TEAEs)**
  - Pharmacokinetics (serum tivozanib concentration)
  - Exploratory efficacy (CST, BCVA)

### Other objectives
- Pharmacokinetics (serum tivozanib concentration)
- Exploratory efficacy (CST, BCVA)

### Inclusion criteria
- **Healthy volunteers in cohorts 1 and 2**
  - **Inclusion criteria**
    - Age ≥ 20 to < 50 years
    - Visual acuity ≥ 20/20
  - **Exclusion criteria**
    - Current illness requiring treatment
    - Current or history of dry eye

- **Patients with nAMD* in cohort 3**
  - **Inclusion criteria**
    - CST ≥ 300 μm
    - BCVA score ≥ 23 letters
  - **Exclusion criteria**
    - Glaucoma, ischemic optic neuropathy, retinitis pigmentosa

* Both treatment-naive and previously anti-VEGF treated patients were enrolled.

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**BCVA:** best corrected visual acuity; **CST:** central subfield thickness; **HVs:** healthy volunteers; **R:** randomization; **TEAE:** treatment-emergent adverse event; **tid:** three times a day.

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**Ph1 study: Dosage regimen**

**Single dose**
- **Cohort 1, HVs**
  - Step 1: 0.5 w/v%, 1 drop Japanese, with NLO
  - Step 2: 1.0 w/v%, 1 drop Japanese, with NLO
  - Step 3: 1.0 w/v%, 2 drops Japanese, with NLO
  - Step 4: 1.0 w/v%, 2 drops White, with NLO
  - Step 5: 2.0 w/v%, 1 drop Japanese, with NLO

**Multiple doses (tid) for 21 days**
- **Cohort 2, HVs**
  - Step 1: 0.5 w/v%, 1 drop Japanese, with NLO
  - Step 2: 1.0 w/v%, 1 drop Japanese, with NLO
  - Step 3: 1.0 w/v%, 2 drops Japanese, with NLO
  - Step 4: 1.0 w/v%, 2 drops Japanese, without NLO
  - Step 5: 1.0 w/v%, 2 drops White, with NLO
  - Step 6: 2.0 w/v%, 1 drop Japanese, with NLO

- **Cohort 3, nAMD patients**
  - Step 1: 0.5 w/v%, 1 drop Japanese, with NLO
  - Step 2: 1.0 w/v%, 1 drop Japanese, with NLO
  - Step 3: 1.0 w/v%, 2 drops Japanese, with NLO

- **Steps for those without NLO**
- **Steps for white subjects**
- **Steps for 2.0 w/v% formulation**

NLO: nasolacrimal duct occlusion or eyelid closure
## Ph1 study: Safety

<table>
<thead>
<tr>
<th>Any TEAE or ocular AE in the study eye</th>
<th>Placebo (tid), HVs (n = 12)</th>
<th>Tivozanib (tid), HVs</th>
<th>Tivozanib (tid), nAMD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE, n (%)</td>
<td>2 (16.7)</td>
<td>3 (50.0)</td>
<td>28 (77.8)</td>
</tr>
<tr>
<td>Death, other serious, or other significant</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders, n (%)</td>
<td>1 (8.3)</td>
<td>2 (33.3)</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>1 (8.3)</td>
<td>2 (33.3)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>0</td>
<td>3 (50.0)</td>
<td>0</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Eye pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>0</td>
<td>1 (16.7)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Pinguecula</td>
<td>0</td>
<td>0</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Swelling of eyelid</td>
<td>0</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
</tbody>
</table>

**Tivozanib (tid), HVs**

- **Step 1**: Jpn with* 0.5 w/v% 1 drop (n = 6)
- **Step 2**: Jpn with* 1.0 w/v% 1 drop (n = 6)
- **Step 3**: Jpn with* 1.0 w/v% 2 drops (n = 6)
- **Step 4**: Jpn without† 1.0 w/v% 2 drops (n = 6)
- **Step 5**: White with* 2.0 w/v% 1 drop (n = 6)
- **HVs Total (n = 36)**

**Tivozanib (tid), nAMD patients**

- **Step 1**: Jpn with* 0.5 w/v% 1 drop (n = 7)
- **Step 2**: Jpn with* 1.0 w/v% 1 drop (n = 10)
- **Step 3**: Jpn with* 1.0 w/v% 2 drops (n = 11)
- **nAMD patients Total (n = 28)**

**Any TEAE or ocular AE in the study eye**

- **Any TEAE**: any adverse event (AE) that occurred or worsened in the period between the first administration of the study drug and the end of the study; death: any AE with an outcome of ‘fatal’; other serious: serious AEs other than death; other significant: non-serious AEs leading to withdrawal of the investigational product.
- *With nasolacrimal duct occlusion or eyelid closure.
- † Without nasolacrimal duct occlusion or eyelid closure. Jpn: Japanese.

No serious adverse events leading to study discontinuation were observed in either HVs or Japanese nAMD patients.
Ph1 study: Serum Drug Concentration

Cohort 2, HVs*

- Mean serum concentrations of tivozanib increased in a dose-dependent manner.
- No significant differences in serum pharmacokinetics were observed between HVs and nAMD patients.

* Healthy volunteers

Cohort 3, nAMD patients
KHK4951 Ph1 study summary

Safety
- There were no serious AEs or AEs leading to discontinuation.
- There were no remarkable differences in its safety profiles between Japanese and White, and between HVs and nAMD patients.

Pharmacokinetics
- Mean serum tivozanib concentration increased in a dose-dependent manner.
- No significant differences in serum concentration were found between HVs and nAMD patients.

+ Exploratory evaluation of efficacy also conducted

Decided to conduct Ph2 study based on the Ph1 study results
Diabetic Macular Edema (DME)

*Target indication for Ph2 study

- As a complication of diabetic retinopathy, high blood sugar causes damage to capillaries in the macula, resulting in edema of the macula and impairment of vision
- VEGF contributes the development of the disease
- Number of patients treated with drugs:
  - Japan: approx. 140K, Global: approx. 1.3M

- Standard of Care:
  - Intravitreal injection of anti-VEGF drugs or steroids, or intraocular implants
  - Ocular surgery (vitrectomy, laser treatment)

References:
https://www.civillink.net/fsozai/eye.html
https://www.eye.med.kyushu-u.ac.jp/patient/question/index3.html

Current treatment methods are all highly invasive
A need for less invasive treatment options
## KHK4951 Ph2 study overview

<table>
<thead>
<tr>
<th>Locations</th>
<th>• (For both studies) JP, US, AU, KR</th>
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<tbody>
<tr>
<td><strong>Study Completion (estimated)</strong></td>
<td>• (For both studies) 2026Q1</td>
</tr>
<tr>
<td><strong>Enrollment (estimated)</strong></td>
<td>• nAMD 180, DME 150</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>• Reduction of 15 or more letters in BCVA (Best corrected visual acuity) as measured by ETDRS² visual acuity chart from baseline</td>
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<table>
<thead>
<tr>
<th>Participant Group/Arm</th>
<th>Intervention/Treatment</th>
</tr>
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</table>
| **Experimental:** Arm A KHK4951 High dose                                 |  • Drug: KHK4951  
KHK4951 eye drop for 44(nAMD)/36(DME) weeks until end of the trial |
| **Experimental:** Arm B KHK4951 Middle dose                                |  • Drug: Aflibercept Injection  
Intravitreal injection (IVT) of aflibercept will be given as specified in the protocol |
| **Experimental:** Arm C KHK4951 Low dose                                   |                                                                                                                                                        |

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1. Clinical Trials.gov ID: NCT06116890 (nAMD), NCT06116916 (DME); jRCT ID: jRCT2031230401 (nAMD), jRCT2031230400 (DME)  
2. Early Treatment Diabetic Retinopathy Study
Toward the Successful Creation and Delivery of Life-changing Value

- **KHK4951** (Ph1 study results and Ph2 studies overview)
- **HSC-GT** (Orchard Therapeutics plc)
**Hematopoietic Stem Cell Gene Therapy (HSC-GT)**

HSC-GT allows delivery of gene-modified blood/immune cells to any part of the body.

Gene Therapy Manufacturing

GMP Cell Product Manufacturing Platform

Lentiviral Vector Manufacturing

- Manufacture gene-specific lentiviral vector

Drug Product Manufacturing (Cell Processing)

- Isolate HSPCs
- Genetically modify HSPCs with lentiviral vector
- Cryopreserve and certify HSPC product
- Transport cells to manufacturing facility
- Transport cryopreserved product to hospital

Local Treatment of Patient

- Collect cells from blood or bone marrow
- Conditioning
- Thaw and infuse product

Orchard Therapeutics Supply Chain

Figure: Created by Orchard Therapeutics plc
Delivering Proteins to Brain
Potential to Treat Multi-System Neurometabolic Diseases via Cross-Correction

Gene modified HSCs

Migration across blood-brain barrier

Distribution throughout brain

Blood vessels

Blood-brain barrier

Gene modified microglia cell expresses enzyme

Engraftment in CNS as microglial-like cells

Defective neuron

Enzyme uptake by neuronal cells to potentially correct underlying genetic cause of disease

Figure: Created by Orchard Therapeutics plc
Libmeldy® (OTL-200, atidarsagene autotemcel)

- **MLD (Metachromatic Leukodystrophy)**
  - Fatal genetic CNS disorder
  - Rapid and irreversible loss of motor and cognitive function
  - In its most severe form, most children pass away within five years of symptom onset

### Severe Motor Impairment Free Survival (sMFS)

<table>
<thead>
<tr>
<th>Status</th>
<th>Next Catalyst</th>
<th>Expected timing of Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Launched in Europe</td>
<td>Filed in US</td>
<td>FDA approval</td>
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</tbody>
</table>

*Ref. Orchard Therapeutics plc, Q2 2023 Financial Results and Webcast [https://ir.orchard-tx.com/static-files/9fed8b65-2fd9-491a-97c0-69bf6595c0c3]*

OTL-200 100% NHx 0% ESEJ 11.2% PSEJ 11.2% PSLI 87.5% MLD subgroups compared to disease natural history.

**Data presented at the at the Society for the Study of Inborn Errors of Metabolism (SSIE) Annual Symposium 2023, August 2023**

### Treatment with OTL-200 resulted in statistically significant and clinically meaningful improvement in sMFS in the PSLI (p<0.001), PSEJ (p=0.042) and ESEJ (p<0.001) MLD subgroups compared to disease natural history.

Potential annual market opportunity for Libmeldy® across all patient segments assuming an average per patient net price of $2.5M and universal newborn screening

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2. The sale price of Libmeldy® will vary from jurisdiction to jurisdiction and could vary for a variety of reasons, some of which are outside of the company’s control. The net price utilized on this slide is for illustrative purposes only and is not an estimate or prediction of the average net price of Libmeldy® globally.
Development Pipelines: OTL-203, OTL-201

OTL-203

- **Indication:** MPS-IH\(^1\)
  - Multisystemic neurometabolic condition affecting cognition, growth and skeletal function
  - ~1:100,000 live births; NBS\(^2\) established in some geographies, incl. U.S.

- **Current Status**
  - Interim PoC results published in NEJM\(^3\)
  - Moving into a Pivotal (Ph3) study in 2H 2023

OTL-201

- **Indication:** MPS-III A\(^4\)
  - Accumulation of substrate heparan sulfate leading to severe CNS degeneration w/ somatic manifestations
  - Development slows from 3 years of age, followed by cognitive decline, behavioral disturbances, loss of skills and eventual death, No successful treatment options

- **Current Status**
  - PoC study (Ph1/2) is ongoing
  - Biochemical/clinical data reported in 2023 ASGCT meeting

Neuropsychological Tests over Time

<table>
<thead>
<tr>
<th>Cognitive Age-Equivalent Score (Overall)</th>
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<tbody>
<tr>
<td>Interim Proof-of-Concept (PoC) Study Results Published in NEJM</td>
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Developmental Age Equivalent\(^2\)

<table>
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<th>MPSIII A natural history (Shapira et al. 2016)</th>
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\(^1\) Mucopolysaccharidosis type I, Hurler syndrome; \(^2\) Newborn Screening; \(^3\) Engl J Med 2021; 385:1929-1940 DOI: 10.1056/NEJMoa2106596; \(^4\) Mucopolysaccharidosis type IIIA (Sanfilippo Syndrome type A)
Expected Synergy

Further Development as a Japan-Based Global Specialty Pharmaceutical Company

- To be a Japan-based Global Specialty Pharmaceutical Company providing life-changing value to high unmet medical needs in concert with our existing business through Crysvita and Poteligeo

Reinforcement of Innovative New Drug Discovery & Development

Kyowa Kirin
- Experience and expertise of R&D and commercialization in Biologics and Antibody Drugs
- Proprietary next-generation antibody technology
- Continuous efforts on new modalities

Orchard Therapeutics
- Experience and know-how in the marketing HSC-GT1 in EU
- High technology in HSC-GT1 (Research, CMC, SCM, etc.)
- Patient access and collaboration with medical institutions
- Efforts and experience in new modalities

A key step toward delivering advanced value to patients
- Pursuing the potential for “One-time treatment in life”
- Challenge to correct the underlying cause of a genetic disease
- Personalized medicine / Precision medicine
- Providing treatment beyond the existing drugs

Address a broader range of UMNs

1. Hematopoietic Stem Cell Gene Therapy

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Innovative New Drug Creation by Kyowa Kirin Drug Discovery Technology

- **KHK4951** (tivozanib eyedrop)
- **KK2260**
- **KK2269**
- **POTELLIGENT**
- **REGULGENT™** (Bispecific antibody technology)
- Approach to eyedrop formulation utilizing nanocrystallization
- **POTELIGENT®**
- Fully human antibody production technology
- **OTL-200 (Libmeldy®)**
- **OTL-203**
- **OTL-201**
- **HSC-GT (Orchard Therapeutics plc)**

Kyowa Kirin will realize the successful creation and delivery of life-changing value that ultimately makes people smile