



**Kyowa Kirin Co., Ltd.**

40th Annual J.P. Morgan Healthcare Conference

January 10, 2022 (EST)

## Event Summary

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<b>[Event Name]</b>	40th Annual J.P. Morgan Healthcare Conference
<b>[Date]</b>	January 10, 2022 (EST)
<b>[Speaker]</b>	Masashi Miyamoto, Ph.D. Representative Director of the Board, President and Chief Executive Officer

# Delivering Life-changing Value as a Global Specialty Pharma

J.P. Morgan Healthcare Conference  
January 10, 2022

**Masashi Miyamoto, Ph.D.**

Representative Director of the Board,  
President and Chief Executive Officer



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# Agenda

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| 4  | Who We Are                                   |
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## Vision

### Our New 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

Address  
patient-centric  
healthcare needs

Retain the trust  
of society

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In order to make this vision a reality by 2030, we focus on: Provide pharmaceuticals for unmet medical needs, Address patient-centric healthcare needs, and Retain the trust of a society.

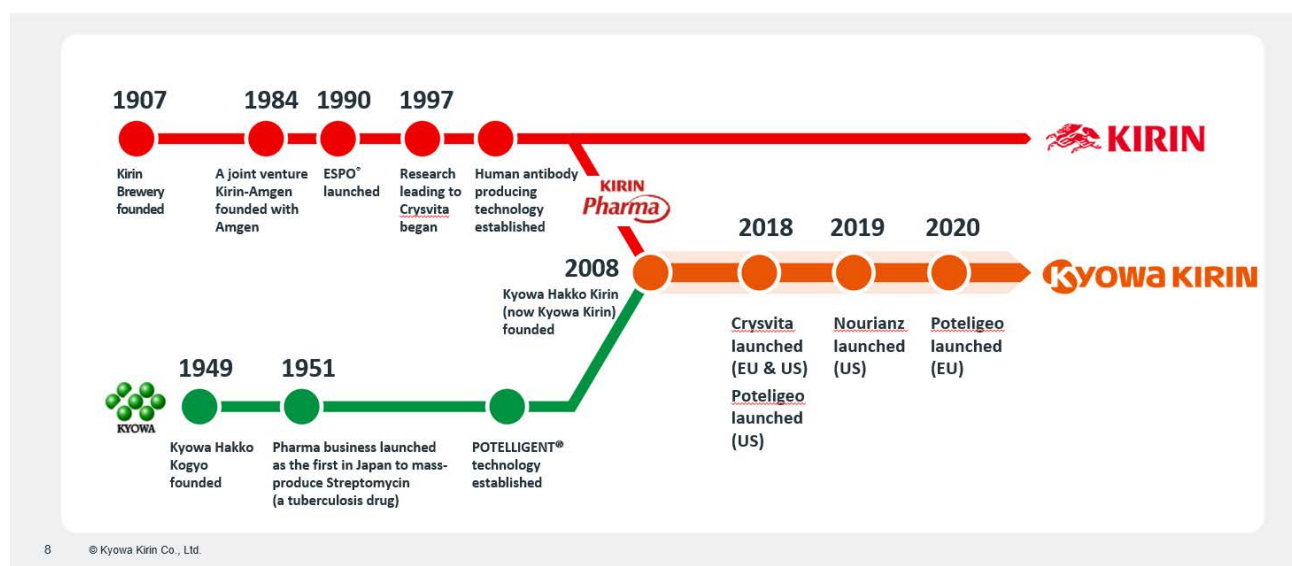
## Overview



## Global Network



# History



Kyowa Kirin was created from the merger of Kyowa Hakko and Kirin Pharma in 2008. At that time, both companies had this long legacy of fermentation technology applied to pharmaceutical manufacturing and also enjoyed long-lasting relationship with research institutions and biotech companies.

For example, Kirin Pharma had a 30-year joint venture with Amgen. Both companies established antibody technologies such as POTELLIGENT and fully human antibody producing technologies, which have spurred innovations in our portfolio.

After the merger, the company began to seek to expand its operation globally. Over the past 13 years, we have followed that plan expanding through organic growth and targeted acquisitions.

Since 2018, we have received FDA approval on three medicines discovered and developed in-house, Crysvida, Poteligeo, and Nourianz.

## Key Marketed Products

Nephrology	Oncology	Immunology/Allergy	Central Nervous System	Others
<b>NESP®</b> Erythropoiesis Stimulating Agent Japan and Asia	<b>POTELIGEO®</b> (mogamulizumab) Anti-CCR4 mAb Japan, US and EU	<b>Allelock®</b> Anti-allergic agent Japan and Asia	<b>NOURIANZ®</b> (istradefylline) tablets Adenosine A <sub>2A</sub> R antagonist Japan and US	<b>CRYSVITA®</b> Anti-FGF23 mAb Japan, US* <sup>2</sup> and EU
<b>REGPARA®</b> Calcium receptor agonist Japan and Asia	<b>Abstral®</b> Sublingual fentanyl Japan and EU	<b>パタノール®</b> Ophthalmic Anti-allergic agent Japan	<b>デパケン®</b> Antiepileptic agent Japan	<b>Romiploste®</b> Romiplostim Thrombopoietin R agonist Japan and Asia
<b>オルケディア®</b> Calcium receptor agonist Japan	<b>ジ-ラスト GRAN™</b> Long-lasting G-CSF/G-CSF Japan and Asia* <sup>1</sup>	<b>ルミセフ®</b> Anti-IL17R mAb Japan	<b>トピナ®</b> Antiepileptic agent Japan	<b>Coniel®</b> Calcium channel blocker Japan and Asia
<b>オングリザ®</b> DPP-4 inhibitor Japan	<b>リツキシマブ BS</b> Rituximab biosimilar Japan	<b>ドボバット®</b> Vitamin D3/Corticosteroid Japan		

9 © Kyowa Kirin Co., Ltd. \*1 Pegfilgrastim only available in Japan, \*2 Marketed by Ultragenyx Pharmaceutical Inc.

## Proprietary Technologies for Life-changing Value Creation

**POTELLIGENT® Technology**

An ADCC-enhancing technology that realizes effective target cell elimination by antibody afucosylation

**POTELIGEO®**  
(mogamulizumab)

**KHK4083/AMG 451**

**Antibodies**

(1) Sugar chains are in the tail of antibodies called Fc portion.

**Fucose**

(2) They contain fucose, a kind of sugar.

(3) The removal of fucose allows increased antibody-dependent cellular cytotoxicity (ADCC) activity.

Antibody concentration (μg/mL)	Potelligent® (low/no fucose)	Conventional (highly fucosylated)
0.0001	~10	~5
0.001	~40	~10
0.01	~60	~20
0.1	~75	~35
1	~75	~40

**Human Antibody Producing Technology**

A technology that enables to generate fully human antibodies with the same diversity as natural antibodies using chromosome engineering

**KHK4083/AMG 451**

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As you may know, ADCC is a critical function of the immune system that enhances the ability of antibodies to kill target cell. This POTELLIGENT technology has been used for our products and rug candidates. In addition,



it has been licensed out and utilized by numerous major pharmaceutical and biotech companies in their pipelines.

The marketed products in which we have applied this technology include Poteligeo, our drug for cutaneous T-cell lymphoma; Fasenra, an asthma drug licensed out to AstraZeneca; and GSK's Blenrep, a drug for multiple myeloma.

We also have our proprietary human antibody producing technologies applied for several drugs and drug candidates. The products launched using this technology include Crystiva, a treatment for X-linked hypophosphatemia.

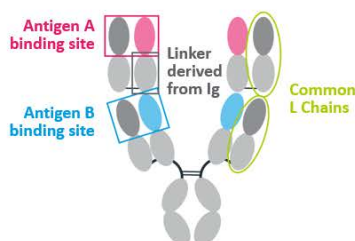
In addition, KHK4083, as known as AMG 451, is being developed for the treatment of atopic dermatitis by applying both technologies.



## Next-Generation Technologies for Life-Changing Value Creation

### Bispecific Antibody Technology

- Selection of linkers derived from Immunoglobulin (Ig) and the common sequence of L Chains
- Versatility equivalent to wild type IgG
- Unique biology based on bivalent x bivalent binding



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### Drug Discovery Collaborations

- Revolutionary small molecule drug discovery (with [Axcelead](#))
- Data-driven drug discovery (with [InveniAI](#))
- RNA structure-targeted drug discovery (with [xFOREST](#) and [Axcelead](#))



The first is our bispecific antibody technology that would create a rich drug pipeline. We are working hard to have this technology to enter clinical trials. Also, we hope that open innovation will lead to the discovery of innovative new drugs and the creation of fundamental technologies to support them.

We value our partnership with outside collaborators as they are essential to reinforce the strength of our technologies into life-changing value.



## Strong Growth of Global 3 Brands (G3B)



### CRYSVITA

(Burosumab, an anti-FGF23 fully human monoclonal antibody)

X-linked hypophosphatemia (XLH)  
Tumor-induced osteomalacia (TIO)



### POTELIGEO

(Mogamulizumab, an anti-CCR4 humanized antibody)

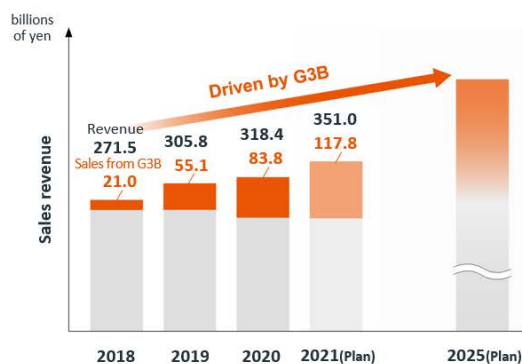
Mycosis fungoides (MF)  
Sézary syndrome (SS)



### NOURIAST/NOURIANZ

(Istradefylline, an Adenosine A<sub>2A</sub> receptor antagonist)

Parkinson's disease (PD)  
experiencing "off" episodes



## CRYSVITA



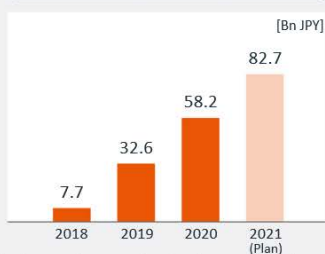
Burosumab, an anti-FGF23 fully human monoclonal antibody



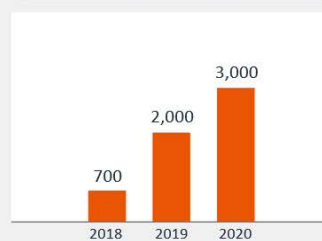
### Indications

US	EU	JP
XLH TIO	XLH (TIO)	FGF23-related hypophosphatemic rickets and osteomalacia

### Annual sales growth<sup>\*2</sup> (NA+EMEA+JP)



### Number of patients<sup>\*2</sup> (global total)



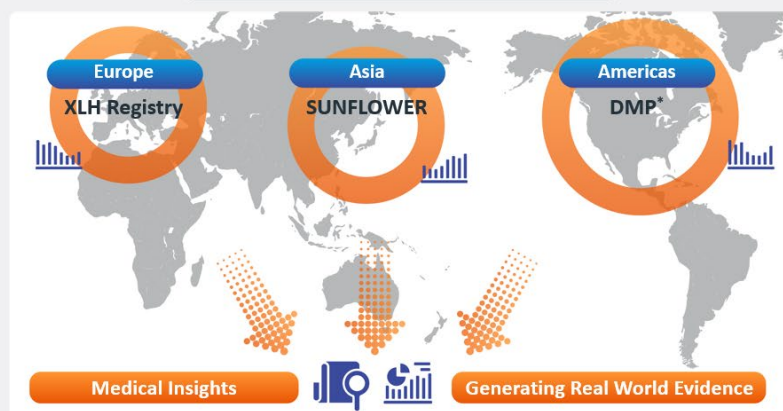
# Crysvita



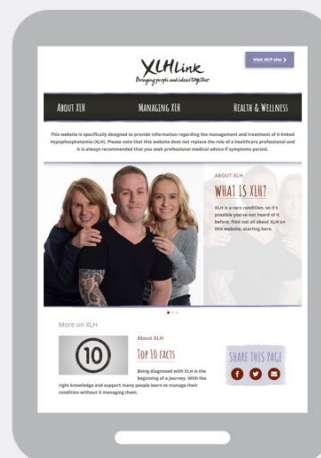
Burosumab, an anti-FGF23 fully human monoclonal antibody

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## Global Evidence Generation Project



\* Disease Monitoring Program



<https://xlhlink.eu/>

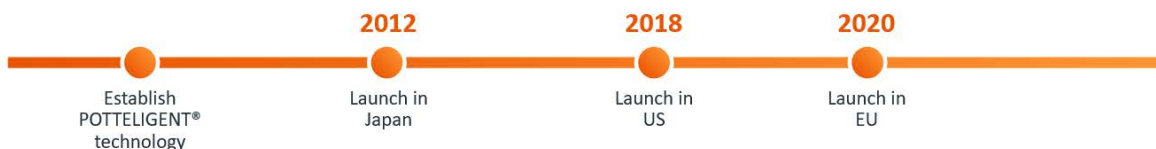
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# Poteligeo



Mogamulizumab, an anti-CCR4 humanized antibody

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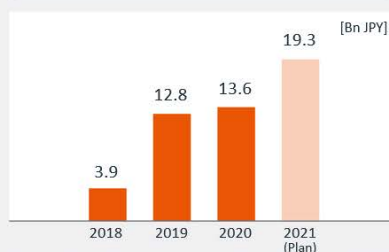


- The first glyco-engineered antibody to reach the market
- Indications

US	EU	JP
MF SS	MF SS	ATL PTCL CTCL

ATL: adult T-cell leukemia/lymphoma; PTCL: peripheral T-cell lymphoma; CTCL: cutaneous T-cell lymphoma

## Annual sales growth\* (NA+EMEA+JP)



\* Excl. patients under Early Access Program and patients who have not started the reimbursement process

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# Nourianz/Nourias

**NOURIANZ**  
(istradefylline) tablets

Istradefylline, an Adenosine A<sub>2A</sub> receptor antagonist

**KYOWA KIRIN**



## MOA (Simple illustration)

Levodopa replaces lost dopamine, like pressing down on the gas



Istradefylline blocks A<sub>2A</sub> receptors, like lifting the brake

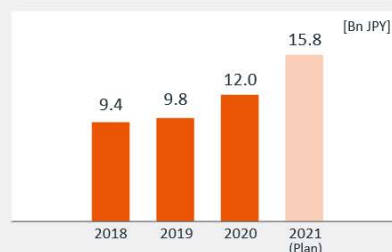


## Indications

US / JP

PD  
experiencing  
"off" episodes

## Annual sales growth (NA+JP)



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Nourianz is the first new mechanism of action drug for Parkinson's disease treatment in decades and is an innovative adenosine A<sub>2A</sub> receptor antagonist that we discovered.

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## Next-generation Strategic Products

	Country / region* <sup>1</sup>	Indication* <sup>2</sup>	Approval year* <sup>3</sup>	Total addressable market* <sup>4</sup>	No. of patients* <sup>5</sup>
<b>KHK4083/AMG 451</b>	NA/EU/JP	Atopic dermatitis	2025/2026	★★★	16,000K
<b>KW-6356</b>	NA/EU/JP	Parkinson's disease	2025	★★★	3,500K
<b>ME-401 Zandelisib</b>	NA/EU/JP	Follicular lymphoma Marginal zone lymphoma	2023	★★★	~800K
<b>RTA 402 Bardoxolone methyl</b>	JP/Asia	Alport syndrome Diabetic kidney disease (DKD) Autosomal dominant polycystic kidney disease (ADPKD)	2022 2023 2025	★★★	2,500K ~
<b>KHK7791 Tenapanor</b>	JP	Hyperphosphatemia under maintenance dialysis	2023	★★☆	250K

As of Feb 4, 2021

\*<sup>1</sup> Countries or regions where Kyowa Kirin currently has marketing rights and will launch products (or will conduct marketing activities); products may not be launched in all countries or regions shown in the table

\*<sup>2</sup> Expected indications as of the date of this document; indications may ultimately differ to expectations due status of approvals from regulatory authorities

\*<sup>3</sup> Expected year of first approval

\*<sup>4</sup> Expected total addressable market, which is the sum of all products for the indications shown in \*<sup>2</sup>, in all countries or regions defined in \*<sup>1</sup>, not projected sales or the Company's targets;

★ = less than ¥50bn, ★★ = ¥50-100bn, ★★★ = Over ¥100bn

\*<sup>5</sup> Total number of estimated patients in all countries or regions defined in \*<sup>1</sup>.

\*<sup>6</sup> The size of the total addressable market and patient numbers are based on our estimates

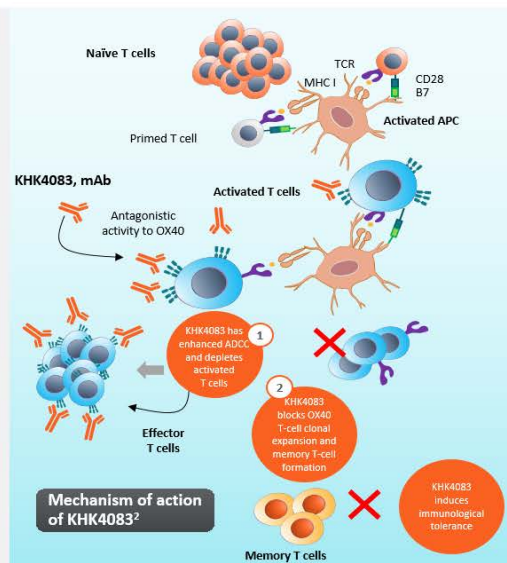
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## KHK4083/AMG 451 targets OX40 as a potential novel target for AD treatment

- Activation of Th2 and other T-cell subsets is central in atopic dermatitis (AD)
- The OX40–OX40L axis plays a critical role in long-lasting T-cell responses
  - OX40 is expressed by activated T cells after antigen recognition and binds OX40L on APCs, facilitating the effector function of T cells
- KHK4083/AMG 451 is a fully human, anti-OX40, non-fucosylated IgG1 mAb with enhanced ADCC<sup>1</sup> that acts by
  - Partially depleting activated T cells<sup>2</sup> ①
  - Blocking T-cell clonal expansion and memory T-cell formation<sup>2</sup> ②

AD, atopic dermatitis; ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cell; CD28, cluster of differentiation 28; IgG, immunoglobulin G; MHC, major histocompatibility complex; mAb, monoclonal antibody; TCR, T-cell receptor; Th2, T-helper 2  
<sup>1</sup>Nakagawa H et al. J Dermatol Sci. 2020; 99(2):82–89; <sup>2</sup>Papp KA et al. J Eur Acad Dermatol Venereol. 2017; 31(8):1324–1332.

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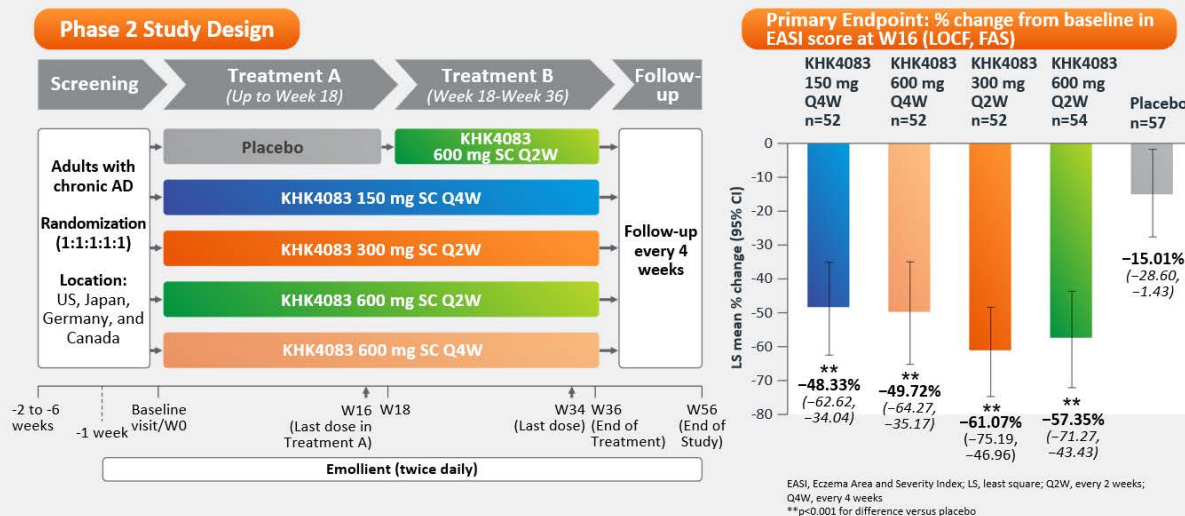


KHK4083/AMG 451 is a human anti-OX40 monoclonal antibody created with our POTELLIGENT technology and the human antibody producing technology.

As is commonly known, activation of Th2 cells is central in atopic dermatitis. KHK4083 blocks the OX40 signaling pathway, which plays a major role in upstream T-cell activation by OX40 inhibition or OX40 positive cell depletion.

As expected, clinical results based on this mechanism of action have been obtained to date.

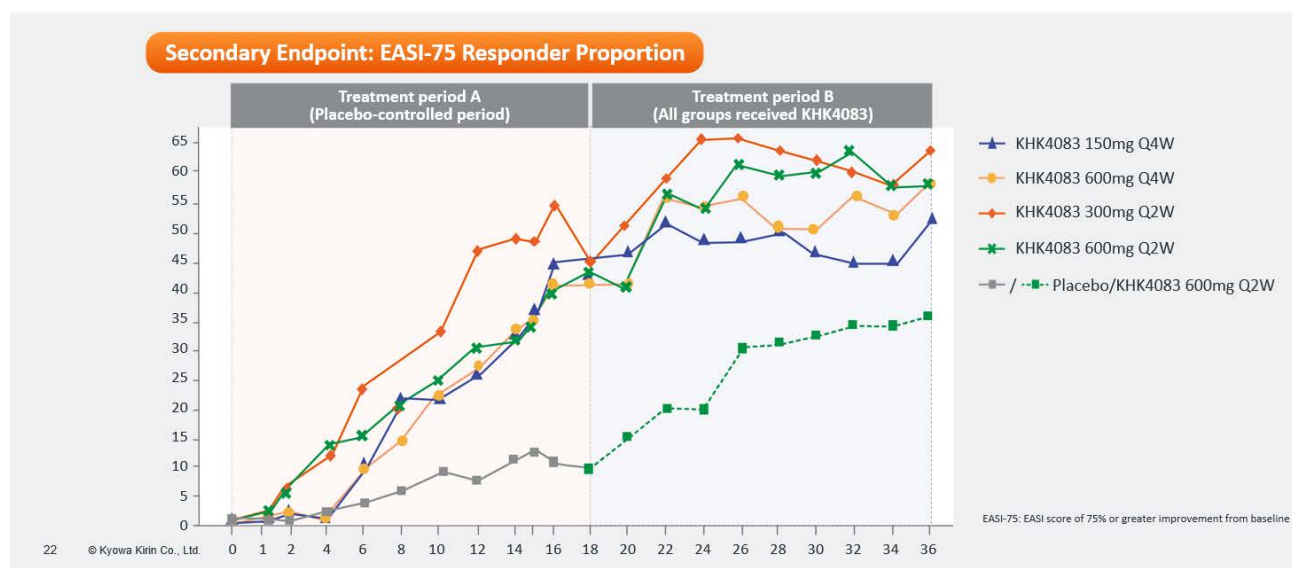
## KHK4083/AMG 451: Achieved Primary Endpoint in Phase 2 Study



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## KHK4083/AMG 451: Durable EASI-75 Response Confirmed



## KHK4083/AMG 451: Collaboration with Amgen

	US	Europe and Asia (ex. JP)	JP
<b>Development</b>	<ul style="list-style-type: none"> <li>Amgen leads development</li> <li>Share development cost</li> </ul>	<ul style="list-style-type: none"> <li>Amgen leads development</li> <li>Share development cost</li> </ul>	<ul style="list-style-type: none"> <li>Kyowa Kirin leads development</li> </ul>
<b>Commercialization</b>	<ul style="list-style-type: none"> <li>Amgen commercializes and books sales</li> <li>Kyowa Kirin co-promotes and shares promotion cost</li> </ul>	<ul style="list-style-type: none"> <li>Amgen commercializes and books sales</li> <li>Kyowa Kirin has opt-in rights for co-promotion</li> </ul>	<ul style="list-style-type: none"> <li>Kyowa Kirin commercializes and books sales</li> </ul>
<b>Sales royalties</b>	<ul style="list-style-type: none"> <li>Double-digit royalty to Kyowa Kirin</li> </ul>	<ul style="list-style-type: none"> <li>Double-digit royalty to Kyowa Kirin</li> </ul>	
<b>Commercial supply</b>	<ul style="list-style-type: none"> <li>Amgen supplies</li> </ul>	<ul style="list-style-type: none"> <li>Amgen supplies</li> </ul>	<ul style="list-style-type: none"> <li>Kyowa Kirin supplies</li> </ul>

Amgen makes a \$400 million up-front payment to Kyowa Kirin and future contingent milestone payments potentially worth up to an additional \$850 million, as well as royalty payments on future global sales.

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To maximize the product value of KHK4083/AMG 451 for atopic dermatitis and its potential in other autoimmune disease treatments, Kyowa Kirin and Amgen have entered into an agreement to develop and commercialize KHK4083/AMG 451 jointly.

Our agreement to co-development and co-commercialize KHK4083 made news in 2021. With Amgen, we are planning to initiate a Phase 3 study of KHK4083 in the first half of 2022. We will also explore the potential use of KHK4083 in indications beyond atopic dermatitis.

## Zandelisib (ME-401): Clinical and Commercial Opportunity

>8,000 U.S. Patients  
With Relapsed/Refractory  
Follicular Lymphoma

**\$1B  
Addressable  
Market**

### Market Opportunity

- PI3Kδ inhibitors deliver potent efficacy, but utility limited by the extensive T-reg mediated toxicity
- R/R FL has several treatment options but no standard of care
- PI3Kδ inhibitors limited to modest ≥ 3<sup>rd</sup> Line FL use due to risk/benefit of current therapies

### Zandelisib Opportunity

- Product attributes and novel treatment schedule could reset expectations of PI3Kδ inhibitors
- Compelling emerging profile supports best-in-class opportunity in 3L+ FL
- Unique zandelisib properties and combinability could expand utility to earlier lines of FL and into other BCMs



Global License, Development and Commercialization Agreement to Optimize Zandelisib Value (April 2020)

US: cost-sharing, co-promotion, MEI Pharma books sales

Ex-US: Kyowa Kirin has exclusive rights, escalating tiered sales royalty payments to MEI starting in teens

BCMs: B-cell malignancies

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Zandelisib has innovative molecular and biologic properties that show the potential to avoid the safety issues that are common among other PI3K treatments.

On November 4th, 2021, FDA granted orphan drug designation to Zandelisib for follicular lymphoma.

## Zandelisib: Emerging Profile

### Phase 2 study (TIDAL) in patients with r/r FL

**Overall Response Rate (ORR)**  
95% CI (59.8, 79.5)

**70.3%**

**Complete Response Rate (CR)**  
95% CI (25.4, 45.9)

**35.2%**

**Duration of Response:**  
Insufficiently mature to estimate final DOR: with median follow-up time for response of 8.4 months, median DOR had not been reached

N=91 in the primary efficacy population for the evaluation of ORR and DOR.

Note: ORR assessed by IRC after a minimum follow-up of 6 months and represents the primary endpoint of the TIDAL study. Safety and duration of response data are as of the data cutoff date; the data cutoff date is approximately 6 months after the last patient in the primary efficacy population received their first dose of zandelisib. With exception of the ORR and CR data reported in the primary follicular lymphoma efficacy population of 91 patients, the data reported today provides an initial look at the data as of the data cutoff date and is interim and subject to change as more patient data become available. Because the data reported today is from an ongoing study, the final data may differ materially from the data reported in this presentation.



**Discontinuation Rate Due to Any Drug Related Adverse Event**

**9.9%**

**Adverse Events of Special Interest (Grade ≥3)**

- 1.7% ALT/AST Elevation
- 1.7% Colitis
- 5.0% Diarrhea
- 2.5% Mucositis
- 0.8% Pneumonitis
- 3.3% Rash

**≤ 5% each**

**Median Follow-up of 9.4 Months (0.8-24)**

N=121 in the total study population for the evaluation of safety.

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## Zandelisib: Exploring Full Potential as Backbone Therapy

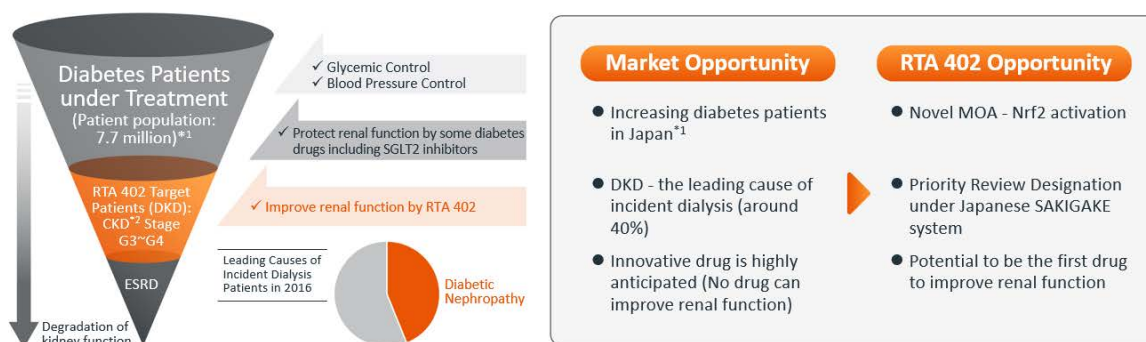


**Additional Studies in Active Planning and More Under Consideration**

CLL: chronic lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; iNHL: indolent B-cell non-Hodgkin lymphoma; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; R-CHOP: rituximab-cyclophosphamide/doxorubicin/prednisone/vincristine; Ven-R: venetoclax-rituximab

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## Bardoxolone Methyl (RTA 402): Clinical and Commercial Opportunity



License Agreement on Bardoxolone Methyl for Japan and Certain Asian Markets (January 2010)  
Kyowa Kirin has exclusive rights, sales royalty payments to Reata ranging from the low teens to the low 20%

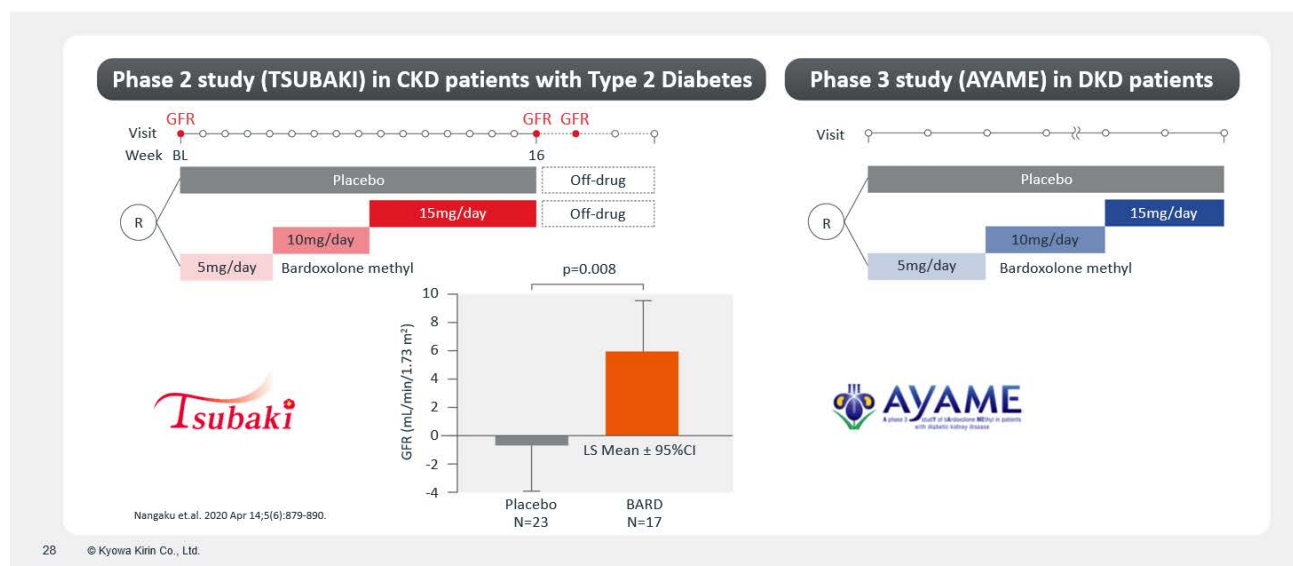
\*1 National Health and Nutrition Survey (2016), MHLW/Ministry of Health, Labour and Welfare; \*2 CKD: chronic kidney disease

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Given this, bardoxolone methyl has opportunities as it activates the system that plays an important role in defense responses against oxidative stress as its convincing clinical data and the priority review designation support its potential market opportunity in Japan, and as it could be the first drug addressing the need for renal function protection and improvement.



## Bardoxolone Methyl: Increase GFR in CKD Patients with Type 2 Diabetes



The Phase 3 AYAME study is scheduled to be complete this year, and then the topline data is available.

## Expected News Flow in FY2022

As of Nov 1, 2021

Code generic name	Target disease	2022
KHK4083/AMG 451	Atopic dermatitis	P3 FPI
KW-6356	Parkinson's disease	P2b detailed data P3 FPI
ME-401 Zandelisib	FL/MZL (2L, R combo) iNHL (3L, mono) CLL (Ven-R combo)	Enrollment ongoing P2 Topline data P2 FPI
RTA 402 Bardoxolone methyl	Alport syndrome Diabetic kidney disease	Regulatory decision (JP) P3 LPO
KHK7791 Tenapanor	Hyperphosphatemia under maintenance dialysis	Marketing application (JP)

FPI: first patient in; FL: follicular lymphoma; MZL: marginal zone lymphoma; iNHL: indolent B-cell non-Hodgkin lymphoma; CLL: chronic lymphocytic leukemia; Ven-R: venetoclax-rituximab; LPO: last patient out

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There are various catalysts for 2022, so please stay tuned. In particular, I hope you will look forward to the start of several Phase 3 clinical trials including KHK4083 and KW-6356. We will announce in a timely manner when Phase 3 studies actually start.

## Outlook toward 2030



In order to do so, we will work on open innovation by developing our own technologies as well as successfully incorporating useful technologies from outside, and we will surely produce life-changing value that will make patients smile. We will continue to strive for this goal.

## FY2021-2025 Medium Term Business Plan



Thank you very much for your time and attention for Kyowa Kirin.

[END]