



Kyowa Kirin Co., Ltd.

Updates on Nourianz Marketing Strategy in the US and KW-6356 Development

November 19, 2019

Event Summary

[Event Name]	Updates on Nourianz marketing strategy in the US and KW-6356 development		
[Date]	November 19, 2019		
[Number of Speakers]	2		
	Len Paolillo	Executive Vice President & CCO, Kyowa Kirin, Inc.	
	Mitsuo Satoh	Vice President & Head of R&D Division, Kyowa Kirin Co., Ltd.	

Presentation

Moderator: Now, I would like to begin the Kyowa Kirin's explanatory meeting for Nourianz launch strategy and also KW-6356 development. First of all, I would like to invite Len Paolillo, our Executive Vice President and Chief Commercial Officer, Kyowa Kirin, Inc, to present the Parkinson's disease product, Nourianz. He's going to explain the North American sales strategy of Nourianz, followed by Dr. Mitsuo Satoh, who will present on the next-generation drug candidate of Nourianz, which is the KW-6356. And he's going to present on the results of the Phase IIa study.

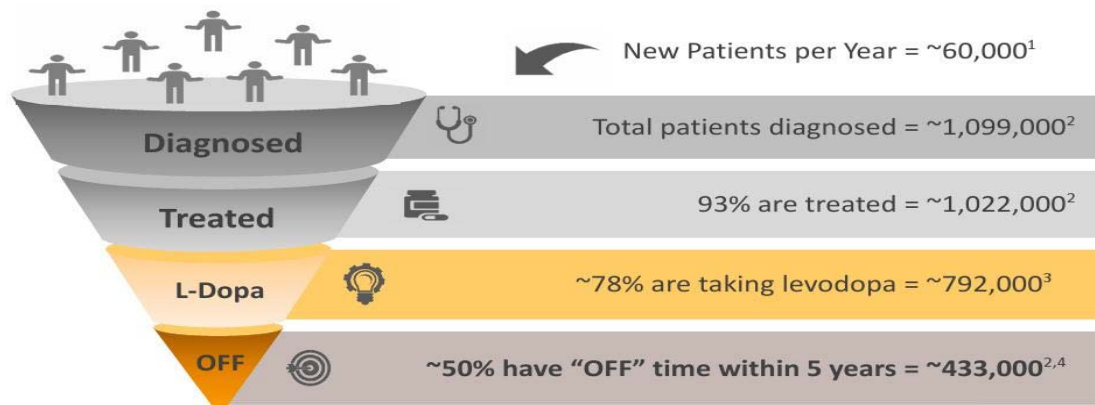
Mr. Len Paolillo, please present on the sales strategy of Nourianz.

Paolillo: Good afternoon, and thank you very much for having me. I am from New York. I tend to speak rather rapidly, but I'll do my best to allow the translator to keep up.

Today, I'll cover the US Parkinson's market dynamics, as well as Nourianz's launch priorities, and a bit of an overview of the 2020 Nourianz brand strategy.

Patients with off-time are a subset of the PD population

Up to ~433k Patients are on Levodopa therapy and have “OFF” time in the US



1. Parkinson's Foundation. <https://parkinson.org/Understanding-Parkinsons/Statistics>. Accessed May 16, 2019. 2. Decision Resources Group. Parkinson's Disease. Epidemiology Mature Markets. 3. Decision Resources Group – Market Forecast Assumptions March 2019. 4. Hickey P, et al. *Drug Des Devel Ther*. 2011;5:241-254.

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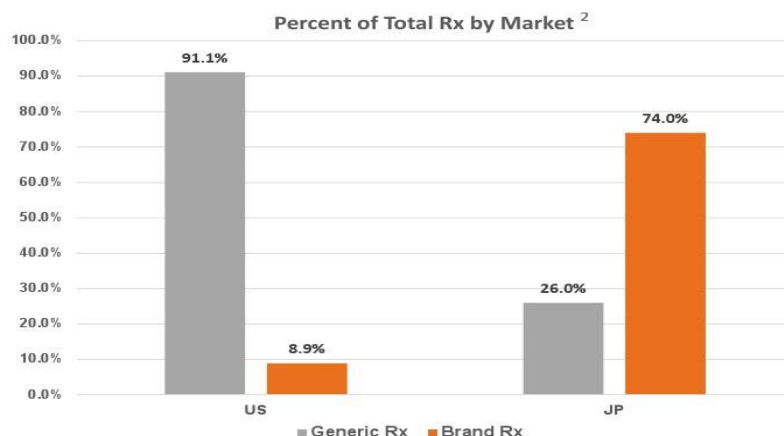
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I'll start with our addressable patient population. There are approximately 1 million patients in the United States with Parkinson's disease. However, as you follow the funnel, you recognize that there are approximately 433,000 patients that have off episodes. These are the addressable patients for Nourianz.

With 60,000 new patients per year, it is a slow, but growing market. Of the patients that you see, once they initiate Levodopa, 50% of them will experience off episodes within five years.

US PD market is dominated by generic prescriptions

In the U.S., Brand volume accounts for ~8.9% of 3.8M PD prescriptions a year¹



Sources: Data compiled from Decision Resource Group report: Parkinson's Disease: Disease Landscape and Forecast, 2017.

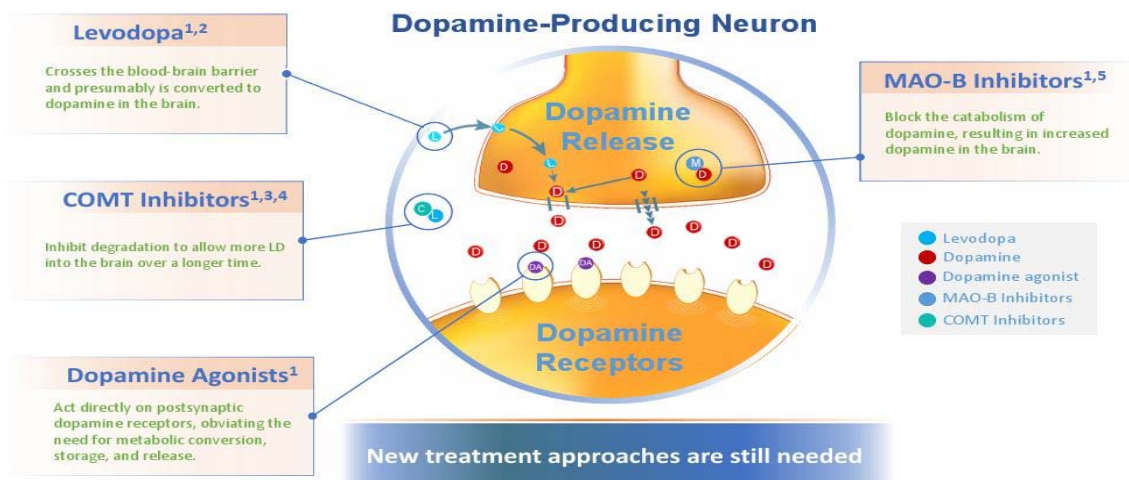
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Turning to the products and how these patients are cared for in the US, in contrast to the Japanese market, 91.1% of the prescriptions in the US are generic. That's compared to 74.0% of the prescriptions in Japan being branded.

When you break down this down on a payor level, 66% of the prescriptions are paid for by Medicare, which is the US insurance for those over 65 years old; 28% are commercial, which is the insurance for people in the workforce, who get that insurance through an employer, or you can purchase it on the exchange; and approximately 6% are Medicaid, which is for the indigent population.

Current treatment options enhance or mimic dopamine to address the symptoms of PD, but wearing off occurs as condition progresses



MAO-B, monoamine oxidase type B.
 1. Hauser RA. Medscape. <https://emedicine.medscape.com/article/1831191-overview>. Accessed June 24, 2019. 2. Gandhi KR, et al. <https://www.ncbi.nlm.nih.gov/books/NBK482140/>. Accessed June 24, 2019. 3. COMT Inhibitors. <https://parkinsonsdisease.net/medications/comt-inhibitors>. Accessed June 24, 2019. 4. NICE. Parkinson's disease in adults. <https://www.nice.org.uk/guidance/ng71/resources/parkinsons-disease-in-adults-pdf-1837629189061>. Accessed June 24, 2019. 5. Mayo Clinic. <https://www.mayoclinic.org/diseases-conditions/depression/in-depth/maois/art-20043992>. Accessed June 24, 2019.

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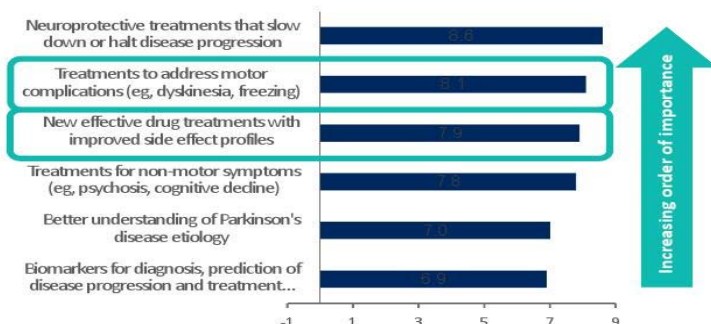
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Looking at the currently available treatment options, you'll notice that most of what's available right now focuses on replacing, mimicking, or enhancing dopamine.

In the top left corner, you see Levodopa. This is the gold standard in the United States, and it is the backbone of therapy. As you go around the neuron here, you can see COMT inhibitors, dopamine agonists, and MAO-B inhibitors. These are adjunct therapies that are often used in combination with Levodopa. All of them are dopaminergic in nature and focus on this neuron here in the synapse.

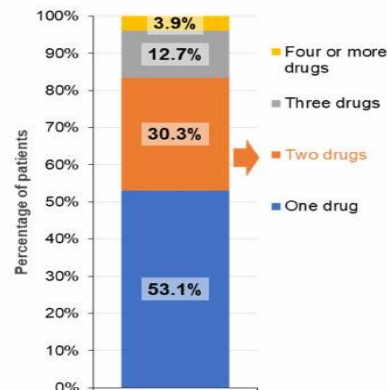
Surveys indicate off-time remains an unmet need, yet many patients are only treated with 1-2 PD medications

Survey Unmet Needs in Parkinson's Disease¹



Note: Respondents were asked how drug developers should prioritize addressing each of the treatment challenges listed above. They rated the treatment challenges using a scale of 1 to 10, where 1 is very low priority and 10 is very high priority. The bar chart displays the mean rating attributed to each treatment challenge across the seven surveyed markets.

Drug Burden for Parkinson's Disease²



Source: 1. Datamonitor Healthcare's Treatment: Parkinson's disease proprietary survey, June 2016, p. 60
2. Decisions Resource Group – Landscape and Market Forecast Apr 2019

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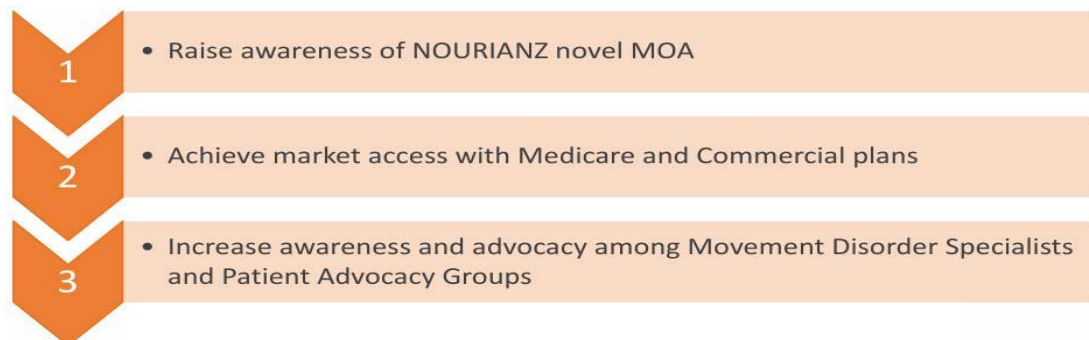
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Interestingly, with these options, and there are numerous options, surveys indicate that motor fluctuations are still an area of high unmet needs, second only to neuroprotective agents and disease-modifying agents. Of the products that you saw there, most of them are available in both generic and brand form. When looking at the right-hand side, you'll notice that physicians in the United States oftentimes treat patients with one or two products with their Parkinson's disease. Only 16% of patients are receiving three or more products for Parkinson's.

If you take a step back and you look at a competitive US market, it's genericized, many of the mechanisms of action for both the brands and generic are similar, and you have still a rather high unmet need in this market, which we believe leaves a good position for a product with a novel mechanism of action.

2020 NOURIANZ™ Launch Success Factors

NOURIANZ is an adenosine receptor antagonist indicated as adjunctive treatment with levodopa/carbidopa in adult patients with Parkinson's Disease (PD) experiencing "off" episodes



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[Click here to see Important Safety Information and full US Prescribing Information](#)

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Let's talk a bit about our Nourianz launch success factors.

This is our indication. Nourianz is an adenosine receptor antagonist indicated as adjunctive therapy with Levodopa/Carbidopa in adult patients with Parkinson's disease experiencing off time.

As you can imagine, our first priority is to raise awareness and understanding of our novel mechanism of action. Second is to achieve market access through both Medicare and commercial payors. And finally, we want to increase awareness and advocacy among movement disorder specialists and patient advocacy groups.

Aim to position NOURIANZ™ to be the **FIRST ADJUNCT tx**

Build understanding of new Mechanism of Action (MOA) and product profile

				
Mechanism of Action	Safety & Tolerability	Improved OFF Time	Simple Dosing	Manageable DDI
• A novel MOA • First and only Adenosine A_{2A} receptor antagonist approved as adjunctive treatment for “off” episodes in U.S.	• Well characterized safety and tolerability in clinical trials	• A non-dopaminergic product that reduces off-time	• Once daily dosing	• Can be used in combination with common medications used by PD patients

Source: Summary of Full Prescribing Information available at <https://www.nourianzhcp.com/assets/pdf/nourianz-full-prescribing-information.pdf>

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As we aim to position Nourianz, you could understand why we would be looking to become the first adjunct. Thinking back to a bit of the market dynamics, if only 16% of patients are on three or more PD medications, it's important for an adjunct therapy to be selected early on in the treatment algorithm.

We think keys to this obviously center around our mechanism of action. We were the first and only adenosine A_{2A} antagonists approved in the United States. We have well-characterized safety and tolerability in our clinical trials. And, we have a non-dopaminergic option now for patients looking to reduce off time. Simple, once-daily dosing and manageable drug-drug interactions make this an easy selection for physicians and easy for patients to take.

Launch Campaign Materials – “Pathways”

EXPLORE A DIFFERENT PATH

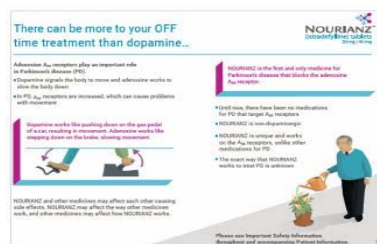
The first and only adenosine
 A_{2A} receptor antagonist
in Parkinson's disease (PD)

NOURIANZ™
(istradefylline) tablets
20 mg | 40 mg

- Educate physicians and patients on the alternative to dopaminergic adjunct treatments



Online ads



Brochures

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Our launch campaign materials, called Pathways, are designed to do just that: educate physicians and patients on the alternative to dopaminergic adjunct therapies.

This campaign that you see here is being brought to physicians both by our medical reps, as well as digitally through banner ads, websites, direct emails, and also direct-to-patients, which is one of the unique things that you can do in the United States market, which is directly marketed to patients.

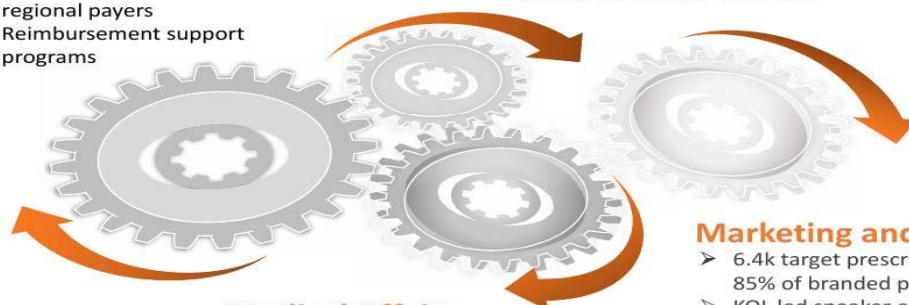
Cross-Functional Execution for Launch Success

Market Access

- Kyowa Kirin is engaged with key PBM's as well as national and regional payers
- Reimbursement support programs

Corporate Communications

- Patient Advocacy Group collaboration
- Patient events and education



Medical Affairs

- Publication of key Nourianz clinical data
- Scientific Exchange

Marketing and Field sales

- 6.4k target prescribers covering 85% of branded prescriptions
- KOL led speaker events
- Digital education for physicians, patients and caregivers
- Sample Program

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Cross-functionally, we've had quite a bit of a lead-up to the launch. Our medical affairs team, our pricing and access team, have had extensive meetings with both KOLs, as well as key payors in the United States, in order to prepare the market for the launch of Nourianz. Now that we are approved and in the market, it's important that this cross-functional team continues to execute to provide access to patients.

I'll start in the top left with market access. Our payor team has been engaged with key PBMs, as well as national and regional payors. We've established a patient services hub that will help patients through the reimbursement process, provide financial assistance to eligible patients, and also provide disease education services.

From corporate communications, we work closely with patient advocacy groups, as well as attend patient events and education. As I've mentioned before, we even market directly to patients in the United States.

Medical affairs is a key function in the United States for scientific exchange. This is not a promotional group. Medical affairs is dedicated to furthering the science of the products and the disease states in which we work. They are focused on the publication of Nourianz's data. Given Nourianz has a wealth of clinical data available that is outside of the US label, the medical affairs team is focused on making that information available for physicians in the United States to better understand the mechanism of action, as well as the properties of the drug.

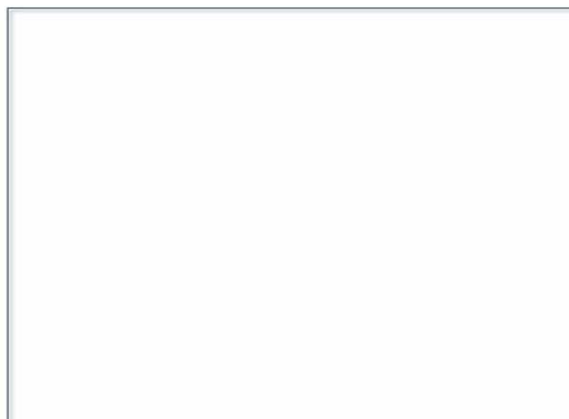
Our marketing and field sales, which is now fully deployed, is covering 6,500 prescribers, and very importantly, we targeted prescribers that prescribe branded medications. This was a key strategy for us in order to have an efficient yet effective deployment.

Through our pre-launch activity, we've identified key opinion leaders who do peer-to-peer programs, known as speaker events, in the United States, to articulate our mechanism of action directly to their peers in a scientific environment. We have digital education for physicians, patients, and caregivers. And, we have a sample program, which for a new product is important for both physicians and patients to ensure the patient can tolerate the medication before they fill their prescription.

Direct to patient education-empowering people affected by Parkinson's disease

*"It has to be patient-led in order to get a change in treatment. Neurologists don't offer treatment switch, **it's up to the patient to ask.**"*

- Neurologist



Source: Final Mile Consulting. (2017). DRIVE – Research to understand the Behavioural Drivers and the Subconscious Influences of Treatment Decisions in Parkinson's Disease. Retrieved from https://ucb-cms.krankikom.de/up/ucb_com_patients/documents/DRIVE%20Report%20EXT%20use-GCCApproved%20as%20HQ-1017-NU-0079-04DEC2017.pdf.

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Direct-to-patient education is central. If you look at the quote on the left-hand side here, it has to be patient-led in order to get a change in treatment. Neurologists don't offer treatment switches. It's up to the patients to ask.

In the United States, there is a very well-established patient advocacy foundation, and patients advocate for themselves. They go in and they tell the neurologists how they feel and that they want to feel better. We want to ensure that they understand Nourianz, they understand our mechanism of action, and that they advocate for themselves when they talk to their neurologists.

We're also working closely with the patient advocacy groups that you see on the right-hand part of the slide. These groups are a trusted source to patients. They don't promote for us, but they do help educate patients on options that are there and help patients advocate for themselves with their neurologists.

Wide Coverage of NOURIANZ™ news

*"In my clinical practice, I see patients who experience the troublesome effects of Parkinson's disease and 'off' episodes that interfere with activities of daily living. **NOURIANZ represents an important milestone** – providing U.S. patients and their caregivers with a nondopaminergic, once-a-day oral treatment option to significantly decrease the amount of 'off' time."*

Peter A. LeWitt, M.D.,
Professor of Neurology, Wayne State University School of Medicine and Director,
Parkinson's Disease and Movement Disorders Program, Henry Ford Hospital.

Press releases received **72M** total impressions and **412** NOURIANZ mentions on social media

*"Options such as NOURIANZ are a step forward in treating 'off' episodes... **We encourage patients to speak with their healthcare providers** if they are experiencing 'off' episodes."*

Rachel Dolhun, M.D.,
Vice President, Medical Communications at The Michael J. Fox Foundation.

We're quite optimistic about the reception that Nourianz received upon its approval and subsequent announcement of its availability. Here, we have quotes from Dr. Peter LeWitt, a well-recognized key opinion leader in the United States, as well as from the Michael J. Fox Foundation, recognizing that Nourianz is a breakthrough for patients.

This is an innovation because it's one of the first new mechanisms of action in Parkinson's disease in a number of decades, and it's something that we're very proud of and that patients and physicians are very excited about.

Summary

- **US PD market is competitive, however NOURIANZ provides a novel MOA**
- **Launch readiness activity was robust and well executed, providing foundation for launch**
- **KOL support will continue to grow with clinical experience**
- **Field teams are built, trained and now calling on physicians**
- **Patient education initiatives are being executed**
- **Negotiations with key payers are ongoing**

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In summary, we do have a competitive market in the United States. However, Nourianz provides a novel MOA that allows us to differentiate ourselves. Our launch readiness activity was robust, well-executed, and provides a strong foundation for launch.

Our KOL support is strong, but it will continue to grow as they gain clinical experience in the market, and as more and more physicians attend speaker events led by our faculty.

Our field teams are built, trained, and now calling on physicians. Many of the sales representatives that we hire come with previous Parkinson's experience, as well as extensive central nervous system sales experience.

Our patient education initiatives are being executed, we are attending patient events, and negotiations with key payors are ongoing.

Thank you very much, and I look forward to your questions.

Moderator: Thank you, Len. Now, I would like to invite Dr. Mitsuo Satoh to give you an update of the KW-6356. Please give us a moment to switch the presentation.

Satoh: I, Satoh, would like to present on the update on KW-6356. This is a next-generation of Istradefylline that's in development, and I would like to introduce it.

Here's the background information.

Background Information

- KW-6356 is a next generation of A_{2A} receptor antagonist. It was selected through Kyowa Kirin's drug discovery platform for Parkinson's disease (PD) therapy. This compound has many attractive and favorable profiles, leading expectation to bring much more clinical benefits through non-dopaminergic mode of action.
- KW-6356 showed good anti-parkinsonian activities in MPTP-treated common marmosets, either with or without adjunct L-DOPA treatment.
- In a Phase 1 study (6356-001), KW-6356 showed favorable safety and pharmacokinetics profiles in healthy Japanese subjects.
- A Phase 2a study (6356-002) with early PD patients as monotherapy has been completed with positive outcomes.
- We are conducting a dose finding study in PD patients under L-DOPA therapy (Phase 2b), and its future development plan will be also discussed.

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As many of you may know, we had failed in a way with regard to Istradefylline's approval process in the US, I mean, in terms of gaining the significance in the Phase III study, but our stance then was that we didn't think of giving up. In the Phase III study in the US, we enrolled the kinds of subjects who couldn't control "off" time, that is period the dopaminergic drug doesn't work well. When an A_{2A} receptor antagonist (Istradefylline) was administered, off-time seemed to be controlled. That's why we have never given up.

We had some challenges of getting the significant superiority in terms of statistics. However, we believed that there was significance in the launching of this novel MOA product.

As a result, we continued on with the negotiation with the FDA, and then this October, we have managed to launch the product.

A_{2A} receptor antagonist is only one product approved globally, which is istradefylline. So, what we are preparing is the next-generation drug candidate, which is KW-6356. Today I'd like to introduce the differences between those two items.

There are some key points listed here on the slide. For example, there is one thing I would like to note.

Istradefylline is the drug that can shorten the "off" time by being adjunctively used with dopaminergic drugs. Actually, we conducted the clinical study of Istradefylline to see the efficacy as a monotherapy for early-phase PD patients, but we could not come up with a good result clearly. However, it seems KW-6356 has an efficacy as a monotherapy. That is a major difference we have.

As a compound how is it different? For example, in terms of affinity as an A_{2A} receptor antagonists, it is over 100 times as potent. In terms of selectivity, it's 10-fold more potent.

However, assuming these potency differences give impact to the quality of pharmacologic efficacy, then, you may think if istradefylline is provided in higher doses, it should be the same. However, this KW-6356 potentially has inverse activities, that not only antagonize for adenosine, but it can decrease antagonizing activities of receptors. In that sense, it's different from istradefylline. So, we can expect a potent efficacy with the KW-6356.

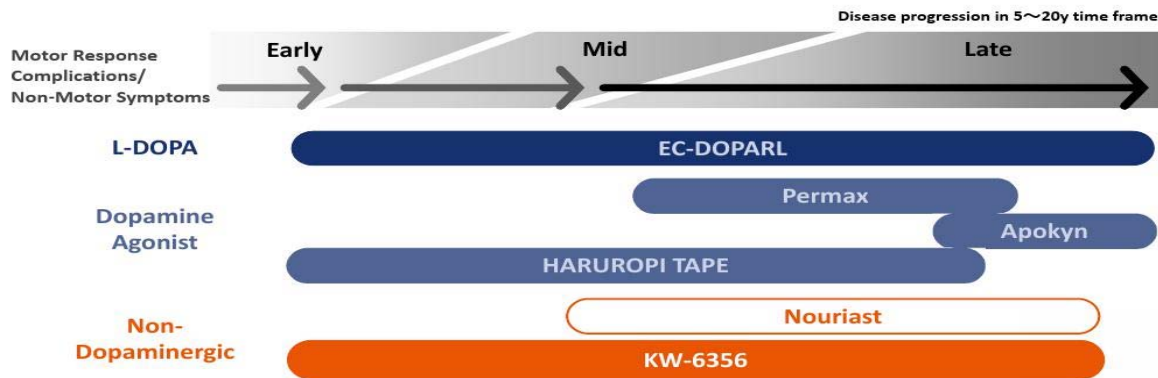
As listed here as one of the facts, we do have non-clinical data that KW-6356 showed good activities in the marmoset model, either with or without the adjunct L-DOPA treatment therapy.

For Phase I, we confirmed the safety, and in Phase IIa, it has been completed with a positive outcome in terms of efficacy as a monotherapy. Currently, we are ongoing with Phase IIb as a dose-finding study under L-DOPA therapy. That's what we are studying at the moment.

Target Product Profile of KW-6356

KW-6356 is expected to bring new treatment options and clinical benefits

- to improve motor symptoms, and potentially non-motor symptoms and disease modification
- for broader target patients (from early to late stage as both monotherapy and adjunct therapy)
- with safer profile through non-dopaminergic mode of action



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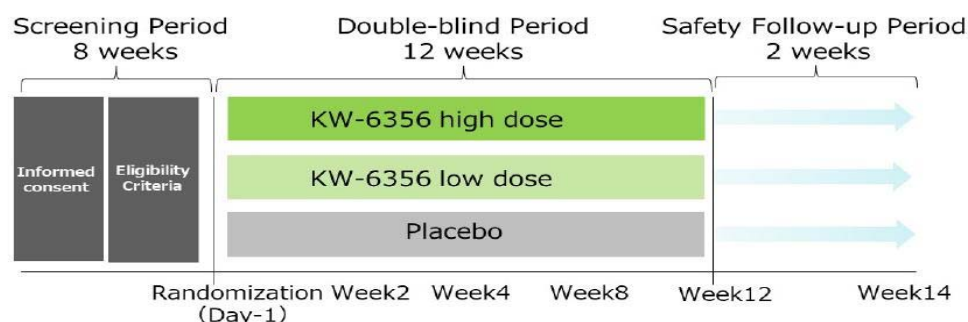
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Here is the range of the coverage. Istradefylline is for the later phase of Parkinson's disease patients. It's used as adjunct therapy, but the 6356, it can be effective for early monotherapy stage of PD patients. If the progress of Parkinson's disease can be delayed by 6356, that can be expressed as a disease modifier, and if we could do that, it's going to be an epic-making medication to Parkinson's disease patients.

Phase 2a Study Design (6356-002)

NCT02939391

Study design	Double-Blind, Placebo-Controlled, Randomized, Parallel-Group, Multicenter study
Target	early Parkinson's disease patients
Treatment	KW-6356 Low dose, High dose or placebo for 12 weeks once a day, p.o. Planned 50 pts/arm, total 150 pts (Actual enrollment: 168 pts)
Primary endpoint	Change from baseline to Week 12 in the MDS-UPDRS part III score
Secondary endpoint	MDS-UPDRS part I ~ IV, CGI-I, PGI-I, PDQ-39



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Next is the design of Phase IIa study. We conducted this as a monotherapy study for early Parkinson's disease patients with motor dysfunctions observed, and here is the regimen.

There are two doses: low-dose and high-dose. In Phase I, we investigated the antagonization ratios in A2A receptors. We set dosage of this PIIb based on the sense it is likely to provide a good inhibition effect even with the low dose, and after 12 weeks, we monitored and observed the motor functions. More specifically, we have utilized the MDS-UPDRS as a scale, as a primary endpoint.

Subjects Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Subject meets the UK Parkinson's Disease Society brain bank clinical diagnostic criteria
- PD stages 1 to 3 on the Modified Hoehn and Yahr Scale
- MDS-UPDRS part III score of ≥ 15

Key Exclusion Criteria

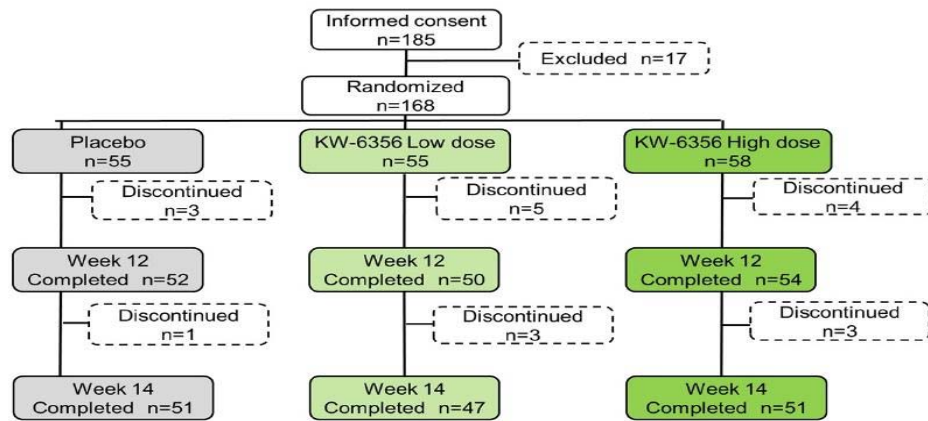
- Use of any CYP3A4/5-related drugs within 2 weeks prior to randomization (Day-1).
- Use of any of the specified anti-parkinsonian drugs and dopamine antagonists during the specified period.
- Treatment with levodopa/DCI at any time in the past for a period of 4 weeks or more.
- Neurosurgical operation for Parkinson's disease (stereotactic surgery, deep brain stimulation or gamma knife), or treatment by TMS.

As mentioned earlier, all included subjects had motor dysfunctions with the MDS-UPDRS part III of over 15.

Next is exclusion criteria. KW-6356 is a compound related to the metabolism of CYP3A4, therefore we have set the criteria based on it.

Enrollment and Rates of Study Completion

- Of 185 subjects screened, 168 subjects were randomized; 55, 55, and 58 subjects were assigned to treatment with placebo, KW-6356 low dose, and KW-6356 high dose, respectively.
- Study completion rates were high (around 90%) across the treatment arms.



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And, here's the enrollment situation. For each arm, we enrolled about 50 cases, and we randomized evenly. During the following 12-week treatment and 2-week follow up, we did not see any skewed data as for the dropout rate.

Baseline Characteristics

- The demographic and baseline characteristics of the subjects were generally well balanced among the three treatment groups.

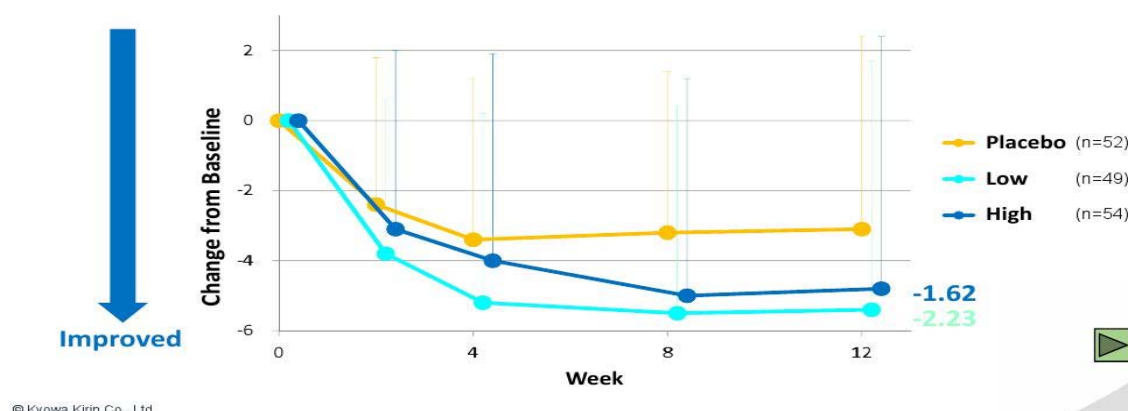
	Placebo N = 55	KW-6356 low dose N = 55	KW-6356 high dose N = 58
Age, years; mean (SD)	66.6(8.0)	67.2(10.0)	65.9(9.2)
>=65 years, n (%)	40 (72.7)	38 (69.1)	40 (69.0)
Male gender, n (%)	34 (61.8)	29 (52.7)	26 (44.8)
Duration of PD, <=6, n (%)	46 (83.6)	47 (85.5)	46 (79.3)
Modified Hoehn and Yahr Scale; mean (SD)	2.17(0.46)	2.19(0.52)	2.11(0.51)
MDS-UPDRS Part I; mean (SD)	4.9(3.4)	5.6(3.9)	4.5(3.0)
MDS-UPDRS Part II; mean (SD)	6.6(4.4)	6.4(4.5)	5.5(4.7)
MDS-UPDRS Part III; mean (SD)	27.6(9.5)	29.7(9.7)	28.3(10.6)
PDQ-39 total score; mean (SD)	15.7(13.5)	19.0(18.7)	15.3(17.4)

Here's the demography. As you can see, for each arm, there were no significant differences. in terms of motor dysfunctions, there were similar baseline characteristics in each group.

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Primary Outcomes: MDS-UPDRS part III

- The LS mean changes from baseline in MDS-UPDRS part III were -4.76 (95% CI, -6.55 to -2.96) for high dose, -5.37 (95% CI, -7.25 to -3.48) for low dose, and -3.14 (95% CI, -4.97 to -1.30) for placebo.
- Both of the KW-6356 groups showed a greater reduction in the primary outcome measure than placebo throughout 12-week study period.



Here are the primary outcomes of the MDS-UPDRS part III data.

As for both low and high-dose arms, we can see the trend of improvement of motor function compared to placebo.

For the reference of the improvement level, I would like to show one example. Rasagiline was approved for early-stage Parkinson's disease in 2018. How much improvement do you think Rasagiline achieved in the study? It's minus four to minus six, in absolute values.

We had higher response in placebo arm in our study, but our product had certainly shown kind of efficacy. The design of the study is not to gain the statistical significance. So this is the study to see a trend or tendency.

A similar study was conducted with istradefylline, but we didn't reach a good outcome.

Safety : KW-6356 was safe and well-tolerated

- Overall rate of TEAEs were similar across the study treatment groups.
- The most common TEAE was nasopharyngitis (7.3% for placebo, 7.3% for low dose, and 8.6% for high dose), none of which were considered to be related to the KW-6356.
- The incidences of drug-related TEAEs for placebo, KW-6356 low dose and KW-6356 high dose were 29.1%, 34.5%, and 27.6%, respectively.
- A total of three serious adverse events occurred in three subjects receiving KW-6356 low dose (three events; rhabdomyolysis ,cerebral hemorrhage and pneumonia, each occurred once). Of these events, causality of rhabdomyolysis and cerebral hemorrhage to KW-6356 was considered to be unknown, and pneumonia was judged not to be drug-related.
- No clinically meaningful changes in vital signs, body weight, laboratory results, or ECGs.

Event	Placebo N=55		Low dose N=55		High dose N=58	
	n	(%)	n	(%)	n	(%)
Subjects with any TEAE	24	(43.6%)	26	(47.3%)	29	(50.0%)
Nasopharyngitis	4	(7.3%)	4	(7.3%)	5	(8.6%)
Constipation	1	(1.8%)	4	(7.3%)	6	(10.3%)
Nausea	1	(1.8%)	0	(0.0%)	3	(5.2%)

TEAEs reported by 5% or more of subjects by preferred term — Safety Analysis Set

As for safety, as you can see on the slide, constipation was seen a few more in KW-6356 compared to placebo. But in total, we judged that there were no big safety issues.

Summary of Phase 2a study

- KW-6356 was safe and well-tolerated during 12-week treatment.
- The clinical efficacy* of KW-6356 was confirmed in early Parkinson's disease as monotherapy.
- The results of this study suggest that KW-6356 improves motor symptoms in early Parkinson's disease.

*Patients under KW-6356 (low or high dose) treatment consistently showed the lower scores of MDS-UPDRS II, III, and II+III than placebo throughout the study period (12 weeks). Means for "Δ MDS-UPDRS II" and "Δ MDS-UPDRS II+III" of KW-6356 (low dose) and their 95% CI were - 1.32 (-2.57, -0.07) and -3.53 (-6.64, -0.43), respectively.

These are the summary of the Phase IIa study. In 12 weeks of treatment, safety and toleration were observed. In terms of efficacy, we felt it was efficacious enough as MAO inhibitors. Since it was used as a monotherapy, we expect that it can be applied for a broad range of patients and expand the market opportunity of this A2A inhibitor.

Future Direction

- Phase 2b study to evaluate efficacy and safety of KW-6356 as adjunctive therapy with L-DOPA is ongoing, in parallel with clinical pharmacology studies required for Phase 3 program.
- Options for global development are under evaluation, depending on outcomes from the ongoing studies.

NCT03703570

Objectives	To evaluate the efficacy of KW-6356 and confirm clinically recommended dosage for Parkinson's disease patients (with/without wearing off) being treated with levodopa by comparing the change in MDS-UPDRS Part III score to the placebo group.
# of patients	Total 486 pts (162 pts/arm)
Primary endpoint	Change from baseline in the MDS-UPDRS part III score
Key Secondary endpoint	Change from baseline in the total hours of awake time per day spent in the OFF state



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Looking towards the future, at the moment, we are conducting a dose-finding study as a Phase IIb study. This is a combination therapy with L-DOPA. In each arm of the placebo, low-dose, and high-dose, there are 162 patients. The treatment period is 26-week.

For KW-6356, study updates are as I presented. There is only one drug with A2A antagonist MOA globally, which is istradefylline, and a high efficacy can be expected of KW-6356. We are undergoing this study, and we would like to deliver this product to Parkinson's disease patients around the globe.

This concludes my presentation.

Question & Answer

Moderator: Thank you very much. We would like to answer any questions from the floor.

Yamaguchi: I am Yamaguchi from Citigroup. The first question is on the marketing. Nourianz has been approved in the condition with no successful clinical study in the US, and for the KOLs, I guess they have probably felt no enough clinical experience on this drug. I know other products in the market, which have similar issue and feel difficulties in marketing. Do you think that is also the truth for Nourianz? –The second one is about KW-6356. Dr. Satoh mentioned the probability of inverse agonist activities of this drug. Do you expect that this drug can control the dopamine's range by this inverse agonist activity?

Moderator: Len will address the first question.

Paolillo: Can the translator please repeat the first question? Sorry.

Translator: Because the clinical study was not successful conducted in the US, doctors don't have enough experience using it – the physicians. That may have some kind of repercussions. We see similar products like that in the market. Are there any opinions about it?

Paolillo: Thank you. So, two of the trials in the US, with the FDA label from North America, were conducted in the United States, and there are many KOLs that remember that experience on the trial. There was also the 6002-014 trial that was conducted in the United States, which missed its primary endpoint. However, anecdotal feedback from KOLs has been that they had positive experience with their patients during that trial. Whereas the lead up to launch was not what you would call "traditional," in the sense that you had a large Phase III trial with a readout, active investigators going into commercialization, there was still a lot of interest in seeing a new mechanism of action come to the market. There was still a base of key opinion leaders who have had experience with istradefylline in clinical practice through the clinical trials, and they were excited to speak to other physicians about it.

Satoh: Thank you very much. With the KW-6356 and the istradefylline, what was the difference between these two? We have some difference between the two, but how it is going to be linked through the efficacy? It is not just the symptom basis, the outcome basis, on it. We have different frameworks, and there is a difference. There is the fact that the monotherapies' outcome was different, especially for these two. There is the part that we are expecting a lot for the wider indications of this KW-6356.

Hashiguchi: This is Hashiguchi from Daiwa Securities. I have questions about the marketing and also about the development. I have one question for each. How is it proceeding with the payors' negotiations for istradefylline in the US? And is it going to contribute to the uptick of Kyowa Kirin as a whole from the early timing of next year, or you are just accumulating experience at the moment? Is it going to be slowly penetrated in a market and fostered, or developed, to become a bigger product? Please share your perspective or outlook.

The second question is about the KW-6356 and its efficacy as a monotherapy, but I didn't quite understand the reason for that. Sorry for my lack of understanding. Just because it's potent, it works as a monotherapy? or it's not just about the potency of the product, but are there any other reasons? I'd like to know.

Paolillo: Thank you very much. So, our progress with payors is on track as we expected. We have done what's called a clinical presentation with the most significant payors in the United States. There are eight that we classify as a Tier 1 payor. They have influence over the majority of the lives in the United States. We've done a clinical presentation for them, as well as what's called a budget impact model presentation,

where we share with them how utilization of Nourianz by their plan would impact them financially. Since then, we've been in what's called a bidding process, where we submit contracts with the payors and begin negotiations. It's still in the early days of that process.

Overall, the Medicare and commercial are on two different schedules. Given the time of year that we are in, and when Nourianz was approved, the bids that were going out from Medicare payors right now are for 2021. That does not mean that we cannot secure coverage in 2020. It just means that the bids that we are receiving now are for 2021; whereas, the commercial plans are in a much tighter timeline. It's hard to say exactly specific timepoints when we would have "coverage" because it is a fragmented market where you have a number of different payors. So whereas we may be gaining coverage on payors further down the line.

If I could understand your question regarding the uptake of Nourianz, and whether it will contribute to Kyowa Kirin in 2020, it will certainly contribute to Kyowa Kirin in 2020. However, we don't at this point disclose what the forecast is or what our expectations are for sales.

Satoh: Istradefylline and KW-6356, the difference between those two — is it just potency? That's something actually I don't know myself. Looking at the clinical study results, the istradefylline as a monotherapy study we have conducted in the past, but we didn't achieve the same results. That's the fact. However, with the KW-6356, we do have an expectation. Affinity and selectivity binding to receptors can be different. But we need to see the clinical data to prove the difference between two drugs and that's the only way to prove the value of these products. So, with istradefylline, we had been pursuing many things to prove the value of it. So far, the results we gained with the KW-6356 look more promising as a monotherapy. That's how we understand, so please understand that way too.

Tanaka: This is Tanaka from Mizuho Securities. I have two questions. For the pricing, the 50 dollars-per-day, compared to the other brand products for Parkinson's disease, it is relatively higher pricing. In the presentations, it is already the generic product-centered market in the US. That is quite different from Japan. Do you think that still the 50 dollars-per-day would be acceptable? And also, the prescriptions data is not available. It is blocked. Are there any reasons you are not disclosing it to the competitors?

The second question is with the KW-6356. If Phase IIb is successful as assumed, are you going to have Phase III for both types of the models, monotherapy as well as the combination?

Paolillo: Thank you very much. Regarding the price of Nourianz at 50 dollars a day, it is not the most expensive product in the PD market. In fact, it's priced in line with recently approved branded products. We feel it's priced in line, even though it is an innovator and it is a new mechanism of action. Regarding the highly genericized market, it is a genericized market. However, when physicians and patients are looking to make a choice in what products they take, they evaluate the differences between the brands and the generic. As I went through some of the different mechanisms of action that are available for patients, there are generic MAO-B inhibitors and there are branded MAO-B inhibitors. There are generic dopamine agonists, and there are branded dopamine agonists. For out-of-pocket costs for patients, what they have to pay at the pharmacy, can vary greatly between a brand and a generic. If they're both the same mechanism of action, very often a payor is going to drive the patient in that direction, and the patient with the money they need to spend is going to choose to go in that direction. Having a unique mechanism of action that is not available in a generic differentiates us, our price is in line with the more recent Parkinson's launches, and we feel that we're well-positioned to achieve our goals with that price.

Regarding the data being blocked, you are correct. It was to hide that, particularly at launch, from our competitors, as we both contract with payors, and as we penetrate the market.

Satoh: With the KW-6356 and the Phase II and onwards, our strategy of clinical studies has not been decided yet, but as a background, we need to consider the patent expirations in the Japanese market. Our

istradefylline has the label of adjunctive therapy with the dopaminergic products. We need to protect this market segment first. Then, with the monotherapy segment, if the label expansion is possible for such indication, this would be a very good product to be used by the doctors and patients. Once we get the results of the Phase IIb, we would like to have another discussion.

Tanaka: For the Nourianz patent period, is it until 2026 in Japan? And then, if a five-year extension is possible, then in the US, it would be 2028. Is this the correct understanding?

Satoh: I don't remember the details about the date. If we can extend, yes, in the US, it is possible. At what point, what developmental strategies we are going to make should also be decided based on the protection period in the U.S.

Sakai: This is Sakai from Crédit Suisse. I'd like to ask you for general information about Parkinson's disease. There is no radical cure product, and even in the future, it's difficult to expect that curable treatment would be launched. The challenge with physicians, the wearing off, and the dyskinesia, is how to reduce that, how to control that. And if you develop KW-6356 as a monotherapy, you need to have a longer term of data, three, four, five years of data? I think that's the timeline of the onset of wearing off and dyskinesia.

And the FDA, do they have any new benchmarks? For example, for Nourianz approval, if they were to say maybe they were lenient when handling the application or I'm not sure. But based on the Nourianz approval, what is your stance, and what is your approach and for the future development of this product?

Satoh: Actually, we did not meet the primary endpoint in the last Phase III, that's true. For the later phase PD patients, like you said, they have challenges of the wearing off and the dyskinesia. It can be controllable with dopaminergics at first, but then those symptoms become poor-controlled. Whether they can shorten the time of those symptoms among those patients is the value of the products. That's the index for evaluation, and I don't think that's going to change. With the A2A antagonist, istradefylline, because it has a good prospect or possibility, that's why it was approved by the FDA.

For monotherapy, for the earlier stage, it can be controlled by the dopamine. Of course, in cases when dosage with limitations is there. With the A2A monotherapy for the earlier stage, the index would be the same. Symptoms, dyskinesia, can be controlled or not. For the later phase patients with dopamine, they have wearing off and dyskinesia, and for the later stage, it can be measured by those indices. If it can control wearing off and dyskinesia. With Parkinson's disease medications, the evaluation index is consistent.

Sakai: Thank you. Can I ask you another question? I believe Len, you presented in your slides the 6,400 prescribers that you introduced on page 10. I think they prescribe 85% of the branded prescriptions. In other words, in the US, for PD medication prescribers, how many in total are there? I think there are so many who prescribe the generics, but 6,400 of them, they are prescribing branded products. Does this data indicate that? Please elaborate.

Paolillo: Thank you. If I understand the question correctly, there are more physicians that write just generics. Interestingly enough, many of the physicians that write only generic are also what's called a lower decile, meaning they don't see as many patients. There are approximately 500 movement disorder specialists in the United States that are really the epicenter of Parkinson's treatment for patients, and you'll find that in those facilities, and under the guidance of those physicians, there's far more patients under management, and there's far more utilization of brands. Whereas we don't necessarily proactively target physicians that are writing nothing but generic, those physicians are often not seeing as many patients. We feel we cover a very good portion of the addressable market.

Sakai: Do you have the exact numbers of the actual target out of 6,400 physicians? How many of them are actually your target?

Paolillo: All 6,400 are our targets. There are more than 6,400 physicians that prescribe Parkinson's disease medications. That number is our target number.

Kotani: Kotani of Nomura Securities. I have two questions. With Nourianz, the clinical studies were successful but the sales don't look so good. In the US, Phase III was not successful, and probably, we would not expect it to be a great success in the market. Probably, there are certain patients treated with four or more drugs, and they could be the target. I think 10 billion yen of sales in Japan is moderate, but in the US, do you think more sales are expected? Maybe due to the market difference, that would make a difference? Do you have any reason to believe that it would be also successful in the US?

Paolillo: We certainly believe that it will be successful in the US. If I can contextualize some of the question, there was a failed Phase III trial. However, there is still a lot of excitement and optimism around having Nourianz approved. The majority of physicians look at that FDA approval as the gold seal, that this is an effective product that I could prescribe. In terms of comparing it to the sales in Japan, at this point, we're not going to discuss our long-term forecasts. But we are confident in the success of Nourianz in the United States.

Kotani: With KW-6356, we can expect a lot from this. According to the data now, patients with L-DOPA are expected to experience wearing off and if we use 6356 as a monotherapy, it will delay the symptom onset. I think that there will be great demand for this product, when it comes around. And Phase IIb, probably you don't have to wait for the outcome. You should start Phase III. And also, you have used the word "disease modifying," with the PD drug. I think that the cells that produce the dopamine, substantia nigra, are dying with PD patients. In the pre-clinical studies those cells' survival was confirmed by this drug? Or aggregation of alpha-synuclein protein was reduced? Is such kind of information disclosable?

Satoh: Thank you very much for your questions. As for the information of the non-clinical studies, I need to confirm with our researchers before talking about it.. I'm not sure whether we can prove those effects by using PD animal models in the laboratory. Let me confirm things afterward, and we will discuss it at a later time.

As for the disease modifying impact, if we are to have this as a monotherapy, instead of using L-Dopa first, then that wearing off over time, or the timing could be reduced and also probably put off, that would be great. That is what we would like to see with the KW-6356. But with the Japanese market, with the istradefylline, patent expirations have to also be considered. We have much experience about developing adjunctive therapies in this area. We know much about it. So, we conducted a dosage finding study first with the adjunctive. We need to define entire clinical study design and strategy about the next Phase III and onward.

Muraoka: This is Muraoka from Morgan Stanley. For KW-6356, I have two questions. One is about what is shown on the last slide, Phase IIb's design. For 26 weeks, that's for MDS-UPDRS, and if you achieve a good result, the Phase III would be the same design, referring to the other products' Phase III. I think that's what's going to happen. If the Phase IIb's results are good, and Phase III results will be good. Is that the right understanding? This is my first question.

The other question is that KW-6356, let's say it's a good product. Is it possible to apply it for other diseases other than Parkinson's disease? I believe it's just on the ideation phase but could you give us a hint if possible.

Satoh: To respond to your question, if the Phase IIb result is good, then is the Phase III going to be a bigger study? I think it depends on the result. In this dose finding study of the combination therapies, we need to find the appropriate dose selection. And for the A2A antagonists, other companies developed them as well (for PD). But these competitors struggled in development A2A. With the istradefylline, we struggled as well

to develop this far. But we strongly feel that A2As are different in terms of pharmacology compared to the dopaminergic. The monotherapy and the combination therapy, what to do with the pivotal study, we need to make a good judgment after the Phase IIb, and then, we can talk about it in the future.

In terms of indication expansion, we do have some ideas, including from KOLs. First of all, with Parkinson's disease, monotherapy would be the focus. That's an area with much unmet needs. We need to pursue that possibility. In the meantime, there are so many different ideas, but we haven't come to a conclusion. I would like to refrain from disclosing any specific indications, but we do have some ideas in mind.

Muraoka: The indication meaning in neurology, probably? Is that the right understanding?

Satoh: Yes.

Muraoka: Okay, thank you.

Wakao: This is Wakao from Mitsubishi UFJ Morgan. I have a question about the KW-6356. For example, the Mitsubishi Tanabe's ND0612, ABBV-951 of AbbVie, they are also under development. If these drugs come to the market, what will the positioning of your drug among those types of the products?

According to what you have described, the new MOA is the requirement, there are unmet needs. But if such kind of new dopaminergic products become available, I think patients just switch from old dopaminergic to new one. If every new dopaminergic product is launched, what would happen?

Satoh: L-DOPA's controls in the blood was also the target of the development and research activity, and wearing off time control is the endpoint. I think with the different MOA, different types of products might be necessary, and that is what we felt in R&D activities. Of course, with L-DOPA, the related products would be also available in the future with the new product profiles, but with the new MOA, I think that we will be able to bring the benefit to the patients with the KW-6356.

Moderator: This is going to be the last question. Anyone?

Mizuno: This is Mizuno from Tokio Marine Asset Management. I have two questions. The first question is, with the existing prescription for PD, is it possible to distinguish from the primary care to the specialists? What's the portion of primary care physicians? What I want to ask is that, with the new mode of action, I thought it might be more difficult for primary care physicians to accept a new mode of action. So, that's why.

The second question is about, you might have talked about it, but how is KW-6356 more efficacious? Is it because it's more highly selective to A2A? You said you are considering the indication expansion in neurology area basically. But there could be any other areas that other companies are interested in developing your product. Is it possible to license it out to other companies for other therapeutic carriers?

Paolillo: The overwhelming majority of our targets are neurologists. In the United States, the data is available that allows us to distinguish between the specialty of the different physicians. That being said, when we do our targeting exercises, we see the profile, the prescribing profile, of neurologists. If there is a physician that has a primary care specialty but is in a rural area and there aren't neurologists there, we may still call on that physician because they have the profile and the prescribing habits that are similar to a neurologist. So, we can differentiate. We do differentiate. I do agree that, especially for new mechanisms of action, you want to go to movement disorder specialists first and neurologists, and once they have a clear understanding, you could use those specialists to help educate the primary care physicians who oftentimes are caring for PD patients for other ailments.

Satoh: Thank you for your question. How is the KW-6356 different is your question? As I explained, for in vitro, the potency is 100-fold and its selectivity is 10-fold and the possibility of the inverse agonist activation,

based on the in vitro studies, we can see those. But that kind of profiling, when we administer to humans as a treatment, what's going to be responding is different and difficult to show clearly. To explain the reason for clinical response difference between istradefylline and KW-6356 is quite difficult at present.

Let's say we get an approval of KW-6356, and then, working along with those clinicians, we need to spend a lot of time to see the exact relationship of the (type of) A2A antagonist with the Parkinson's disease to be able to provide authentic explanation. But for us, with the in vitro basis, we have two different characters of A2A antagonists, and they seem to be different (in clinical stage). We see some points of differentiation and we want to develop differently. That's our intention, and I'd like you to understand it that way. With A2A antagonists, with the oncology, well, we are aware of that, as well for the oncology field. For immuno-oncology, it is said that there might be synergies. We are trying to see that in our study as well. But, on our end, we are not really feeling that's very potent in that way. This dyskinesia improvement would be the most efficacious indication, and that's the area we would like to develop first, and that's our strategy.

Moderator: Okay, it's about time. We would like to conclude the explanatory meeting of Nourianz and KW-6356. Thank you very much for gathering to our event. Thank you.

[END]