ONO PHARMACEUTICAL CO., LTD.

R&D Briefing

September 7, 2021

[Number of Speakers]	3	
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Compounds to be presented

Compound	Mechanism	Target indication	Stage
ONO-2910	Schwann cell differentiation promoter	Diabetic polyneuropathy	P2
ONO-2909	Prostaglandin receptor (DP1) antagonist	Narcolepsy	P1
ONO-2808	S1P5 receptor agonist	Neurodegenerative disease	P1
ONO-4578	Prostaglandin receptor (EP4) antagonist	Solid tumor	P1
ONO-2017 (cenobamate)	Voltage-gated sodium currents inhibition/ $GABA_A$ modulation	Epilepsy	Clinical Trial preparation

This slide shows the projects I will be presenting today.

These projects are in Phase I and II. We are going to establish the PoC of these projects, which will support the future of Ono. We are aiming to receive the approvals for these compounds not only in Japan but also in Europe and the US.

The drug at the very bottom is an epilepsy drug, ONO-2017, in-licensed from SK Biopharmaceuticals. I will introduce 4 neurology project including ONO-2017 and 1 oncology project, ONO-4578.

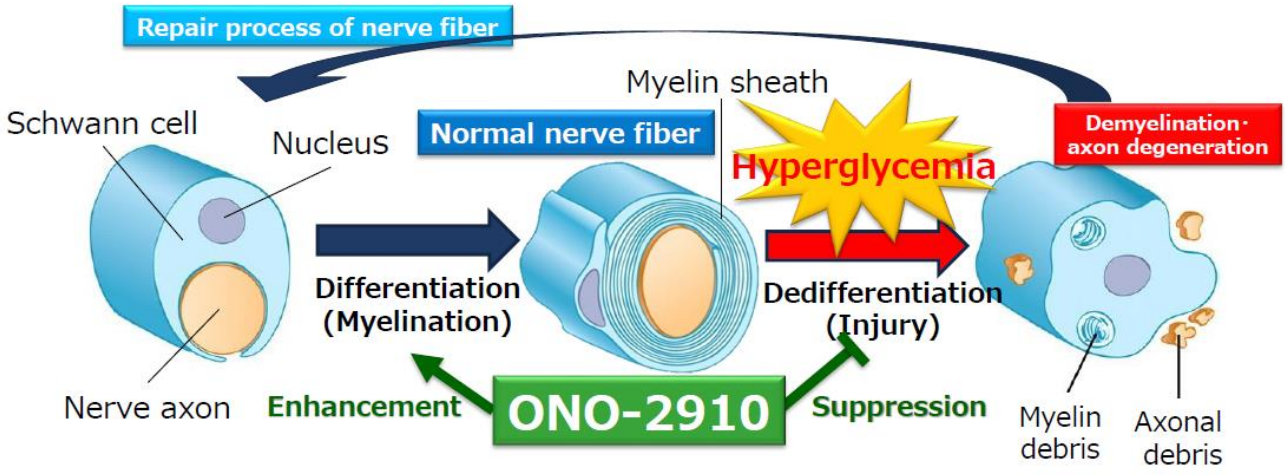
ONO-2910

Compound	ONO-2910
Company	Ono
Mechanism	Schwann cell differentiation promoter
Formulation	Tablet
Indication	Diabetic polyneuropathy
Stage	Phase 2 (Japan)

First of all, ONO-2910.

This is a compound that acts on Schwann cells. Based on the non-clinical study results, we believe that it may restore peripheral nerves injury. We have just started Phase II trial for the treatment of diabetic polyneuropathy.

ONO-2910 Mechanism of Action



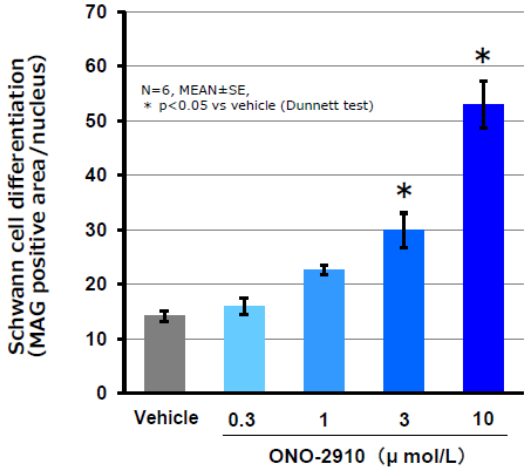
Prepared based on J. Cell Biol. 2008; 181: 575–577

Neurons, specifically nerve cells, axons are surrounded by layers of lipid membrane called myelin. In the case of peripheral nerves, myelin is formed from differentiated Schwann cells. When myelin is damaged by hyperglycemia or chemicals, such as anticancer drugs, it causes dedifferentiation and demyelination. This causes nerve axon degeneration, and is thought to be one of the causes of various neurological disorders.

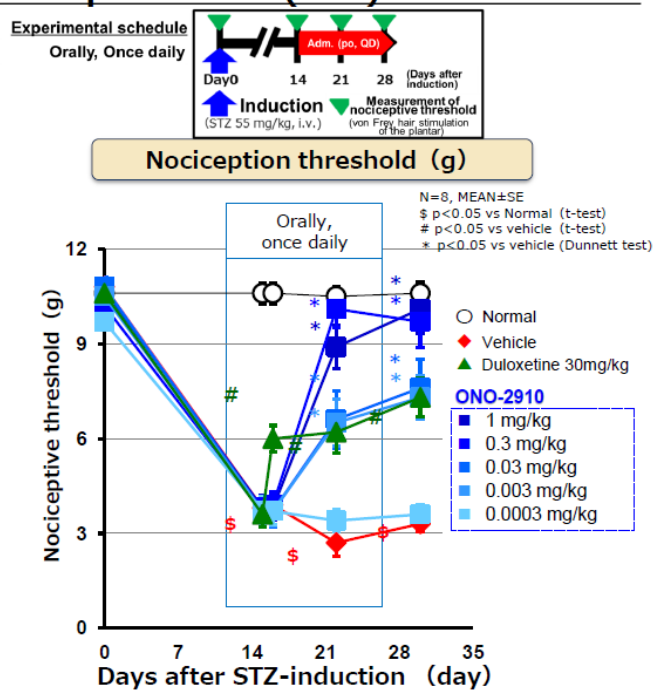
ONO-2910 accelerates the differentiation of Schwann cells into myelin and suppresses dedifferentiation.

ONO-2910 Pharmacological study result

Human Schwann cell



Rat streptozotocin (STZ)induced model



ONO-2910 suppresses pain-related behavior by promoting Schwann cell differentiation.

This shows the results from the non-clinical studies. The left side is the result of in vitro study of human Schwann cells. MAG is a glycoprotein which increases as myelination progresses. It is an index of myelination.

It is thought that ONO-2910 increases the concentration of MAG in a dose-dependent manner and promotes myelination. In addition, although I cannot show you today, a different experiment shows that ONO-2910 suppresses demyelination.

Next, on the right, we measured nociceptive thresholds, using a rat streptozotocin (STZ)-induced diabetes model. When the disease progresses, the nociceptive threshold decreases and rat feels pain with a little stimulus. In this study, ONO-2910 was given at dose range from 0.0003 mg to 1 mg, and duloxetine is used as a positive control.

Duloxetine had a quick onset of effect and superior quick-acting effect.

On the other hand, ONO-2910 showed the improving effect in a dose-dependent manner and maximum effect was superior to positive control. From these results, we expect that ONO-2910 may be a potential radical treatment, but not a symptomatic treatment.

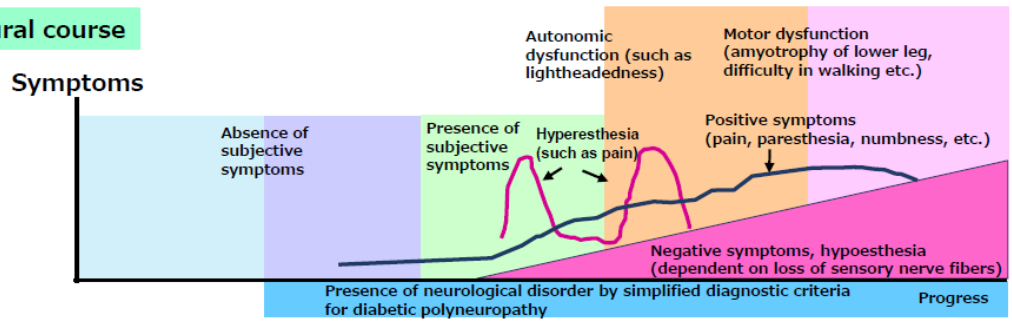
Diabetic Polyneuropathy

Simplified diagnostic criteria

Prerequisite conditions (the following two must be met)
1. Diagnosed as diabetes 2. Neuropathies other than diabetic neuropathy can be excluded
Criteria (any two of the following three must be met)
1. Presence of symptoms considered to be due to diabetic polyneuropathy 2. Decrease or disappearance of bilateral ankle reflex 3. Decreased vibration sensations in bilateral medial malleoli
Note
Subjective symptoms of diabetic polyneuropathy are characterized as: 1. Bilateral 2. Paralysis, pain and paresthesia in the toe and sole 3. Not inclusive of upper limb symptoms alone
Findings of interest (diabetic neuropathy is to be confirmed if one of the following two has been met, despite failure to meet the criteria described above)
1. Abnormal nerve conduction findings on one or more parameters (i.e., conduction velocity, amplitude and latency) in two or more nerves 2. Presence of clinically apparent diabetic autonomic neuropathy (preferably to be confirmed by tests to assess autonomic nerve function)

Japanese Clinical Practice Guideline for Diabetes 2019

Natural course



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A Phase II trial has been started for diabetic polyneuropathy. In diabetic polyneuropathy, bilateral symptoms are observed and characterized by symptoms such as numbness, pain, hypersensibility, paresthesia and so on.

When it comes to hypersensibility such as spontaneous pain, existing drugs such as Pregabalin and Cymbalta, are effective. On the other hand, it is reported that with these treatments, positive symptoms like spontaneous pain, abnormal sensations or numbness tend to remain where we believe that there is an unmet need here. Since ONO-2910 repairs the nerve itself, we expect it to be effective in treating these symptoms as well.

Next is about the number of patients with diabetic polyneuropathy.

It is estimated that there are 10 million patients with diabetes mellitus in Japan in 2016. Among them, it is estimated that 76.6% of patients are receiving treatment, so approximately 7.7 million people are being treated for diabetes.

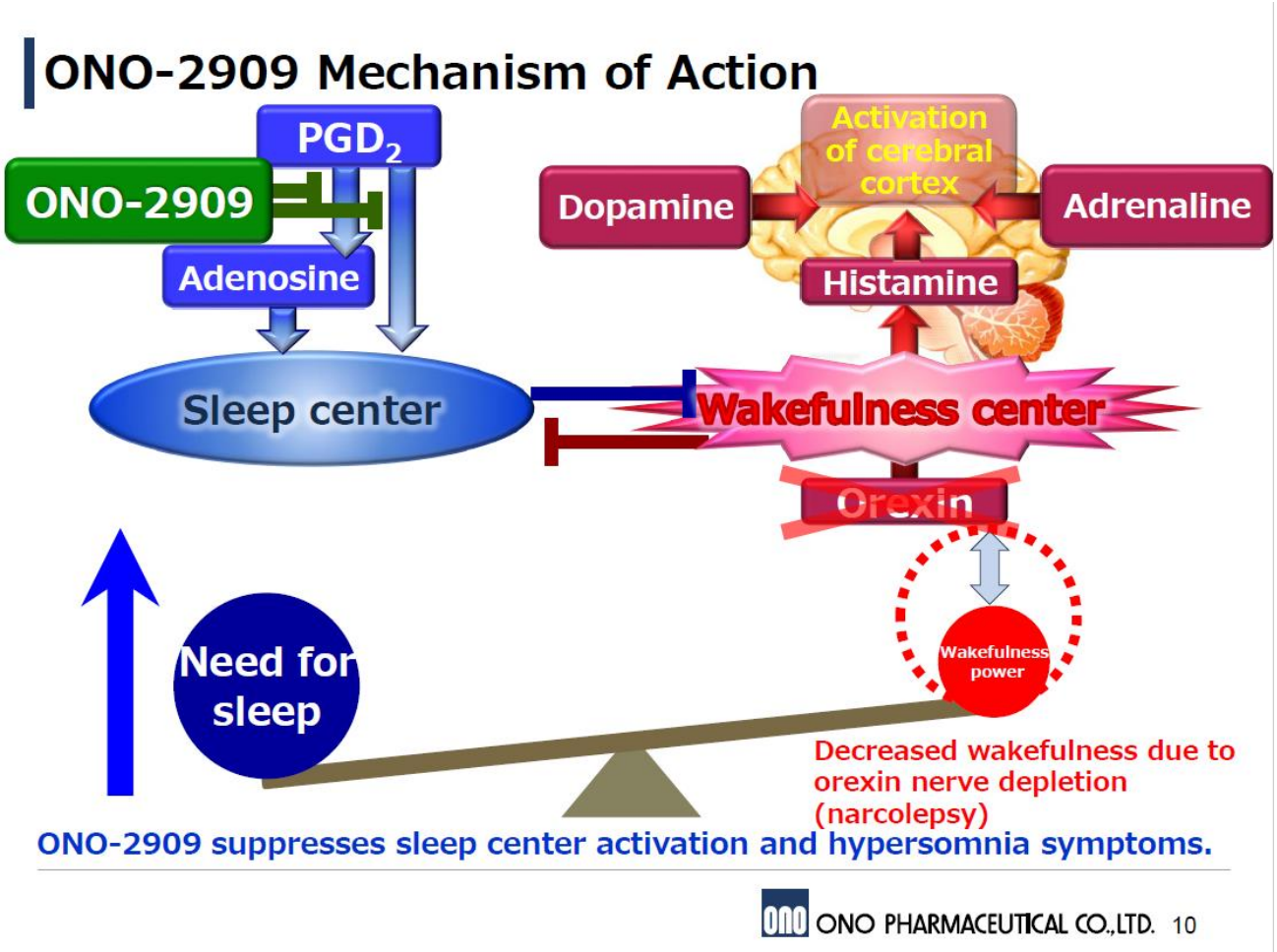
There is data showing that 16.2% of Type 2 diabetes patients are associated with diabetic polyneuropathy. It is estimated that there are over 1.2 million patients with diabetic polyneuropathy or at least about 1 million patients.

ONO-2909

Compound	ONO-2909
Company	Ono
Mechanism	Prostaglandin receptor (DP1) antagonist
Formulation	Tablet
Indication	Narcolepsy
Stage	Phase 1 (Japan)

Next, ONO-2909.

ONO-2909 is a prostaglandin D_2 receptor antagonist, and we are considering development for narcolepsy.



Sleep and wakefulness are thought to be regulated with the balance between the effect of sleep substances such as prostaglandin D_2 and adenosine on the sleep center, and the effect of substances such as orexin, as well as monoamines, eg. dopamine, adrenaline and histamine, etc.

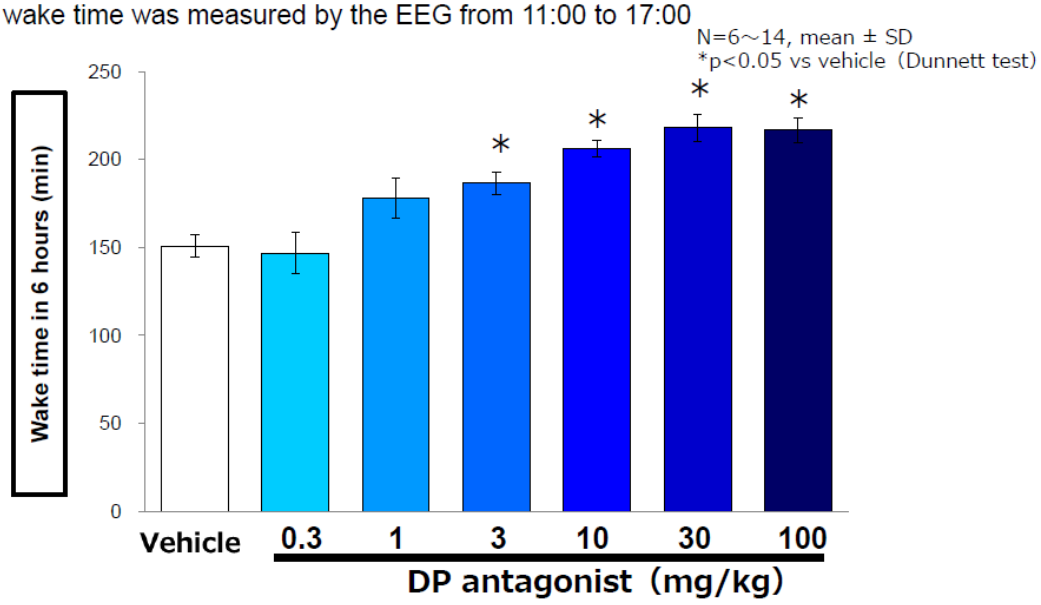
By the way, it is discovered by Dr. Osamu Hayaishi, a pioneer of biochemistry in Japan that prostaglandin D_2 has an effect of inducing sleep. We expect that ONO-2909 suppresses the activation of the sleep center and hypersomnia by blocking the effect of prostaglandin D_2.

On the other hand, research and development focusing on the wakefulness center is also being carried out. By focusing on the sleep center, we expect that ONO-2909 will be a superior drug from the safety viewpoint, considering that it can avoid excitatory side effects, such as insomnia, headache, etc.

DP antagonist (Pharmacological study result 1)

Effect on wake time in normal rats

DP antagonist was administered at 11:00 am, which corresponds to the sleep phase for rodents, and the wake time was measured by the EEG from 11:00 to 17:00



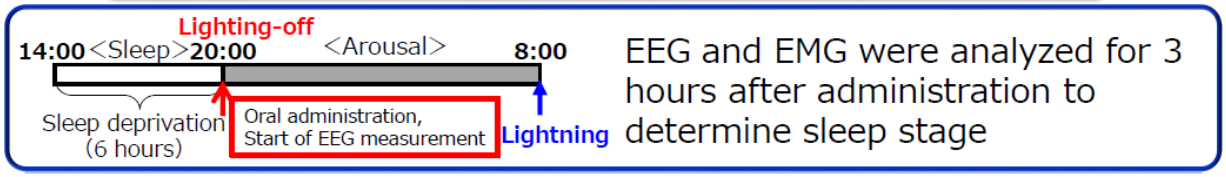
DP antagonist prolonged wake time during rat sleep phase (light period).

Here are the results of animal experiments using DP antagonists.

When a DP antagonist was administered to normal rats, wake time was extended in a dose-dependent manner.

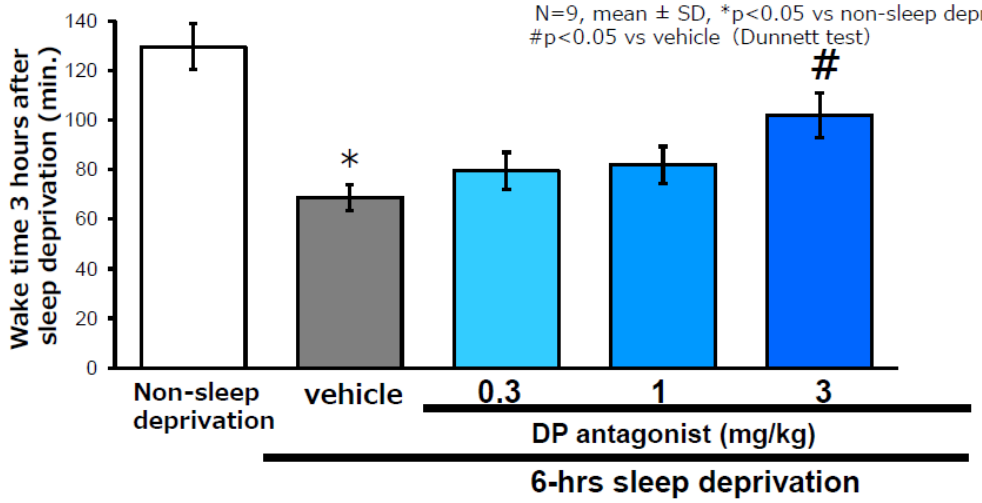
DP antagonist (Pharmacological study result 2)

Effect on wake time in sleep deprivation rats



EEG and EMG were analyzed for 3 hours after administration to determine sleep stage

N=9, mean ± SD, *p<0.05 vs non-sleep deprivation (t-test), #p<0.05 vs vehicle (Dunnett test)



DP antagonist prolonged wake time after sleep deprivation.

The slide shows the result when a DP antagonist was administered to the sleep deprivation rat. Wake time was extended in a dose-dependent manner.

Narcolepsy

2 Major symptoms

Major symptoms ① : Hypersomnia

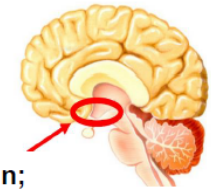
First-line : Modafinil

Falling asleep when unable to remain awake

Major symptoms ② : Cataplexy (Type 1 only)

Feelings are high, and muscles throughout the body become weak

Tricyclic antidepressants, Sodium Oxybate （US）



Orexin;
hormones involved in maintaining awakening

Narcolepsy type1 patients are loss of the nerves producing and secreting orexin.

Narcolepsy type1 (Narcolepsy with cataplexy)	● Persistent excessive daytime sleepiness for at least 3 months ● Mean sleep latency (mean sleep onset) within 8 minutes ● SOREM (REM sleep that occurs within 15 minutes) ● History of cataplexy ● Orexin level in CSF ≤ 110 pg/mL
Narcolepsy type2 (Narcolepsy without cataplexy)	● Persistent excessive daytime sleepiness for at least 3 months ● Mean sleep latency (mean sleep onset) within 8 minutes ● SOREM (REM sleep that occurs within 15 minutes) ● No history of cataplexy ● No decrease orexin level in CSF

International Classification of Sleep Disorders, Third Edition, Central Disorders Hypersomnolence 2018; 97-106.

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Narcolepsy has 2 types of symptoms. One is a symptom of falling asleep without being able to maintain wakefulness, and the other is cataplexy, in which the whole body suddenly loses power when emotional excitement occurs. Some dogs have a genetic cataplexy. Feeding causes weakness in the muscles of the limbs and causes them to collapse.

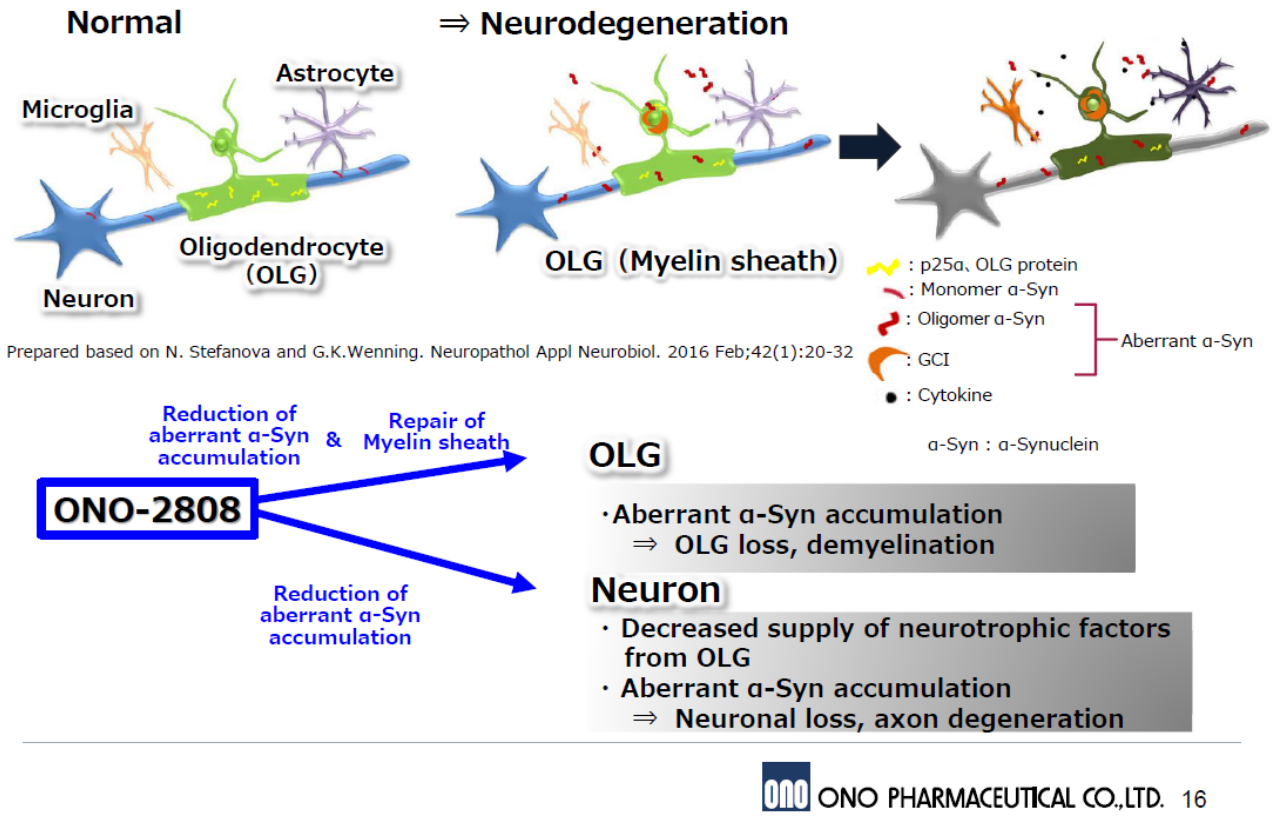
Cases with cataplexy are classified as Type 1, and cases without cataplexy are classified as Type 2. Today we only show some data, but from non-clinical data, we believe that ONO-2909 may be effective for both hypersomnia and cataplexy, Type 1 and Type 2.

Regarding the number of patients, the prevalence rate is 0.05%, or 1 in 2,000 people. It is said there are about 150,000 people with narcolepsy in the US. By the way, the prevalence is higher in Japan, with the rate of 0.16%.

ONO-2808

Compound	ONO-2808
Company	Ono
Mechanism	S1P5 receptor agonist
Formulation	Tablet
Indication	Neurodegenerative disease
Stage	Phase 1 (Europe/ Japan)

Next, I'll talk about ONO-2808.



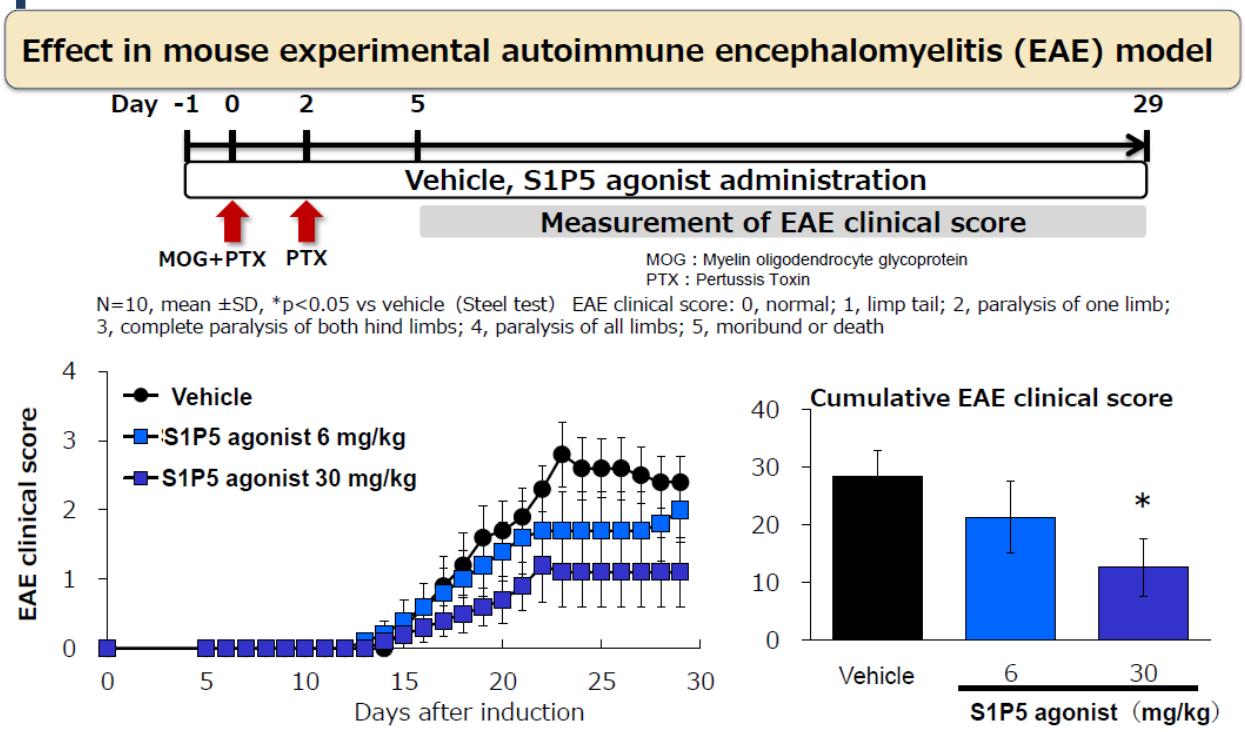
Among neurodegenerative diseases, there are diseases where abnormal aggregates of protein called α-synuclein accumulate in the brain.

In the introduction of ONO-2910, I explained that Schwann cells differentiate to form myelin sheaths in the case of peripheral nerves. But, in the case of central nerves, these oligodendrocytes differentiate to form myelin sheaths.

When abnormal α-synuclein accumulates in oligodendrocyte-derived myelin sheath and neurons themselves, the myelin undergoes demyelination, and neurons themselves degenerate and die.

ONO-2808 is an agonist of S1P5 receptor, one of receptors of a lipid called sphingosine 1-phosphate. Results have shown that S1P5 receptor agonist prevents the accumulation of abnormal α-synuclein in oligodendrocytes and neurons.

S1P5 agonist (Pharmacological study result)

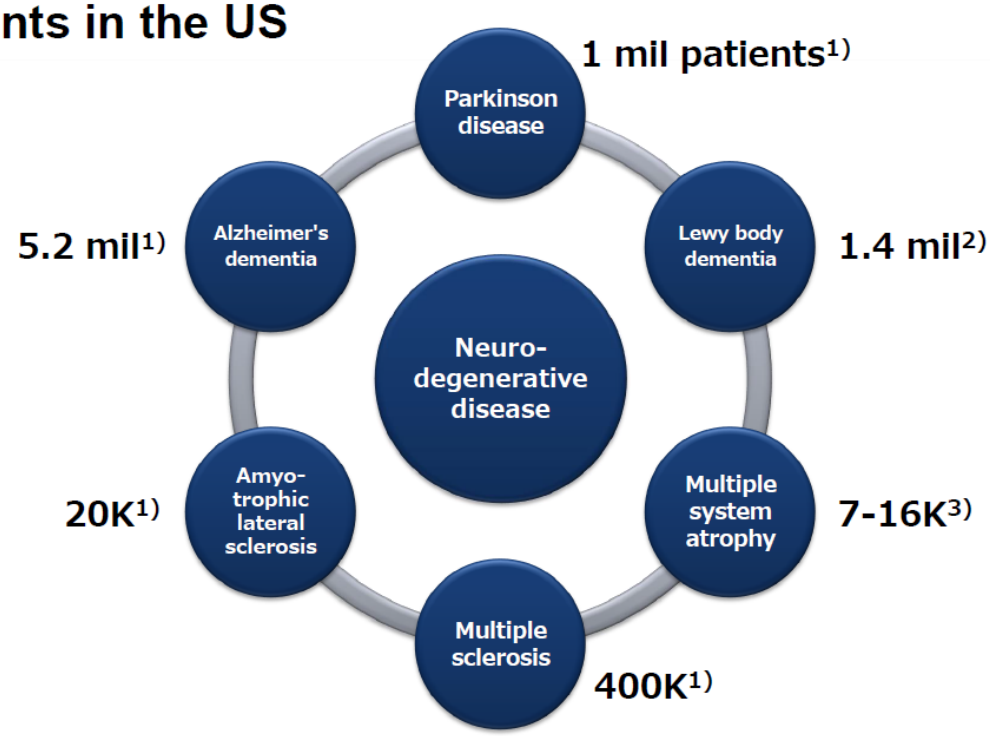


S1P5 agonist suppressed aggravation of EAE clinical score.

Experimental results using S1P5 agonist are shown here. This is an experimental autoimmune encephalomyelitis model commonly known as EAE. In this model, no accumulation of abnormal α-synuclein itself was observed, but worsening of the neurological symptom score was suppressed in a dose-dependent manner by preventive administration of S1P5 agonist.

We believe that this is a result of suppressing neuronal degeneration, and that S1P5 agonist has a promoting effect on oligodendrocyte differentiation and an inhibitory effect on oligodendrocyte demyelination.

Main neurodegenerative disease and number of patients in the US



1) : Thermo Fisher SCIENTIFIC Web https://www.thermofisher.com/blog/learning-at-the-bench/neuro_disease1/
2) : Lewvy Boday Dementia Association Web https://www.lbda.org/about-lbd/
3) : The portal for rare diseases and orphan drugs web https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN

There are various types of neurodegenerative diseases. Among these diseases, those in which accumulation of abnormal α-synuclein is observed are Parkinson's disease, Lewy-body dementia, and multisystem atrophy. ONO-2808 is currently in the final stage of Phase I. While considering the compound profile, we are going to conduct Phase II trial with selected appropriate diseases.

ONO-4578

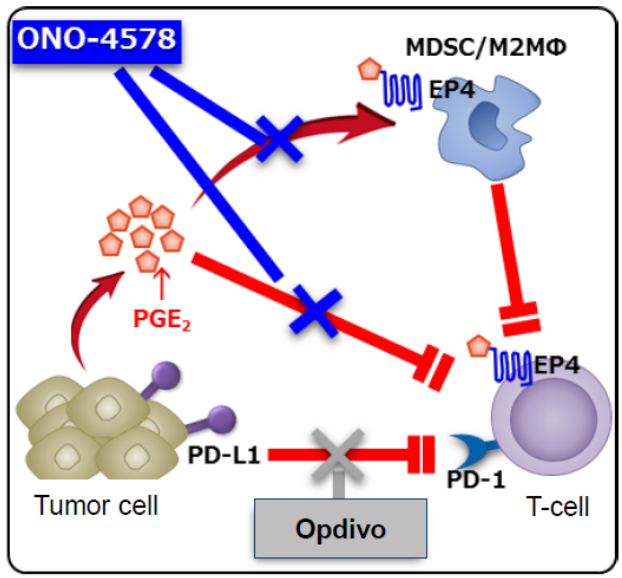
Compound	ONO-4578
Company	Ono
Mechanism	Prostaglandin receptor (EP4) antagonist
Formulation	Tablet
Indication	Solid Cancer
Stage	Phase 1 (Japan) Colorectal cancer, pancreatic cancer, Non-small cell lung cancer, gastric cancer

Next, ONO-4578.

This is the only compound in the oncology area. ONO-4578 is a prostaglandin receptor EP4 antagonist.

ONO-4578 Mechanism of Action

- Prostaglandin E_2 (PGE_2) is produced from arachidonic acid through cyclooxygenase-2 (COX-2)
- COX-2 is overexpressed in solid cancer[1]. PGE_2 has been reported to induce myeloid-derived suppressor cells (MDSC) and M2 macrophages in the tumor microenvironment through one of its receptors, EP4, and suppress activation of cytotoxic T cells[2].
- ONO-4578, a novel selective EP4 antagonist, is expected to have an antitumor effect by abolishing the tumor immunosuppressive mechanism that PGE_2 constructs via EP4.



1) Bing L, et al. Cancer Cell Int; 2015:15:106
2) Yukinori T, et al. Front Immunol. 2020;11:324

Prostaglandin E_2 (PGE_2) is produced by the cyclooxygenase (COX) 2 from arachidonic acid. COX2 has been reported to be overexpressed in tumor cells. It has been reported that the produced PGE_2 directly and indirectly suppresses the activity of cytotoxic T cells through EP4 receptor expressed on MDSC and M2 macrophages. ONO-4578 is expected to release PGE_2-mediated immunosuppressive mechanism and enhances tumor immunity.

ONO-4578 Non-clinical data

- In syngeneic mouse tumor-bearing model, ONO-4578 improved immunosuppressive tumor microenvironment and showed antitumor effects (Figs. 1 and 2).
- Furthermore, ONO-4578 enhanced its antitumor effect by co-administration with anti-mouse PD-1 antibody (αPD-1) (Fig. 1).

Fig 1. Time course of median tumor volume in syngeneic mouse colorectal cancer MC38 tumor-bearing model

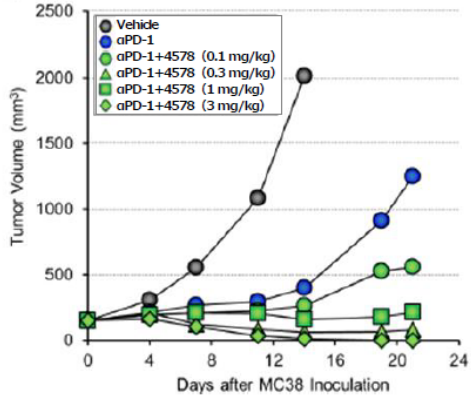
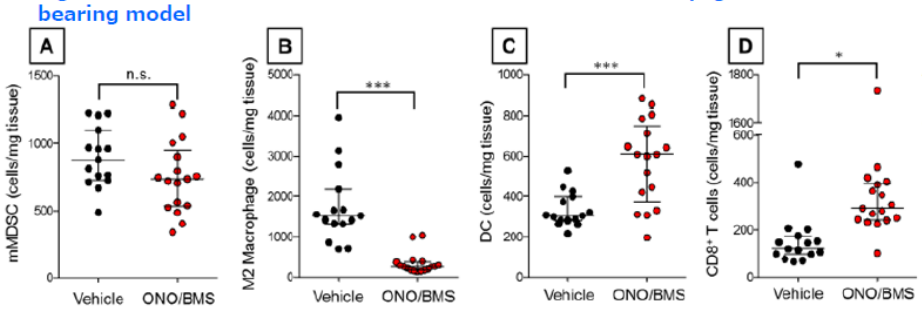


Fig 2. Effect of ONO-4578 on intra-tumoral immune cells in syngeneic mouse colorectal cancer MC38 tumor-bearing model



A : No. of mMDSC
B : No. of M2 macrophage
C : No. of dendritic cells
D : No. of CD8-positive T cells

AACR 2020: Poster # 4443

The results of non-clinical experiments with ONO-4578 are shown here.

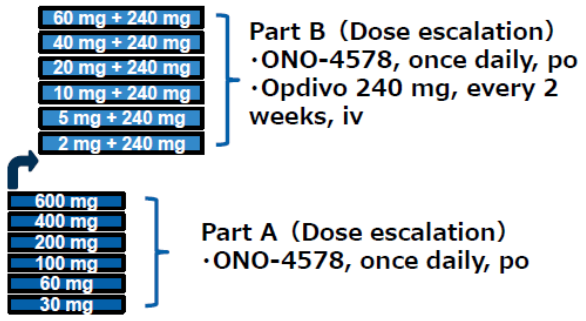
In the mouse tumor-bearing model, ONO-4578 showed an improvement in enhancing tumor immunity, by reducing the number of MDSC and M2 macrophages that suppress tumor immunity, while increasing the number of dendritic cells and CD8-positive T cells .

Next, this is the result of an experiment assessing the anti-tumor activity in combination treatment of ONO-4578 and anti-PD1 antibody in in vivo.

ONO-4578 in combination with anti-PD1 antibody reduced the tumor size in a dose-dependent manner and enhanced the antitumor effect.

ONO-4578 Clinical data

- In the ONO-4578-01 study in Japanese patients with solid tumors, the tolerability and safety of ONO-4578 alone (Part A) and in combination with Opdivo (Part B) were evaluated.
- In Part A and B, the maximum tolerated dose (MTD) was not reached.
- CR and PR were not observed in 10 cases of Part A, and SD was observed in 3 cases.
- In 21 cases of Part B, PR was observed in 1 case of small cell lung cancer and unconfirmed PR was observed in 1 case of pancreatic cancer. In addition, SD was observed in 5 cases.



Main inclusion criteria:
- Age: 20 years or above, ECOG PS 0 or 1
- Advanced or metastatic solid tumors
  - ✓ Refractory or intolerant to standard treatment or no standard treatment (Part A)
  - ✓ Refractory or intolerant to standard treatment except anti-PD-1 antibody or no standard treatment (Part B)
  - ✓ No previous treatment with immune checkpoint inhibitors (Part B)

Cut-off date : February 5, 2020
ECOG PS, Eastern Cooperative Oncology Group Performance Status;
CR: Complete response PR: Partial response SD: Stable disease

ESMO 2020: # 504

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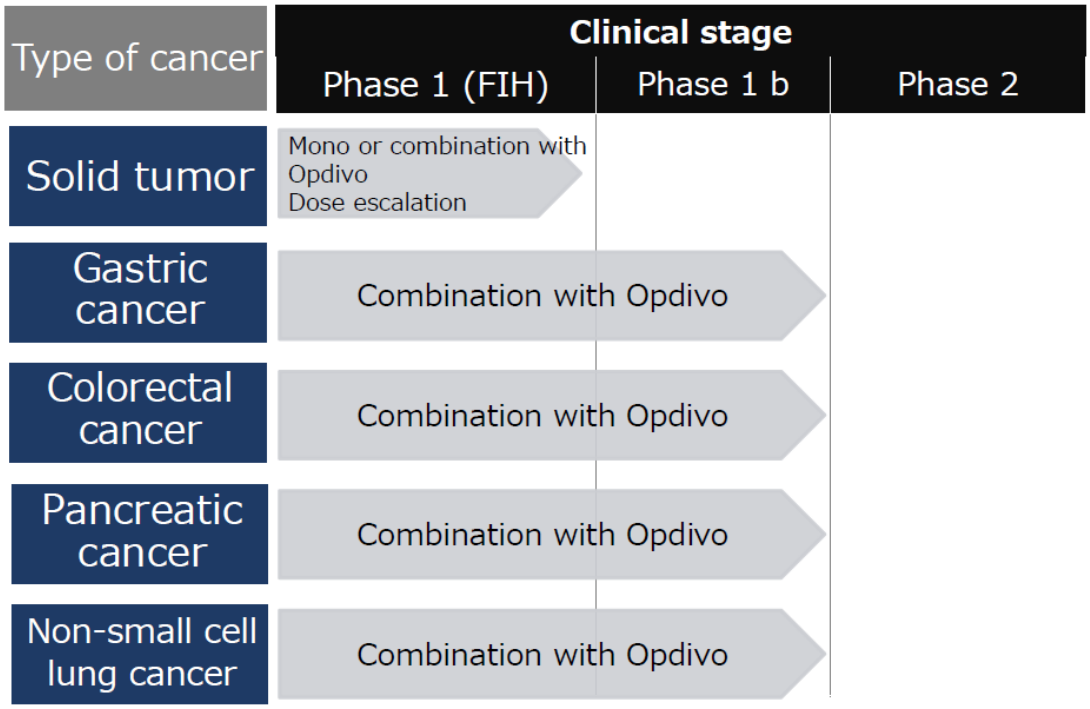
We have been conducting Phase I trial to evaluate a tolerability and safety with monotherapy of ONO-4578, followed by in combination with OPDIVO.

ONO-4578 Development stage



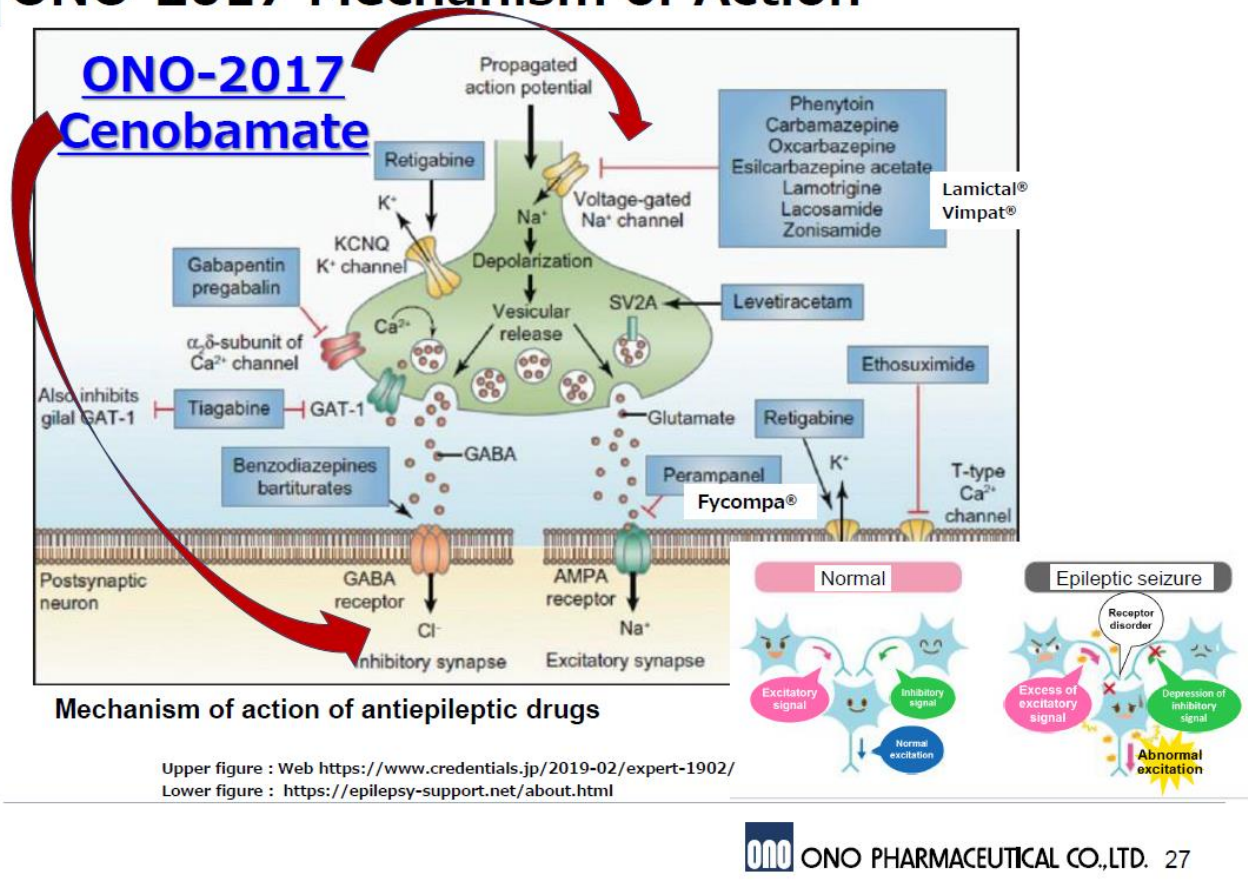
As we have confirmed the safety profile, we are now conducting Phase Ib trial as an expansion part for various types of cancers, gastrointestinal cancers such as gastric cancer, colorectal cancer and pancreatic cancer, as well as non-small cell lung cancer.

ONO-2017

Compound	ONO-2017 (Cenobamate)
Company	SK Biopharmaceuticals Co., Ltd.
Mechanism	Voltage-gated sodium currents inhibition/$GABA_A$ modulation
Formulation	Tablet
Indication	Epilepsy (Partial seizure, tonic-clonic seizure)
Stage	US: Launched by SK Life Science Europe: Launched by Angelini Pharma Japan: Under preparation for clinical trial

Finally, ONO-2017 is an antiepileptic agent in-licensed from SK Biopharmaceuticals in Korea.

ONO-2017 Mechanism of Action



Mechanism of action of antiepileptic drugs

Upper figure : Web https://www.credentials.jp/2019-02/expert-1902/
Lower figure : https://epilepsy-support.net/about.html

Regarding mechanism of action, in addition to inhibiting sodium channels, this compound also enhances the function of GABA receptors, thus suppressing abnormal excitation of neurons in the brain.

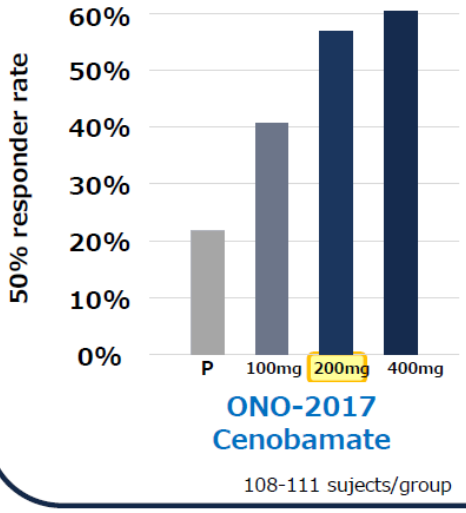
ONO-2017 Clinical Results

Partial seizure, Patients with poor seizure control, Combined use with existing drugs

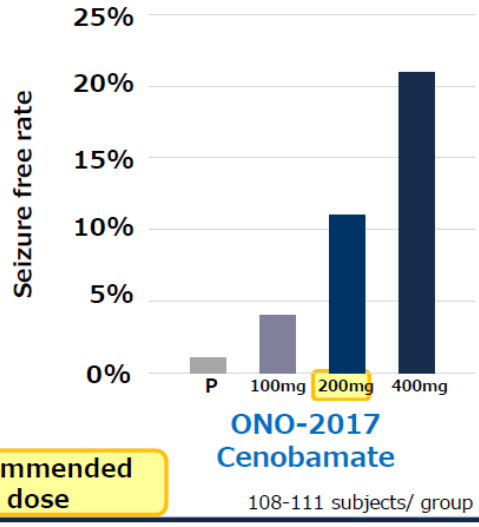
Treatment period: Dose-escalation period + 12 or 13 weeks maintenance period

Patients: **Adult epilepsy patients with partial seizures for which existing antiepileptic drugs are not fully effective**

50% responder rate :
Percentage of cases in whom the number of partial seizure improved by ≧50% compared to the observation period



Seizure free rate:
Percentage of cases in whom no partial seizure was observed during the maintenance period



Recommended dose

Krauss GL, et al. Lancet Neurol. 2020 Jan;19(1):38-48

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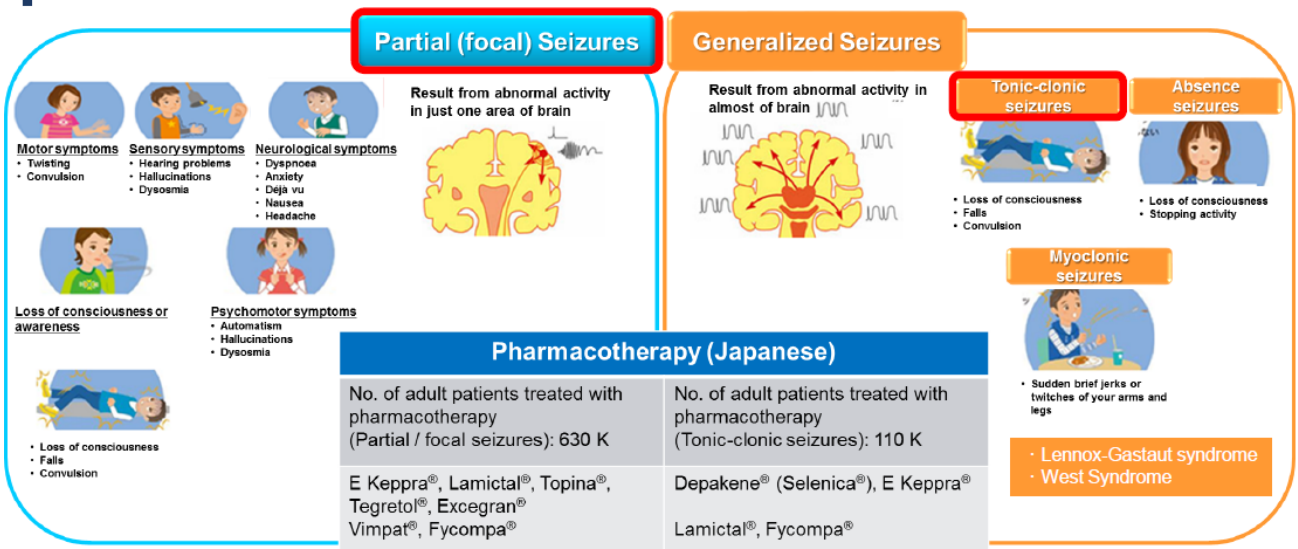
Cenobamate has already been approved and launched in the US, and has shown very high clinical efficacy. I will show you the results of clinical study in partial seizures in combination with existing drugs. Looking at the 50% responder rate, it was 57% at the recommended dose of 200 mg, and 60% at a dose of 400 mg. If we look at the result of other drugs, we can see the rate of approximately 30% at the recommended dose and up to 50% at the higher dose

It may not be adequate here, as it is a comparison between different trials, but we see that cenobamate shows very high efficacy. Then on the right are data on the disappearance rate of seizures, that is, the percentage of cases in which seizures were not observed at all. Regarding the disappearance rate of seizures, it was more than 10% at the recommended dose of 200 mg, and over 20% at 400 mg.

Again, when we look at similar tests of other drugs, it's around 5%. Note that again, this is a comparison between trials, but for patients with epilepsy, it is very meaningful to reduce seizures to zero. From these data, Cenobamate is expected to be able to address these unmet needs.

Epilepsy



Patients refractory to existing treatments: 20-30%

- Partial (Focal) seizures: 130-190 K
- Tonic-clonic seizures: 20-30 K

- Prepared based on materials for training of epilepsy for school.
- Epidemiology of epilepsy. Epilepsy 2020.; 14: 7-10.
- JAMA Neurol, 2008; 75: 279-86.
- MHLW Study Report, Research on Pathology and Treatment of Intractable Epilepsy, 1991.
- Epilepsy Research. 2005; 23: 249-53.

Finally, about the number of patients with epilepsy.

Epilepsy can be divided into partial seizures and generalized seizures.

There are said to be 630,000 patients treated for partial seizures, and 110,000 treated for generalized seizures.

It is said that about 20% to 30% of those patients are resistant to existing drugs, representing a significant unmet medical need. It accounts for 130,000 to 190,000 patients with partial seizures, and 20,000 to 30,000 patients with generalized seizures.

As I mentioned earlier, cenobamate is already on the market in the US and has been confirmed to be effective and safe. In collaboration with SK Biopharmaceuticals, we hope to efficiently develop and obtain approval in Japan as soon as possible, and are currently preparing for clinical trials.

Question & Answer

Questioner 1: The presentation helped me go over the basics. It was very helpful. Regarding your 4 in-house products excluding the last epilepsy drug, three neurology and one oncology, although it may be a little early, could you tell us about the development policy for these products?

How far does your company intend to proceed in-house development, and from what stage would you look into partnerships? If possible, could you give any details about conditions you would favor, such as reducing upfront payments in exchange for a 50/50 profit share in the US? Or would you prefer to leave the whole development to your partner, so that the project is out of your own control? It may be a little early to ask about these things, but could you give us an idea of your thoughts for these 4 products?

Idemitsu: Basically, we would like to proceed with the development by ourselves, including in Europe and the United States. We would like to carry out the PoC study where it can be carried out as soon as possible, and proceed with the global development of the verification study to obtain approval in Japan, Europe and the United States.

Regarding the marketing in Europe and the United States, we will consider it on a product-by-product basis, but basically are considering in-house sales.

Questioner 1: Thank you. Regarding narcolepsy and cancer, I appreciate that. As for diabetic polyneuropathy, do you intend to move forward with the development and sales in-house in Europe and the United States? I'd just like to confirm that.

Idemitsu: It will be considered for each project. We think that we will be able to do it by ourselves, at least for Parkinson's disease, Lewy body dementias, multiple system atrophy and multiple sclerosis, as well as ALS.

Questioner 1: Okay. This will not be a question of waiting for partnerships, but rather, waiting for results of trials to come in.

Idemitsu: Establishing a PoC is first, then, we are considering developing in-house in Europe and the United States.

Questioner 1: Okay. Regarding timing of these 4 products, when do we expect to ask you about the next important clinical update? Could you comment about each one individually?

Idemitsu: ONO-2910 is already in Phase II, so I think the result will come out in a few years. ONO-2909 is still in Phase I, so it may take a little more time. ONO-2808 is now in the final stage of Phase I. The next step is to enter into the following Phase after selecting the target diseases. Since it targets neurodegenerative diseases, I think that the administration period will be longer and it will take a few years to get the POC.

ONO-4578 is depending on the result from the extension part of the ongoing Phase I study.

Questioner 1: Okay. Thank you very much. If ONO-4578 is going well, the result will be available next year or in one year. Then, the result of Phase I of ONO-2808 for narcolepsy will come out in about 2 years. May I imagine that the Phase II result of ONO-2910 is coming out by that time?

Idemitsu: Sorry, I cannot tell you about the details of the schedule, but ONO-4578 is at most advanced stage.

Questioner 1: Okay. There's one more thing I'd like to ask. I'm not sure if it's okay to ask about a drug that wasn't discussed today, but regarding the anti-CD47 antibody in-licensed from Forty Seven, which Gilead acquired recently. Similarly, Pfizer also acquired Trillium Therapeutics, which also has an anti-CD47 antibody, with about $ 2 billion. It made me think that your company has a swift eye for this. How do you think the advantage of your company's anti-CD47 antibody compares to the Trillium Therapeutics one, beside the timing?

Idemitsu: I think that it is ahead and the amount of data is overwhelmingly different. In addition, when considering the enhancement of tumor immunity in combination with anti-PD-1 / PD-L1 antibody, we believe that we have abundant data on OPDIVO. I believe that is our strength.

Questioner 2: First of all, some potential indications for ONO-2808 are listed on page 18. It was mentioned in the previous question that perhaps the stage of determining indications is approaching. Based on previous research in non-clinical studies, what indications appear to be the most likely candidates?

Idemitsu: Interesting data is coming out, but I can't tell you at this stage. I'm very sorry.

Questioner 2: Is there some exciting data or great potential that you're not able to talk about?

Idemitsu: Yes, interesting data is coming out.

Questioner 2: I see. Understood. This is a similar question, but considering the mechanisms of both ONO-2910 and ONO-2909, I get the impression that they can be used for a variety of indications. ONO-2910 is now in Phase II for diabetic polyneuropathy, but what do you think about the possibility of exploring other indications?

In parallel, I think it is being considered in the non-clinical stage, but could you tell us how promising the second indication is, the timing, and when you may be able to tell us more about it?

Idemitsu: ONO-2910 acts on peripheral nerves. We think that neuropathy associated with anticancer drug, paclitaxel etc. will be targeted. We have obtained results that suggest an efficacy in non-clinical studies, and think that it may be applicable to neuropathy such as numbness caused by paclitaxel. We are still exploring the possibility of other indications in the research institute.

As for ONO-2909, we think that narcolepsy may be a potential target disease to maximize the potential value of this compound. If the PoC is established, it may be applied to jet lag or sleep disorders associated with day and night shift work etc.

Questioner 2: Thank you. Finally, regarding ONO-4578, what do you think about why Bristol redeemed the rights? Based on the reason, could you tell us your thoughts about the significance of proceeding with global development independently?

Idemitsu: At the time that ONO-4578 rights were returned from Bristol Myers Squibb, there was not enough clinical data available. After that, Phase I trial in Japan progressed to confirm safety and are now proceeding to an expanded cohort.

It's not a clear situation yet, but if the effectiveness is firmly recognized, I think it is worth developing ONO-4578 in combination with OPDIVO, including in the United States.

Questioner 2: I'm sure, but it wasn't that you got promising data after it was returned, so I think if some promising data comes out in future, it's worth continuing development.

Idemitsu: Yes.

Questioner 3: Of the compounds introduced this time, I think ONO-2910 is in the most advanced development stage. As you mentioned, I think it's been comparing it with Cymbalta in a rat model, but I think Mr. Idemitsu mentioned the effect of repairing nerves. The point is that you are checking the action of repairing peripheral nerves somewhere.

As it may have been in the question at the beginning, I think that it is also overseas in-house, but especially in the United States, this kind of drug is very difficult to get approval for, judging from past cases. I think maybe clinical trials with thousands of subjects are needed. Based on that aspect, I think that there is a considerable potential from this current profile, and are you considering that approach to capture it? Please let me know this point first.

Idemitsu: We have confirmed the restoration of nerves in non-clinical study. We think it is not a direct effect on nerves, but effect on the myelin to promote differentiation of Schwann cells and suppress dedifferentiation.

As you pointed out, we think that it is very difficult to evaluate diabetic polyneuropathy, especially the symptoms. So we will ask the experts who are accustomed to the measurement of subjective symptoms and nerve conduction velocity to conduct the study. After establishing a POC in Japan, we think we are moving to a global development.

Questioner 3: Do you mean you are thinking about in-house development while reducing development costs to some extent?

Idemitsu: If the ongoing PoC study confirms a clear improvement in nerve conduction velocity and subjective symptoms, we would like to carry out subsequent studies by ourselves, as well.

Questioner 3: Thank you very much. Another thing, regarding narcolepsy which has an attracting attention, your approach is different from the approach that other companies in Japan are doing, in terms of central nervous system action. I believe that your approach for ONO-2909, that is, targeting the sleep center directly, will give results close to radical treatment, regardless of whether it’s type 1 or 2 of narcolepsy. That was my impression.

Of course, this is still in Phase I, so POC study and others have to be done in the future, but at this stage, what are your feelings about how much potential is there?

Idemitsu: In the non-clinical experiment results, I am feeling the potential. However, as was pointed out, we do not know honestly until it is tested in humans. As such, we would like to proceed with clinical trials as soon as possible.

I don't know which target is better, wakefulness or sleep, but in the wakefulness approach, you can be awake in the daytime, but you can't sleep at night if the effect lasts. The same is true for blocking the sleep center, depending on the PK profile, but I think it's easier to adjust. Of course, even if it acts on the wakefulness center, it depends on the adjustment of PK. Regarding which is better, we think it is better to suppress the sleep center.

Questioner 3: Since it is related to sleep and wakefulness, I think that the side effect profile may be a bit different, but that will become clear to some extent in the POC.

Idemitsu: First of all, after confirming whether sleep can be prevented, we will try to differentiate.

Questioner 4: I would like to ask you about cenobamate first. As was mentioned, it's been launched in the United States, and the clear data is also available. When you develop it in Japan, I feel it is important for you how to accelerate the development of the compound by omitting and simplifying duplicate parts of clinical studies as much as possible.

On the other hand, I think there are some parts with which you cannot enter into clinical study for epilepsy. You have not yet started any clinical study, while you are continuously preparing clinical study for a long time. Do you have any development strategies, for example to conduct only one Phase II/III from the beginning to skip other ordinal clinical study? Please let me know if you have decided the strategy for the development.

Idemitsu: While considering the business strategy, I would like to refrain from answering, but I will tell you the facts. Regarding partial seizures, SK Biopharmaceuticals has already been conducting Phase III clinical study for the treatment of partial seizure in Asia, including Japan. I think we can use the results from the study in filing an application in Japan.

As for generalized tonic-clonic seizures, we would like to do it in a reasonable way, while consulting with the authorities.

Questioner 4: Although you say that it is in preparation for clinical trials, but in effect, if you get data in Asia including Japan from SK, you can apply it as it is.

Idemitsu: In addition to the ongoing study, we are reviewing how much additional data is needed about the partial seizures. I think it's as minimal and appropriate as possible. Regarding partial seizure, one Phase III study including in Japan is ongoing.

Questioner 4: Considering the fact you said right now, it's not about starting from scratch in clinical preparation, but a lot of things are moving.

Idemitsu: We have not yet started Ono sponsored-study, but are preparing to do an adequate trial at the appropriate time so that we can get an approval as soon as possible.

Questioner 4: I also had several questions about narcolepsy, ONO-2909. It's quite difficult to compare the test with the other test. Here is the data of the sleep-deprived rat, and Takeda is presenting a mouse model. The base wakefulness time can't be compared because it's totally different, and the animals are also subtly different. I know this, but taking a quick look, the way Takeda's wakefulness time is extended to some extent in humans, and it seems to be significant, almost doubling in the mouse model. It seems that your compound does not have a big impact, while I understand that it is still in dose-finding stage.

In other words, if you look at it, the impact of your compound on wakefulness time is somewhat milder, compared to the data from Takeda. Can you generally say that sleep block and waking effect have a different impact on wakefulness time?

Idemitsu: The non-clinical study results presented today are data for a DP antagonist that differ from ONO-2909. Regarding ONO-2909, there are many unpublished data, so I cannot introduce all of them including the data on the effect of prolonging the awakening time. However, we have also confirmed the suppressive effect on cataplexy. Regarding the strength of effectiveness, I will refrain from commenting because the experimental model is different. We expect that ONO-2909 will show potentially sufficient effectiveness in a clinical setting.

Questioner 4: And this is the general thing that narcolepsy Type 2 does not cause a decrease in orexin levels. Given the situation, is it more likely that your approach of stopping sleep rather than elevating orexin is effective?

Idemitsu: It would be difficult for me to give a simple answer to that. It is also reasonable approach to increase orexin.

Questioner 4: Treatment approaches are different between them. Therefore, will it be possible to combine both of treatment approaches, namely one acting on the sleep system and the other acting on wakefulness system, in the future, for the treatment of patients having severe symptoms?

Idemitsu: I think it depends on the data.

Questioner 4: Regarding α-synuclein, I think Takeda Pharmaceutical is doing with antibodies with AstraZeneca, and in short, I feel that there are quite a lot of approaches in terms of these targets. Do you think the data for ONO-2808 will be competitive to that kind of thing?

Idemitsu: I don't know which one works. Neurodegenerative diseases, such as multiple system atrophy and ALS are associated with movement disorders, so in that sense, I think oral preparations that can be taken at home may be better than injection of antibody preparations.

Questioner 5: First, regarding products in your pipeline, including the ones you introduced this time, could you tell us about the general feeling at the moment? I get the impression that there are several compounds in Phase I and Phase II, and that things look promising. I think these products are drugs that will contribute after the patent for OPDIVO has expired, but now, including in-house products in Phase I, do you feel as if the pipeline has been beefed up enough to bring in enough after the patent for OPDIVO expires?

Or do you think you still need to put more of your in-house products into Phase I? I would like you to tell me the overall sense of the current situation.

Also, for the 4 in-house products introduced this time, do you think you could rank them in terms of how much potential you feel they have?

Idemitsu: I don’t think we ever feel this is enough. In order to introduce as many new drugs as possible to the worldwide market, I would like to bring as many compounds as possible to clinical phase. We also want to expand the pipeline including in-licensed products even more.

If we can confirm the efficacy and safety of these compounds as expected and launch them in Europe and the United States, I think there is a potential to surpass the patent cliff you mentioned. However, since it depends on the degree of the efficacy and safety, we cannot unequivocally state the potential at this time. On the other hand, for example, ONO-4578 is being developed in combination with OPDIVO. I think that sales will increase depending on the target type of cancer.

We are currently targeting gastric cancer, where OPDIVO has already shown an efficacy, and expect an additional effect in combination treatment. On the other hand, OPDIVO has not been approved for colorectal cancer, excluding MSI-H one of colorectal cancer, but we can enter into further market if we can show the efficacy in combination with OPDIVO. In addition, we believe that there is great potential if we can show the efficacy of ONO-4578 in combination with OPDIVO for non-small cell lung cancer, which is highly marketable.

Questioner 5: The second is the S1P5 agonist, ONO-2808. In today’s explanation, it was mentioned about noticing something novel, and I was wondering that as many companies are working on multiple sclerosis, perhaps it is something other than that. Might I be on the right track?

Idemitsu: Compounds acting on different subtypes of the S1P receptors have been developed for multiple sclerosis. For multiple sclerosis, this is an approach where a compound acting on the S1P1 receptor suppresses the export of lymphocytes from the lymph nodes. On the other hand, we take a different approach, since the target of ONO-2808 is not the S1P1 receptor.

Questioner 5: Regarding narcolepsy, ONO-2909 is in Phase I right now. What's the dosing schedule and what kind of regimen will it be? Will it be a once-daily, morning dose?

Perhaps it is early to ask, and you may need to look at the results of Phase I, but please tell me what the dosing regimen will be, if possible.

Idemitsu: I think that the ideal administration method is that if it is taken once a day in the morning, we will not feel drowsy during the day without cataplexy.

Questioner 5: Basically, this would be taken once a day in the morning. Is that correct?

Idemitsu: Yes. It doesn't have to work at night, so I think it's best to take it once in the morning and last the effect during the day. If the PK is short, we may need to take an option of twice a day.

Questioner 6: I have 2 questions about the oncology area. ONO-4578 was presented in ESMO last year, and an expert from the National Cancer Center presented something related to dose escalation phase. At that time, it was in combination with OPDIVO, and I think the PR was observed in small cell lung cancer and pancreatic cancer. From that, I got the impression that gastric cancer is the most advanced in dose expansion phase, but is my understanding correct?

Idemitsu: As you remembered, it was presented at the ESMO in 2020, the Part A of Phase I trial is a monotherapy. Part B is the part to investigate tolerability and safety in combination with OPDIVO.

CR and PR was not observed in the Part A, monotherapy and SD was observed in 3 cases. Part B had 21 cases, where PR was found in 1 case of small cell lung cancer, and unconfirmed PR in 1 case of pancreatic cancer and SD in 5 cases. Since then, the expansion part has been sequentially conducted in gastric cancer, colorectal cancer, pancreatic cancer and non-small cell lung cancer. The part for gastric cancer has first started and advanced.

Questioner 6: What do you anticipate to make a presentation about gastric cancer? Is it possible around ASCO next year?

Idemitsu: I think it would be good, but it may take a little longer.

Questioner 6: Why do you preceded with those 3 cancer types? Is it because OPDIVO doesn't work for colorectal cancer of course? But after all, are you choosing 3 cancer types considering the market size?

Idemitsu: The selection of cancer types is determined by comprehensive judgment, including scientific aspect such as findings of the expression of PGE_2 and COX, and market aspects.

Questioner 6: The second question, and this wasn’t mentioned today, but your company is partnering with Fate Therapeutics to develop cell therapy in cancer. I think your company was the first company to sign a contract for iPS cell-derived CAR-T, but could you tell us a little more about progress here?

Takino: It hasn't entered the clinical stage yet, so I will explain about it. I think that everyone is already aware of the merits of iPS CAR-T, so I will not go into details. iPS CAR-T is expected to enhance the cell-killing effect by gene editing and enable multiple doses necessary for application to solid tumors as an off-the-shelf product. So, we are currently tuning around that area. It will take a little longer to get into clinical practice. Since we are expecting it, we are trying to make a clinical transition as soon as possible.

Questioner 6: Is it correct that your company is contracted with a specific target, and CAR-NK is not contracted?

Takino: I can say that it is a contract-centered around CAR-T, but we ourselves are also somewhat interested in CAR-NK. We are keeping an eye on it and considering future possibilities.

Questioner 4: I'm sorry to ask another question regarding narcolepsy, but it was mentioned that with a wakefulness approach, headaches and insomnia occurred. Is this a reference to the current Jazz Pharmaceuticals product? Or is it an inevitable consequence in treating orexin?

I believe the Takeda product can result in an increase in heart rate or something like that, but I haven't heard about headaches. Could you comment on that?

Idemitsu: My previous explanation was referring to the general theory that when acting on the wakefulness center, an exciting side effect, ex, insomnia easily occurs. I wasn't referring to any particular products.

Questioner 7: Just 1 question, regarding ONO-2808. What is known about how the cells in which α-synuclein accumulates differ according to disease? For example, in Alzheimer's disease, tau protein and beta amyloid accumulate in a variety of cells.

In the case of α-synuclein, the cells in which it accumulates would be localized. I wonder if there is data available about the localization by disease, or if your partner company has got the data from their research. Is there any possibility that the action of this drug will be unique if the cells that accumulate are localized? I would like to ask you about this.

Idemitsu: I think your question is whether the cells and sites where α-synuclein accumulates differ depending on the disease or not. For example, in the case of Parkinson's disease, α-synuclein may or may not be accumulated. I explained that ONO-2808 suppresses the accumulation of α-synuclein, but ONO-2808 also has the effect of suppressing myelin sheath degeneration and promoting regeneration. As introduced earlier, it is also effective in models, like an EAE model, that there are no accumulation of α-synuclein.

We are considering which disease to choose from those with and without accumulation of α-synuclein.

Questioner 7: After all, when it comes to focusing only on the accumulation of α-synuclein, or finding indications that include regenerative effects, which one is more attractive to your company so far?

Idemitsu: I think that diseases with accumulation of α-synuclein are promising candidates.

Questioner 7: By the way, I feel that the first Phase I trial is almost over. Haven't you got any results?

Idemitsu: ONO-2808 is at the final stage of Phase I. We haven't got any final result yet.