R&D Briefing

September 7, 2021

ONO PHARMACEUTICAL CO.,LTD.

Cautionary Notes

Forecasts and other forward-looking statements included in this document are based on information currently available and certain assumptions that the Company deems reasonable.
Actual performance and other results may differ significantly due to various factors. Such factors include, but are not limited to:

(i) failures in new product development
(ii) changes in general economic conditions due to reform of medical insurance system
(iii) failures in obtaining the expected results due to effects of competing products or generic drugs
(iv) infringements of the Company's intellectual property rights by third parties
(v) stagnation of product supply from the delay in production due to natural disasters, fires and so on
(vi) onset of new side effect of post-licensure medical product
and, (vii) currency exchange rate fluctuations and interest rate trend.

Information about pharmaceutical products (including products currently in development) included in this document is not intended to constitute an advertisement of medical advice.

Compounds to be presented

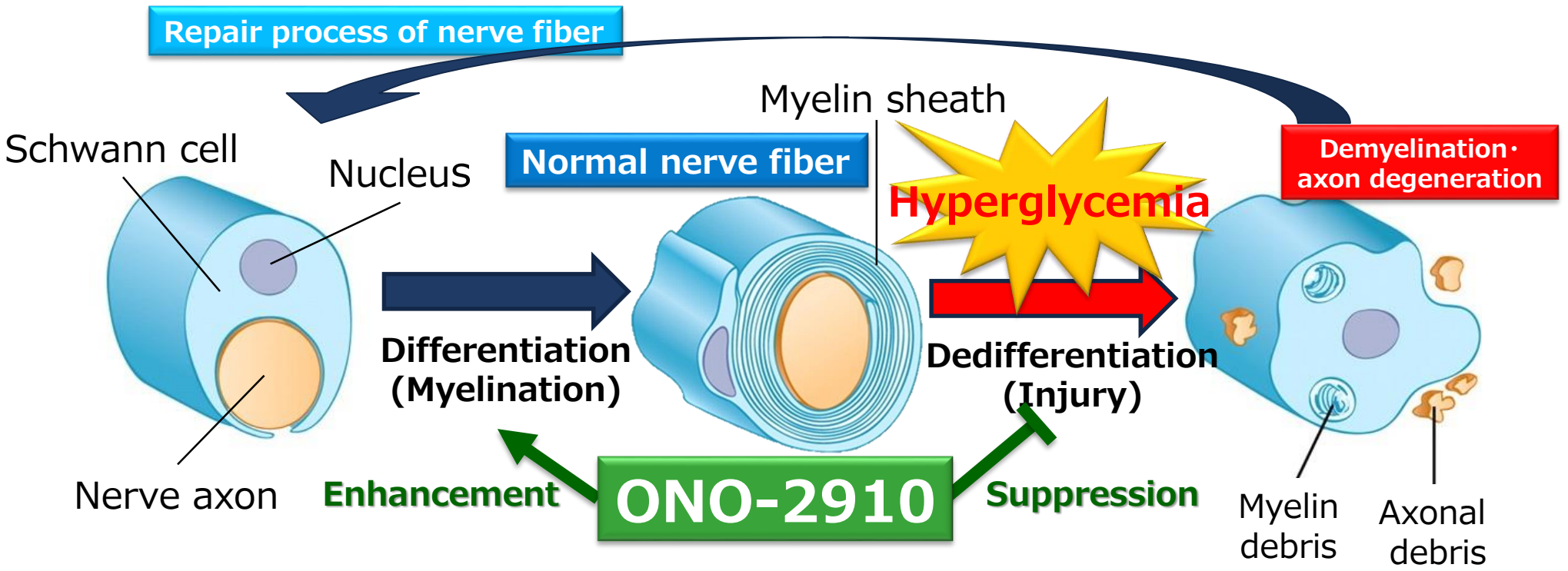
Compound	Mechanism	Target indication	Stage
ONO-2910	Schwann cell differentiation promoter	Diabetic polyneuropathy	P2
ONO-2909	Prostaglandin receptor (DP1) antagonist	Narcolepsy	P1
ONO-2808	S1P5 receptor agonist	Neurodegenerative disease	P1
ONO-4578	Prostaglandin receptor (EP4) antagonist	Solid tumor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

ONO-2910
Schwann cell differentiation promoter

ONO-2910

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

ONO-2910 Mechanism of Action

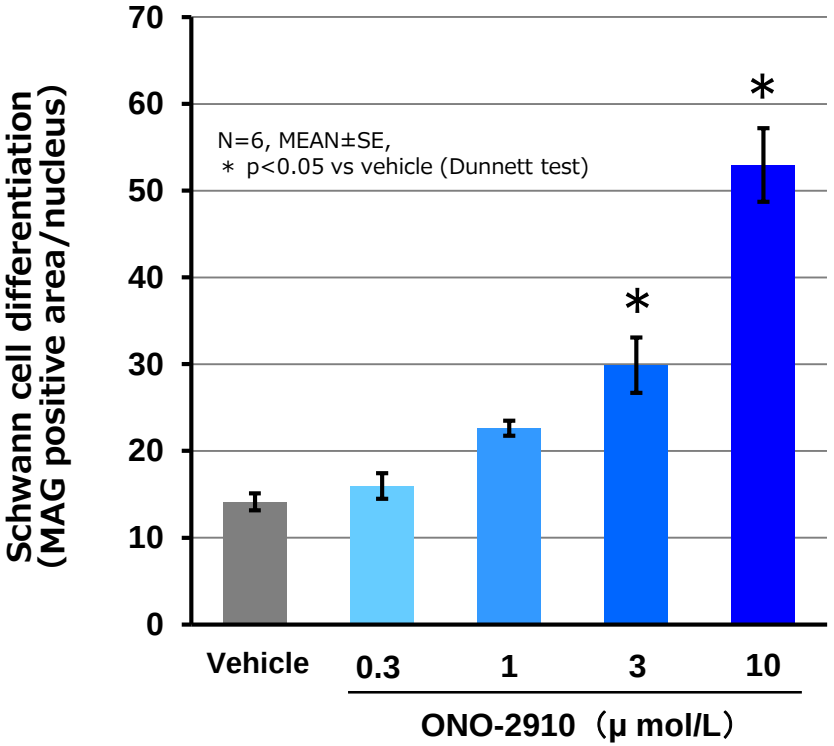


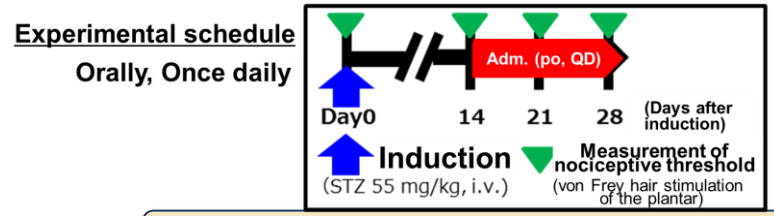
Prepared based on J. Cell Biol. 2008; 181: 575–577

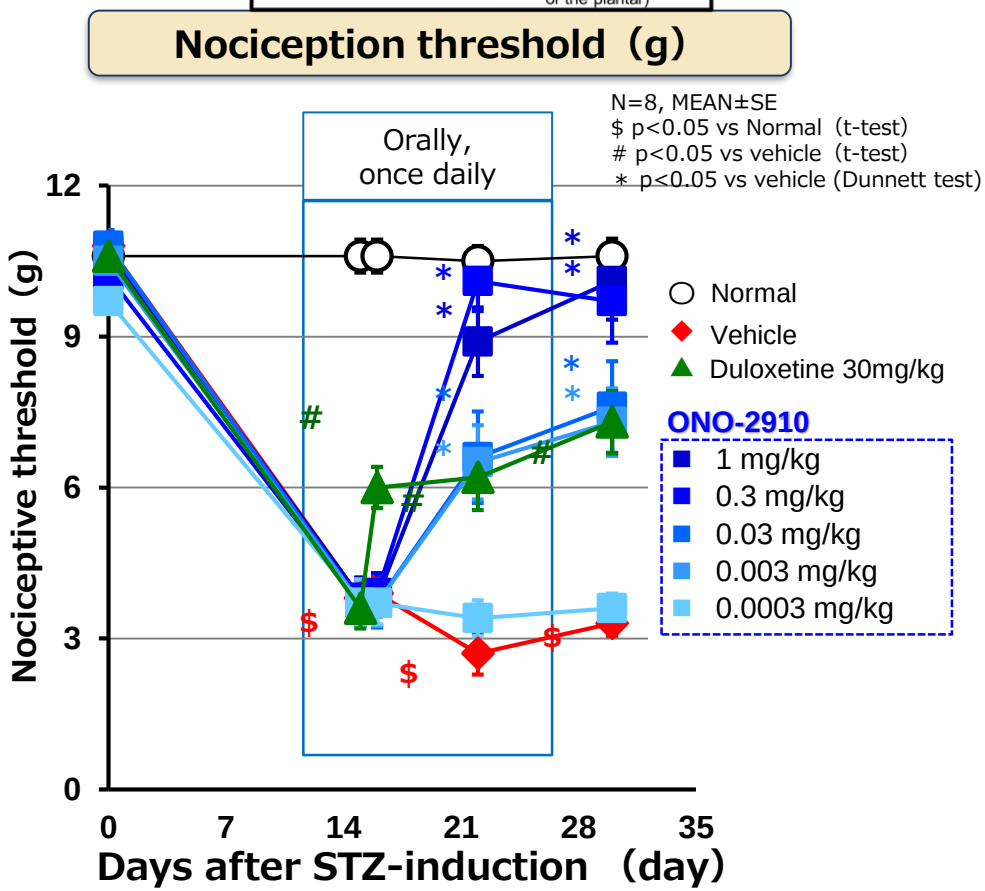
ONO-2910 Pharmacological study result

Rat streptozotocin (STZ)induced model

Human Schwann cell







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

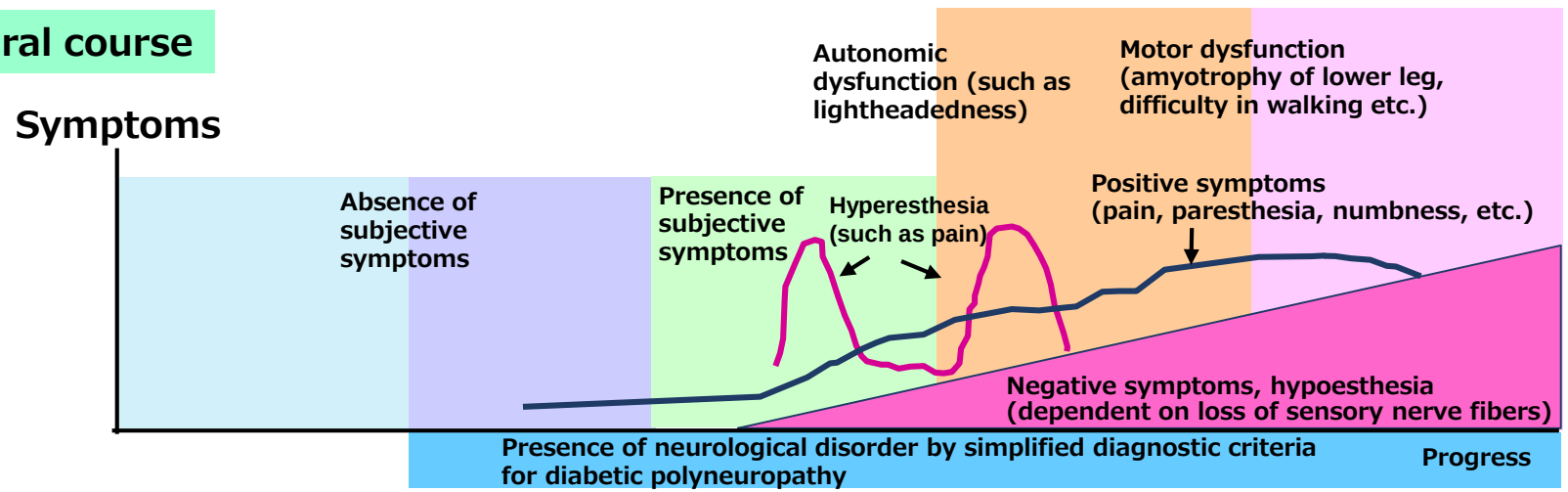
Diabetic Polyneuropathy

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

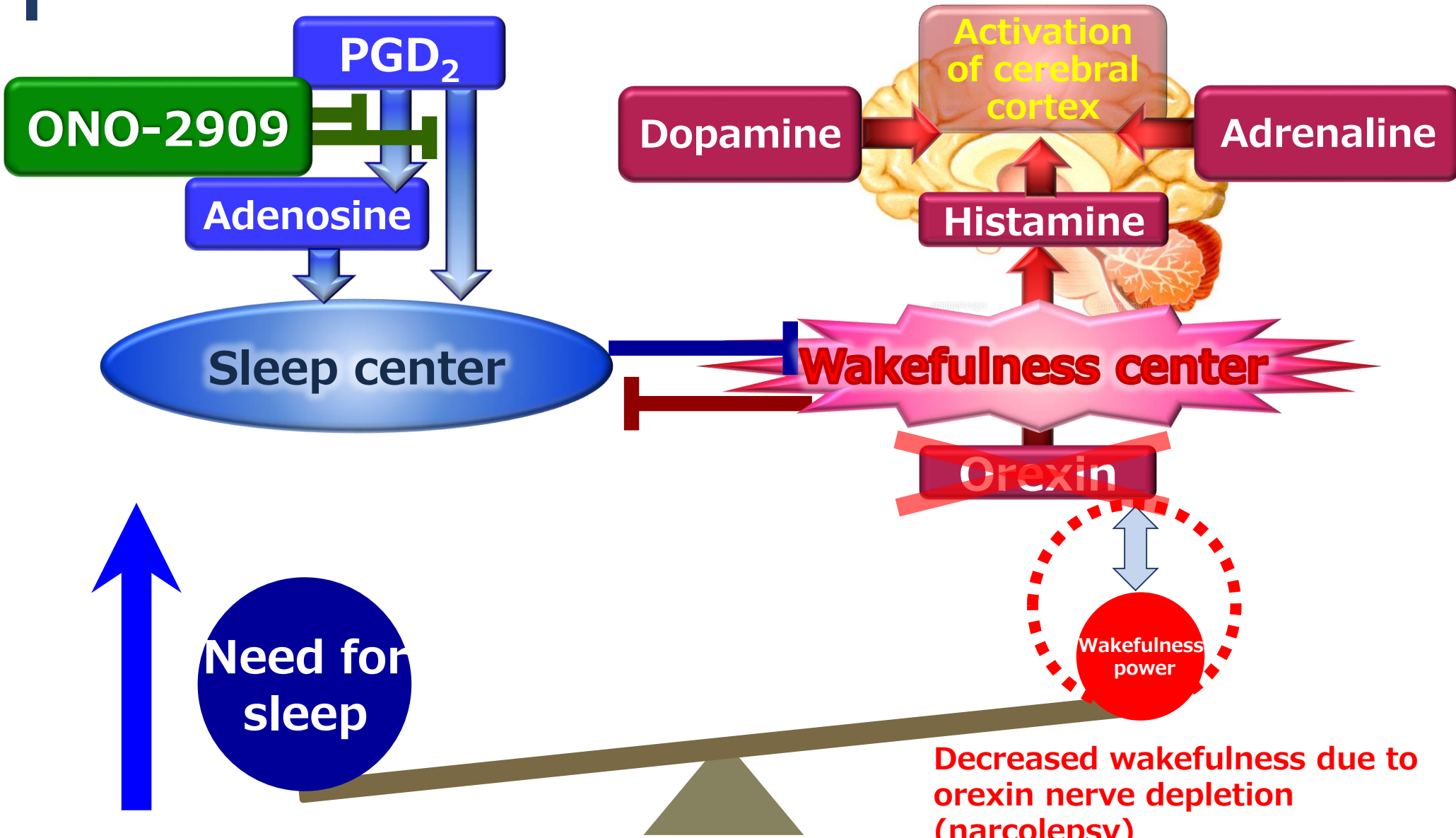


ONO-2909
Prostaglandin receptor (DP1) antagonist

ONO-2909

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

ONO-2909 Mechanism of Action

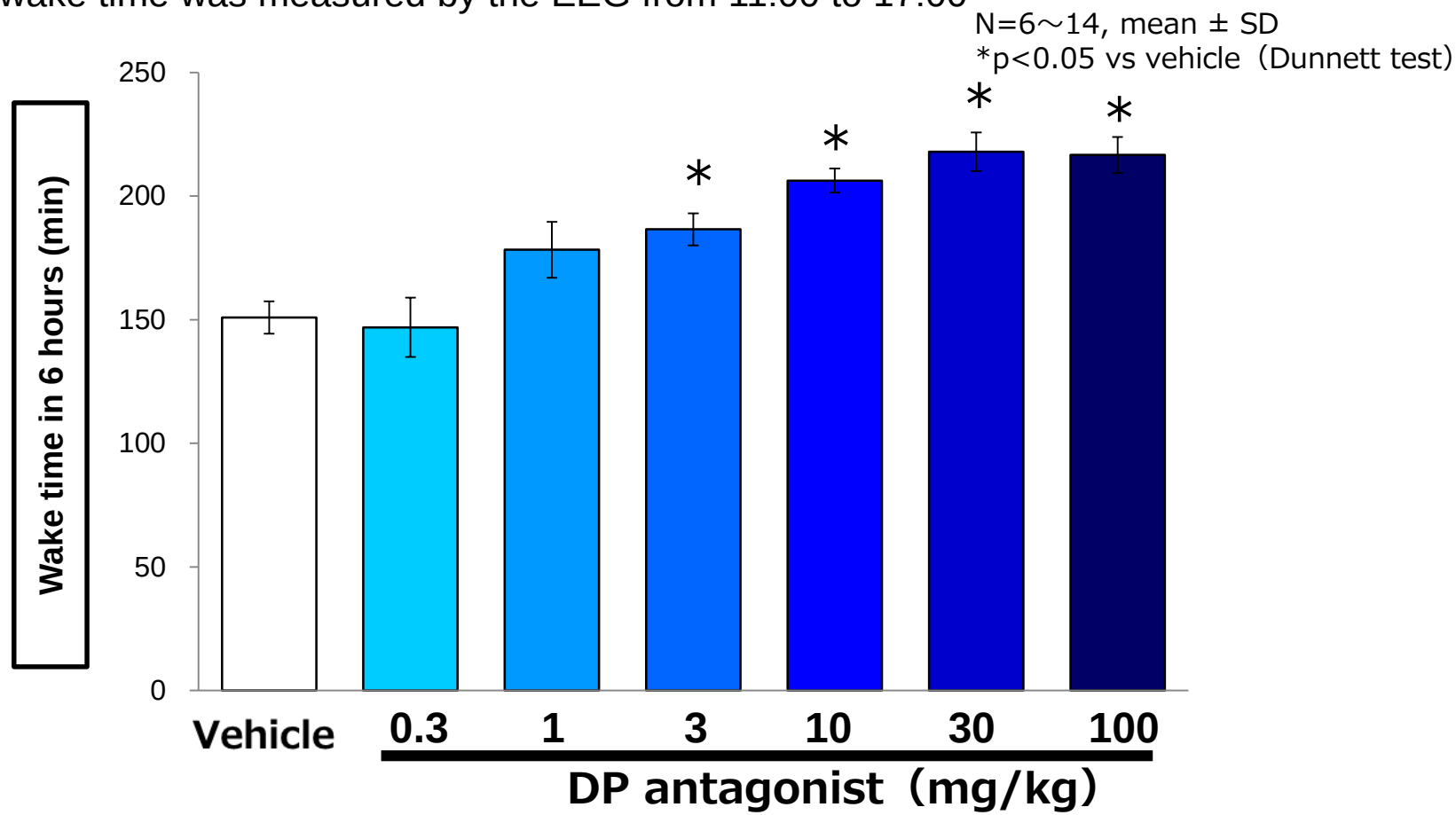


ONO-2909 suppresses sleep center activation and hypersomnia symptoms.

DP antagonist (Pharmacological study result 1)

Effect on wake time in normal rats

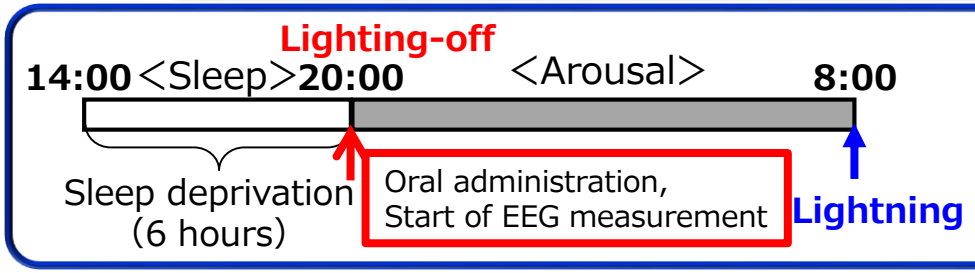
DP antagonist was administered at 11:00 am, which corresponds to the sleep phase for rodents, and the wake time was measured by the EEG from 11:00 to 17:00



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

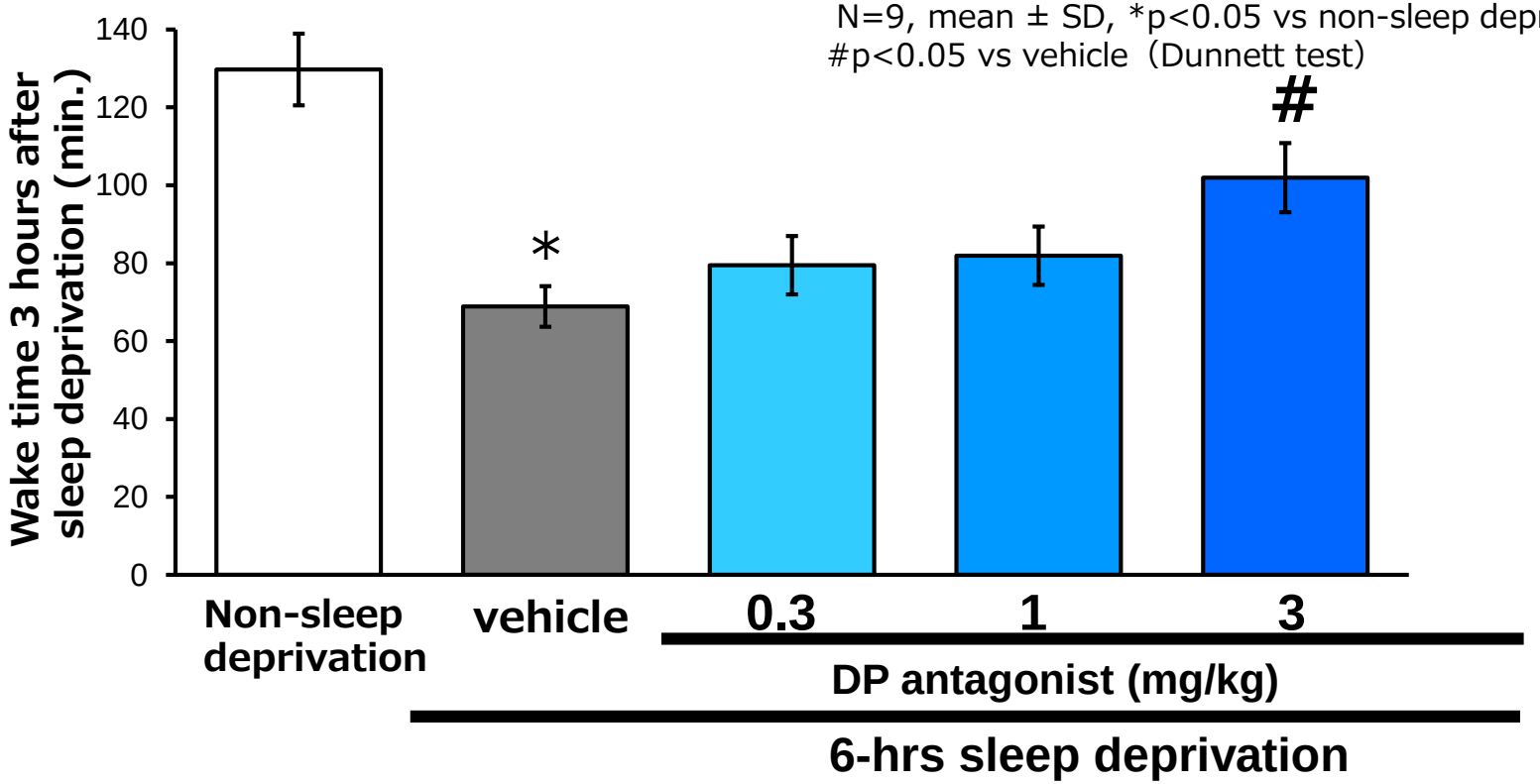
DP antagonist (Pharmacological study result 2)

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.

Narcolepsy

2 Major symptoms

Major symptoms ①： Hypersomnia

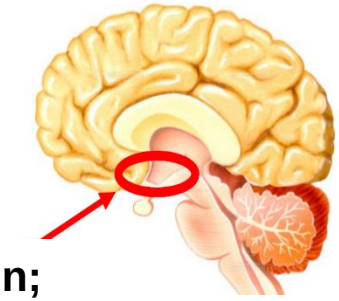
First-line：Modafinil

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.

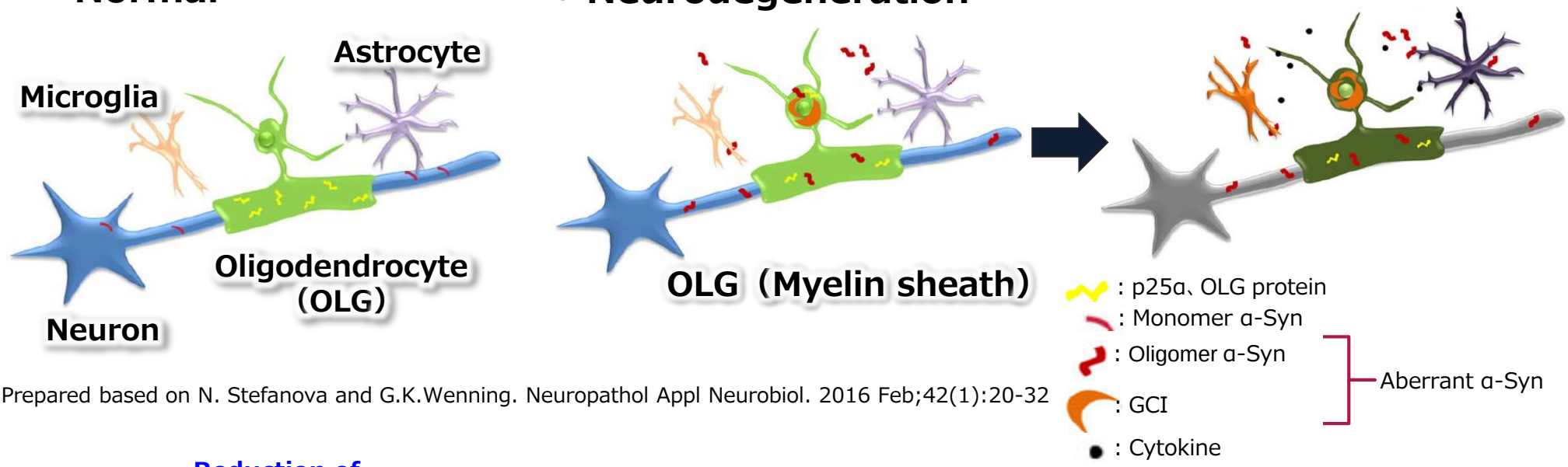
ONO-2808
S1P5 receptor agonist

ONO-2808

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

ONO-2808 Mechanism of Action

Normal ⇒ **Neurodegeneration**



Prepared based on N. Stefanova and G.K.Wenning. Neuropathol Appl Neurobiol. 2016 Feb;42(1):20-32

α-Syn : α-Synuclein

ONO-2808

Reduction of aberrant α-Syn accumulation & **Repair of Myelin sheath**

Reduction of aberrant α-Syn accumulation

OLG

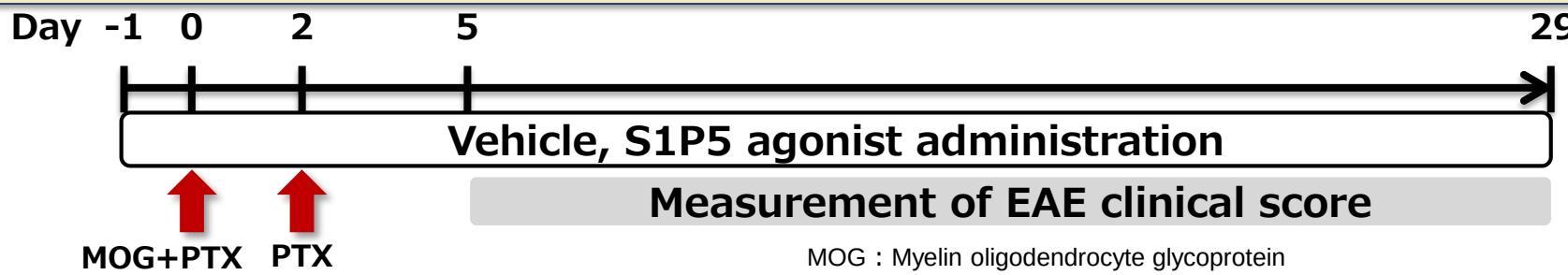
- **Aberrant α-Syn accumulation**
  ⇒ OLG loss, demyelination

Neuron

- **Decreased supply of neurotrophic factors from OLG**
- **Aberrant α-Syn accumulation**
  ⇒ Neuronal loss, axon degeneration

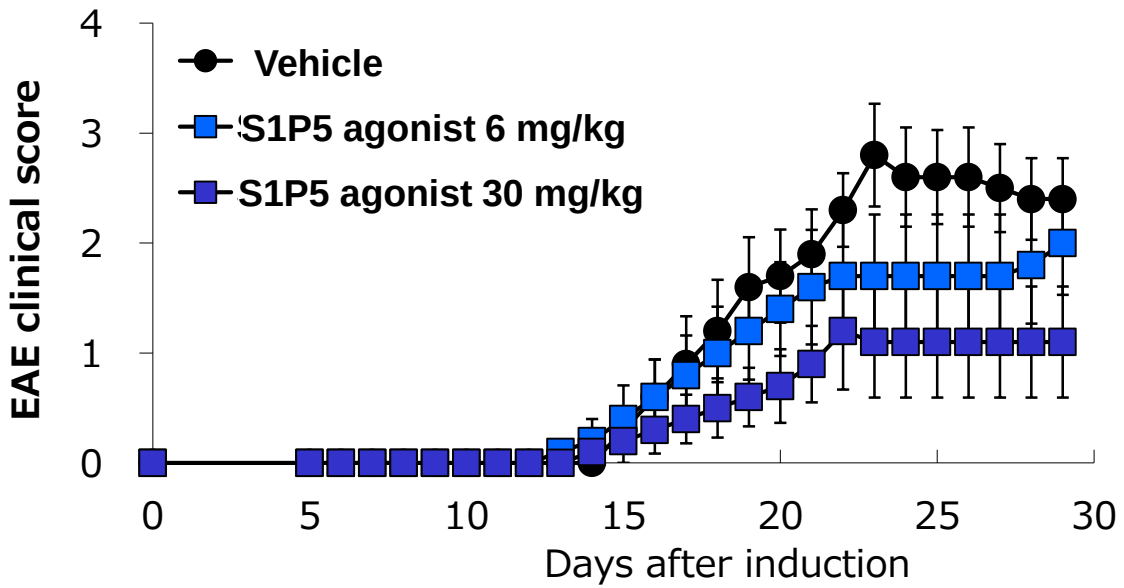
S1P5 agonist (Pharmacological study result)

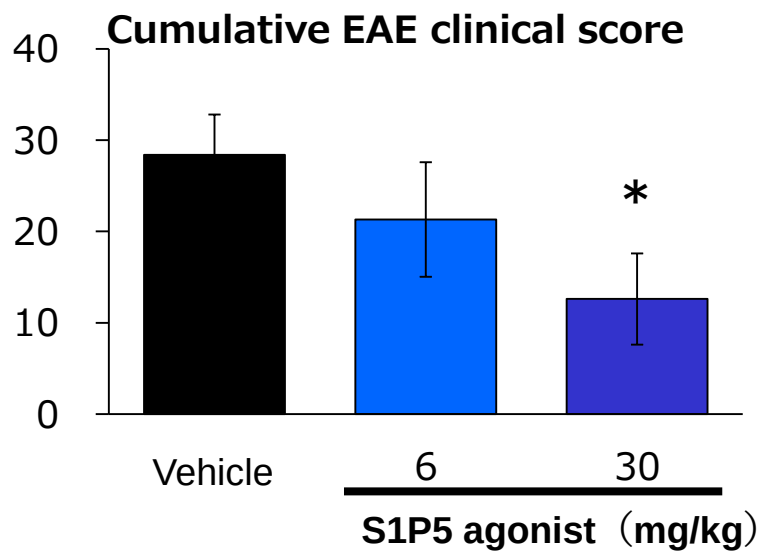
Effect in mouse experimental autoimmune encephalomyelitis (EAE) model



MOG : Myelin oligodendrocyte glycoprotein
PTX : Pertussis Toxin

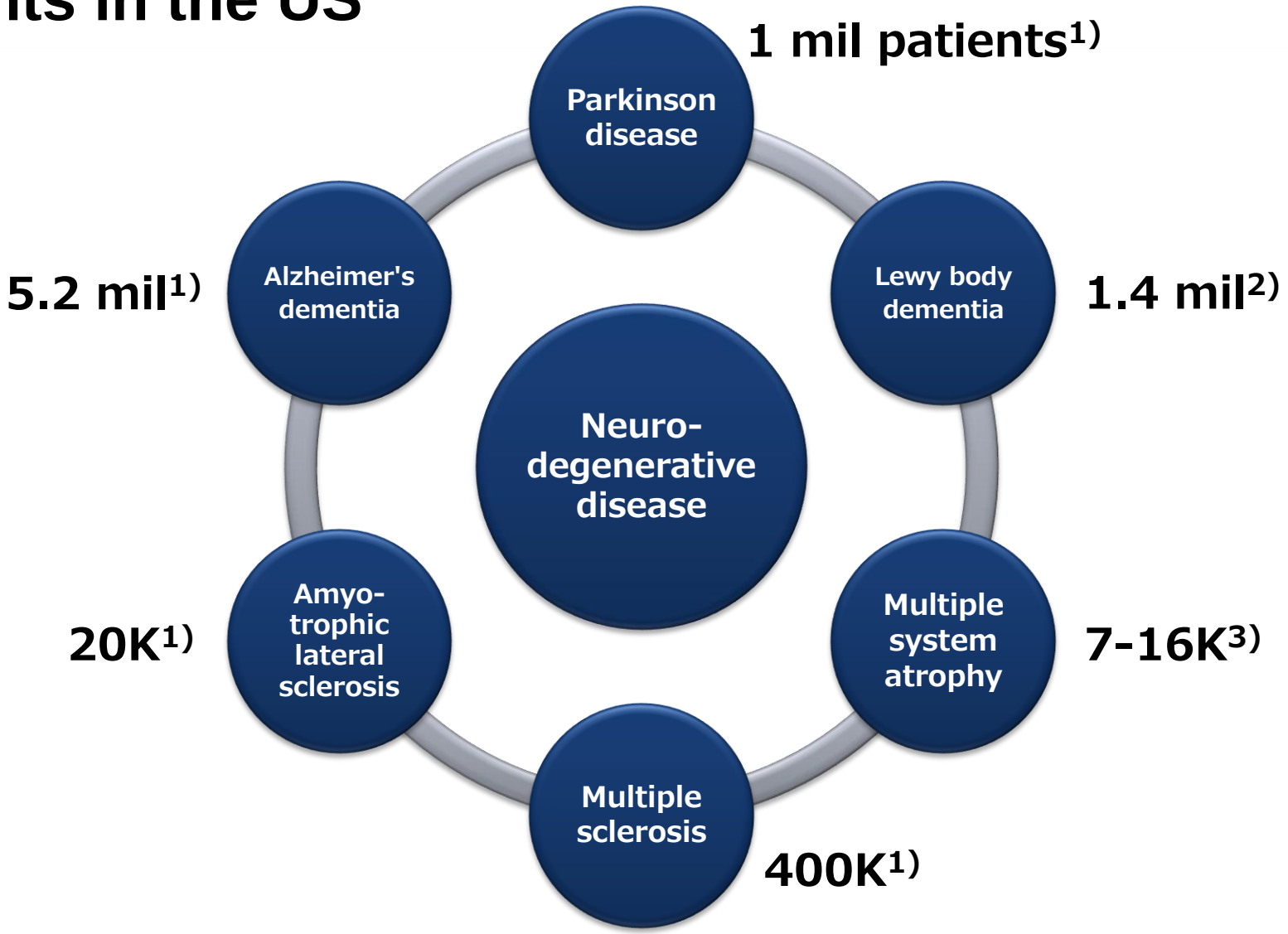
N=10, mean ±SD, *p<0.05 vs vehicle（Steel test） EAE clinical score: 0, normal; 1, limp tail; 2, paralysis of one limb; 3, complete paralysis of both hind limbs; 4, paralysis of all limbs; 5, moribund or death





S1P5 agonist suppressed aggravation of EAE clinical score.

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

ONO-4578

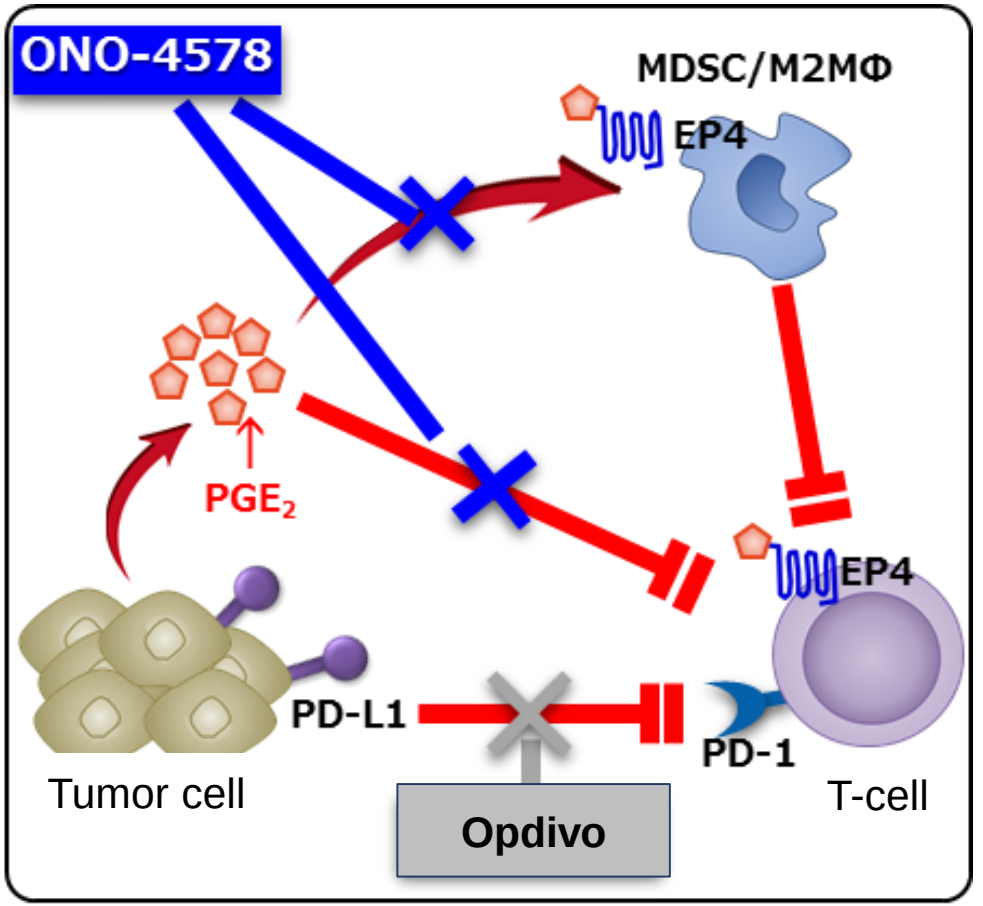
Prostaglandin receptor (EP4) antagonist

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

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

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

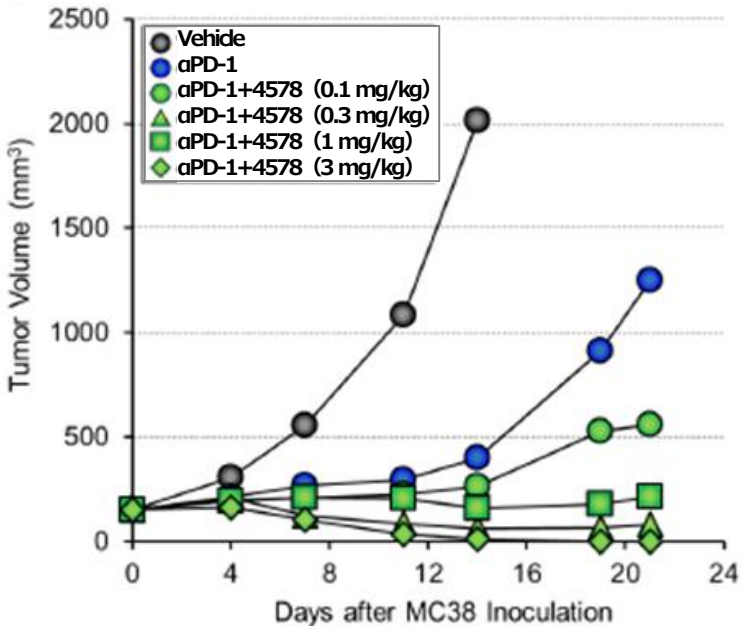
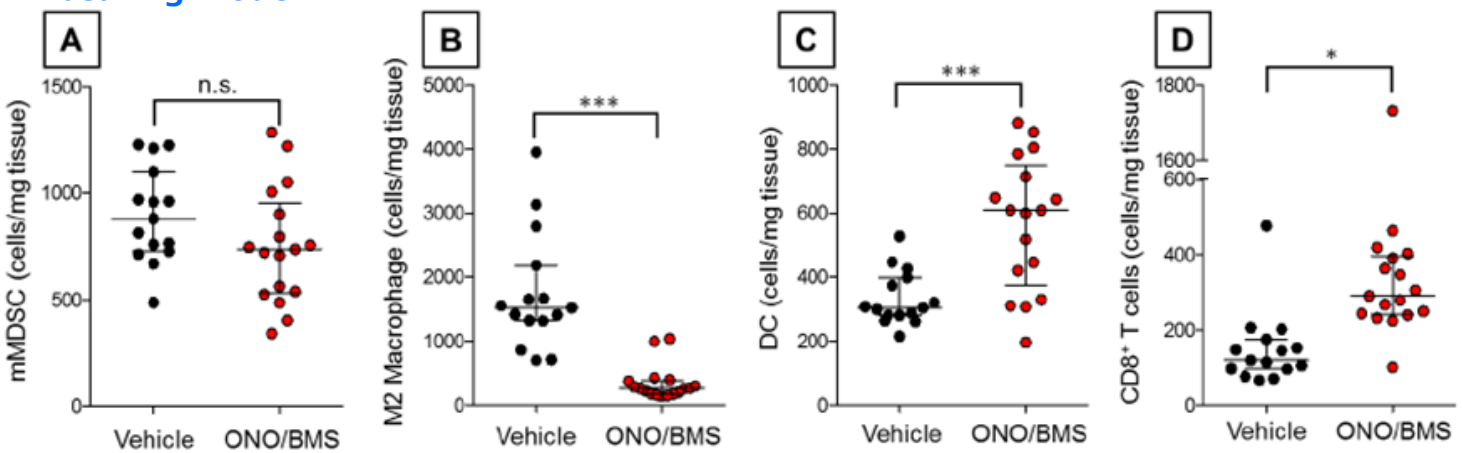


Fig 2. Effect of ONO-4578 on intra-tumoral immune cells in syngeneic mouse colorectal cancer MC38 tumor-bearing model

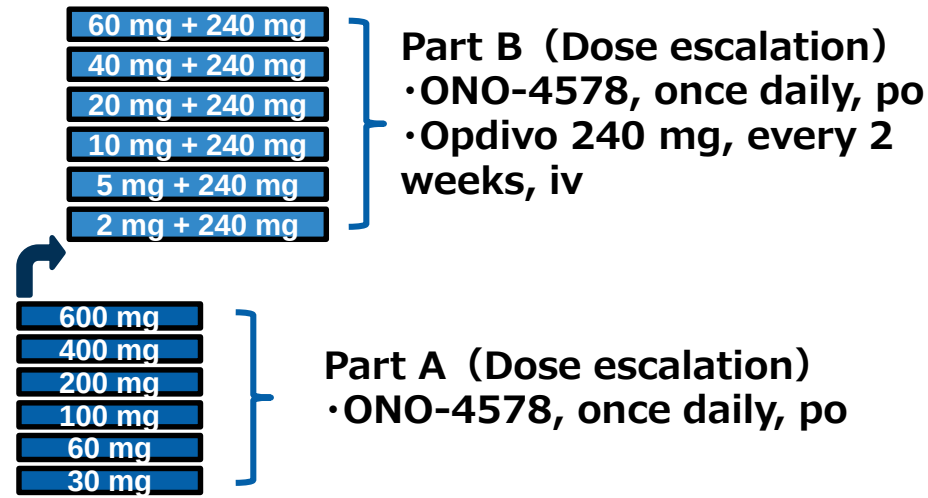


A : No. of mMDSC
B : No. of M2 macrophage
C : No. of dendritic cells
D : No. of CD8-positive T cells

AACR 2020: Poster # 4443

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.



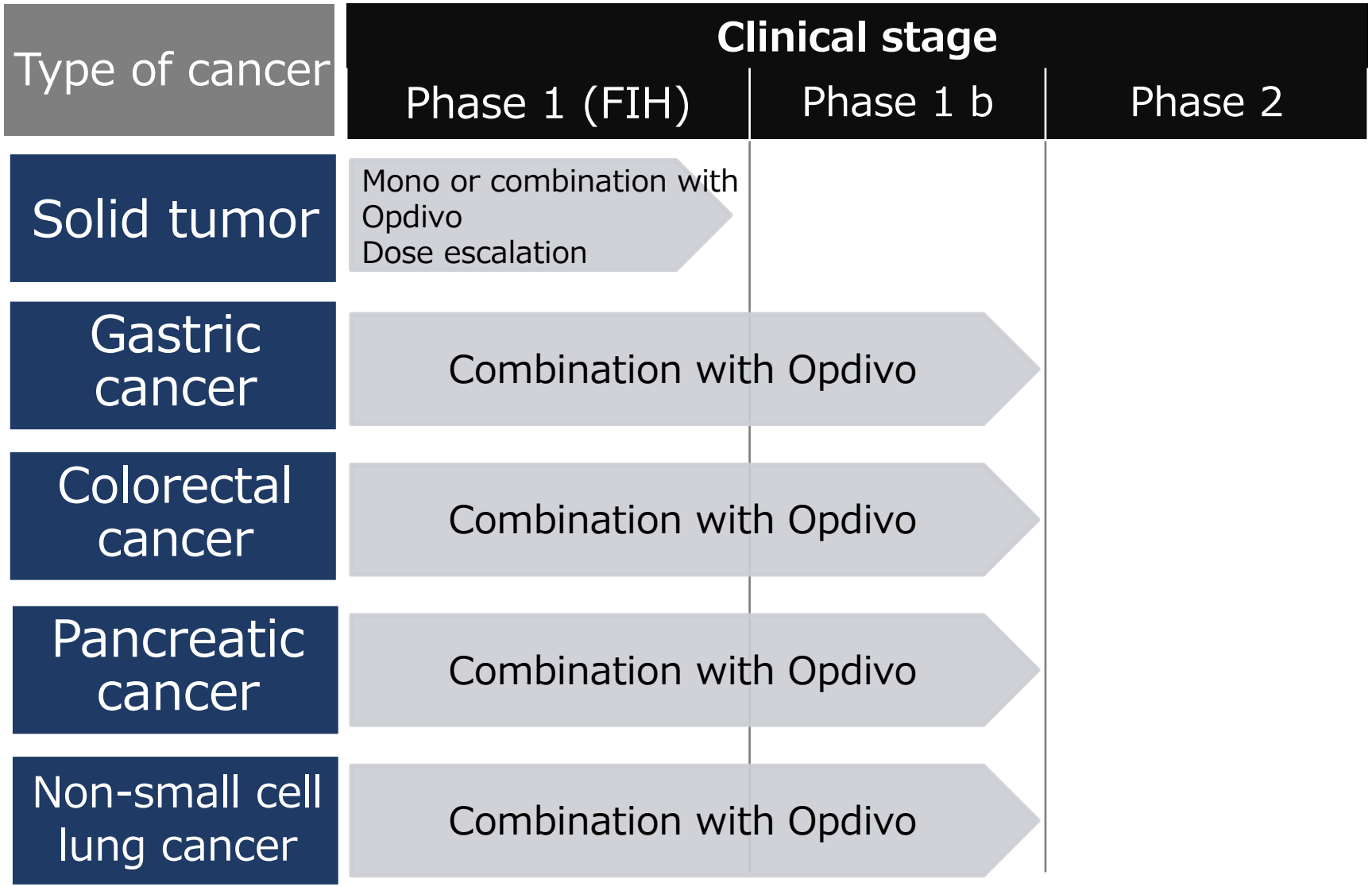
Main inclusion criteria:
- Age: 20 years or above, ECOG PS 0 or 1
- Advanced or metastatic solid tumors
  - ✓ Refractory or intolerant to standard treatment or no standard treatment (Part A)
  - ✓ Refractory or intolerant to standard treatment except anti-PD-1 antibody or no standard treatment (Part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

ONO-4578 Development stage



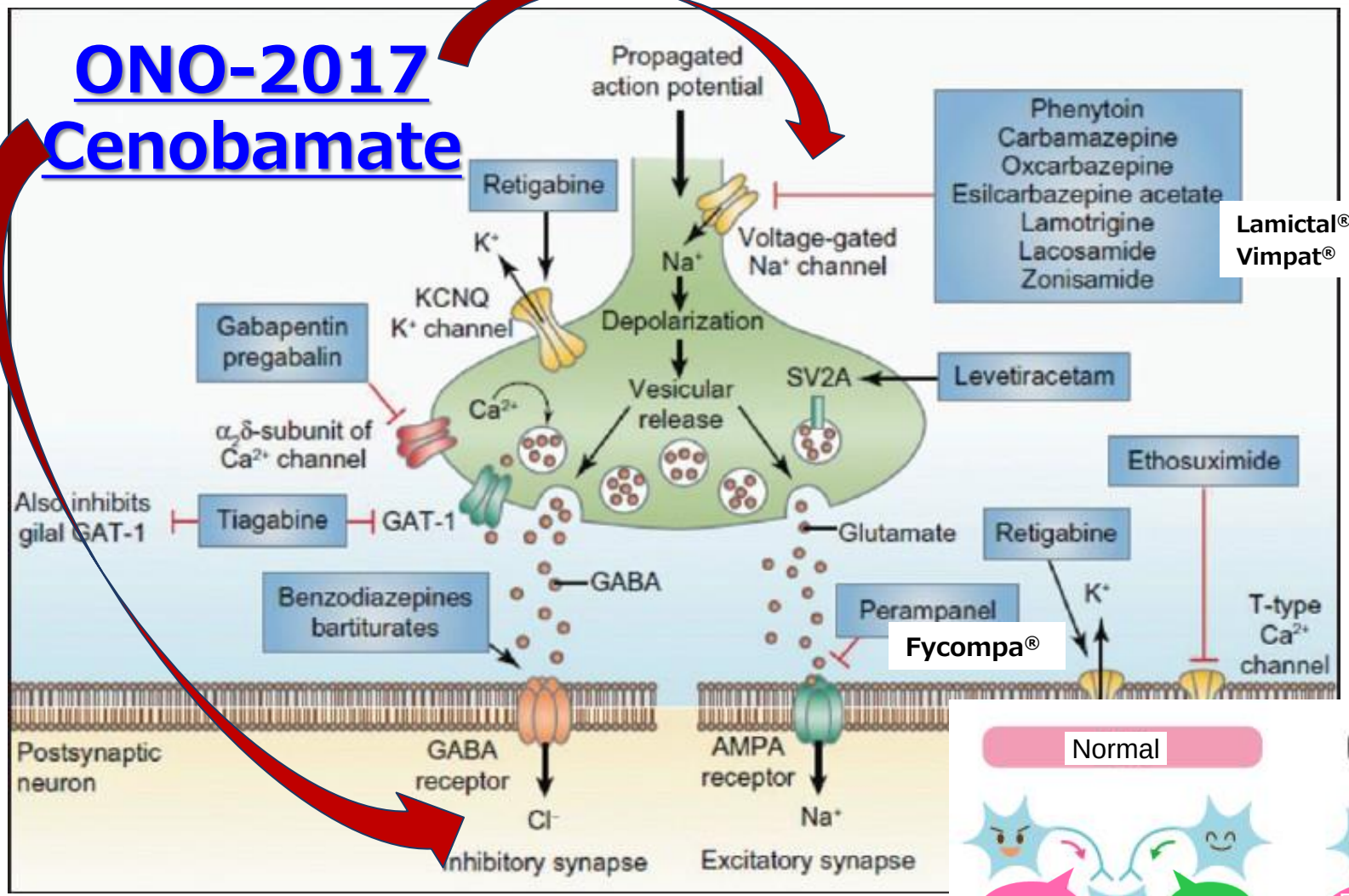
ONO-2017 (cenobamate)

Voltage-gated sodium currents inhibition/ $GABA_A$ modulation

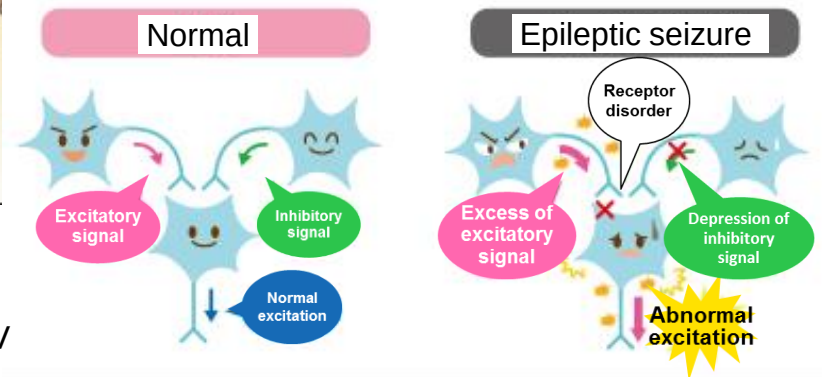
ONO-2017

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

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

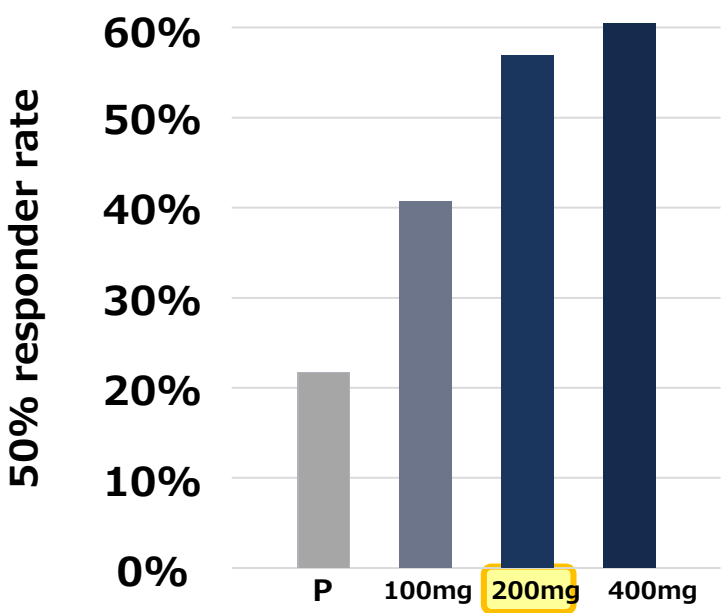
ONO-2017 Clinical Results

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**

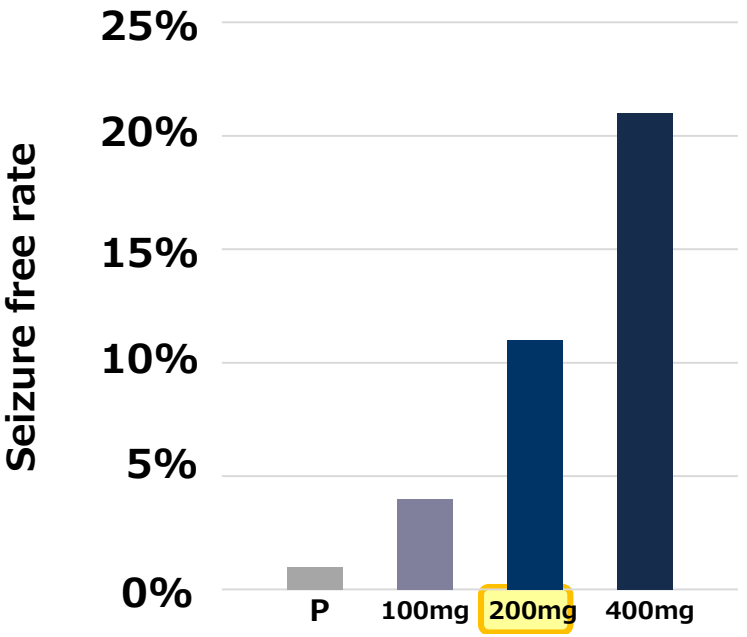
50% responder rate :
Percentage of cases in whom the number of partial seizure improved by ≧50% compared to the observation period



ONO-2017
Cenobamate

108-111 sujects/group

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



ONO-2017
Cenobamate

108-111 subjects/ group

Recommended dose

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

Epilepsy

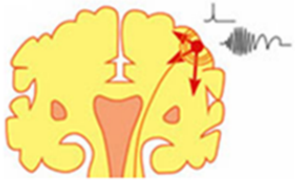
Partial (focal) Seizures

Motor symptoms
- Twisting
- Convulsion

Sensory symptoms
- Hearing problems
- Hallucinations
- Dysosmia

Neurological symptoms
- Dyspnoea
- Anxiety
- Déjà vu
- Nausea
- Headache

Result from abnormal activity in just one area of brain



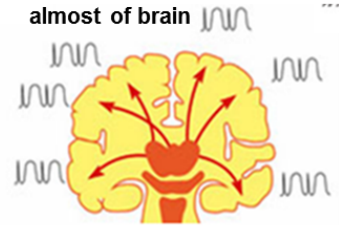
Loss of consciousness or awareness

Psychomotor symptoms
- Automatism
- Hallucinations
- Dysosmia

- Loss of consciousness
- Falls
- Convulsion

Generalized Seizures

Result from abnormal activity in almost of brain



Tonic-clonic seizures

- Loss of consciousness
- Falls
- Convulsion

Absence seizures

- Loss of consciousness
- Stopping activity

Myoclonic seizures

- Sudden brief jerks or twitches of your arms and legs

- Lennox-Gastaut syndrome
- West Syndrome

Pharmacotherapy (Japanese)

No. of adult patients treated with pharmacotherapy (Partial / focal seizures): 630 K	No. of adult patients treated with pharmacotherapy (Tonic-clonic seizures): 110 K
E Keppra®, Lamictal®, Topina®, Tegretol®, Excegran® Vimpat®, Fycompa®	Depakene® (Selenica®), E Keppra® Lamictal®, Fycompa®

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.

ONO PHARMACEUTICAL CO.,LTD.

Dedicated to the Fight against Disease and Pain