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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism</th>
<th>Target indication</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONO-2910</td>
<td>Schwann cell differentiation promoter</td>
<td>Diabetic polyneuropathy</td>
<td>P2</td>
</tr>
<tr>
<td>ONO-2909</td>
<td>Prostaglandin receptor (DP1) antagonist</td>
<td>Narcolepsy</td>
<td>P1</td>
</tr>
<tr>
<td>ONO-2808</td>
<td>S1P5 receptor agonist</td>
<td>Neurodegenerative disease</td>
<td>P1</td>
</tr>
<tr>
<td>ONO-4578</td>
<td>Prostaglandin receptor (EP4) antagonist</td>
<td>Solid tumor</td>
<td>P1</td>
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<tr>
<td>ONO-2017 (cenobamate)</td>
<td>Voltage-gated sodium currents inhibition/GABA&lt;sub&gt;Α&lt;/sub&gt; modulation</td>
<td>Epilepsy</td>
<td>Clinical Trial preparation</td>
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</table>
ONO-2910
Schwann cell
differentiation promoter
<table>
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<th>ONO-2910</th>
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</thead>
<tbody>
<tr>
<td>Company</td>
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<tr>
<td>Mechanism</td>
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<td>Formulation</td>
<td>Tablet</td>
</tr>
<tr>
<td>Indication</td>
<td>Diabetic polyneuropathy</td>
</tr>
<tr>
<td>Stage</td>
<td>Phase 2 (Japan)</td>
</tr>
</tbody>
</table>
ONO-2910 Mechanism of Action

Schwann cell
Nucleus
Nerve axon

Normal nerve fiber
Differentiation (Myelination)
Enhancement

ONO-2910
Suppression

Hyperglycemia
Demyelination - axon degeneration
Myelin debris
Axonal debris

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

## Simplified diagnostic criteria

<table>
<thead>
<tr>
<th>Prerequisite conditions (the following two must be met)</th>
</tr>
</thead>
</table>
| 1. Diagnosed as diabetes  
2. Neuropathies other than diabetic neuropathy can be excluded |

<table>
<thead>
<tr>
<th>Criteria (any two of the following three must be met)</th>
</tr>
</thead>
</table>
| 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)

## Natural course

**Symptoms**

- Absence of subjective symptoms
- Presence of subjective symptoms
- Hyperesthesia (such as pain)
- Positive symptoms (pain, paresthesia, numbness, etc.)
- Negative symptoms, hypoesthesia (dependent on loss of sensory nerve fibers)

**Presence of neurological disorder by simplified diagnostic criteria for diabetic polyneuropathy**

**Progress**

**Autonomic dysfunction (such as lightheadedness)**

**Motor dysfunction (amyotrophy of lower leg, difficulty in walking etc.)**

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*Japanese Clinical Practice Guideline for Diabetes 2019*
ONO-2909
Prostaglandin receptor (DP1) antagonist
<table>
<thead>
<tr>
<th>Compound</th>
<th>ONO-2909</th>
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<tbody>
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<td>Mechanism</td>
<td>Prostaglandin receptor (DP1) antagonist</td>
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<tr>
<td>Formulation</td>
<td>Tablet</td>
</tr>
<tr>
<td>Indication</td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>Stage</td>
<td>Phase 1 (Japan)</td>
</tr>
</tbody>
</table>
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.

N=6~14, mean ± SD
*p<0.05 vs vehicle (Dunnett test)

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

- 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

**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)**

### Narcolepsy type 1

(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 type 2

(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

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Orexin; hormones involved in maintaining awakening

**Narcolepsy type 1 patients are loss of the nerves producing and secreting orexin.**

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ONO-2808
S1P5 receptor agonist
<table>
<thead>
<tr>
<th>Compound</th>
<th>ONO-2808</th>
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<tbody>
<tr>
<td>Company</td>
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<td>Mechanism</td>
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<td>Formulation</td>
<td>Tablet</td>
</tr>
<tr>
<td>Indication</td>
<td>Neurodegenerative disease</td>
</tr>
<tr>
<td>Stage</td>
<td>Phase 1 (Europe/ Japan)</td>
</tr>
</tbody>
</table>
ONO-2808 Mechanism of Action

Normal ⇒ Neurodegeneration

- Decreased supply of neurotrophic factors from OLG
- Aberrant α-Syn accumulation

⇒ Neuronal loss, axon degeneration

ONO-2808

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

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

Day -1  0  2  5  29

Vehicle, S1P5 agonist administration

Measurement of EAE clinical score

MOG+PTX  PTX

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

- Parkinson disease: 1 mil patients\(^1\)
- Alzheimer's disease: 5.2 mil\(^1\)
- Lewy body dementia: 1.4 mil\(^2\)
- Amyotrophic lateral sclerosis: 20K\(^1\)
- Multiple system atrophy: 7-16K\(^3\)
- Multiple sclerosis: 400K\(^1\)

1) : Thermo Fisher SCIENTIFIC Web [https://www.thermofisher.com/blog/learning-at-the-bench/neuro_disease1/](https://www.thermofisher.com/blog/learning-at-the-bench/neuro_disease1/)
2) : Lewvy Boday Dementia Association Web [https://www.lbda.org/about-lbd/](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](https://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN)
ONO-4578
Prostaglandin receptor (EP4) antagonist
## ONO-4578

<table>
<thead>
<tr>
<th>Compound</th>
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<tbody>
<tr>
<td>Company</td>
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<td>Mechanism</td>
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<td>Formulation</td>
<td>Tablet</td>
</tr>
<tr>
<td>Indication</td>
<td>Solid Cancer</td>
</tr>
</tbody>
</table>
| Stage          | Phase 1 (Japan)  
Colorectal cancer, pancreatic cancer, Non-small cell lung cancer, gastric cancer |
**ONO-4578 Mechanism of Action**

- Prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) is produced from arachidonic acid through cyclooxygenase-2 (COX-2)
- COX-2 is overexpressed in solid cancer\textsuperscript{1}). PGE\textsubscript{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\textsuperscript{2}.
- ONO-4578, a novel selective EP4 antagonist, is expected to have an antitumor effect by abolishing the tumor immunosuppressive mechanism that PGE\textsubscript{2} constructs via EP4.

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
## ONO-4578 Development stage

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Clinical stage</th>
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<tbody>
<tr>
<td></td>
<td>Phase 1 (FIH)</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>Mono or combination with Opdivo</td>
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<tr>
<td></td>
<td>Dose escalation</td>
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<tr>
<td>Gastric cancer</td>
<td>Combination with Opdivo</td>
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<tr>
<td>Colorectal cancer</td>
<td>Combination with Opdivo</td>
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<tr>
<td>Pancreatic cancer</td>
<td>Combination with Opdivo</td>
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<tr>
<td>Non-small cell lung cancer</td>
<td>Combination with Opdivo</td>
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ONO-2017 (cenobamate) Voltage-gated sodium currents inhibition/ GABA_A modulation
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<th><strong>Compound</strong></th>
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<tbody>
<tr>
<td><strong>Company</strong></td>
<td>SK Biopharmaceuticals Co., Ltd.</td>
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<tr>
<td><strong>Mechanism</strong></td>
<td>Voltage-gated sodium currents inhibition/GABA&lt;sub&gt;A&lt;/sub&gt; modulation</td>
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<tr>
<td><strong>Formulation</strong></td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Epilepsy (Partial seizure, tonic-clonic seizure)</td>
</tr>
</tbody>
</table>
| **Stage** | US: Launched by SK Life Science  
Europe: Launched by Angelini Pharma  
Japan: Under preparation for clinical trial |
**ONO-2017 Mechanism of Action**

**ONO-2017 Cenobamate**

Mechanism of action of antiepileptic drugs

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 $\geq 50\%$ compared to the observation period

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

50% responder rate

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
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<th>60%</th>
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</table>

Seizure free rate

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
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<tbody>
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ONO-2017 Cenobamate

Recommended dose

108-111 subjects/group

Epilepsy

Patients refractory to existing treatments: 20-30%

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

Pharmacotherapy (Japanese)

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

- Prepared based on materials for training of epilepsy for school.
- JAMA Neurol, 2008; 75: 279-86.
ONO PHARMACEUTICAL CO., LTD.
Dedicated to the Fight against Disease and Pain