1. **Psychiatry & Neurology**

**Ulotaront (SEP-363856)**

- Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral
- Ulotaront (SEP-363856) is a TAAR1 (trace amine-associated receptor 1) agonist with serotonin 5-HT\textsubscript{1A} agonist activity. Ulotaront does not bind to dopamine D\textsubscript{2} or serotonin 5-HT\textsubscript{2A} receptors. Sunovion discovered ulotaront in collaboration with PsychoGenics using its in vivo phenotypic SmartCube\textsuperscript{®} platform and associated artificial intelligence algorithms. Phase 2 results in patients with schizophrenia support the efficacy of ulotaront in treating both positive and negative symptoms of schizophrenia, while demonstrating a side effect profile with notable similarities to placebo: extrapyramidal symptoms, weight gain, lipid and glucose derangements or prolactin elevation.
- Development stage: (Co-development with Otsuka Pharmaceutical Co., Ltd.) Schizophrenia: Phase 3 in the U.S. Parkinson’s disease psychosis: Phase 2 in the U.S.

**EPI-589**

- Origin: PTC Therapeutics, Inc. (Acquired from BioElectron Technology Corporation), Formulation: oral
- EPI-589 is expected to show efficacy by removing the oxidative stress that is generated excessively by decreased mitochondrial function. It is expected to be developed for neurodegenerative indications arising through redox stress.
- Development stage:
  - Parkinson’s disease: Phase 2 in the U.S.
  - Amyotrophic lateral sclerosis (ALS): Phase 2 in the U.S.
  - Amyotrophic lateral sclerosis (ALS): Phase 2 (Investigator-initiated study\textsuperscript{*}) in Japan
- Sponsor: Tokushima University

**SEP-4199**

- Origin: in-house (Sunovion Pharmaceuticals Inc.), Formulation: oral
- SEP-4199 is a non-racemic ratio of amisulpride enantiomers. Sunovion discovered that the pharmacology of amisulpride is enantiomer-specific, and that increasing the ratio of R-amisulpride to S-amisulpride increases the potency for serotonin 5-HT\textsubscript{7} receptors relative to dopamine D\textsubscript{2} receptors. SEP-4199 was designed with an 85:15 ratio of R-amisulpride to S-amisulpride to increase levels of serotonin 5-HT\textsubscript{7} activity intended to enhance antidepressant efficacy and produce reduced levels of D\textsubscript{2} receptor occupancy appropriate for the treatment of bipolar depression.
- Development stage: (Co-development with Otsuka Pharmaceutical Co., Ltd.)
  - Bipolar I depression: Phase 3 in the U.S.
  - Bipolar I depression: Preparing for Phase 3 in Japan

**DSP-6745**

- Origin: in-house, Formulation: oral
- DSP-6745 is a serotonin 5-HT\textsubscript{2A} and serotonin 5-HT\textsubscript{2C} receptors dual antagonist, which is expected to be effective for Parkinson’s disease psychosis and one or more Parkinson’s disease non-motor symptoms (depression, anxiety, or cognitive impairment). In addition, DSP-6745 has negligible affinity for dopamine D\textsubscript{2} receptors.
- Development stage: Parkinson’s disease psychosis: Phase 1 in the U.S.
SEP-378608  
Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral  
- SEP-378608 is a novel CNS-active molecule. Sunovion discovered SEP-378608 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms. Pre-clinical studies suggest that it may modulate neuronal activity in key areas of the brain associated with the regulation of mood.
- Development stage: Bipolar disorder: Phase 1 in the U.S.

DSP-3905  
Origin: in-house, Formulation: oral  
- DSP-3905 is an agent that selectively inhibits voltage-gated sodium channels Nav1.7. Based on its inhibitory mode of action, the agent is expected to show a potent analgesic effect on the pain occurring when neurons get excessively excited. In addition, DSP-3905 has a high selectivity for Nav1.7 expressed in peripheral neuron and may not produce central nervous system or cardiovascular system side effects, which are present with the current drugs for neuropathic pain.
- Development stage: Neuropathic pain: Phase 1 in the U.S.

SEP-378614  
Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral  
- SEP-378614 is a novel CNS-active molecule. Sunovion discovered SEP-378614 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms. Pre-clinical studies suggest that it may have rapid onset and long lasting antidepressant-like activity and enhance neuroplasticity.
- Development stage: Phase 1 in the U.S. (Co-development with Otsuka Pharmaceutical Co., Ltd.)

SEP-380135  
Origin: in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral  
- SEP-380135 is a novel CNS-active molecule. Sunovion discovered SEP-380135 in collaboration with PsychoGenics using its in vivo phenotypic SmartCube® platform and associated artificial intelligence algorithms. Pre-clinical studies showed a broad range of in vivo activities suggesting efficacy against a number of behavioral and psychological symptoms in dementia, including agitation/aggression, psychomotor hyperactivity, depression and deficits in social interaction.
- Development stage: Phase 1 in the U.S. (Co-development with Otsuka Pharmaceutical Co., Ltd.)

DSP-1181  
Origin: in-house (Joint research with Exscientia Ltd.), Formulation: oral  
- DSP-1181 is a novel compound created by Sumitomo Dainippon Pharma using Exscientia’s AI technologies. In contrast to conventional serotonin 5-HT1A receptor partial agonists (non-benzodiazepine anxiolytics), DSP-1181 has a potent full agonistic activity for serotonin 5-HT1A receptors and is expected to have a long half-life, and therefore it is suggested that DSP-1181 has strong efficacy over a long period of time. In obsessive compulsive disorder (OCD) model mice manipulated OCD-related neural circuit, DSP-1181 is expected to have an earlier onset of efficacy than a standard medication, a selective serotonin reuptake inhibitor (SSRI).
- Development stage: Obsessive compulsive disorder: Phase 1 in Japan.

DSP-0038  
Origin: in-house (Joint research with Exscientia Ltd.), Formulation: oral  
- DSP-0038 is a novel compound discovered at Sumitomo Dainippon Pharma using Exscientia’s AI technologies. DSP-0038 is a serotonin 5-HT2A receptor antagonist and a serotonin 5-HT1A receptor agonist. DSP-0038 is expected to demonstrate a greater antipsychotic effect, based on the additive effect of 5-HT2A receptor antagonist and 5-HT1A receptor agonist. The compound could also have a broader efficacy in the treatment of behavioral and psychological symptoms of dementia (BPSD) which include agitation, aggression, anxiety, and depression. Furthermore, DSP-0038 has negligible affinity.
for dopamine D2 receptors, and therefore it can be expected to show improved safety and tolerability compared to existing antipsychotic.

- Development stage: Alzheimer's disease psychosis: Phase 1 in the U.S.

**DSP-9632P**
- Origin: in-house, Formulation: patch
  - DSP-9632P is a serotonin 5-HT1A receptor partial agonist. It is expected to exert an effect on dyskinesia expressed after administration of levodopa by suppressing the excessive release of levodopa-derived dopamine. Pre-clinical studies suggest DSP-9632P suppresses the dyskinesia symptom induced by levodopa. The transdermal patch formulation of DSP-9632P could potentially have an effective treatment option for levodopa-induced dyskinesia in Parkinson's disease by showing stable blood concentration, and may also lead to improved convenience for patients in terms of drug administration.
  - Development stage: Levodopa-induced dyskinesia in Parkinson's disease: Phase 1 in Japan

2. Oncology

**adegramotide/nelatimotide (DSP-7888)**
- Origin: in-house, Formulation: injection
  - DSP-7888 is an immunotherapeutic cancer peptide vaccine targeting Wilms' tumor gene 1 (WT1) protein. DSP-7888 is a vaccine containing peptides that induces WT1-specific cytotoxic T lymphocytes (CTLs) and helper T cells. DSP-7888 is expected to become a treatment option for patients with various types of hematologic malignancies and solid tumors that express WT1 by inducing WT1-specific CTLs that attack WT1-expressing cancer cells. By adding a helper T cell-inducing peptide, improved efficacy over that observed with a CTL-inducing peptide alone may be achieved. DSP-7888 is expected to be an option for a wide range of patients.
  - Development stage:

<table>
<thead>
<tr>
<th>Proposed indication</th>
<th>Combination products</th>
<th>Country/Area</th>
<th>Stage</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>bevacizumab</td>
<td>U.S., Japan</td>
<td>Phase 3</td>
<td>BBI-DSP7888-201G</td>
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<tr>
<td>Solid tumors</td>
<td>nivolumab, pembrolizum</td>
<td>U.S.</td>
<td>Phase 1/2</td>
<td>BBI-DSP7888-102CI</td>
</tr>
</tbody>
</table>

**dubermatinib (TP-0903)**
- Origin: University of Utah, Formulation: oral
  - Dubermatinib (TP-0903) is an inhibitor of multikinase including AXL receptor tyrosine kinase inhibitor, which is known to be involved in acquiring resistance to conventional agents and developing metastatic capacity in cancer cells. Dubermatinib may have anti-cancer activities on various cancer types through blocking transition from epithelial to mesenchymal phenotype by inhibiting AXL. Dubermatinib has been shown to inhibit AXL signaling and reverse the mesenchymal to epithelial phenotype in preclinical studies.
  - Development stage: Acute Myeloid Leukemia: Phase 1/2 (Research group-initiated study*) in the U.S.
  * One arm in the Beat AML study led by the U.S. non-profit organization LLS (The Leukemia & Lymphoma Society)

**guretolimod (DSP-0509)**
- Origin: in-house, Formulation: injection
  - Guretolimod (DSP-0509) is a novel Toll-like receptor (TLR) 7 agonist. Guretolimod may promote the cytokine induction and cytotoxic T lymphocyte (CTL) activation mediated by agonistic effect of TLR 7 expressing in plasmacytoid dendritic cell. Furthermore, guretolimod is expected to sustain the immune-mediated anti-cancer activity by induction of immune system memory T cells.
  - Development stage: Solid tumors: Phase 1/2 in the U.S.
Profiles of Major Products under Development

**itacnosertib (TP-0184)**  
*Origin: in-house (former Tolero Pharmaceuticals, Inc.), Formulation: oral*
- Itacnosertib (TP-0184) has an inhibitory effect against kinase such as ALK2 and ALK5, part of the transforming growth factor beta (TGFβ) receptor superfamily. In myelodysplastic syndromes, the ALK5 pathway is activated and caused abnormal erythroid differentiation. Itacnosertib is expected to show anti-cancer activities through the kinase inhibitory effect decrease hepcidin expression, increase bioavailable iron, and restore normal levels of hemoglobin.
- Development stage:  
  Anemia associated with myelodysplastic syndromes: Phase 1/2 in the U.S.

**DSP-5336**  
*Origin: in-house (Joint research with Kyoto University), Formulation: oral*
- DSP-5336 is a small molecule inhibitor against the binding of menin and mixed-lineage leukemia (MLL) protein. Acute leukemia with MLL rearrangements or nucleophosmin 1 (NPM1) mutations rely on the menin-MLL interaction for upregulation of genes instrumental to leukemogenesis. DSP-5336 has been shown to have anti-cancer activity through downregulation of the genes by inhibition of menin-MLL interaction in pre-clinical studies.
- Development stage: Hematologic malignancies: Phase 1/2 in the U.S.

**TP-1287**  
*Origin: in-house (former Tolero Pharmaceuticals, Inc.), Formulation: oral*
- TP-1287 is a small molecule oral agent that inhibits cyclin-dependent kinase 9 (CDK9). TP-1287 has shown favorable oral bioavailability in pre-clinical studies. It is enzymatically cleaved, yielding alvocidib, a potent inhibitor of CDK9. The oral administration of TP-1287 may allow for administration for a prolonged period, which may lead to a continuous inhibition of CDK9.
- Development stage: Solid tumors: Phase 1 in the U.S.

**TP-3654**  
*Origin: in-house (former Tolero Pharmaceuticals, Inc.), Formulation: oral*
- TP-3654 inhibits the inflammatory signaling pathways through inhibition of PIM (proviral integration site for Moloney murine leukemia virus) kinases. PIM kinases are frequently overexpressed in various hematologic malignancies and solid tumors, allowing cancer cells to evade apoptosis and promoting tumor growth.
- Development stage: Myelofibrosis: Phase 1 in the U.S. and Japan

**TP-1454**  
*Origin: in-house (former Tolero Pharmaceuticals, Inc.), Formulation: oral*
- TP-1454 inhibits tumor growth through activation of PKM2 (pyruvate kinase M2) which lead to the inhibition of tumor cell proliferation and enhances antitumor immune response in tumor microenvironment. TP-1454 induces the activity of PKM2 through tetramerization of the enzyme which mainly exists in enzymatically less active dimer state in cancer cells. Tetramerization of PKM2 lead to the reduction of aerobic glycolysis in cancer cells and revert the immunosuppressive microenvironment. TP-1454 is expected to show synergistic effect with immune checkpoint inhibitor.
- Development stage:  
  Solid tumors: Phase 1 in the U.S.

**DSP-0390**  
*Origin: in-house, Formulation: oral*
- DSP-0390 is an inhibitor of Emopamil Binding Protein (EBP), which is one of cholesterol biosynthetic enzymes. EBP is an endoplasmic reticulum membrane protein involved in cholesterol biosynthesis. When functional, EBP mediates de novo cholesterol synthesis for cell membrane structure and signaling, enabling aberrant growth of tumors. Inhibition of EBP causes an efficient cellular cholesterol depletion and it is expected to show anti-cancer activities.
- Development stage: Solid tumors: Phase 1 in the U.S. and Japan
3. Regenerative medicine / cell therapy

Allo iPS cell-derived products

- In cooperation with the partners in the industry-academia collaboration, we are promoting toward the commercialization of regenerative medicine / cell therapy using allo iPS (induced pluripotent stem) cell (healthy patients) for AMD (age-related macular degeneration), Parkinson’s disease, retinitis pigmentosa, and spinal cord injury.

- Development stage:

<table>
<thead>
<tr>
<th>Development code</th>
<th>Partnering</th>
<th>Proposed indication</th>
<th>Area</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>Kyoto University</td>
<td>Parkinson’s disease</td>
<td>Japan</td>
<td>Phase 1/2 (Investigator-initiated study, Sponsor: Kyoto University Hospital)</td>
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<tr>
<td>HLCR011</td>
<td>RIKEN, Healios</td>
<td>Age-related macular degeneration (AMD)</td>
<td>Japan</td>
<td>Preparing for start of clinical study</td>
</tr>
</tbody>
</table>

4. Others

relugolix

- Relugolix is a once-daily, oral gonadotropin-releasing hormone (GnRH) receptor antagonist that reduces testicular testosterone production, the hormone primarily responsible for stimulating prostate cancer, and ovarian estradiol production, hormones known to stimulate the growth of uterine fibroids and endometriosis. Myovant received approval in the U.S. in December 2020 for a relugolix single agent tablet (120 mg) for men with advanced prostate cancer and in May 2021 for a distinct product, a relugolix combination tablet (relugolix 40 mg plus estradiol 1.0 mg and norethindrone acetate 0.5 mg) for uterine fibroids. Myovant submitted sNDA for the relugolix combination tablet in the U.S. for endometriosis.

- Development stage:
  Prostate cancer: MAA submitted in Europe in March 2021
  (New indication) Endometriosis: sNDA submitted in the U.S. in July 2021

GEMTESA® (vibegron)

- Vibegron is an oral, once-daily, small molecule β3 adrenergic receptor agonist. Vibegron selectively acts on the β3 adrenergic receptor in the bladder that relax the bladder, enhance urinary storage, and improve symptoms of urgency, urinary frequency, and urge urinary incontinence in patients with overactive bladder. Urovant has received approval for overactive bladder in the U.S in December 2020.

- Development stage:
  (New indication) Overactive bladder in men with BPH: Phase 3 in the U.S.

lefamulin

- Lefamulin is an antimicrobial agent of pleuromutilin class and a novel treatment for infectious diseases with a mechanism of action that differs from existing antibiotics. Lefamulin is designed to inhibit the synthesis of bacterial protein, which is required for bacteria to grow. Lefamulin’s binding occurs with high affinity, high specificity and at molecular sites that are distinct from other antibiotic classes. Lefamulin has been marketed by Nabriva Therapeutics in the U.S. since 2019.

- Development stage:
  Bacterial community-acquired pneumonia: NDA submitted in China in October 2021
Rodatristat ethyl  
Origin: Karos Pharmaceuticals, Inc., Formulation: oral  
- Rodatristat ethyl is a prodrug of tryptophan hydroxylase (TPH) inhibitor designed to reduce peripheral production of serotonin without entering the brain. It is believed that rodatristat ethyl may halt or reverse the pathology of diseases that are driven by excessive serotonin production, such as PAH, idiopathic pulmonary fibrosis (IPF) and sarcoidosis.  
- Development stage: Pulmonary arterial hypertension (PAH): Phase 2 in the U.S.

MVT-602  
Origin: Takeda Pharmaceutical Company Ltd, Formulation: oral  
- MVT-602 is an oligopeptide kisspeptin-1 receptor agonist. Activation of kisspeptin in upstream hypothalamic neurons is hypothesized to lead to the transmission of a signal that stimulates downstream neurons to increase the secretion of GnRH. However continued stimulation of kisspeptin is thought to result in the desensitization of receptor transduction, which is anticipated to result in a complete cessation of the signaling pathway. Myovant is developing MVT-602 as part of the hormonal preparation for women with infertility undergoing in vitro fertilization. MVT-602 is believed to stimulate GnRH which in turn increases secretion of luteinizing hormone (LH) that acts as a trigger for egg maturation prior to oocyte collection.  
- Development stage: Female infertility: Phase 2 in Germany

URO-902  
Origin: Ion Channel Innovations, LLC., Formulation: injection  
- URO-902 is a novel gene therapy for patients with overactive bladder symptoms who have failed oral pharmacologic therapy. URO-902 is a plasmid vector containing a human cDNA encoding the pore-forming component of the Maxi-K ion channel. Expression of the Maxi-K protein in muscle cells is hypothesized to increase potassium ion flow across the cell membrane, reducing excitability of smooth muscle cells. This mechanism could potentially normalize the heightened detrusor smooth muscle tone in overactive bladder, thereby reducing the related symptoms.  
- Development stage: Overactive bladder: Phase 2 in the U.S.

5. Frontier business  

SMC-01 (mobile app for management of type 2 diabetic patients)(medical device)  
Origin: Save Medical Corporation  
- The purpose of the App is to promote behavioral change in patients and improve clinical parameters by managing their daily activities related to type 2 diabetes care (meals, exercise, body weight, medication, blood pressure, and glucose level). Unlike other apps, the App is intended to be used under the guidance and endorsement of a physician, which will motivate patients to continue with their treatment and support their efforts to change their behavior.  
- Development stage: Type 2 diabetes: Phase 3 in Japan (Co-development with Save Medical Corporation)