Profiles of Major Products under Development (As of July 29, 2019)

1. Psychiatry & Neurology

**dasotraline (SEP-225289)** Developed in-house (Sunovion Pharmaceuticals Inc.), Formulation: oral
- SEP-225289 is a dopamine and norepinephrine reuptake inhibitor (DNRI). SEP-225289 has an extended half-life (47-77 hours) that supports the potential for plasma concentrations yielding a continuous therapeutic effect over the 24-hour dosing interval.
- Development stage:
  - Binge eating disorder (BED): NDA submitted in the U.S. in May 2019
  - Attention-deficit hyperactivity disorder (ADHD):
    - U.S.: NDA submitted in August 2017, Complete Response Letter received in August 2018, development strategy under consideration
    - Japan: Phase 1 in Japan

**apomorphine hydrochloride (APL-130277)** Developed in-house (Sunovion Pharmaceuticals Inc., from former Cynapsus Therapeutics), Formulation: sublingual film
- APL-130277 is a sublingual film formulation of apomorphine, a dopamine agonist, which is the molecule approved for acute intermittent treatment of OFF episodes associated with Parkinson’s disease. It is designed to rapidly, safely and reliably convert a Parkinson’s disease patient from the OFF to the ON state while avoiding many of the issues associated with subcutaneous delivery of apomorphine.
- Development stage: NDA submitted in the U.S. in March 2018. Complete Response Letter received in January 2019

**SEP-363856** Developed in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral
- SEP-363856 is an antipsychotic agent with a novel mechanism of action discovered using a variety of preclinical models, including the PsychoGenics’ SmartCube® System phenotypic screening platform and doesn’t show affinity to dopamine D2 receptors. The molecular target(s) responsible for the profile of effects is unknown, but may include agonist effects at serotonin 5-HT1A and TAAR1 (trace amine-associated receptor 1) receptors. Results obtained with the preclinical models suggest that SEP-363856 may be able to treat the positive and negative symptoms of schizophrenia as well as Parkinson’s disease psychosis. SEP-363856 is expected to have high efficacy in the treatment of schizophrenia and Parkinson’s disease psychosis, with an improved safety profile compared with currently marketed antipsychotics.
- Development stage:
  - Schizophrenia: Phase 3 in the U.S.
  - Parkinson’s disease psychosis: Phase 2 in the U.S.
  - Schizophrenia: Phase 1 in Japan

**vatiquinone (EPI-743)** In-licensed from BioElectron Technology Corporation (former Edison Pharmaceuticals, Inc.), Formulation: oral
- EPI-743 is expected to show efficacy by removing the oxidative stress that is generated excessively by decreased mitochondrial function. It is expected to be the world’s first treatment for mitochondrial diseases, beginning with Leigh syndrome, for which there is no effective therapy.
- Development stage:
  - A Phase 2 / 3 study for Leigh syndrome in Japan completed, development strategy under consideration
Profiles of Major Products under Development

**EPI-589**  
In-licensed from BioElectron Technology Corporation  
(former Edison Pharmaceuticals, Inc.), 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. by BioElectron Technology Corporation
  - Amyotrophic lateral sclerosis (ALS): Phase 2 in the U.S. by BioElectron Technology Corporation
  - Amyotrophic lateral sclerosis (ALS): Phase 1 in Japan

**SEP-4199**  
Developed in-house (Sunovion Pharmaceuticals Inc.), Formulation: oral

- SEP-4199 is investigated for the treatment of major depressive episodes associated with bipolar I disorder. The mechanism of action is not disclosed at this time.
- Development stage:
  - Bipolar I depression: Phase 2 in the U.S. and Japan

**DSP-6745**  
Developed 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**  
Developed in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral

- SEP-378608 is a novel CNS-active molecule discovered using a variety of preclinical models, including the PsychoGenics’ SmartCube\textsuperscript{®} System phenotypic screening platform. 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**  
Developed 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**  
Developed in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral

- SEP-378614 is a novel CNS-active molecule discovered using a variety of preclinical models, including the PsychoGenics’ SmartCube\textsuperscript{®} System phenotypic screening platform. Pre-clinical studies suggest that it showed rapid onset and long lasting antidepressant-like activity and neuroplasticity effects.
- Development stage: Treatment resistant depression: Phase 1 in the U.S.

**SEP-380135**  
Developed in-house (Joint research with Sunovion Pharmaceuticals Inc. and PsychoGenics Inc.), Formulation: oral

- SEP-380135 is a novel CNS-active molecule discovered using a variety of preclinical models, including the PsychoGenics’ SmartCube\textsuperscript{®} System phenotypic screening platform. Pre-clinical studies suggest that it showed a broad range of in vivo activities suggesting efficacy against a number of behavioral
Profiles of Major Products under Development

and psychological symptoms in dementia, including agitation/aggression, psychomotor hyperactivity, depression and deficits in social interaction.

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

### 2. Oncology

**napabucasin (BBI608)**

- Developed in-house (Boston Biomedical, Inc.), Formulation: oral
- BBI608 is an orally administered small molecule agent with a novel mechanism of action which is bioactivated by the enzyme NQO1 in cancer cells, which generates reactive oxygen species (ROS) to inhibit cancer stemness and tumor progression-related pathways including STAT3, which is expected to result in cancer cell death.
- Development stage:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proposed indication</th>
<th>Country/Area</th>
<th>Combination products</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>Colorectal cancer (combination therapy)</td>
<td>U.S., Japan</td>
<td>FOLFIRI&lt;sup&gt;3&lt;/sup&gt;, FOLFIRI&lt;sup&gt;3&lt;/sup&gt; + bevacizumab</td>
<td>CanStem303C</td>
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<tr>
<td>Phase 2</td>
<td>Colorectal cancer (combination therapy)</td>
<td>U.S.</td>
<td>cetuximab, panitumumab, capecitabine</td>
<td>224</td>
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<tr>
<td></td>
<td>Solid tumors&lt;sup&gt;1&lt;/sup&gt; (combination therapy)</td>
<td>U.S.</td>
<td>paclitaxel</td>
<td>201</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma&lt;sup&gt;2&lt;/sup&gt; (combination therapy)</td>
<td>U.S.</td>
<td>sorafenib</td>
<td>HCC-103</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>ipilimumab, pembrolizumab, nivolumab</td>
<td>201CIT</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal cancer (combination therapy)</td>
<td>U.S., Canada</td>
<td>FOLFOX&lt;sup&gt;3&lt;/sup&gt;, FOLFOX&lt;sup&gt;3&lt;/sup&gt; + bevacizumab, CAPOX&lt;sup&gt;3&lt;/sup&gt;, FOLFIRI&lt;sup&gt;3&lt;/sup&gt; + bevacizumab, sorafenib, irinotecan</td>
<td>246</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Pancreatic cancer (combination therapy)</td>
<td>U.S.</td>
<td>gemcitabine + nab-paclitaxel, FOLFIRINOX&lt;sup&gt;3&lt;/sup&gt;, FOLFIRI&lt;sup&gt;3&lt;/sup&gt;, irinotecan liposome injection + fluorouracil + leucovorin</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>amcasertib</td>
<td>401-101</td>
</tr>
</tbody>
</table>

<sup>*1</sup> Phase 2 stage: Ovarian cancer, Breast cancer, Melanoma, etc.
<sup>*2</sup> Phase 2 stage
<sup>*3</sup> FOLFOX: Combination therapy with fluorouracil, leucovorin, oxaliplatin
CAPOX: Combination therapy with capecitabine, oxaliplatin
FOLFIRI: Combination therapy with fluorouracil, leucovorin, irinotecan
FOLFIRINOX: Combination therapy with fluorouracil, leucovorin, irinotecan, oxaliplatin

**amcasertib (BBI503)**

- Developed in-house (Boston Biomedical, Inc.), Formulation: oral
- BBI503 is an orally administered small molecule agent with a novel mechanism of action designed to inhibit cancer stemness pathways, including Nanog, by targeting stemness kinases. By inhibiting pathways involved in the maintenance of cancer stemness, it may provide a new therapeutic option against the challenges in cancer treatment such as treatment resistance, recurrence and metastasis.
- BBI503 has been shown to inhibit multiple kinases in pre-clinical studies.
- Development stage:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proposed indication</th>
<th>Country/Area</th>
<th>Combination products</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
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<td>Phase 2</td>
<td>Hepatocellular carcinoma, Cholangiocarcinoma (monotherapy)</td>
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<td>Phase 1/2</td>
<td>Solid tumors&lt;sup&gt;1&lt;/sup&gt; (monotherapy)</td>
<td>U.S.</td>
<td>-</td>
<td>101</td>
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<tr>
<td></td>
<td>Hepatocellular carcinoma (combination therapy)</td>
<td>U.S.</td>
<td>sorafenib</td>
<td>HCC-103</td>
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Profiles of Major Products under Development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proposed indication</th>
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<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1/2</td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>capecitabine, doxorubicin, nivolumab, pembrolizumab, paclitaxel, sunitinib</td>
<td>201</td>
</tr>
<tr>
<td></td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>napabucasin</td>
<td>401-101</td>
</tr>
</tbody>
</table>

* Phase 2 stage: Colorectal cancer, Head and neck cancer, Ovarian cancer, etc.

**alvocidib (DSP-2033)**

In-licensed from Sanofi S.A., Formulation: injection

- Alvocidib is a small molecule inhibitor of cyclin-dependent kinase 9 (CDK9), a member of cyclin-dependent kinase family, which activates transcription of cancer-related genes. The subsequent down-regulation of MCL-1, an anti-apoptotic gene, may be responsible for the potential clinical anticancer activity observed with Alvocidib.

- Development stage:

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Acute myeloid leukemia (combination therapy) (refractory or relapsed patients)</td>
<td>U.S.</td>
<td>cytarabine, mitoxantrone</td>
<td>TPI-ALV-202</td>
</tr>
<tr>
<td></td>
<td>Acute myeloid leukemia (monotherapy/combination therapy (refractory or relapsed patients following treatment with venetoclax combination therapy)</td>
<td>U.S.</td>
<td>cytarabine</td>
<td>TPI-ALV-201</td>
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<tr>
<td>Phase 1/2</td>
<td>Myelodysplastic syndromes (combination therapy)</td>
<td>U.S.</td>
<td>decitabine</td>
<td>TPI-ALV-102</td>
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<tr>
<td>Phase 1</td>
<td>Acute myeloid leukemia (combination therapy) (newly diagnosed patients)</td>
<td>U.S.</td>
<td>cytarabine, daunorubicin</td>
<td>TPI-ALV-101</td>
</tr>
<tr>
<td></td>
<td>Acute myeloid leukemia (combination therapy) (newly diagnosed and refractory or relapsed patients)</td>
<td>Japan</td>
<td>newly diagnosed: cytarabine, daunorubicin refractory or relapsed : cytarabine, mitoxantrone</td>
<td>DC850101</td>
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<tr>
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<td>Acute myeloid leukemia (combination therapy) (refractory or relapsed patients)</td>
<td>U.S.</td>
<td>venetoclax</td>
<td>M16-186*</td>
</tr>
</tbody>
</table>

* Co-development with AbbVie

**adegramotide/nelatimotide (DSP-7888)**

Developed in-house, Formulation: injection

- DSP-7888 is a therapeutic cancer peptide vaccine derived from 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>
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</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Glioblastoma (combination therapy)</td>
<td>U.S., Japan</td>
<td>Bevacizumab</td>
<td>BBI-DSP7888-201G</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>Myelodysplastic syndromes (monotherapy) *</td>
<td>Japan</td>
<td>-</td>
<td>DB650027</td>
</tr>
<tr>
<td></td>
<td>Pediatric malignant gliomas (monotherapy) *</td>
<td>Japan</td>
<td>-</td>
<td>DB601001</td>
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### Profiles of Major Products under Development

<table>
<thead>
<tr>
<th>Stage</th>
<th>Proposed indication</th>
<th>Country/Area</th>
<th>Combination products</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Solid tumors, Hematologic malignancies (monotherapy)</td>
<td>U.S.</td>
<td>-</td>
<td>BBI-DSP7888-101</td>
</tr>
<tr>
<td></td>
<td>Solid tumors (combination therapy)</td>
<td>U.S.</td>
<td>nivolumab, atezolizumab</td>
<td>BBI-DSP7888-102CI</td>
</tr>
</tbody>
</table>

* Phase 2 stage

**TP-0903**
In-licensed from University of Utah, Formulation: oral
- TP-0903 is an AXL receptor tyrosine kinase inhibitor, which is known to be involved in acquiring resistance to conventional agents and developing metastatic capacity in cancer cells. TP-0903 may have anti-cancer activities on various cancer types through blocking transition from epithelial to mesenchymal phenotype by inhibiting AXL. TP0903 has been shown to inhibit AXL signaling and reverse the mesenchymal to epithelial phenotype in pre-clinical studies.
- Development stage:
  - Chronic lymphocytic leukemia (monotherapy / combination therapy): Phase 1/2 in the U.S.
  - Solid tumors (monotherapy / combination therapy): Phase 1 in the U.S. and Japan

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

**TP-0184**
Developed in-house (Tolero Pharmaceuticals, Inc.), Formulation: oral
- TP-0184 inhibits activin A receptor type 1 (ACVR1, also known as ALK2), part of the transforming growth factor beta (TGFβ) receptor superfamily. Mutations in the ACVR1 gene have been identified in various tumors, including diffuse intrinsic pontine glioma (DIPG; one of common pediatric brain tumors). TP-0184 has been shown to inhibit the growth of tumors harboring ACVR1 mutations in the pre-clinical studies.
- Development stage: Solid tumors (monotherapy): Phase 1 in the U.S.

**DSP-0337**
Developed in-house, Formulation: oral
- DSP-0337 is a small molecule oral prodrug of napabucasin. DSP-0337 is expected to be stable and dispersed in the stomach, and converted to napabucasin in the intestine, which may be absorbed and exert its pharmacologic activities.
- Development stage: Solid tumors (monotherapy): Phase 1 in the U.S.

**TP-1287**
Developed in-house (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 preclinical 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 (monotherapy): Phase 1 in the U.S.

**TP-3654**
Developed in-house (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: Solid tumors (monotherapy): Phase 1 in the U.S.
3. Regenerative medicine / cell therapy

**SB623**
- In-licensed from and co-developed with SanBio, Inc., Formulation: injection
- SB623 is an allogeneic cell product, derived from bone marrow stromal cells isolated from healthy donors. SB623 is expected to be effective for chronic stroke, which has no effective treatments available, by promoting regeneration of central nerve cells. Unlike autologous cell therapies that require individualized cell preparation at the clinical site, SB623 production can be scaled up from a single donor’s cells, enabling delivery of uniform-quality products to a large number of stroke patients.
- Development stage: Chronic stroke: Phase 2 in the U.S. (Co-development with SanBio)

**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 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 CiRA</td>
<td>Parkinson’s disease</td>
<td>Japan</td>
<td>Phase 1/2 (Investigator-initiated clinical study)</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

**imeglimin (PXL008)**
- In-licensed from and co-developed with Poxel SA, Formulation: oral
- Imeglimin is the first clinical candidate in a new chemical class of oral agents called the Glimins by the World Health Organization. Imeglimin has a unique mechanism of action that targets mitochondrial bioenergetics. Imeglimin acts on all three key organs which play an important role in the treatment of type 2 diabetes: the liver, muscles, and the pancreas, and it has demonstrated glucose lowering benefits by increasing insulin secretion in response to glucose, improving insulin sensitivity and suppressing gluconeogenesis.
- Development stage: Type 2 diabetes: Phase 3 in Japan (Co-development with Poxel)