R&D Meeting

December 9, 2015

Sumitomo Dainippon Pharma Co., Ltd.
Today’s Agenda

◆ Quest for Further Innovation

Hiroshi Noguchi, Ph.D.
Representative Director, Senior Executive Vice President, Chief Scientific Officer

◆ Development products topics

Nobuyuki Hara, Ph.D.
Executive Officer, Deputy Executive Director, Drug Development

✓ Obeticholic acid (Nonalcoholic steatohepatitis (NASH))
  Phase II study results

✓ Ranirestat (Diabetic neuropathy)
  Phase III study results

✓ Lurasidone hydrochloride (Schizophrenia)
  Phase III study plan

◆ Oncology

Chiang J. Li, MD, FACP
Executive Officer, Head of Global Oncology for Sumitomo Dainippon Pharma Group
President, Chief Executive Officer and Chief Medical Officer, Boston Biomedical, Inc.
Quest for Further Innovation

Hiroshi Noguchi, Ph.D.
Representative Director,
Senior Executive Vice President
Chief Scientific Officer
Executive Director, Drug Research; Global R&D Office;
Global Oncology Office
Vision

- Aim to global, R&D-based company
- Venture into leading-edge Science and Technology

First Phase MTBP FY2007 to FY2009
- Strengthening and maintaining our business foundation towards globalization
- Focus resources on four strategic products
- Early maximization of new products
- Establish US marketing org.
- Expand US/EU clinical development organization
- Start-up US business in our own sales organization
- Strengthen new drug discovery activities and in-licensing activities

Second Phase MTBP FY2010 to FY2014
- Creation and transformation toward a new stage of globalization
- Transform domestic business foundation
- Expand North America business through our own sales organization
- Expand new product pipeline

Third Phase MTBP FY2013 to FY2017
- Quest for Further Innovation
- Establish strong domestic business foundation
- Strengthen profitability in North America.
- Expansion into Europe and Asia
- Expand global pipeline
- Develop leading-edge science fields

Aspire to be a globally active R&D-based company
Contribute to medical care through leading-edge technologies
R&D: Accomplishments in the past 10 years

- Own development of LATUDA in the U.S.
  Acquisition of Sepracor (’09), LATUDA approved (’10)
  Enhanced capacities for clinical studies and regulatory science

- R&D strategy redefined to take the U.S. market in consideration: Entry into Oncology Area
  In-licensing of BBI608 (’11) and Acquisition of Boston Biomedical, Inc. (’12)

- Focus on innovative drugs
  R&D organizations and management restructured
  In-licensing team realigned
R&D Strategy-1: Basic Approach

Discover first-in-class drugs or drugs that can make the difference

Innovative Drug Discovery Laboratories has been created
Take on the challenge of unmet medical needs; “from point to plane” (from one rare disease solution to broader indication additions)
Implant and nurture a new R&D culture and mindset; a new human resource management scheme

- **Early POC demonstration and prompt application for late-stage development**
  - Focus on Killer Experiments (minimum required experiments and tests to move on to the next R&D stage)
  - Enhance the success ratio of late-stage development products

- **Focus on priority areas and venturing into new areas**
  - Adopt business unit structure (oncology area and regenerative/cell therapy area)

- **Strategies according to the development stage**
  - Early-stage: focus on innovation, individual strengths, from out to in
  - Late-stage: team strength, collaboration
R&D Strategy—2: Early-stage drug discovery

- **Build up “autonomous” units**
  - Innovative Drug Discovery Laboratories: Concentrate on “Delivering 1 from 0”
  - Multiple arrows: multiple units compete with respective strengths
  - Venture capital-like management
  - Hub (Osaka) & Spoke (Units in Japan and abroad)

- **Pursue originality (make use of original technologies)**
  - In-silico drug discovery, iPS drug discovery, nucleic acid medicine (aiRNA)
  - Introduce most leading-edge Science and Technology (mitochondria drug discovery, cerebral DDS, etc.)

* A drug discovery strategy to use phenotype as screening index
R&D Strategy–3: Late-stage drug discovery and clinical studies

- **Show team strength through collaboration, seek speed and quality**
  - Collaboration among drug discovery, clinical studies, CMC as well as among division headquarters
  - Collaboration with Sunovion Pharmaceuticals Inc. and Boston Biomedical, Inc. Established of development integrated organization GCD (Global Clinical Development)
  - Develop products efficiently and quickly
  - Improve thematic quality by portfolio management

- **Intensify translational research (TR) approaches**
  - Make use of non-human primates (NHP)
  - Translational research using EEG (brain waves), PET and other non-invasive methods
  - Promote biomarker research with clinical samples

- **Use novel techniques**
  - Get pharmacologic/pharmacodynamics signals by f-MRI (functional MRI) (non-clinical and clinical)
  - Improve success ratio by pharmacokinetic/pharmacodynamics modelling and simulation

- **Re-positioning & PLCM**
R&D organization

CEO

Board of Directors

Global R&D Office

Drug Research Division (include External Innovation Development Office)

Drug Development Division*

Technology Research & Development Division

Regenerative & Cellular Medicine Office (RACMO)

Global Corporate Planning

Global Business Development

日本

Overseas

Sunovion Pharmaceuticals Inc. (Research・Development*・CMC)

Boston Biomedical, Inc. (R&D&CMC in the Oncology area)

Sumitomo Pharmaceuticals (Suzhou) Co., Ltd (Development)

Global Oncology Office (GOO) DSP Cancer Institute (DCI)

*GCD: Global Clinical Development

- 3 Divisions: Research, Development, Technology R&D
- Established GCD* regarding Clinical Development
- Oncology and Regenerative medicine / Cell therapy independent of the 3 divisions
- R&D bases in group companies in the U.S., China
- R&D personnel: approx.1,360 (consolidated)
Area strategy and R&D investment strategy

Priorities: Innovation, Competition, Market, Growth potential

- Take on the challenge to unmet medical needs
  From point to plane

- Timespan
  Needs of the time
  Rapid advance of Science and Technology

- Own strengths
  Past accomplishments & experiences

- Toward the future
  High-growth areas

Image of R&D investment
R&D activity making use of our strengths

**Psychiatry & Neurology**
- EXCEGRAN/TRERIEF
- DOPS, SEDIEL, LULLAN, LONASEN

**Oncology**
- SUMIFERON CALSED MIRIPLA

**Disease field where no approved drugs exist**
- GENOTROPIN/GROWJECT REPLAGAL

**Regenerative medicine / Cell therapy**
- Research of nerve regeneration
- Cell mass culture technology
- Cell culture techniques, QC/QA

**Sumitomo Dainippon Pharma created in 2005**

**Acquired Sepracor Inc. (current Sunovion) (2009)**
- LATUDA (Development in-house)
  - SEP-225289 (Ph3) ADHD¹¹, BED
  - SEP-363856 (Ph1) Schizophrenia
  - DSP-2230 (Ph1) Neuropathic pain
  - DSP-3748 (Ph1) CIAS¹²

**Acquired Boston Biomedical, Inc. (2012)**
- Post LATUDA (Development in-house)
  - BBI608 (Ph3) Gastric and GEJ Colorectal cancer
  - BBI503 (Ph2) Solid tumors
  - DSP-7888 (Ph1) Solid tumors, Hematologic malignancies

**In-license and alliance with venture companies**
- In-licensed and alliance with venture companies
  - Acquired Boston Biomedical, Inc. (2012)
  - Acquired Sepracor Inc. (current Sunovion) (2009)

**Partnerships with academia and venture (SanBio, Healios)**
- Acquired Boston Biomedical, Inc. (2012)
- Acquired Sepracor Inc. (current Sunovion) (2009)

**Development products**
- EPI-743/EPI-589
  - Neurodegenerative disease
- DSP-1747
  - Nonalcoholic steatohepatitis (NASH)
- SB623 (Ph2b)
  - Chronic stroke

*1 ADHD: Attention-deficit hyperactivity disorder
*2 CIAS: Cognitive impairment associated with schizophrenia
Trends in R&D costs and allocation to therapeutic areas

- Trends in R&D costs

<table>
<thead>
<tr>
<th>Year</th>
<th>Net sales (Billions of yen)</th>
<th>R&amp;D costs (Billions of yen)</th>
<th>R&amp;D costs / Net sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2006</td>
<td></td>
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<tr>
<td>FY2008</td>
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<td></td>
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<td>FY2010</td>
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<td>FY2012</td>
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<tr>
<td>FY2014</td>
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</tr>
</tbody>
</table>

- R&D area resource (Direct costs)

- Psychiatry & Neurology
- Oncology
- Regenerative medicine / Cell therapy
- Cardiovascular and diabetes Area
- Others (Exclude cardiovascular and diabetes area)
- Others (Including cardiovascular and diabetes area)
Activities in Psychiatry & Neurology and Disease fields where no approved drugs exist

- Psychiatry/neurology: Capitalize on our strengths, take in leading-edge Science and Technology
  - Monoamine drug discovery, disease iPS, in-silico, phenotype
  - Channel technique, omics technology
  - Non-human primate (NHP)
- More weight on diseases of higher unmet medical needs
- Promote research cooperation with other companies
- Early POC demonstration for early-stage development products and early application for approval of late-stage development products

### Targeted diseases
- **Psychiatry**
  - Treatment resistant segment (Schizophrenia, Depression)
  - Autism spectrum, Developmental disability

- **Neurology**
  - Alzheimer disease, Parkinson’s disease, ALS
  - Intractable epilepsy, Pain

- **Disease fields where no approved drugs exist**
- **Mitochondria-related diseases**
Development Pipeline: Psychiatry & Neurology and Disease fields where no approved drugs exist

- **Invest in high priority late-phase products to seek fastest approval**
  - Dasotraline (SEP-225289): ADHD (Ph3)·BED (Ph2/3)/U.S.
  - TRERIEF: Parkinsonism in Dementia with Lewy Bodies (DLB) (Ph3)/Japan
  - Obeticholic acid (DSP-1747): NASH/Japan (Ph2)

- **Aim to obtain early POC of early-phase products**
  - EPI-589: Parkinson’s disease, ALS
  - DSP-2230: Neuropathic pain
  - SEP-363856: Schizophrenia
  - DSP-3748: Cognitive impairment associated with schizophrenia (CIAS)

<Products under consideration of development strategy >

- Ranirestat: Diabetic neuropathy/Japan
  \(\Rightarrow\) Development strategy to be determined after additional data analysis

- Lurasidone: Schizophrenia/Japan
  \(\Rightarrow\) Another Ph3 study to be implemented

- Vatiquinone (EPI-743): Leigh syndrome/Japan
  \(\Rightarrow\) development strategy under consideration
Oncology area: Background of full entry and challenges

Consistent with Management Mission and Strategy
- Cancer drug development is a mission of R&D-based pharmaceuticals company
- Not always determined by company size; medium-sized company could be successful
  - Highly competitive market but product-driven
- A typical specialty area
  - No heavy sales force required

Externals: opportunities, market attractiveness
- High unmet medical needs, drugs based on innovative concept are required
- Rapid science and technology advances in the area, the time is calling for change from an incurable disease to curable
- Market growing medium- to long-term

- Very competitive market (over 800 compounds being developed, rush for patients recruit), speed is critical
- Complex indication strategy (cancer type X line X combined drug), unprecedented development strategy and emergent design are necessary

Internals: Change in business climate
- US market became accessible (2009)
- The next step following LATUDA launch (2011), post LATUDA strategy, pipeline enrichment

- A pillar for Sumitomo Dainippon Pharma Group on a long-term basis
- Limited management resources
Oncology area: R&D strategy

- Advanced technology to capitalize on our strengths
  - Cancer stem cells medicine
  - Cancer peptide vaccines
  - New technology (aiRNA, etc.)

- Boston Biomedical, Inc. and DSP cancer institute together expand drug discovery activities through cooperation and competition
Oncology area: Development pipeline

- **Napabucasin (BBI608)**
  - **Phase 3:**
    - Colorectal cancer (Monotherapy) (CO.23 study)
    - Gastric and Gastro-esophageal junction adenocarcinoma (Combination therapy) (BRIGHTER study)

  **Candidate for new pivotal studies:**
  - Colorectal cancer (Combination therapy) (from 246 study)
  - Solid tumors (Non-small cell lung cancer, Pancreatic cancer, Ovarian, Breast cancer) (Combination therapy) (from 201 study)
  - Pancreatic cancer (Combination therapy) (from 118 Study)

- **BBI503:**
  - Plan pivotal study in FY2016
Cancer peptide vaccine (DSP-7888)

<table>
<thead>
<tr>
<th>Product code</th>
<th>Characteristics</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSP-7888</td>
<td>Therapeutic peptide vaccine candidate containing peptides which induce WT1-specific cytotoxic T lymphocytes (CTLs) and helper T cells</td>
<td>Myelodysplastic syndromes (MDS), Solid tumors, Hematologic malignancies</td>
</tr>
</tbody>
</table>

**MOA of DSP-7888**

- Injection of DSP-7888
- Peptides are presented on antigen presenting cell
- CTLs and helper T cells are induced. Helper T cell enhance the activity of CTL
- Clonally expanded WT1-specific CTLs attack WT1-expressing cancer cells

Cancer cell killing
Cancer peptide vaccine (WT4869/WT2725)

<table>
<thead>
<tr>
<th>Product code</th>
<th>Characteristics</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT4869</td>
<td>Therapeutic cancer peptide vaccine candidate derived from Wilms’ tumor gene 1 (WT1) protein</td>
<td>Myelodysplastic syndromes (MDS), Solid tumors</td>
</tr>
<tr>
<td>WT2725</td>
<td>Therapeutic cancer peptide vaccine candidate derived from WT1 protein</td>
<td>Solid tumors, Hematologic malignancies</td>
</tr>
</tbody>
</table>

- Phase 1/2 study of WT4869 in Patients with Myelodysplastic Syndromes (MDS)

**Clinical response** (N=22, evaluable)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*</td>
<td>18.2% (4/22)</td>
</tr>
<tr>
<td>DCR</td>
<td>59.1% (13/22)</td>
</tr>
</tbody>
</table>

* included hematological improvement

**Overall survival (OS) of higher risk Azacitidine (AZA)-failure (N=11)**

- Median OS of higher risk AZA failure
  - WT4869 (N=11): 55.71 week (aprox. 13 months)\(^1\)
  - Historical data (N=435): 5.6 months\(^2\)

\(^1\) ASH 2015 (Abstract 2868) Suzuki T et. al.
\(^2\) J Clin Oncol 2011;29:3322-7 Prebet T et. al.

WT1: Wilms’ tumor gene 1
CTL: Cytotoxic T lymphocyte
Regenerative medicine / Cell therapy: R&D strategy

- High unmet medical needs and incurable diseases
- An area of big market potential
- Our longstanding R&D expertise and our group strengths can be utilized in this area
  ⇒ Cooperate with regulatory authority, academia and venture firms to promote development

- Progress & change in the last 12 months
  ✓ Pharmaceuticals and Medical Devices Act became effective
  ✓ SB623 (for chronic stroke): A Ph2b study begun in the U.S. [156 patients (3-group double-blinded test)]
  ✓ Age-related macular degeneration: suspension chosen as formulation
  ✓ Parkinson’s disease: Study begun on evaluation method of auto-culture (selected as an AMED project)
  ✓ iPS cells: Production begun of master cell bank for clinical iPS cells
  ✓ A cell production center (CPC) under construction in Kobe (estimated investment: 2.2 billion yen)
# Regenerative medicine / Cell therapy of Business Plan

(Updated December 2015)

<table>
<thead>
<tr>
<th>Partnering</th>
<th>Region (planned)</th>
<th>Cell type</th>
<th>Schedule for practical use (Calendar year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Stroke</td>
<td>SanBio</td>
<td>North America</td>
<td>2015: Ph2b, 2016: Ph3, 2019: Approval Target</td>
</tr>
<tr>
<td>Chronic Stroke</td>
<td>SanBio</td>
<td>North America</td>
<td>2015: Ph2b, 2016: Ph3, 2019: Approval Target</td>
</tr>
<tr>
<td>AMD (age-related macular degeneration)</td>
<td>Healisos RIKEN</td>
<td>Japan</td>
<td>2015: Clinical research, 2016: Investigator initiated clinical trial, 2019: Approval Target</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Kyoto Univ CiRA</td>
<td>global</td>
<td>2015: Clinical research or clinical trial</td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>RIKEN</td>
<td>global</td>
<td>2015: Clinical research or clinical trial</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>Keio Univ, Osaka National Hospital</td>
<td>global</td>
<td>2015: Clinical research (allogeneic)</td>
</tr>
</tbody>
</table>
# Product Launch Plan (Updated December 2015)

<table>
<thead>
<tr>
<th>Area</th>
<th>FY2015 (Launched)</th>
<th>FY2016</th>
<th>FY2017</th>
<th>FY2018</th>
<th>FY2019～FY2021</th>
</tr>
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<tbody>
<tr>
<td>Japan</td>
<td>REMITCH® (Pruritus)</td>
<td>※ EPI-743 (Leigh)</td>
<td>ranirestat</td>
<td>LONASEN® (Schizophrenia / Bipolar maintenance)</td>
<td>DSP-1747 (NASH)</td>
</tr>
<tr>
<td></td>
<td>(chronic liver disease)</td>
<td>syndrome)</td>
<td>(Gastric)</td>
<td>(Schizophrenia / Bipolar maintenance)</td>
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<td></td>
<td>(Promotion)</td>
<td></td>
<td>(Transdermal patch)</td>
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<tr>
<td></td>
<td>Trulicity® (GLP-1 receptor agonist)</td>
<td></td>
<td>napabucasin</td>
<td>Lurasidone (Colorectal cancer, etc.)</td>
<td>DSP-6952 (IBS with constipation, Chronic idiopathic constipation)</td>
</tr>
<tr>
<td></td>
<td>(Marketing)</td>
<td></td>
<td>(Gastric)</td>
<td></td>
<td>IPS cell-derived RPE cells</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(Transdermal patch)</td>
<td></td>
<td>(Age-related macular degeneration)</td>
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<tr>
<td>U.S.</td>
<td>APTIOM® (Epilepsy-)</td>
<td>napabucasin</td>
<td>dasotraline</td>
<td>SB623 (Chronic stroke)</td>
<td>napabucasin (Colorectal cancer, etc.)</td>
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<tr>
<td></td>
<td>monotherapy)</td>
<td>(Gastric)</td>
<td>(ADHD)</td>
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<td>(Transdermal patch)</td>
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<td>SUN-101 (COPD)</td>
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<tr>
<td>China</td>
<td>LONASEN® (Schizophrenia)</td>
<td></td>
<td></td>
<td>lurasidone</td>
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<tr>
<td></td>
<td>CALSED® (Small cell lung cancer)</td>
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</tbody>
</table>

- **P&N**: P&N
- **Oncology**: Oncology
- **Respiratory**: Respiratory
- **Liver/Digestive**: Liver/Digestive
- **New Chemical Entities**: New Chemical Entities
- **New Indication**: New Indication
- **etc.**: etc.
- ※: Development strategy under consideration
Summary

Serve medical community with most leading-edge technology, and grow to be an R&D-based and globally operating pharmaceuticals group

- Concentrate to the target disease and research area
  Identify targets to fill unmet medical needs

**Focus Therapeutic Areas**
- Psychiatry & Neurology
- Oncology

**New fields**
- Disease fields where no approved drugs exist
- Regenerative medicine / Cell therapy

- Stage-focused R&D strategy and management

  **Early drug discovery**
  - Value creation (0 → 1)
  - Venture approach
  - Individuality-focused
  - Innovation-oriented

  **Late discovery, development**
  - Value enhancement (1 → 10)
  - Medium-sized pharma approach
  - Team strength-focused
  - Speed/POC-oriented

  **Emphasis on speed and quality**

  ✓ Contribute to medicine by preempting science and technology advances and commercializing them
  ✓ Take on the challenge of first-in-class drug discovery
  ✓ Promote open innovation and collaboration (joint R&D, in-licensing)
Looking ahead...
Venture into new areas by the application of most advanced science and technology

- Era of nucleic acid medicine and cell therapy is sure to come
- Small molecule drug discovery will make progress

- Cancer will no longer be an incurable disease in near future
- Population aging and stressful life will increase cases of psychiatric diseases as well as Alzheimer’s and other neurological diseases, causing a serious social problem

- Treatment of rare or segmented diseases will advance
- Integration technologies will improve diagnosis, prevention and treatment
Development products topics

Nobuyuki Hara, Ph.D.
Executive Officer
Deputy Executive Director, Drug Development
Obeticholic acid (DSP-1747) and NASH

- **Mode of Action for DSP-1747:** FXR agonist
  - Improvement on NASH is expected by improvement of liver accumulation, anti-inflammatory effect, and anti-fibrosis effect

- **Prognosis of NASH/NAFLD**

  [Diagram showing progression from NAFLD to NASH, Cirrhosis, and Hepatocellular Cancer]

  - Number of NASH patients in Japan: approximately 200 to 300 millions (estimate 2 to 3% of adult population)
  - Five to 20% of NASH progress to cirrhosis in 5 to 10 years.
  - The 5-year survival rates of NASH cirrhosis is comparable to that of Hepatitis C

NASH

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NAFLD: Non-Alcoholic Fatty Liver Disease
NAFL: Non-Alcoholic Fatty Liver
NASH: Non-Alcoholic Steatohepatitis

1) Japan Society of Hepatology : NASH/NAFLD practice guideline 2015
2) The Journal of the Japan Medical Association: 2010; 139(9); 1880
DSP-1747 Phase II study

Study Design

✓ Randomized, Double-blind, Parallel-group, Placebo-controlled Study of DSP-1747 in Patients with NASH

✓ The number of dosed subjects: 200 (50 subjects/arm)

✓ Arms: DSP-1747 10mg/day, 20mg/day, 40mg/day, and Placebo

✓ Primary endpoint: Improvement of liver pathological findings from baseline to week 72

  The improvement was defined as: a) No worsening of Kleiner’s fibrosis staging, and b) Decrease in NAFLD activity score (NAS) by 2 or more points.

  • Factors of NAS are steatosis (3 points), inflammation (3 points) and ballooning (2 points); total NAS is 8 points at maximum

  • Evaluating liver fibrosis with Kleiner’s fibrosis staging (stage 0-4). Stage 4 was excluded from the study because stage 4 is liver cirrhosis.
**DSP-1747 Phase II study: Results**

- **Efficacy:** The percentages of improvement increased dose dependently
  
  [Primary analysis with Stratified Cochran-Armitage test with multiple contrast coefficients: p=0.053]

<Primary endpoint>

<table>
<thead>
<tr>
<th>Arms (ITT)</th>
<th>Placebo (N=50)</th>
<th>10mg/day (N=50)</th>
<th>20mg/day (N=50)</th>
<th>40mg/day (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved*¹</td>
<td>10 (20%)</td>
<td>11 (22%)</td>
<td>14 (28%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.807*²</td>
<td>p=0.338*²</td>
<td>p=0.0496*²</td>
</tr>
<tr>
<td>Decrease in NAS by 2 or more points</td>
<td>12</td>
<td>13</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>No worsening of liver fibrosis</td>
<td>31</td>
<td>30</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Unimproved</td>
<td>40 (5)</td>
<td>39 (6)</td>
<td>36 (6)</td>
<td>31 (13)</td>
</tr>
</tbody>
</table>

*¹ The subjects for whom the fibrosis stage or NAS or both at Week 72 were missing were classified as “unimproved”

*² vs placebo, CMH test stratified by baseline fibrosis stage, There is no adjustment for multiplicity.

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**Analyzed with the subjects who conducted 2nd biopsy at 72 W**

<table>
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<th>Arms</th>
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<th>20mg/day</th>
<th>40mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>10/45 (22.2%)</td>
<td>11/44 (25.0%)</td>
<td>14/44 (31.8%)</td>
<td>19/37 (51.4%)</td>
</tr>
<tr>
<td></td>
<td>p=0.764*²</td>
<td>p=0.291*²</td>
<td>P=0.006*²</td>
<td></td>
</tr>
</tbody>
</table>
# DSP-1747 Phase II study: Efficacy (liver fibrosis)

<table>
<thead>
<tr>
<th>Arms (ITT)</th>
<th>Placebo</th>
<th>10mg/day</th>
<th>20mg/day</th>
<th>40mg/day</th>
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<tr>
<td>No worsening of liver fibrosis</td>
<td>31/50</td>
<td>30/50</td>
<td>29/50</td>
<td>28/50</td>
</tr>
<tr>
<td></td>
<td>(62%)</td>
<td>(60%)</td>
<td>(58%)</td>
<td>(56%)</td>
</tr>
<tr>
<td>Fibrosis improvement (1 stage or more improvement of liver fibrosis)*1</td>
<td>12/50</td>
<td>12/44</td>
<td>15/49</td>
<td>10/49</td>
</tr>
<tr>
<td></td>
<td>(24.0%)</td>
<td>(27.3%)</td>
<td>(30.6%)</td>
<td>(20.4%)</td>
</tr>
</tbody>
</table>

<Analyzed with the subjects who conducted 2nd biopsy at 72 W*2>

<table>
<thead>
<tr>
<th>Arms</th>
<th>Placebo</th>
<th>10mg/day</th>
<th>20mg/day</th>
<th>40mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>No worsening of liver fibrosis</td>
<td>31 / 45</td>
<td>30 / 44</td>
<td>29 / 44</td>
<td>28 / 37</td>
</tr>
<tr>
<td></td>
<td>(68.9)</td>
<td>(68.2%)</td>
<td>(65.9%)</td>
<td>(75.7%)</td>
</tr>
<tr>
<td>Fibrosis improvement (1 stage or more improvement of liver fibrosis)*3</td>
<td>12 / 45</td>
<td>12 / 38</td>
<td>15 / 43</td>
<td>10 / 36</td>
</tr>
<tr>
<td></td>
<td>(26.7%)</td>
<td>(31.6%)</td>
<td>(34.9%)</td>
<td>(27.8%)</td>
</tr>
</tbody>
</table>

*1 Percentages are based on the number of ITT subjects for whom the Kleiner’s fibrosis stage at baseline are not stage 0.
*2 Post-hoc analyses.
*3 Percentages are based on the number of the subjects, who conducted 2nd biopsy at 72 W, for whom the Kleiner’s fibrosis stage at baseline are not stage 0.
DSP-1747 Phase II study: Efficacy (NASH resolution, ITT)

<table>
<thead>
<tr>
<th>Arms (ITT)</th>
<th>Placebo (N=50)</th>
<th>10mg/day (N=50)</th>
<th>20mg/day (N=50)</th>
<th>40mg/day (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NASH in Matteoni classification*¹</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>p value (vs placebo)*²</td>
<td>p=0.317</td>
<td>p=0.075</td>
<td>p=0.079</td>
<td></td>
</tr>
<tr>
<td>Resolution of hepatocyte ballooning and residual inflammation (0-1)*³</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>p value (vs placebo)*²</td>
<td>p=1.000</td>
<td>p=0.379</td>
<td>p=0.082</td>
<td></td>
</tr>
<tr>
<td>Resolution of hepatocyte ballooning</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
<td>7 (14%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>p value (vs placebo)*²</td>
<td>p=0.694</td>
<td>p=0.163</td>
<td>p=0.064*⁴</td>
<td></td>
</tr>
</tbody>
</table>

*¹ NASH diagnosis method which is used in Japan widely. NAFLD (Non-Alcoholic Fatty Liver Diseases) patients are classified in type 1 to 4 and type 3 and 4 are diagnosed as NASH.

*² vs placebo, CMH test stratified by baseline fibrosis stage. There is no adjustment for multiplicity.

*³ As a part of surrogate histological primary endpoint of pivotal Phase 3 study planned by Genfit, NASH resolution is defined as “ballooning = 0, inflammation = 0-1” (press release by Genfit on Nov.16, 2015)

*⁴ Analyzed with the subjects who conducted 2nd biopsy at 72 W as post-hoc analysis: placebo 3/45 (6.7%) vs 40mg/day 9/37 (24.3%), p=0.030 (vs placebo, CMH test stratified by baseline fibrosis stage. There is no adjustment for multiplicity)
Adverse events reported more than 10% incidence in any DSP-1747 arms

<table>
<thead>
<tr>
<th>Adverse events (PT; Preferred Terms)</th>
<th>Placebo N=50</th>
<th>10 mg/day N=50</th>
<th>20 mg/day N=50</th>
<th>40 mg/day N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Dental caries</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>27 (54%)</td>
<td>21 (42%)</td>
<td>23 (46%)</td>
<td>21 (42%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
<td>8 (16%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
<td>6 (12%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (4%)</td>
<td>0</td>
<td>5 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (8%)</td>
<td>10 (20%)</td>
<td>12 (24%)</td>
<td>25 (50%)</td>
</tr>
</tbody>
</table>
NASH Diagnostic Marker: Exploratory Study

- Original article “Identification of novel noninvasive markers for diagnosing nonalcoholic steatohapatitis and related fibrosis by data mining” (“Hepatology” accepted on Sep. 21) http://onlinelibrary.wiley.com/doi/10.1002/hep.28226/abstract;jsessionid=42FA284E0BD5D00BE38F2B50947DB3BC.f01t03

- Collaborative study with Saiseikai Suita Hospital
- The purpose of the study was to identify noninvasive diagnosing marker differentiating NASH or NASH-related liver fibrosis from NAFLD patients.
- 261 blood molecules were examined for 132 Japanese NAFLD patients.
- The two markers by using combinations of a few molecules respectively appropriate to diagnosing NASH and NASH-related liver fibrosis were established.
- Reproducibility of diagnosis by the NASH-related liver fibrosis marker has been confirmed by examinations of an independent validation group at the same hospital consisting of 62 Japanese NAFLD patients.
- While the novel markers seem promising, the study has several limitations due to single institution and limited number of subjects => Additional multicenter study is needed

<table>
<thead>
<tr>
<th>Markers for diagnosing NASH related liver fibrosis</th>
<th>Clinical Parameters/Blood molecules</th>
<th>AUROC of Exploratory Group</th>
<th>AUROC of Validation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM-fibro Index (Novel)</td>
<td>VCAM1, Type IV collagen 7S</td>
<td>0.896</td>
<td>0.852</td>
</tr>
<tr>
<td></td>
<td>VCAM1, Hyaluronic acid</td>
<td>0.867</td>
<td>0.878</td>
</tr>
<tr>
<td></td>
<td>Hyaluronic acid, Type IV collagen 7S</td>
<td>0.917</td>
<td>0.892</td>
</tr>
<tr>
<td>FIB4 Index (Existing)</td>
<td>Age, AST, ALT, Platelet</td>
<td>0.809</td>
<td>0.831</td>
</tr>
</tbody>
</table>

AUROC: Area Under the Receiver Operator Characteristic curve; which is used as a basis for evaluation of diagnostic markers. If the value is closer to “1”, it means more sensitive marker for diagnosis.
Clinical Research on NASH diagnosis markers

1. External validation study of diagnostic accuracy for NASH by the serum biomarkers vs histopathological Diagnosis (Dx): cross-sectional, retrospectively collected samples

2. Investigation on the prognosis of NASH/NAFLD

Past 2-year samples are eligible
Target number: N=400

* NASH here means “NASH with fibrosis (type 4 patients of Matteoni’s classification)”
Ranirestat (AS-3201) Phase III study top-line results

Study design

- Randomized, double-blind, parallel-group, placebo-controlled study with diabetic neuropathy patients
- Arms and subject number: Ranirestat 40 mg/day: 277 pts, Placebo: 278 pts
- Treatment period: 1 year treatment
- Co-primary endpoints: Changes in tibial motor nerve conduction velocity (TMNCV) and modified Toronto Clinical Neuropathy Score (mTCNS)

Study results

Efficacy: In comparison with placebo treatment, ranirestat 40 mg/day treatment significantly improved the TMNCV although did not improve the mTCNS with statistical significance.

Safety: The incidences of TEAEs and treatment-related TEAEs in 40mg/day treatment group were comparable to those in placebo treatment group, respectively.

p-value were calculated using ANCOVA with the baseline value as a covariate.
Ranirestat (AS-3201) Phase III study results

- In comparison with placebo, ranirestat 40 mg/day treatment significantly improved not only NCV of tibial motor nerve, but also other motor and sensory nerves.
- Additional data analysis ongoing, development strategy under consideration.

p-value were calculated using ANCOVA with the baseline value as a covariate.
### Lurasidone: Schizophrenia
#### New Phase III study plan

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Randomized, double-blind (6 weeks) , placebo-controlled, parallel-group study in patients with Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries</td>
<td>Multinational study including Japan</td>
</tr>
<tr>
<td>Primary efficacy variable</td>
<td>Change from baseline in PANSS total score at week 6</td>
</tr>
<tr>
<td>Target sample size</td>
<td>About 450 – 550 subjects</td>
</tr>
<tr>
<td>Study period</td>
<td>About 2.5 years from Clinical trial notification (FY2015) to Data base lock (FY2018)</td>
</tr>
</tbody>
</table>

- **Target Doses:** 40mg/d and 80mg/d
- Simultaneous J-NDA submission with Bipolar I depression and Schizophrenia is planned (To avoid the off label use when BP indication would be approved prior to Schizophrenia)
- The first study collaborated with Sunovion since GCD establishment
- Based on the past experiences, the study will be conducted in the countries which can be expected speedy enrollment with high quality
Development products topics: Summary

● DSP-1747
  ✓ NASH Phase II study results:
    • Efficacy: Improvements of histological findings were shown in 40mg/day
    • Safety: Incidences of reported adverse events of DSP-1747 groups were generally similar to placebo group except pruritus
  ✓ Tolerability against pruritus needs to be improved at Phase 3

● Ranirestat
  ✓ Phase III study with diabetic neuropathy patients results: in comparison with placebo treatment, ranirestat 40 mg/day treatment significantly improved the TMNCV although did not improve the mTCNS with statistical significance.
  ✓ Development strategy under consideration

● Lurasidone hydrochloride
  ✓ New Phase III study with schizophrenia patients will be initiated in FY 2015
Oncology

Chiang J. Li  MD FACP

Executive Officer, Head of Global Oncology for Sumitomo Dainippon Pharma Group
President, Chief Executive Officer and Chief Medical Officer, Boston Biomedical, Inc.
GLOBAL ONCOLOGY

A LEADER IN MEDICAL INNOVATION FOR TARGETING CANCER STEM CELLS

OUR TEAM, SCIENCE, AND STRATEGY
Location and Organization in Global Oncology

- Oncology Clinical Development Unit (OCU)
- Oncology Marketing Unit (OMU)
- Global Oncology Office (GOO) (Tokyo)

- DSP Cancer Institute (DCI)
- Global Oncology Office (GOO) (Osaka)

- Boston Biomedical, Inc. (BBI)
- Boston Biomedical Pharma, Inc. (BBP)
- Global Oncology Office (GOO)

Japan
- GOO: Tokyo, Osaka
- DCI: Osaka
- OCU: Tokyo
- OMU: Tokyo

USA
- GOO: Cambridge
- BBI: Cambridge
- BBP: Cambridge
Challenges in Cancer Therapy

• Chemotherapy/XRT
  Mainstay for over 50 years…still so!
  Toxicity, very limited efficacy

• Targeted Therapy (1998- )
  Efficacy is limited for most cancer types and patients

• Cancer Immunotherapy Therapy (2015- )
  Unprecedented prolonged disease control in about 20-30% in responding tumor types

Relapsed Cancer Enriched with CSC and Stemness Phenotype
CSC Science Update I
Targeting Cancer Stemness

Cancer Stem Cells
Cancer Stem Cells (CSC)
Fundamentally responsible for
malignant growth
recurrence
metastasis
resistance

Heterogeneous Cancer Cells

Cancer Stemness Inhibitor

CSC Science Update II
Cancer Stemness Mediates Drug Resistance

- Cancer stem cells and cancer cells with stemness are resistant to current therapies
- Conventional therapies can induce cancer stemness
- Relapsed cancer, after initial response to current therapies, display stemness phenotypes
CSC Science Update III
Cancer Stemness Gene Mediates Resistance to Immune Checkpoint Inhibitors

Clinical Development Strategy
For Cancer Stemness Inhibitors

**Quality, Timeline, and Cost**

- Novel and Efficient Clinical Trial Design and Conduct
  - Adaptive multi-arms Ph1/2 studies
    - Efficient and economical way to enrich or to kill an indication
    - Data-driven selection and prioritization of indications
  - Multiple pivotal Ph2/3 studies in parallel
    - “Built-in” flexibility for quality, speed and cost-efficiency
    - Capture broad potential of cancer stemness inhibitors
Pipeline Growth

2012

Launch

Phase III
\(/\) Registration

2015

Phase I/II

Notes:

Napabucasin and BBI503 are investigational agents.

Combo: combination

IO: Immuno-Oncology

Cancer vaccines: MDS, Hematogolic

Solid tumors, mono

Solid tumors, combo

Colorectal, combo

Solid tumors, combo BB503

Hematologic, combo

Glioblastoma, combo

Colorectal, combo

Pancreatic, combo

Hepatocellular, combo

Gastrointestinal, combo SoC

Solid tumors, mono

Colorectal, combo

Gastrointestinal, combo SoC

Solid tumors, combo

Colorectal, combo

Solid tumors, combo

Mesothelioma, combo

Gastrointestinal, combo SoC

Solid tumors, mono

Colorectal, combo

Hepatocellular, combo

Gastrointestinal, combo SoC

Solid tumors, mono

Colorectal, combo

Hepatocellular, combo

Gastrointestinal, combo SoC

Solid tumors, combo

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Gastrointestinal, combo SoC

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Hepatocellular, combo

Gastrointestinal, combo SoC
Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness
Napabucasin Targets Stat3

- Boston Biomedical successfully visualized the direct binding of napabucasin to p-Stat3
- Identification of a novel binding site
- Discovery of a novel mechanism of transcription factor inhibition
Stat3 is a Key Regulator of Cancer Stemness

Tumor Types with Activated Stat3
- Breast Cancer
- Head and Neck Cancer
- Ovarian Cancer
- Lung Cancer
- Colorectal Carcinoma
- Prostate Cancer
- Renal Cell Carcinoma
- Melanoma
- Hepatocellular Carcinoma
- Cervical Cancer
- Sarcoma
- Brain Tumors
- Gastric Cancers
- Multiple Myeloma
- Leukemia
- Lymphoma

Cancer stemness
- Nanog
- Sox2
- c-Myc
- CD133
- β-Catenin
- Twist
- Zeb1

Immune checkpoint
- IDO1
- PD-L1
- MHC class II
- IL-10 (Th1 response)
- Effector T cell infiltrate
Unlike Current Therapeutics, Napabucasin Suppresses CSC Gene Expression

Napabucasin Targets CSC and Spares Normal Stem Cells

Napabucasin Inhibits Cancer Relapse and Metastasis in Mice

Napabucasin Enhances Efficacy of Current Therapies (Paclitaxel as an Example)

**In-Vivo Biomarker Response in Xenograft Tumor**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Napabucasin</th>
<th>Paclitaxel</th>
<th>Napabucasin + Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P-Stat3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P-Stat3 + DAPI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD44</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Human lung cancer xenograft, A549**

![Graph showing MTV (mm^3) vs. Days post inoculation for different treatments](image-url)

- Control
- Napabucasin, 100mg/kg qd po
- Taxol, 10mg/kg q3d iv
- Napabucasin + Taxol

Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

— Colorectal Cancer (CRC) —
Colorectal Cancer: Napabucasin as Monotherapy

Signs of Clinical Activity in CRC

Progression Free Survival
(CRC patients with q12h dosing regimen)

Overall Survival
(CRC patients with q12h dosing regimen)

Median PFS: 17 weeks
Median OS: 40 weeks

Predictive Biomarkers

**p-STAT3**

High p-STAT3

Low p-STAT3

<table>
<thead>
<tr>
<th>p-STAT3 Levels</th>
<th>OS (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>54</td>
</tr>
<tr>
<td>Negative or Low</td>
<td>16</td>
</tr>
</tbody>
</table>

HR = 0.406, p value = 0.152

**β-Catenin**

Nuclear β-Catenin

Membrane bound β-Catenin

<table>
<thead>
<tr>
<th>β-Catenin Pattern</th>
<th>Median OS (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear</td>
<td>53</td>
</tr>
<tr>
<td>Membranous</td>
<td>11</td>
</tr>
</tbody>
</table>

HR = 0.043, p value = 0.001
Colorectal Cancer: Napabucasin as Monotherapy CO.23 Study

The analysis results including Overall Survival and Biomarker have not been obtained yet.

Sponsor: National Cancer Institute of Canada - Clinical Trial Group (NCIC-CTG)
Patients: Failed or intolerant to all recommended therapies (TS inhibitor, Oxaliplatin, Irinotecan + EGFR inhibitor if KRAS WT)

Interim Analysis I Interim analysis II

DCR OS

napabucasin + BSC* Unacceptable toxicity or No longer benefiting from protocol therapy, per Investigator opinion

Placebo + BSC* *BSC: Best Supportive Care

Biomarkers Stratification:
- KRAS (WT vs MUT)
- ECOG PS (0 or 1)
- Prior anti-VEGF (y vs n)
- Time from dx mets (<18 mo vs >18 mo)

Randomize 1:1

napabucasin 480 mg PO BID

• Primary Objective: Overall Survival (5% alpha, 90% power, HR=0.75)
• Secondary: Progression Free Survival, Disease Control Rate, Safety, Quality of Life, Health Economics, PK, Correlative Biomarkers

ASCO 2014 (Abstract TPS3660)

Note: Further enrollment of new patients was stopped and all patients discontinued study therapy in May 2014.
Colorectal Cancer: Preclinical Rationale for Napabucasin in Combo with Chemo

The combination of napabucasin with Chemo showed strong synergy in-vitro and in-vivo.

Effect of Treatments on Cancer Stem Cells

Effect of Treatments on Cancer Stemness Biomarker Response in Xenograft Tumor

ASCO 2015 (Abstract 3616)
Colorectal Cancer: Signs of Activity for Napabucasin in Combo with FOLFIRI

FOLFIRI +/- bevacizumab as the second line treatment of CRC has DCR ~50 to 68%, and ORR ~ 5% in FOLFIRI-naive patients. Phase Ib study has been conducted to use napabucasin plus FOLFIRI in CRC patients (Total 9 Patients, 6 patients had failed FOLFIRI)

- Signs of tumor regression observed in every patient (100%)
- Disease control (Partial Regression and Stable Disease) achieved in all patients (100%)
- 56% (5 of 9 evaluable pts) had prolonged SD (≥ 6 months).

Further data update: ASCO-GI 2016 (Abstract 569)  First Author: Joleen Hubbard
Colorectal Cancer: BBI608-303CRC Study in Advanced Colorectal Cancer

Phase III study of BBI608 in combination with FOLFIRI with or without bevacizumab in patients with advanced colorectal cancer who have failed first line chemotherapy.

Primary Endpoint: Overall Survival
Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

— Gastric/GEJ Cancer —
Gastric/GEJ Cancer: Preclinical Rationale

Stat3 and β-catenin in gastric cancer

- Elevated expression p-Stat3 and nuclear β-catenin associated with advanced disease
- Gastric cancer patients with positive p-Stat3 expression have a poorer overall survival

**Gastric/GEJ Cancer: Signs of Activity of Napabucasin**

**BBI608-201: A Phase Ib/II Clinical Study of BBI608 Administered With Paclitaxel in Adult Patients With Advanced Malignancies**

<table>
<thead>
<tr>
<th>Total Daily Dose (mg)</th>
<th>Diagnosis</th>
<th>Weeks on Study</th>
<th>Best Response (RECIST 1.1)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>Small Cell Lung Cancer</td>
<td>8</td>
<td>PD</td>
<td>Lesion growth</td>
</tr>
<tr>
<td>400</td>
<td><strong>Gastric adenocarcinoma</strong></td>
<td>25</td>
<td>SD</td>
<td><strong>24% regression, 90% CEA decrease</strong></td>
</tr>
<tr>
<td>400</td>
<td>Non-small cell lung cancer</td>
<td>7</td>
<td>SD</td>
<td>Minimal change in target lesions</td>
</tr>
<tr>
<td>1000</td>
<td>Bladder cancer</td>
<td>17</td>
<td>SD</td>
<td>Minimal change in target lesions, PFS 16 weeks</td>
</tr>
<tr>
<td>1000</td>
<td>Ovarian cancer</td>
<td>20</td>
<td>PR</td>
<td>40% regression, 40% CA–125 decrease</td>
</tr>
<tr>
<td>1000</td>
<td>Melanoma</td>
<td>4</td>
<td>SD</td>
<td>11% regression, elected to receive vemurafenib</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>8</td>
<td>PD</td>
<td>Brain metastases not previously imaged</td>
</tr>
<tr>
<td></td>
<td>Ovarian cancer</td>
<td>5</td>
<td>PD</td>
<td>Pathologic fractures</td>
</tr>
<tr>
<td>1000</td>
<td><strong>Melanoma</strong></td>
<td>25</td>
<td>SD</td>
<td>0% lesion change, prolonged stable disease</td>
</tr>
<tr>
<td>1000</td>
<td>GEJ adenocarcinoma</td>
<td>9</td>
<td>PR</td>
<td>44% regression</td>
</tr>
<tr>
<td>1000</td>
<td>GEJ adenocarcinoma</td>
<td>21</td>
<td>PR</td>
<td>48% regression</td>
</tr>
<tr>
<td>1000</td>
<td>GEJ adenocarcinoma</td>
<td>21</td>
<td>SD</td>
<td>0% lesion change, prolonged stable disease</td>
</tr>
<tr>
<td></td>
<td>Bladder cancer</td>
<td>8</td>
<td>PD</td>
<td>Lesion growth</td>
</tr>
<tr>
<td></td>
<td>Bladder cancer</td>
<td>8</td>
<td>PD</td>
<td>Lesion growth</td>
</tr>
<tr>
<td></td>
<td>GEJ adenocarcinoma</td>
<td>23</td>
<td>SD</td>
<td>60% CEA decrease, prolonged stable disease</td>
</tr>
</tbody>
</table>

- 5 patients total with gastric/GEJ adenocarcinoma enrolled:
  - all 5 responded to treatment
  - 3 patients had tumor regression (44%, 48%, 24%)
  - 2 patients who failed prior taxane had prolonged stable disease (>5 months)
Gastric/GEJ Cancer: Early Signs of Clinical Activity

Early signs of anti-cancer activity in patients with gastric/GEJ adenocarcinoma were confirmed in an expansion cohort of heavily pre-treated gastric/GEJ patients.

Baseline

2.2 cm RLL metastasis

8 weeks

Resolved

Revised on December 28th, 2015: deleted the images of CT-scan

ASCO 2015 (Abstract 4069)
BB608-201 (Gastric/GEJ adenocarcinoma) Patient

- Gastric Adenocarcinoma, metastatic to liver
- Failed first line therapy

100% regression of hepatic lesion
Complete Response per RECIST

BASELINE

Metastatic lesion in liver

8 Weeks

Resolved

Revised on December 28th, 2015: deleted the images of CT-scan
Gastric/GEJ Cancer: Signs of Clinical Activity

Efficacy-Summary (BBI608-201)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Prior lines (ave.)</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>mPFS (weeks)</th>
<th>mOS (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>46</td>
<td>2.4</td>
<td>15%</td>
<td>54%</td>
<td>13.0</td>
<td>31.6</td>
</tr>
<tr>
<td>Total Evaluated Per-Protocol</td>
<td>35</td>
<td>2.4</td>
<td>20%</td>
<td>71%</td>
<td>14.6</td>
<td>34.0</td>
</tr>
<tr>
<td>Received Taxane in Metastatic Setting</td>
<td>19</td>
<td>2.6</td>
<td>11%</td>
<td>68%</td>
<td>12.6</td>
<td>33.1</td>
</tr>
<tr>
<td>No Taxane in Metastatic Setting</td>
<td>16</td>
<td>2.1</td>
<td>31%</td>
<td>75%</td>
<td>20.6</td>
<td>39.3</td>
</tr>
</tbody>
</table>

ASCO2015 (Abstract 4069)

• **In 6 patients evaluated who received 1 prior line of therapy that did not include a taxane, an objective response rate of 50% was observed.**

• **Napabucasin plus weekly paclitaxel for the treatment of patients with gastric/GEJ adenocarcinoma who have failed first line platinum-based therapy is being evaluated in a phase III randomized controlled trial, the BRIGHTER study.**
Gastric/GEJ Cancer: BRIGHTER Study of Napabucasin

Interim Analysis (OS): Test for Superiority at 2/3 of required events (380)

Death

Primary
• Overall survival (OS) in general study population

Secondary
• Overall survival in predefined biomarker-positive sub-population
• Progression-Free Survival (PFS) in general study population
• Progression-Free survival in predefined biomarker-positive sub-population
• Objective response rate (OR) in general study population
• Disease Control Rate (DCR)
• Safety profile

Planned sample size: 700 patients (350 pts on napabucasin arm and 350 pts on Placebo arm)

ASCO 2015 (Abstract TPS4139)
Napabucasin

First-in-Class inhibitor of Stat3, a critical pathway in cancer stemness

— Combination with Immune Checkpoint Inhibitors —
Napabucasin Inhibits Cancer Immune Evasion

CCL4
Dendritic cell (DC)
CD8+ T-cell

Active β-catenin signaling

Phenotype change

T cell-inflamed phenotype
Immune Checkpoint Inhibitors-sensitive

Non-T cell-inflamed phenotype
Immune Checkpoint Inhibitors-resistant

β-catenin
Chemoattractant
Infiltration

Immune Checkpoint Inhibitors sensitization

Stat3
Napabucasin

β-catenin
Chemoattractant
Infiltration
Targeting Stemness May Sensitize Cancer to Immune Checkpoint Drugs

BBI608-201CIT: A Phase Ib/II Clinical Study of BBI608 Administered in Combination with Immune Checkpoint Inhibitors to Adult Patients with Advanced Cancers

Primary objective: Safety, Tolerability, RP2D
Secondary objective: PK profile, preliminary anti-tumor activity

(Clinical Trial .gov  NCT02467361)
Clinical Strategy to Develop Cancer Stemness Inhibitors

Phase 1/2
(Each study tests multiple tumor types and/or regimens)

- BBI608-101
  Explore tumor types in monotherapy

- BBI608-224 (3-arm)
  Explore best combination regimens in CRC

- BBI608-246 (6-arm)
  Explore best combination regimens in GI cancers

- BBI608-201
  Explore tumor types in combination w paclitaxel

- BBI608-201CIT
  Explore tumor types in combination w ICIs

Phase 2/3
(Multiple pivotal studies run in parallel)

- CO.23
  CRC, monotherapy

- BBI608-336 (BRIGHTER)
  Gastric/GEJ, combo w paclitaxel

- BBI608-303CRC
  Combo w FOLFIRI+/-bev

To be selected

- NSCLC
- Breast Cancer
- Ovarian Cancer
- Pancreatic Cancer

Pancreatic Cancer Data Presentations
ASCO-GI, 2016
# Napabucasin – Clinical Trials

Napabucasin is an orally-administered investigational agent designed to inhibit cancer stem cell pathways by targeting Stat3.

<table>
<thead>
<tr>
<th>Proposed indication</th>
<th>Development Location</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer (Monotherapy)</td>
<td>Global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric / GEJ adenocarcinoma (Combination therapy)</td>
<td>Global</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal Cancer (Combination therapy)</td>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple solid tumors (NSCLC, ovarian, breast, melanoma) (Combination therapy)</td>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant pleural mesothelioma (Combination therapy)</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal cancer (Combination therapy)</td>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancer (Combination therapy)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (Combination therapy)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma (Combination therapy)</td>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancies (MM, lymphoma, AML, MDS, CML) (Monotherapy / Combination therapy)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple solid tumors (Combination with BBI503)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple solid tumors (Combination with immune checkpoint inhibitors)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (Combination therapy)</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Napabucasin is investigational agent and not approved by the U.S. FDA.
Upcoming Presentation

Gastrointestinal Cancers Symposium (ASCO-GI)
Jan 21-23, 2016, San Francisco, CA

(Pancreatic Cancer)

**Poster Session B: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract**
Friday, January 22, 2016: 12:30 PM–2:00 PM and 5:30 PM–7:00 PM

A phase Ib study of cancer stem cell (CSC) pathway inhibitor BBI-608 in combination with gemcitabine and nab-paclitaxel (nab-PTX) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC).  (Abstract 284)  First Author: Safi Shahda

A phase Ib/II study of BBI608 combined with weekly paclitaxel in advanced pancreatic cancer.  (Abstract 196)  First Author: Tanios Bekaii-Saab

(Colorectal Cancer)

**Poster Session C: Cancers of the Colon, Rectum, and Anus**
Saturday, January 23, 2016: 7:00 AM–7:55 AM and 12:30 PM–2:00 PM

Phase Ib study of cancer stem cell (CSC) pathway inhibitor BBI-608 administered in combination with FOLFIRI with and without bevacizumab (Bev) in patients (pts) with advanced colorectal cancer (CRC).  (Abstract 569)  First Author: Joleen Hubbard
BBI503

First-in-Class Kinase Inhibitor of Cancer Stem Cell Pathways, including Nanog
BBI503: First-in-Class Kinase Inhibitor of Cancer Stem Cell Pathways

Cancer stem cells
- Highly tumorigenic
- Responsible for continued malignant growth
- Initiators of metastases
- Chemoresistant

BBI503
- Inhibits multiple kinases responsible for cancer cell stemness
- Has demonstrated inhibitory activity in cancer stem cell assays
- Has demonstrated antitumor activity in preclinical models

BBI503
• Inhibits multiple kinases responsible for cancer cell stemness
• Has demonstrated inhibitory activity in cancer stem cell assays
• Has demonstrated antitumor activity in preclinical models

ASCO 2015 (Abstract 3615)
BBI503 Inhibits Cancer Stemness Pathways in Patients

Nanog in Pre-Treatment and On-Treatment Tumor Biopsies

Baseline Biopsy  On-Treatment Biopsy

% fluorescence remaining plotted as function of total daily dose

ASCO 2015 (Abstract 3615)
Cancer Stemness Gene Nanog as a Predictive Biomarker for BBI503

Nanog Staining of Archival Tissue

Positive

Negative

Overall Survival Stratified by Nanog Status

<table>
<thead>
<tr>
<th>Nanog Status mOS (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive: 38.0</td>
</tr>
<tr>
<td>Negative: 15.9</td>
</tr>
</tbody>
</table>

Tissue considered positive if ≥ 20% of tumor cells have 2+ Nanog staining or ≥ 5% tumor cells have 3+ intensity of Nanog staining.

ASCO 2015 (Abstract 3615)
BBI503 is an orally-administered investigational agent designed to inhibit cancer stem cell pathways, including Nanog by targeting kinases

<table>
<thead>
<tr>
<th>Proposed indication</th>
<th>Development Location</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple solid tumors (Monotherapy)</td>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary cancer (Monotherapy)</td>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors (Monotherapy)</td>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urologic malignancies (Monotherapy)</td>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer (Monotherapy)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (Combination therapy)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple solid tumors (Combination therapy with napabucasin)</td>
<td>U.S.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple solid tumors (Combination therapy)</td>
<td>North America</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple solid tumors (Monotherapy) (Combination therapy in Hepatocellular carcinoma)</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BBI503 is investigational agent and not approved by the U.S. FDA.
New Product Development Opportunities
Major Product Platform Technologies

- **Small Molecules (1950s-1980s)**
  - 1000 products
- **Antibody/Protein (1980s-2000s)**
  - 200 products
- **RNA Interference <Gene-Targeted Platform>**
  - Major Therapeutic Product Platform of the 21st century
  - RNA interference discovered in 1998.
  - Can potentially target any disease gene, including “non-druggable” targets.
  - Over 20 clinical trials had launched.

<table>
<thead>
<tr>
<th></th>
<th>RNAi</th>
<th>Small molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specificity</strong></td>
<td>High, sequence driven</td>
<td>Low-medium, conformation driven</td>
</tr>
<tr>
<td><strong>Potency</strong></td>
<td>Typically pM-nM</td>
<td>Variable</td>
</tr>
<tr>
<td><strong># of accessible targets</strong></td>
<td>&gt;&gt;1000</td>
<td>500 to 1,000</td>
</tr>
<tr>
<td><strong>Lead discovery timeline</strong></td>
<td>4 to 8 weeks</td>
<td>2 to 4 years</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Common, rapid, scalable methods</td>
<td>Variable, can be complex</td>
</tr>
</tbody>
</table>
Effective RISC loading of aiRNA. Sense strands and anti-sense strands from siRNA are incorporated into RISC and off-target silencing derived from sense strands is induced. By contrast, only antisense strands from aiRNA are incorporated into the RISC increasing specific target gene silencing.
aiRNA Enables Superior Gene Silencing Efficiency

- Super aiRNA shows **pico-molar** activity.
- **20 fold potent** more than siK-Ras used in the recent clinical trials.

*(siG12D RODER trial, NCT01188785)*

AACR 2015 (Abstract LB-14)
Targeting cancer stem cells with diverse approaches

Cancer tissues

- Bulk tumor cells
- Stromal cells
- Immune cells

Cancer stem cells

- Stem cell pathways
- Stemness kinases

Pipeline

<table>
<thead>
<tr>
<th>Research</th>
<th>Preclinical</th>
<th>Phase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>aiRNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSC Kinase Inhibitors</td>
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<tr>
<td>Stemness Inhibitor</td>
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<tr>
<td>Epigenetic targets</td>
<td></td>
<td></td>
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<tr>
<td>Cancer Vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune Response Enhancers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Global Oncology Clinical Development Perspective

**Launch**

Gastric, combo

Colorectal, combo (in preparation)

**Phase III / Registration**

2012

2015

2018

Gastric, combo

Colorectal, combo

Colorectal, mono

Colorectal, combo

**Phase I/II**

Solid tumors, mono

Solid tumors, combo

Colorectal, combo

Solid tumors, mono

Solid tumors, combo

Colorectal, combo

Gastrointestinal, combo SoC

Pancreatic, combo

**Notes:**

Napabucasin and BBI503 are investigational agents.

Combo: combination

IO: Immuno-Oncology
Disclaimer Regarding Forward-looking Statements

The statements made in this presentation material are forward-looking statements based on management’s assumptions and beliefs in light of information available up to the day of announcement, and involve both known and unknown risks and uncertainties.

Actual financial results may differ materially from those presented in this document, being dependent on a number of factors.

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