R&D INVESTOR DAY AGENDA – TOKYO, SEPTEMBER 27, 2018

<table>
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<tr>
<th>Time</th>
<th>Agenda</th>
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                         Christophe Weber        |
| 13:25 – 14:05 | R&D Transformation, Progress To Date, Future Outlook  
                         Andy Plump                |
| 14:05 – 14:40 | Oncology  
                         Phil Rowlands               |
| 14:40 – 15:00 | Gastroenterology  
                         Asit Parikh                |
| 15:00 – 15:15 | Break                  |
| 15:15 – 15:35 | Neuroscience  
                         Emiliangelo Ratti          |
| 15:35 – 15:55 | Vaccines  
                         Choo Beng Goh               |
| 15:55 – 16:10 | Shonan iPark  
                         Toshio Fujimoto            |
| 16:10 – 17:15 | Looking ahead  
                         Andy Plump  
                         Panel Q&A Session          |
DELIVERING ON OUR R&D VISION

TOKYO, JAPAN

ANDY PLUMP MD, PHD
Chief Medical and Scientific Officer
September 27, 2018

Better Health, Brighter Future

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OUTLINE FOR TODAY

• Overview of Takeda, our R&D transformation and progress to date
• Deep dive by Therapeutic Area (Oncology, Gastroenterology, Neuroscience plus Vaccines) and how each is contributing to unlock innovation and deliver meaningful value
• Recurring themes:
  - Focus
  - Robust research engine and capabilities
  - New modalities
  - Differentiated, global partnership approach
  - High-performing teams
• Review Shire acquisition and how it accelerates our R&D momentum

DOING MORE FOR OUR PATIENTS

WHAT WE’VE DELIVERED

WHAT’S NEXT
Takeda is a patient-centric, innovation-driven global pharmaceutical company that builds on a distinguished 237-year history, aspiring to bring better health and a brighter future for people worldwide.
VALUES

TAKEDA-ISM & OUR PRIORITIES

Established by our founding spirit and integral to every part of our business, Takeda-ism and our priorities guide us in our efforts to achieve our Vision 2025.

OUR PRIORITIES

We make decisions and take actions by focusing on our four priorities in this order:

1. Putting the patient at the center
2. Building trust with society
3. Reinforcing our reputation
4. Developing the business

R&D LEGACY: THE CASE FOR CHANGE WAS ABSOLUTE

Period of poor productivity following approval of pioglitazone in 1999

- Fragmented R&D footprint
- Lack of therapeutic area focus
- Inwardly facing
- Regional teams, regional mindset
- Pipeline >85% small molecule

PRODUCT LAUNCHES BY DISCOVERY SOURCE (FY2005 – 2015)

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<thead>
<tr>
<th>Internal (4)</th>
<th>Acquisition (8)</th>
<th>Licensed (10)</th>
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<tr>
<td>DEXILANT</td>
<td>NESINA</td>
<td>ADCETRIS</td>
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<tr>
<td>EDARBI / AZILVA²</td>
<td>COLCRYS²</td>
<td>AMITIZA</td>
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<tr>
<td>ROZEREM</td>
<td>DAXAS³</td>
<td>AZILECT</td>
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<td>TAKECAB</td>
<td>ENTYVIO</td>
<td>BRINTELLIX / TRINTELLIX</td>
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<tr>
<td>NINLARO</td>
<td>CONTRAVE³,⁴</td>
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<td>REVESTIVE³</td>
<td>COPAXONE</td>
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<td>ZAFATEK</td>
<td>REMINYL</td>
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<td>MEPACT</td>
<td>VECTIBIX</td>
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<tr>
<td>XELJANZ³</td>
<td>ULORIC</td>
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</table>

1. For purposes of NME counts, Edarbi and Azilva are combined.
2. Colcrys is counted as an NME, although the product was on-market in generic form.
3. Daxas, Revestive, Contrave, and Xeljanz have since been divested or returned to partner.
4. Contrave counts as an NME, although it is composed of two on-market compounds.
WHAT WE COMMITTED TO
Reinventing R&D

BUILDING AN AGILE R&D ORGANIZATION DRIVEN BY INNOVATIVE SCIENCE

THERAPEUTIC AREA FOCUS
Oncology, Gastroenterology, Neuroscience plus Vaccines

PARTNERSHIPS & CAPABILITIES  TRANSFORM OUR CULTURE

R&D TRANSFORMATION KEY IMPERATIVES
• Agile and lean
• Dynamic and sustainable research and early development engine
• Transformative advances via reciprocally advantageous partnerships
• Laser-focused on purposeful execution
WHAT R&D TRANSFORMATION MEANT...

A STRATEGIC, TECHNICAL, SKILL-SET, STRUCTURAL, GEOGRAPHIC AND CULTURAL CHANGE THAT IMPACTED NEARLY ALL R&D EMPLOYEES.

STRONG LEADERSHIP DRIVING CHANGE

<table>
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<tr>
<th>Name</th>
<th>Role/Unit</th>
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<tbody>
<tr>
<td>ANDY PLUMP</td>
<td>CMSO</td>
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<tr>
<td>ASIT PARIKH</td>
<td>Gastroenterology TAU</td>
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<tr>
<td>STEVE HITCHCOCK</td>
<td>Research</td>
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<td>PHIL ROWLANDS</td>
<td>Oncology TAU</td>
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<tr>
<td>EMILIANGELO RATTI</td>
<td>Neuroscience TAU</td>
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<tr>
<td>RAJEEV VENKAYYA</td>
<td>Vaccines Business Unit</td>
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<tr>
<td>DAN CURRAN</td>
<td>Center for External Innovation</td>
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<tr>
<td>NENAD GRMUSA</td>
<td>R&amp;D Portfolio Strategy &amp; Investment Mgmt</td>
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<tr>
<td>STEFAN WILDT</td>
<td>Pharmaceutical Sciences</td>
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<tr>
<td>COLLEEN BEAUREGARD</td>
<td>R&amp;D Communications</td>
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<tr>
<td>GEORGINA KERESTY</td>
<td>Medical Sciences &amp; Development Operations</td>
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<tr>
<td>TOSHIO FUJIMOTO</td>
<td>iPark</td>
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<tr>
<td>ERIKA MARDER</td>
<td>R&amp;D Human Resources</td>
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<tr>
<td>CHRISS MORABITO</td>
<td>R&amp;D Shire Integration</td>
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TAU: Therapeutic Area Unit

HIRED IN THE LAST 12 MONTHS
WHAT WE’VE DELIVERED
Our innovations are transforming our business and the lives of patients

TWO YEARS INTO A FIVE-YEAR R&D TRANSFORMATION JOURNEY

Focused (3+1) therapeutic area strategy and lean operating model

A pipeline that’s delivering
- Fueled by a robust research engine and a rich, global partner ecosystem

Culture: engaged and empowered teams
WE’VE FOCUSED OUR THERAPEUTIC AREAS

<table>
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<th>ALL IN: 3+1</th>
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<tbody>
<tr>
<td>ONCOLOGY</td>
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<tr>
<td>GASTROENTEROLOGY</td>
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<tr>
<td>VACCINES</td>
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<td>NEUROSCIENCE</td>
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RESEARCH, DIVERSE MODALITIES AND PARTNERSHIPS

WE’VE STREAMLINED OUR GLOBAL FOOTPRINT

**BOSTON, MA**
R&D Center
Oncology, GI Research

**SHONAN, JAPAN**
Neuroscience Research,
T-CiRA, iPark

**SAN DIEGO, CA**
Specialized drug
discovery technologies,
GI and Neuroscience
WE’VE REDIRECTED RESOURCES TO HIGHLY INNOVATIVE MEDICINES

FOCUS AND PRIORITIZATION

- Reduced Drug Discovery Units from 6 to 3
- Changed research from “pipe” to “funnel” along stage-gates*
- Aggressive resourcing of focused portfolio

FOCUS ON EXECUTION

Established a research KPI in FY18 to achieve industry leading cycle-times for candidate selection

On track to achieve 11 planned candidate selections in FY18 of which 5 are non small molecules

* Beginning June 2016

RESEARCH & EARLY CLINICAL ENGINE: KEY CAPABILITIES

THE RIGHT TARGET

- Leveraging human-derived data
- Potential for game-changing patient impact
- Testable translational hypotheses
- First-in-class or best-in-class

THE RIGHT MODALITY

- Patient -> Biology -> Modality
- Embrace innovative platforms
- Expand internal capabilities through partnerships
- Invest in innovative biologics and cell therapies

FLAWLESS EXECUTION

- Human early POC is a key performance indicator
- Optimized partnership model
- Operational effectiveness incentives
- Specialized Pharmaceutical Sciences capabilities
SELECT PARTNERSHIPS

WITH OUR PARTNERS, WE’RE AT THE FOREFRONT OF INNOVATION
Diversity of modalities in the research pipeline*

* As of August 28, 2018, Biologics include proteins, enzymes, antibodies, peptides. Other Modalities include microbiome, drug delivery systems, vaccine.
INVESTING IN THE TRANSFORMATIVE POTENTIAL OF CELL THERAPIES

RESEARCH

NOILE-IMMUNE BIOTECH
GAMMADELTA

7CiRA

Key Academic Collaborations in CAR-T

APPROVED*

ALOFISEL

“We’re at a key point when it comes to cell and gene therapy...for a long time, they were largely theoretical constructs. Now they are a therapeutic reality.”

SCOTT GOTTLIEB, M.D.
Alliance for Regenerative Medicine Annual Meeting | May 22, 2018

2019: Differentiated CAR-Ts in Phase I
2020+: Other Hematologic/Solid Tumor CAR-Ts

* EU launch 2018

WE’VE BUILT A COMPREHENSIVE, DIFFERENTIATED PARTNERSHIP MODEL

CENTER FOR EXTERNAL INNOVATION (CEI)

- Integrated into the innovation system; access to promising, potentially revolutionary platforms prior to validation
- Close alignment of interests/incentives with many engagement mechanisms including: co-creation, in-licensing, out-licensing, Takeda financing, capabilities support, etc.
- Flexibility and optionality in partnership structure with clear two-way accountability
WE EXECUTED 56 PARTNERSHIPS IN FY17

THERAPEUTIC AREA FOCUSED

ONCOLOGY

ONCOLOGY COMPANIES

GASTROENTEROLOGY

GASTROENTEROLOGY COMPANIES

NEUROSCIENCE

NEUROSCIENCE COMPANIES

NOVEL PLATFORMS, NEW CAPABILITIES

External Value Creation

Companies Created

New Capabilities

Rare Disease Initiatives

Strategic Academic Alliances

Takeda Ventures

OBSIDIAN

AND OUR APPROACH TO EXTERNAL INNOVATION IS GLOBAL

Number of ongoing partnerships by region
...RESULTING IN A DYNAMIC AND RE-INVIGORATED PIPELINE

WE’LL CONTINUE TO FOCUS ON CORE THERAPEUTIC AREAS
WITH THE POTENTIAL TO DELIVER MORE VALUE IN THE FUTURE

Note: SHP652 and Natpara classified as “other” and not shown here | **With ongoing clinical development activities. Pipeline as of February 1, 2018

CENTRAL TO EVERYTHING, WE’VE EVOLVED OUR CULTURE AND THE WAY WE WORK

SELECT INITIATIVES

<table>
<thead>
<tr>
<th>METRICS</th>
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<tbody>
<tr>
<td>Staff turnover</td>
</tr>
<tr>
<td>Engagement</td>
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<tr>
<td>Alignment</td>
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</table>

R&D ALIGNMENT AROUND BIG IMPORTANT VALUE INFLECTIONS (BIVIs) FOR R&D FY18

1. Trintellix: Approval of processing speed (important aspect of cognitive function) in U.S. label

2. Alunbrig:
   a) ALTA-1L interim analysis
   b) EU approval for 2nd line in ALK+ non-small cell lung cancer

3. Ninlaro:
   a) Interim analysis
   b) Submission for both newly diagnosed multiple myeloma and maintenance post-transplant

4. Entyvio: Ulcerative colitis subcutaneous submission

5. Dengue vaccine: Successful primary endpoint of Ph3 trial

6. STING agonists: Achieve in vivo POC for a drug delivery system

Internal R&D KPIs established in April 2018

WHAT’S NEXT
Looking Ahead
WHAT WE STILL NEED TO DELIVER

Maximize the value of our current portfolio

Progress our research and early pipeline

Implement improvements to our clinical trial operating model

Develop enhanced capabilities to support rare disease portfolio growth

PROMISING PIVOTAL PROGRAMS

NEAR-TERM PIVOTAL RESULTS

Pevonedistat NAE inhibitor
Phase 1b study of pevonedistat with azacytidine

Bar length reflects duration of response

Registration-enabling results expected in FY19

TAK-003 Dengue vaccine
Antibody-mediated immune response in dengue naive population

Phase 3 results expected in FY18

NEXT PIVOTAL INITIATION

TAK-788 EGFR/HER2 inhibitor
Antitumor activity in all patients treated with TAK-788 at a total daily dose of 280–160 mg

Registration-enabling trial start expected in FY18

1 Blood. 2018;131(13):1415-1424


Neal et al., WCLC 2018
CHINA IS AN IMPORTANT PART OF OUR GLOBAL GROWTH STRATEGY

6 NEW PRODUCTS, 14 NEW INDICATIONS ANTICIPATED BY 2020

SUSTAINED VALUE CREATION

<table>
<thead>
<tr>
<th>FY 2018</th>
<th>FY 2019</th>
<th>FY 2020</th>
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<tbody>
<tr>
<td>Ninlaro, 2L, ALK+ NSCLC post-1st line (EU)</td>
<td>TAK-003 Dengue Vaccine</td>
<td>Pevonedistat, HR-MDS</td>
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<tr>
<td>ADCETRIS, TL, HL (EU, JP)</td>
<td>TAK-788, NSCLC Phase 2</td>
<td>ADCETRIS, VALCL (CN)</td>
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<tr>
<td>Entyvio, UC, HDI vs. adalimumab</td>
<td>ALLUNBRIG, 2L, H2H vs. standard</td>
<td>Ninlaro, ND MM</td>
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<tr>
<td>Entyvio, UC, HDI (EU)</td>
<td>ICLUSIO, Ph+ ALL</td>
<td>Ninlaro, MM maint, non-SCT</td>
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<tr>
<td>ALLUNBRIG, 2L, H2H vs. standard</td>
<td>Entyvio, GvHD prophylaxis</td>
<td>TAK-003, Dengue Vaccine (EM)</td>
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<tr>
<td>ALLUNBRIG, 2L, post-2nd Gen</td>
<td>TAK-214 Nonrulinus Ph2b results</td>
<td>Entyvio SC CD</td>
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<tr>
<td>TAK-214 Nonrulinus Ph2b results</td>
<td>TAK-029 R/R MM EPOC results</td>
<td>TAK-164, GI Cancers EPOC results</td>
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<td>Ninlaro, MM maint, non-SCT (US, EU, JP)</td>
<td>TAK-403, lymphoma EPOC results</td>
<td>Ninlaro, MM maint, non-SCT (US, EU, JP)</td>
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<td>TAK-157 MM EPOC results</td>
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<td>Ninlaro, MM maint, non-SCT (US, EU, JP)</td>
<td>TAK-625 GI Cancers EPOC results</td>
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<td>Ninlaro, MM maint, non-SCT (US, EU, JP)</td>
<td>TAK-925 preliminary NT1 efficacy data</td>
<td>Ninlaro, MM maint, non-SCT (US, EU, JP)</td>
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<td>Ninlaro, MM maint, non-SCT (US, EU, JP)</td>
<td>TAK-931, Friedrich Ataxia Ph2 results</td>
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Projected timelines as of September 23, 2018 and subject to change. Please refer to glossary for disease abbreviations.

* On Aug 8th 2018, a total of 48 products marketed outside of China were selected by the Center Drug Evaluation based on urgent medical needs, companies are encouraged to apply for NDA with overseas data including data demonstrating lack of ethnic differences. Priority review/approval process will be applied.

Projected timelines as of September 23, 2018, subject to change. Please refer to glossary for disease abbreviations.
CONCLUSION:

1. Distinct R&D strategy based on TA focus, sustainable research and partnership engine

2. Delivering an innovative and compelling pipeline with near-term, data-driven inflections across each therapeutic area

3. With the successful execution of R&D transformation complete, we’re now ready to effectively integrate Shire

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ORIENTATION TO OUR ONCOLOGY R&D OVERVIEW

Focused Oncology R&D Strategy
- Building on foundational expertise in hematologic malignancies and a growing portfolio in lung cancer

Novel Discovery Strategy in Immuno-Oncology (I/O) and Advance in Cell Therapies
- Pursuing novel I/O targets and next-generation platforms with world class external partners
- Next-generation cell therapies will bring transformative potential to patients with cancer

Near Term Inflections
- FY2018-FY2020 will be highlighted by several submissions, approvals, pivotal trial starts, and novel assets entering clinical trials
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WE ASPIRE TO CURE CANCER

OUR MISSION
We endeavor to deliver novel medicines to patients with cancer worldwide through our commitment to science, breakthrough innovation, and passion for improving the lives of patients.
BUILDING ON THE TAKEDA ONCOLOGY FOUNDATION IN HEMATOLOGIC MALIGNANCIES

GROWING LEADERSHIP POSITION IN HEMATOLOGIC MALIGNANCIES

Next Generation I/O TAK-573 TAK-981

MDS Phase 3

AML Phase 3

pevonedistat

alisertib

Lymphoma Chronic Myeloid Leukemia

ADCETRIS® brentuximab vedotin

ICLUSIG® ponatinib tablets

Improving Patient Outcomes in Multiple Myeloma

VELCADE® bortezomib

NINLARO® ixazomib capsules

RECENT PROGRESS AND NEXT STEPS

Current Status

Approved in 59 countries for Relapsed/Refractory Multiple Myeloma

First Phase 3 maintenance readout (post-transplant)

Looking Forward

2019 Data Inflections:

MM2 (newly diagnosed)

MM4 (non-transplant maintenance)

AL1 (amyloidosis)

Evolution of real world evidence

Ideal Maintenance Therapies in Multiple Myeloma:

- Easy to administer
- Minimal toxicity
- Maintain response
ADVANCE CD38 BIOLOGY FOR REFRACTORY MULTIPLE MYELOMA

TAK-079
- A fully human, anti-CD38 cytolytic IgG1 lambda antibody
- Potent and selective reduction of plasmablasts and NK cells
- Potential for convenient subcutaneous delivery
- Currently in Phase 1 for refractory multiple myeloma

TAK-573
- Novel immuno-cytokine approach
- Potential to overcome toxicity of unmodified interferon α and realize the true benefit in oncology
- Compelling pre-clinical data; Phase 1 enrolling for patients with refractory multiple myeloma

TAK-169
- 2nd generation Molecular Templates platform
- pM activity against CD38+ cells plus activity in daratumumab-resistant cells
- IND planned in 2019

TAK-079: IMPROVING UPON FIRST GENERATION ANTI-CD38 mAb FOR REFRACTORY MULTIPLE MYELOMA PATIENTS

A potent anti-CD38 mAb administered as a low volume subcutaneous (SC) injection

Plasmablast depletion*

NK cell depletion*

* After a single SC injection of 0.6 mg/kg into healthy volunteers (n=6)

Novel pharmacokinetic properties enhance potency and enable convenient administration
BRINGING NOVEL THERAPIES TO MDS AND AML

PEVONEDISTAT IN HR-MDS

- 1 in 3 MDS patients will progress to AML
- Overall survival 1-1.5 years in the relapse setting
- No new therapies in the last decade

ALISERTIB IN AML

- AML: Current 5 year survival ~30%
- Transplant remains only curative option


DUAL STRATEGY IN LUNG CANCER:
TARGETING DRIVER MUTATIONS AND NEXT-GENERATION I/O

CURRENT PORTFOLIO
- **ALUNBRIG**
  - TAK-788
- **BRIGATINIB**
  - TAK-228
- Sapanisertib (TAK-228)
- Next-generation kinase inhibitors

EMERGING ASSETS

NEXT GENERATION TARGETS AND PLATFORM

**ALUNBRIG ALTA 1L — POTENTIAL BEST-IN-CLASS PROFILE IN ALK+ NSCLC**

Clear superiority to crizotinib and early separation in PFS curve

Primary endpoint (PFS) hazard ratio is 0.49

Risk/benefit profile consistent with the expectations of a best-in-class therapy

Camidge R., WCLC 2018

**TAK-788: ADDRESSING UNMET NEED IN EGFR EXON20 MUTATIONS**

Overall survival <6 months for exon 20 insertions

Current therapies ineffective for these mutations

Robichaux et al. WCLC 2016

Expected to begin registration-enabling Phase 2 trial in FY2018

Neal et al., WCLC 2018
ORIENTATION TO OUR ONCOLOGY R&D OVERVIEW

Focused Oncology R&D Strategy
• Building on foundational expertise in hematologic malignancies and a growing portfolio in lung cancer

Novel Discovery Strategy in Immuno-Oncology (I/O) and Advance in Cell Therapies
• Pursuing novel I/O targets and next-generation platforms with world class external partners
• Next-generation cell therapies will bring transformative potential to patients with cancer

Near Term Inflections
• FY2018-FY2020 will be highlighted by several submissions, approvals, pivotal trial starts, and novel assets entering clinical trials

WORLD CLASS PARTNERS FUELING THE I/O PIPELINE

Re-directed immunity
Targeted payloads
Tumor micro-environment

Key Academic Collaborations in CAR-T

Memorial Sloan Kettering Cancer Center
HaemaLogix
Noile-Immune Biotech
Shattuck Labs
Heidelberg Pharma
Gamma Delta Therapeutics
Maverick Therapeutics
Teva
Crescendo Biologics
Mersana Therapeutics
TAK-573: BRINGING A NOVEL IMMUNO-CYTOKINE APPROACH TO MULTIPLE MYELOMA

Targeted delivery of attenuated interferon α to CD38 - a known target in multiple myeloma

Binds to CD38

Human IgG4 Fc

Attenuated IFNα2b with 2 point mutations

NCI-H929 Myeloma Model

Highly compelling pre-clinical data with TAK-573 in a core area of our clinical development expertise in multiple myeloma

Pogue et al. PLOS ONE 2016

TAKEDA ONCOLOGY AIMS TO BECOME A LEADER IN CELL THERAPIES

TRANSFORMATIVE POTENTIAL UTILIZING NEXT GENERATION CELL THERAPY PLATFORMS

Cell therapy engine for Takeda R&D

FY2019: Differentiated CAR-Ts in Phase I
FY2020+: Other Hematologic Malignancy and Solid Tumor CAR-Ts

Key Academic Collaborations in CAR-T
ORIENTATION TO OUR ONCOLOGY R&D OVERVIEW

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AN INNOVATIVE PIPELINE ENHANCED WITH EXTERNAL PARTNERSHIPS

<table>
<thead>
<tr>
<th>Discovery/preclinical*</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved**</th>
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<tbody>
<tr>
<td><strong>Hematologic Malignancies</strong></td>
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<tr>
<td>TAK-160</td>
<td>CD30 SLTA</td>
<td>TAK-079</td>
<td>RR MM, NSZ CD38 mAb</td>
<td>TAK-655 Lymphoma SYK, FLT-3 Small Molecule Alkertib AML AURORA A Small Molecule Pembrolizumab HR-MDS/ANL NEDD 8 Small Molecule NINJARO Amyloidosis, ND MM, R/R MM NExt combo, R/R MM NExt/dx, Maint MM post-SCT PROTASOME Small Molecule</td>
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<td><strong>Lung Cancer</strong></td>
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<tr>
<td>TAK-788 NSCLC Exon 20 EGFR/HER2</td>
<td>Small Molecule</td>
<td>Sapanisertib Endometrial Cancer Lung Cancer mTORC1/2 Small Molecule</td>
<td>ALUNBRIG 2L post-orientinib ALK+NSCLC (EU, JP, CN), FL ALK+ NSCLC ALC Small Molecule</td>
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<td>TAK-573 PD-L1/0K40L</td>
<td>STING</td>
<td>TAK-676 ATE002 Attenukin mAb/Fusion Protein</td>
<td>TAK-931 Solid Tumors CD7 Small Molecule niraparib*** Ovarian Cancer, HER2+ Breast Cancer Small Molecule cabozantinib*** 1L RCC, 2L HCC, 3L HCC Multi-RTK Small Molecule</td>
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<td><strong>Solid Tumors</strong></td>
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<td>TAK-522</td>
<td>Solid Tumors HER2</td>
<td>mAb 4D4</td>
<td>TAK-364</td>
<td>Solid Tumors GCC mAb 4D4</td>
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</tbody>
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Pipeline as of September 23, 2018  * Assets shown in discovery/preclinical and Phases 2-3 explicitly refer to new molecular entities
** Some with active development seeking new or supplemental indications, or approvals in new territories
*** In pivotal trial for Japan approval
Note: Takeda holds the right to develop and commercialize Aduron in ex-US/Canada. For Nanoparc and Cabozantinib, Takeda holds the right to develop and commercialize in Japan and selected Emerging Markets
EXPECTED KEY ONCOLOGY PORTFOLIO INFLECTION AND MILESTONES

Dates in fiscal year (FY) starting April 1st

1. **ALUNBRIG EU APPROVAL (2L)**
   ADCETRIS EU/JP APPROVAL (FL)

2. **NINLARO maintenance post-transplant US APPROVAL**

3. **ALUNBRIG US APPROVAL (1L)**

Projected timelines as of September 23, 2018, subject to change

Concluded:

1. Focused on delivering the next approvals for NINLARO, ALUNBRIG, and pevonedistat

2. Expanding transformative treatment options in our focus areas of hematologic malignancies and lung cancer with alisertib, TAK-788 and novel CD38 targeted mechanisms

3. Harnessing the power of external innovation with a diverse set of world-class partnerships, accelerating novel therapies into the clinic
# R&D INVESTOR DAY AGENDA – TOKYO, SEPTEMBER 27, 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda</th>
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<tr>
<td></td>
<td>Christophe Weber</td>
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<td>13:25 – 14:05</td>
<td>R&amp;D Transformation, Progress To Date, Future Outlook</td>
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<td>14:05 – 14:40</td>
<td>Oncology</td>
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<td>Phil Rowlands</td>
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<td>14:40 – 15:00</td>
<td>Gastroenterology</td>
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<td>Asit Parikh</td>
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<td>15:00 – 15:15</td>
<td>Break</td>
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<td>15:15 – 15:35</td>
<td>Neuroscience</td>
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<td>15:35 – 15:55</td>
<td>Vaccines</td>
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<td>Choo Beng Goh</td>
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<td>15:55 – 16:10</td>
<td>Shonan iPark</td>
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<td>Toshio Fujimoto</td>
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<td>16:10 – 17:15</td>
<td>Looking ahead</td>
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<td>Andy Plump</td>
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<td></td>
<td>Panel Q&amp;A Session</td>
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TAKEDA GASTROENTEROLOGY
A GLOBAL LEADER IN GASTROENTEROLOGY

Asit Parikh MD, PhD
Head, Gastrointestinal Therapeutic Area
WE ARE A LEADING GI COMPANY

GASTROENTEROLOGY

OUR VISION
Restore Life to Living for patients suffering with GI and liver diseases

OUR MISSION
 Deliver innovative, life-changing therapeutics for patients with GI and liver diseases

OUR STRATEGY EXPANDS THE PORTFOLIO ACROSS CORE DISEASE AREAS SUPPORTED BY PLATFORM TECHNOLOGIES

IBD
• Build upon success of Entyvio with new formulations
• Expand treatment options with Alofisel

Celiac disease
• Advance approaches for the prevention of immune responses to gluten

Motility disorders
• Focus on select high unmet medical need areas including gastroparesis and enteral feeding intolerance

Liver diseases
• Target early-stage investments in liver fibrosis

Luminal platforms
• Accelerate microbiome investments
• Invest in selective drug delivery technologies

 acid related diseases franchise will continued to be supported, but new pipeline investment will be deprioritized relative to above disease areas.

Abbreviations: IBD, Inflammatory Bowel Disease e.g., Ulcerative Colitis, Crohn’s disease
WE ARE EXECUTING ON OUR STRATEGY THROUGH A RICH, DIVERSIFIED PIPELINE FUELED BY STRONG EXTERNAL PARTNERSHIPS

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<th>IBD</th>
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<th>Approval**</th>
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<td>BEACH</td>
<td>Multiple targets in IBD</td>
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<td>FOCUS THERAPEUTICS</td>
<td>Multiple targets</td>
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<td>FINISH THERAPEUTICS</td>
<td>Multiple targets in IBD</td>
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<td>AMB partnership</td>
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| Celiac    |                        |         |         |         |            |
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|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |

| GI Motility |                        |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |

| Liver      |                        |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |

| Acid disease/Other |                        |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |
|庭外新製　|                       |         |         |         |            |

Abbreviations: IBD, Inflammatory Bowel Disease e.g., Ulcerative Colitis (UC), Crohn’s disease (CD); SC, Subcutaneous; PPI, Proton pump inhibitor

WE ARE BUILDING ON THE SUCCESS OF ENTYVIO TO ADDRESS CONTINUED UNMET NEED IN IBD PATIENTS

1. Geographic expansion
2. New formulations
3. Expanded patient populations
4. New evidence generation

Abbreviations: IBD, Inflammatory Bowel Disease e.g., Ulcerative Colitis, Crohn’s disease
WE ARE CONTINUOUSLY IMPROVING THE VALUE OF ENTYVIO FOR PATIENTS

GEOGRAPHIC EXPANSION
- Japan NDA approval for UC
- Potential China approval in FY2020*
- Approved in 58 countries**
- Nearly 90,000*** IBD patients treated

* On Aug 8th-2018, a total of 48 products marketed outside of China were selected by the CDE based on urgent medical needs, companies are encouraged to apply for NDA with overseas data including data demonstrating lack of ethnic differences. Priority review/approval process will be applied.
** As of April 2018
*** For FY 2017

Abbreviations: IBD, Inflammatory Bowel Disease e.g., Ulcerative Colitis (UC), Crohn’s disease (CD); aGVHD, Acute Graft vs. Host Disease

NEW FORMULATIONS

ENTYVIO SUBCUTANEOUS
- Positive topline results from VISIBLE UC trial; filing Q4 FY2018 in US for UC, and in EU for both UC and CD
- Anticipate readout in H2 FY2019 from VISIBLE CD

Prefilled syringe  Autoinjector pen  Portal needle-free

EXPANDED PATIENT POPULATIONS
- GvHD prophylaxis Ph3 first patient expected Dec 2018
- GvHD prophylaxis Ph3 readout expected H1 FY2021

Phase 1b data (N = 21): 6 month incidence of intestinal aGVHD*

14%  Entyvio  28%
Entyvio  70%  stage 2-4

* The safety profile of Entyvio in the GvHD patient population remains unchanged and is consistent with the approved US labelling
** Adjusted for patient population including allogeneic stem cell transplant characteristics with similar conditioning regimen

Abbreviations: BE, Biologic Equivalent; EU, European Union; FY, Fiscal Year; FY2018, Fiscal Year 2018

ENTYVIO CONTINUES TO DELIVER AGAINST UNMET NEED FOR PATIENTS

NEW EVIDENCE GENERATION

MUCOSAL HEALING IN CROHN’S DISEASE – PREVIOUSLY A GAP FOR ENTYVIO

Complete mucosal healing (absence of ulceration)

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
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<tbody>
<tr>
<td>N=101</td>
<td>15%</td>
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<tr>
<td>N=46</td>
<td>24%</td>
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<tr>
<td>N=55</td>
<td>7%</td>
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</tbody>
</table>

Vedolizumab can induce endoscopic remission and complete mucosal healing over 26 weeks of treatment at levels comparable to other biologic therapies

OTHER DATA
- Head-to-head vs. adalimumab readout expected in H1 FY2019
- Long-term safety data published in Gut
- Real world propensity score matched analyses by the VICTORY Consortium trended favorable to superior profile for Entyvio vs. anti-TNFs

3 References for the VICTORY Consortium Studies:
Bohn et al—CD propensity; [https://academic.oup.com/ecco-jcc/article/12/supplement_1/S018/4807655]
Falagas et al—UC propensity; [https://academic.oup.com/ecco-jcc/article/12/supplement_1/S019/4807661]

Abbreviations: SES-CD, Simple Endoscopic Score for CD; TNFα, tumor necrosis factor alpha.

65

66
ALOFISEL: FIRST AND ONLY APPROVED (EU) MESENCHYMAL STEM CELL THERAPY FOR FISTULIZING CROHN’S DISEASE

ADRESSES THE HIGHEST UNMET NEED IN IBD, PERIANAL CROHN’S

• ~5% of Crohn’s patients experience perianal fistulas, resulting in drainage, pain, and multiple surgeries
• Biologic therapies do not address the depth of unmet need
• Patients experience an average of 4 medical treatments and 5.4 surgeries with >50% failure rate and risk of permanent fecal incontinence
• Patient anxiety regarding maintenance of bodily function, shame, fear of unknown and depression
• ADMIRE-2 Phase 3 study for US registration ongoing in EU/Israel, first US patient expected Q1 FY2019

CX601 MEANINGFULLY IMPROVES STANDARD OF CARE IN ACHIEVING REMISSION (52 WK)*

COMBINED** REMISSION

38.6%

56.30%

CLINICAL REMISSION

41.6%

59.20%

(95% CI): 17.7%

(4.2-31.2)p=0.010

(95% CI): 17.6%

(4.1-31.1)p=0.013

Control group (Placebo + SOC; n=101) ■ Cx601 group (Cx601 + SOC; n=103)
20.4% of patients in the Cx601 group vs. 26.5% in the control group experienced treatment related adverse events

* Panés J, et al., Gastroenterology. Published online 18th December 2017.
** Combined = clinical + radiologic
Abbreviations: SOC, Standard of care

TAK-906: DISTINCTIVE MECHANISM OF ACTION (ORAL D2/D3 RECEPTOR ANTAGONIST) THAT FILLS A LARGE UNMET NEED IN GASTROPARESIS

CURRENT THERAPIES DO NOT MEET THE SIGNIFICANT UNMET NEED IN GASTROPARESIS

• Gastroparesis affects ~45M people globally
• Key symptoms are nausea, vomiting
• No drug approved in the US to treat all forms of gastroparesis, inadequate options elsewhere

TAK-906: PHASE 2A STUDY DEMONSTRATES TARGET ENGAGEMENT AND ENABLES DOSE SELECTION

• No QTc prolongation in Healthy Volunteer study
• No QTc prolongation or drug-related neurological AEs in Phase 2a study in GP patients*
• Phase 2b dose-range finding study expected to initiate in Q4 2018

* Other AEs observed in Phase 2a study not related to TAK-906 administration included a case of tumor in a subject with history of depression, anxiety, T2DM and Neurontin use. Also, acute kidney insufficiency in a patient with urinary tract infection and in a patient with prior chronic renal failure.

Abbreviations: AE, Adverse event; HV, healthy volunteer; GP, Gastroparesis
KUMA062: A HIGHLY POTENT ORAL GLUTENASE THAT COULD CHANGE THE STANDARD OF CARE IN CELIAC DISEASE

CELIAC DISEASE

- Affects ~1% of the population\(^1\), rising prevalence
- Triggered by exposure to omnipresent gluten peptides
- Manifests via immune reaction in gut causing distressing symptoms
- Only existing treatment is a gluten free diet (GFD)

\[\text{As little as 50-100mg of gluten exposure per day can trigger celiac disease}\]

GLUTEN RECOVERY FROM RAT STOMACHS 30MINS AFTER DIGESTION OF A HIGH-GLUTEN BREAD SLURRY

- Kuma062 is a computationally engineered super glutenase
- Proof-of-mechanism (POM) study enabling go/no-go decision initiated July 2018, readout anticipated H1 FY2019

Abbreviations: POM, Proof of mechanism

WE HAVE STRENGTHENED OUR COMMITMENT TO ADDRESSING LIVER DISEASES THROUGH EARLY RESEARCH PARTNERSHIPS

TARGETING LIVER FIBROSIS PREVENTION AND REVERSAL THROUGH NEW PLATFORMS, NEW PROJECTS AND BUSINESS DEVELOPMENT FOCUSED ON PERI-IND OPPORTUNITIES

- Hemoshear Therapeutics: Human cell system for new target identification and validation for liver fibrosis
- Arcturus Therapeutics: Liver-targeted delivery of nucleotide therapeutics with anti-fibrotic MOAs
- Ambys Medicines: Takeda co-founded with Third Rock Ventures to focus on cell and gene therapy for end-stage liver diseases

Abbreviations: MOA, Mechanism of action
EXPECTED KEY GI PORTFOLIO INFLECTIONS AND MILESTONES

Dates in fiscal year (FY) starting April 1st

Abbreviations: FSI, First subject in; SC, Subcutaneous; IV, Intravenous; UC, Ulcerative colitis; CD, Crohn’s disease; GvHD, Graft vs. host disease; POM, Proof of mechanism; EFI, Enteral feeding intolerance; H2H, head to head.

CONCLUSION

1. Maximizing the potential of ENTYVIO and delivering ALOFISEL to global markets

2. Progressing several early to mid-stage assets including TAK-906 for gastroparesis and KUMA062 for celiac disease

3. Continuing to capture opportunities early through industry-leading scientific talent, sophisticated in-house evaluation capabilities and rapid decision-making
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| 15:15 – 15:35 | Neuroscience  
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| 15:35 – 15:55 | Vaccines  
Choo Beng Goh                |
| 15:55 – 16:10 | Shonan iPark  
Toshio Fujimoto              |
| 16:10 – 17:15 | Looking ahead  
Andy Plump  
Panel Q&A Session            |

# TAKEDA NEUROSCIENCE

**BRINGING INNOVATIVE MEDICINES TO PATIENTS FOR WHOM THERE ARE NO TREATMENTS AVAILABLE**

**EMILIANGELO RATTI, PHD**  
Head, Neuroscience Therapeutic Area
WE HAVE TAKEN ON THE CHALLENGE TO ALLEVIATE THE IMMENSE PATIENT NEED IN NEUROSCIENCE

MISSION

To bring innovative medicines to patients suffering from neurologic and psychiatric diseases for whom there are no treatments available

FOCUS

• Treatment Resistant Depression
• Schizophrenia Negative Symptoms & CIAS
• Selected rare CNS diseases
• Alzheimer’s Disease
• Parkinson’s Disease

CIAS: Cognitive Impairment Associated with Schizophrenia

WE HAVE EXECUTED ON THE ROADMAP DESCRIBED IN 2016

FROM 2016 R&D DAY

We are committed to being a global player in CNS

KEY COMPONENTS OF ROADMAP

• Differentiate TRINTELLIX
• Advance early pipeline towards POC
• Further expand in neurology and rare CNS diseases through partnerships
## BUILDING AN INNOVATIVE PIPELINE ENHANCED WITH EXTERNAL PARTNERSHIPS

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<tbody>
<tr>
<td><strong>Depression</strong></td>
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<tr>
<td>TAK-653</td>
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<td>AMPA PAM</td>
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<td>Small Molecule</td>
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<td><strong>Schizophrenia</strong></td>
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<td>GPR139 Agonist, 2xF</td>
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<td>Small Molecule</td>
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<td><strong>Parkinson’s Disease</strong></td>
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<td>AstraZeneca MEDI1341</td>
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<td>α-synuclein mAb</td>
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<td>Monoclonal Antibody</td>
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<td><strong>Alzheimer’s Disease</strong></td>
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<td>TEVA AZILECT</td>
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<td>PD (JP) Launched 2018</td>
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<td><strong>Rare CNS Diseases</strong></td>
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<td>TAK-925, Narcolepsy, OD</td>
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<td>OX2R Agonist Small Molecule</td>
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<td>TAK-935 Epileptic Encephalopathy, OD</td>
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<td>TAK-831, Friedreich’s Ataxia, OD, FT</td>
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<td>DA2D DHmAb Small Molecule</td>
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<td><strong>CTDf37, ATXN1, Multiple Targets</strong></td>
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<td>Stereopure Antisense Oligonucleotide</td>
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<td><strong>C9orf72, ATXN1, Multiple Targets</strong></td>
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<td><strong>TAK-831</strong></td>
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<tr>
<td>Friedreich’s Ataxia, OD, FT</td>
<td></td>
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<tr>
<td>DA2D DHmAb Small Molecule</td>
<td></td>
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</tr>
</tbody>
</table>
| Pipeline as of September 23, 2018

1 Discovery/preclinical phase: Only external collaborations shown, does not include internal programs

**WE HAVE BUILT OUR PORTFOLIO THROUGH THREE MAIN LEVERS**

**EXECUTED ON OPPORTUNITIES WITH LATE-STAGE ASSETS**
- Successful differentiation of TRINTELLIX
- Launched AZILECT in Japan

**ADVANCED EARLY STAGE PIPELINE TOWARDS POC**
- TAK-925 Narcolepsy
- TAK-831 Schizophrenia, Friedreich’s Ataxia
- TAK-935 Epileptic Encephalopathy

**EXPANDED IN NEURODEGENERATION AND RARE DISEASE WITH WORLD CLASS PARTNERS**
- Denali Therapeutics partnership to address extracellular targets with highly brain penetrant monoclonal antibodies
- Wave Life Sciences partnership to address intracellular targets with stereopure oligonucleotides
- AstraZeneca partnership to treat Parkinson’s Disease
TRINTELLIX SHOWS BENEFITS IN PROCESSING SPEED, AN IMPORTANT ASPECT OF COGNITION, AND TREATMENT EMERGENT SEXUAL DYSFUNCTION FOR PATIENTS WITH MDD

COGNITIVE FUNCTION (PROCESSING SPEED)
Digit Symbol Substitution Test (DSST) after 8 weeks of treatment

TREATMENT EMERGENT SEXUAL DYSFUNCTION
Changes in Sexual Functioning Questionnaire (CSFQ-14) after 8 weeks of treatment

• In May 2018, FDA approved sNDA that includes DSST, which most specifically measures processing speed, an important aspect of cognition
• TRINTELLIX® is the first MDD treatment labelled for improvement of processing speed, an important aspect of cognitive function

\[ \text{Total number of correct symbols; mean score with standard deviation} \]

\[ \text{Change from baseline in CSFQ-14 total score; least squares mean, standard error} \]

\[ \text{CONNECT study: Mahableshwarkar AR, et al. Neuropsychopharmacol. 2015} \]

MDD = Major Depressive Disorder

1 Normative data from healthy individuals

***p<0.001 vs baseline
Change from baseline was also significant vs placebo in both FOCUS and CONNECT studies

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DESPITE CURRENT TREATMENTS, PATIENTS WITH NARCOLEPSY TYPE 1 (NT1) SUFFER FROM A RANGE OF DEBILITATING SYMPTOMS

**NARCOLEPSY TYPE 1**
- Affects ~100K patients in US (~400K in G-7), with typical disease onset from 7-25 years old\(^1\)
- Symptoms characterized by:
  - Excessive daytime sleepiness
  - Sleep/wake fragmentation
  - Cataplexy
- Current treatments are only partially effective and only provide benefit for some disease symptoms

“We take our current meds to **survive**. We want new medications to help us **live**.”

Narcolepsy patient advisor
Patient Advisory Board sponsored by Takeda

---

**NARCOLEPSY TYPE 1 IS CAUSED BY LOSS OF OREXIN PRODUCING NEURONS**

**HYPOTHALAMIC OREXIN PRODUCING NEURONS**\(^1\)

\(\text{OX1Rs}: \text{activate brain’s reward systems}\)
\(\text{OX2Rs}: \text{activate arousal and wakefulness}\)

**OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS**\(^2\)

- Orexin mRNA transcripts are detected in control but not in Narcolepsy Type 1 patients
- Orexin receptors may remain functional in Narcolepsy Type 1 patients

**LEADING RESEARCH TO SUPPORT THE OREXIN HYPOTHESIS**

An orexin 2 receptor agonist may mimic the missing endogenous peptide (orexin) and address the neurotransmitter deficiency of Narcolepsy Type 1 leading to reduction in disease specific symptoms

---

\(^1\) Longstreth. Sleep. 2007;30(1),13
\(^3\) Nature Medicine 2000 Vol 6 p 991-997
TAK-925 IS A SELECTIVE OX2R AGONIST SHOWING REDUCTION IN NARCOLEPSY-LIKE SYMPTOMS IN A MOUSE MODEL

**TAK-925 FULLY RESTORED WAKEFULNESS**

Wakefulness time of NT1 mouse model in active phase for one hour

Minutes awake

<table>
<thead>
<tr>
<th>TAK-925 (mg/kg, s.c.)</th>
<th>0</th>
<th>1</th>
<th>3</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>TAK-925</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

* **p<0.05, **p<0.01 vs placebo

**TAK-925 ELIMINATED SLEEP / WAKE TRANSITIONS**

Hypnogram of sleep/wake transitions in NT1 mouse model

EEG recordings

**TAK-925 ABOLISHED CATAPLEXY-LIKE EPISODES**

Cataplexy-like episodes in NT1 mouse model for three hours after chocolate

Count

<table>
<thead>
<tr>
<th>Vehicle 0.3</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-925 1</td>
<td></td>
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</table>

Phase I clinical studies are ongoing to evaluate safety and efficacy of TAK-925

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ADVANCES IN GENETICS, BIOMARKERS AND ALTERNATIVE MODALITIES DROVE OUR EXPANSION INTO NEURODEGENERATION AND RARE DISEASE

Neurodegenerative diseases are proteinopathies that can be addressed by new modalities with greater precision than before e.g., monoclonal antibodies and antisense oligonucleotides

Genetically defined CNS diseases provide the opportunity to develop targeted therapies employing new modalities e.g., antisense oligonucleotides, gene therapy

MANY NEURODEGENERATIVE DISEASES CAN BE ADDRESSED WITH ALTERNATIVE MODALITIES TARGETED TO PATHOGENIC PROTEINS

Antisense oligonucleotides can reduce intracellular expression of toxic proteins

Monoclonal antibodies can clear pathogenic extracellular proteins

ASOs and mAbs could be combined for greater efficacy

Pathogenic protein monomers, oligomers, and fibrils can spread from neuron to neuron and propagate the disease
PARTNERSHIP WITH DENALI HAS REINFORCED OUR ALZHEIMER’S DISEASE PORTFOLIO WITH HIGHLY BRAIN PENETRANT MONOCLONAL ANTIBODIES

Antibody Transport Vehicles (ATVs) enable up to >20X higher brain penetration of monoclonal antibodies than the same antibody without ATV.

Collaboration agreement to co-develop three named programs
- ATV: BACE1 / TAU
- ATV: TREM2
- Additional undisclosed program

PARTNERSHIP WITH WAVE LIFE SCIENCES ENABLES TARGETED THERAPIES TO RARE CNS DISEASES WITH STEREOPURE ANTISENSE OLIGONUCLEOTIDES

SYNTHESIS OF STEREOPURE OLIGONUCLEOTIDES: A SIGNIFICANT IMPROVEMENT IN THE FIELD

STANDARD OLIGONUCLEOTIDE APPROACHES
Racemic mixture up to >500,000 molecules per sequence

WAVE RATIONAL DESIGN
Selection of 1 stereopure molecule per sequence allows a proper optimization of desired drug properties

STEREOPURE APPROACH ENABLES ALLELE-SPECIFIC TARGETING OF DISEASE GENES

PARTNERSHIP PROVIDES:
- Option to co-develop and co-commercialize programs for rare CNS diseases (Huntington’s Disease, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia and Spinocerebellar Ataxia Type 3)
- Exclusive license to research, develop, and commercialize multiple additional programs for CNS indications

Courtesy of Wave Life Sciences
**EXPECTED KEY NEUROSCIENCE PORTFOLIO INFLECTIONS AND MILESTONES**
Dates in fiscal year (FY) starting April 1st

<table>
<thead>
<tr>
<th>2H FY 2018</th>
<th>1H FY 2019</th>
<th>2H FY 2019</th>
<th>FY 2020</th>
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<tbody>
<tr>
<td>TRINTELLIX PDUFA</td>
<td>Treatment Emergent Sexual Dysfunction (s)NDA</td>
<td>TAK-925 preliminary NT1 (s)NDA efficacy data</td>
<td>TAK-831 Schizophrenia Phase II</td>
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<tr>
<td>TAK-831 Friedreich's Ataxia Phase II</td>
<td>TAK-831 JNDA Submission Major Depressive Disorder</td>
<td>MEDI1341 Proof of Mechanism</td>
<td>TAK-935 Pediatric POC in epileptic encephalopathy</td>
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<tr>
<td>TRINTELLIX JNDA Submission Major Depressive Disorder</td>
<td>WVE-120101, WVE-120102 Phase (ib/)Ia top line data</td>
<td>TRINTELLIX JNDA Decision Major Depressive Disorder</td>
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</table>

Projected timelines as of September 23, 2018, subject to change

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**CONCLUSION**

1. Successful differentiation of TRINTELLIX in processing speed, an important aspect of cognitive function, and treatment emergent sexual dysfunction in MDD

2. Progressed TAK-925, the first OX2R agonist, as potential transformative therapy for Narcolepsy Type 1

3. Expanded in neurodegeneration and CNS rare disease with world-class partners (exemplified by Wave and Denali partnerships)
# R&D INVESTOR DAY AGENDA – TOKYO, SEPTEMBER 27, 2018

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**TAKEDA VACCINES**

**INNOVATION FOR GLOBAL IMPACT**

**CHOO BENG GOH, MD**

Regional Lead for Medical Affairs Asia, Global Vaccine Business Unit
OUR MISSION

Develop and deliver innovative vaccines that tackle the toughest problems in public health and improve the lives of people around the world.

WE HAVE BUILT A GLOBAL VACCINE BUSINESS UPON A STRONG FOUNDATION IN JAPAN

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1946</td>
<td>Japan vaccine business established</td>
</tr>
<tr>
<td>1947</td>
<td>1st Takeda manufactured vaccine</td>
</tr>
<tr>
<td>2010</td>
<td>Multiple vaccine products manufactured internally and marketed in Japan</td>
</tr>
<tr>
<td>2012</td>
<td>Global vaccine business established</td>
</tr>
<tr>
<td>2014</td>
<td>Partnered with Japan government to develop and supply pandemic influenza vaccines for people in Japan</td>
</tr>
<tr>
<td>2016</td>
<td>Global pivotal Phase 3 clinical trial of dengue vaccine candidate initiated: 20,100 participants in 8 countries in 2 regions</td>
</tr>
<tr>
<td>2018</td>
<td>Phase 3 clinical trial results of dengue vaccine candidate is expected in H2 FY18</td>
</tr>
</tbody>
</table>

PARTNERSHIPS
- Polio vaccine candidate
- Bill & Melinda Gates Foundation
- Zika vaccine candidate
- U.S. Government- BARDA

ACQUISITIONS
- Inoviragen
- Norovirus vaccine candidate
- LigoCyte Pharmaceuticals Inc.
THE VACCINE MARKET IS AN ATTRACTIVE PLACE FOR INVESTMENT

- Vaccine sales growth projected at 7.1% between 2017 and 2024, reaching $44.6 billions in 2024
- Durability in sales with limited impact of patent expiry
- Blockbuster potential in newly launched vaccines
- Threat of emerging and existing infectious diseases with epidemic potential

1 Evaluate Pharma report 2018

OUR STRATEGY

- Develop vaccines with global relevance and business potential
- Build a global pipeline
- Tackle unmet need
- Leverage partnerships
- Partner to de-risk and drive vaccine development
- Target the greatest opportunity in infectious diseases
**OUR PIPELINE**

<table>
<thead>
<tr>
<th>Discovery/preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Japan Marketed Vaccines</th>
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<tr>
<td></td>
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<td></td>
<td>DENGUE VACCINE (TAK-003)</td>
<td>EGG-BASED SEASONAL FLU DENKA &amp; KM BIOLOGICS</td>
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<td></td>
<td></td>
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<td>NOROVIRUS VACCINE (TAK-214)</td>
<td>MEASLES RUBELLA* BIKEN</td>
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<tr>
<td></td>
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<td></td>
<td>BARDA ZIKA VACCINE (TAK-426)</td>
<td>MUMPS JAPANESE ENCEPHALITIS BIKEN</td>
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<td>ENTEROVIRUS 71 VACCINE (TAK-021)</td>
<td>DIPHTHERIA TETANUS TOXOID^</td>
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<tr>
<td>Zydus Cadila</td>
<td></td>
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<td>Sabin Inactivated Poliovirus Vaccine (TAK-195)</td>
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<tr>
<td></td>
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<td></td>
<td>CHIKUNGUNYA VACCINE (TAK-507)</td>
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Pipeline as of September 23, 2018

+ Takeda has a measles-rubella combined vaccine, a measles vaccine and a rubella vaccine on the Japanese market.
* Takeda has a diphtheria-tetanus combined toxoid vaccine and a tetanus-toxoid vaccine on the Japanese market.
^ Takeda’s varicella vaccine has been approved for an additional indication preventing herpes-zoster.

---

**DENGLUE THREATENS HALF OF THE WORLD’S POPULATION**

- Endemic in more than 120 countries
- Causes an estimated 390M infections
- Causes more than 20K deaths each year
- In 2015, >85M travelers from US, Canada, and Japan travelers to endemic countries

Without safe and effective dengue vaccine, >3.9 BILLION people around the globe are at risk of dengue.

---

A SAFE AND EFFECTIVE DENGUE VACCINE SHOULD BE DESIGNED TO PROTECT AGAINST ALL FOUR STRAINS OF THE VIRUS

- Dengue is a mosquito-borne disease that can be caused by each of the four strains of the dengue virus (DENV) 1-4
- In people previously exposed to dengue, a subsequent infection with a different strain could lead to more severe disease
- A dengue vaccine must provide broad protection against all four strains of dengue, particularly in persons who have never been exposed to the virus (“naïve”)

TAK-003 IS MODELED ON THE COMPLETE DENGUE VIRUS AND ACTIVATES MULTIPLE ARMS OF THE IMMUNE SYSTEM

- Live attenuated dengue vaccine based on the complete DENV-2 genome
- Vaccine virus stimulates robust immune response without causing illness
- Components of immune response that are activated include:
  - Neutralizing antibodies
  - Cell-mediated immunity
  - Antibodies to the NS1 protein (NS1 is implicated in severe disease)
TAK-003 TRIGGERS BOTH ANTIBODY AND CELL-MEDIATED IMMUNE RESPONSES

Antibody-mediated immune response in dengue naïve population¹

- High and sustained antibody response to multiple serotypes after 2 doses (0, 3 month), in participants without prior exposure to dengue

DENV-2 cell-mediated immune response ²

- >90% of TAK-003 vaccinated participants demonstrate a Dengue-specific T-cell response
- Comparable response between seronegative and seropositive participants at baseline
- Demonstrated cross-reactivity to DENV-1, -3, and -4

¹ Lancet Infect Dis 2018; 18: 163–70 Published Online November 6, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30632-1; results from DEN-204, a Phase 2 study in children living in 3 dengue endemic countries
² 6th Pan-American Dengue Research Network Meeting; results from DEN-205, a Phase 2 study

TAK-003 TRIGGERS NS1 ANTIBODIES THAT PREVENT VASCULAR LEAKAGE IN THE LABORATORY¹

- Severe dengue is characterized by vascular leakage in the lungs and abdomen
- This vascular leakage is thought to be mediated by the dengue virus non-structural protein 1 (NS1)
- TAK-003-induced NS1 antibodies block NS1-induced vascular leakage in human pulmonary tissue models

¹ 6th Pan-American Dengue Research Network Meeting; results from DEN-203, a Phase 2 study
HPMEC = Human Pulmonary Microvascular Endothelial Cells
TAK-003 was generally safe and reduced the incidence of dengue in children in a recent phase 2 study

**Study Features**
- 1,800 participants received either TAK-003 (1 dose; 2 doses at 0, 3 months; or 2 doses at 0, 12 months) or placebo
- Mean age 7.3 years, range 2 – 17 years
- Approximately 45% of participants were dengue naive

**Incidence of Symptomatic Dengue Was Significantly Lower in Vaccine Recipients Over 18 Months**

<table>
<thead>
<tr>
<th>Dengue Incidence</th>
<th>Relative risk of dengue in vaccinees (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>TAK-003 (%)</td>
<td>Placebo (%)</td>
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<tr>
<td>1.3</td>
<td>4.5</td>
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<tr>
<td>0.29 (0.13–0.72)</td>
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</table>

These proof-of-concept findings require confirmation in our ongoing phase 3 efficacy study.

**Our Phase 3 Pivotal Trial is Designed to Answer the Most Important Questions About Safety and Efficacy of Our Dengue Vaccine Candidate**

**Study Design**
- 20,100 participants, aged 4 – 16 years old
  - Age range ensures a mix of dengue exposed and naive participants
- Blood sample in all participants at baseline
  - Enables identification of seronegative subjects
- 8 countries in 2 regions
  - Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, Thailand
  - Assesses the safety and efficacy of TAK-003 in diverse populations and epidemiological scenarios

**Primary Endpoint Analysis:** Overall vaccine efficacy against any dengue fever

**Secondary Endpoint Analysis:** Vaccine efficacy in seronegatives and by serotype

**Primary Endpoint Results Expected in H2 FY18 Followed by Regulatory Filing in FY19**
**TAKE DA HAS THE MOST ADVANCED NOROVIRUS VACCINE CANDIDATE (TAK-214) AND RECENTLY COMPLETED PHASE 2B STUDY**

**CHALLENGE**
- Leading cause of acute gastroenteritis – 600M infections per year
- No vaccine available

**OUR PATH**
- Most advanced vaccine in development
- Completed Phase 2b study
- Phase 3 preparations underway

**OUR GOAL**
- Potential for first and best vaccine
- Impact in all markets

**TAKE DA HAS PARTNERED WITH THE U.S. GOVERNMENT TO DEVELOP THE FIRST ZIKA VACCINE (TAK-426)**

**CHALLENGE**
- Devastating impact on newborns
- Potential for recurrent outbreaks
- No vaccine available

**OUR PATH**
- Largest Zika investment by U.S. government
- Proven platform
- Fast track designation

**OUR GOAL**
- Deliver the first Zika vaccine to market
## CONCLUSION

1. **STRONG FOUNDATION AND TOP TALENT**
   - Over 70 years of vaccine manufacturing experience
   - Top talent in vaccine development
   - Built a high impact global pipeline

2. **BEST-IN-CLASS AND FIRST-IN-CLASS POTENTIAL**
   - Dengue vaccine (TAK-003) in Phase 3
   - Norovirus vaccine (TAK-214) in Phase 2b
   - Zika vaccine (TAK-426) in Phase 1

3. **A PARTNER OF CHOICE FOR VACCINES**
   - U.S. Government
   - Japan Government
   - Bill & Melinda Gates Foundation
   - Industry Partners

---

“If you want to save and improve lives around the world, vaccines are a fantastic investment.”
- Bill Gates
# R&D INVESTOR DAY AGENDA – TOKYO, SEPTEMBER 27, 2018

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**SHONAN HEALTH INNOVATION PARK**

**TOSHIRO FUJIMOTO, MD, MBA**  
*General Manager, Shonan Health Innovation Park*
Introduction

Drug R&D is Mainly Focused in ‘Hotspots’ Around the World

*KSP: Kanagawa Science Park, LIC: Life Innovation Center
iPark Vision: Creating an Open Innovation Ecosystem for Life Sciences

iPark will be the first pharma-led open innovative health ecosystem in Japan.

Built on pharmaceutical know-how, industry, government and academia will come together to incubate and accelerate the translation of cutting-edge science into impactful health solutions for patients in Japan and around the world.

Shonan iPark is One of the Largest R&D Facilities in Japan and is Equipped with Cutting-Edge Technologies

- **Established:** February, 2011
- **Floor space:** Approx. 310,000m²
- **Lab space:** Approx. 140,000m²
- **Office space:** Approx. 30,000m²
iPark Nurtures World-Class Bioventures

- Science Mentorship
- Venture Capital Network
- Entrepreneurship Training
- Regulatory / IP Consultation
iPark Generates Co-creation among Life Science Players

Spin-offs
- AXCELEAD
- SCOMIA

Entrepreneurship Venturing Program
- Aikomi
- ARTham
- Chordia Therapeutics
- ChromaJean
- FIMECS

University-origin Startups / Partnership
- GenHeadBio
- GEXVal
- ReboRNA
- SEEDSUPPLY
- T.N.TECHNO., LTD.
- YOKOGAWA

Other Partners
- IBM
- FORESIGHT 
- PHC

COLLABORATE

iPark Accelerating the Frontier of Science

Expand Drug Discovery Platform
Apply IT Tech to Healthcare
Access to Human Data

ACCELERATE
Leverage Local and Global Resources to Develop an Ecosystem

Local Collaboration  Global Ecosystem

Kanagawa Prefecture
Kanagawa Science Park
Life Innovation Center
iPark

Location | Contents
---|---
Boston | • Launching Venture Mentoring Program based the MIT VMS model  
| • Collaboration with Japan MIT Alumni group  
| • Collaborating with Venture Cafe
San Diego | • Collaborating with BioCom to serve as mutual gateways to support ventures for market entries

DEVELOP

Strengthening iPark Organization as Partners to Join and Businesses to Grow

<table>
<thead>
<tr>
<th>Execute strategy</th>
<th>Gain focus area partners</th>
<th>Ensure sustainable revenue through services</th>
<th>Enhance organization for further growth</th>
<th>Become profitable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target partners (#)</td>
<td>40 partners</td>
<td>70 partners</td>
<td>100 partners</td>
<td>130 partners</td>
</tr>
<tr>
<td>Y1 (Current year)</td>
<td>2018</td>
<td>Y2</td>
<td>2019</td>
<td>Y3</td>
</tr>
</tbody>
</table>
# R&D INVESTOR DAY AGENDA – TOKYO, SEPTEMBER 27, 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda</th>
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</table>
Christophe Weber                                      |
| 13:25 – 14:05 | R&D Transformation, Progress To Date, Future Outlook  
Andy Plump                              |
| 14:05 – 14:40 | Oncology  
Phil Rowlands                        |
| 14:40 – 15:00 | Gastroenterology  
Asit Parikh                         |
| 15:00 – 15:15 | Break                                           |
| 15:15 – 15:35 | Neuroscience  
Emiliangelo Ratti                      |
| 15:35 – 15:55 | Vaccines  
Choo Beng Goh                         |
| 15:55 – 16:10 | Shonan iPark  
Toshio Fujimoto                       |
| 16:10 – 17:15 | Looking ahead  
Andy Plump  
Panel Q&A Session                     |

**LOOKING AHEAD**

Shire
RECOMMENDED OFFER FOR SHIRE – TRANSACTION UPDATE

PROGRESS TO DATE
- $7.5 billion term loan agreed with leading global financial institutions
- Regulatory review process commenced
  - U.S. Federal Trade Commission (FTC) clearance received
  - Chinese State Administration for Market Regulation (SAMR) clearance received
  - Brazilian Administrative Council for Economic Defense (CADE) clearance received
- Integration planning underway

KEY NEXT STEPS
- Detailed functional integration planning kicked off; consistent with Takeda’s core values, leveraging both companies’ knowledge and expertise
- Remaining regulatory approvals pending (including EU and Japan)
- Expected to close in first half of calendar year 2019

PENDING ACQUISITION AND INTEGRATION OF SHIRE WILL ACCELERATE TAKEDA R&D

- Increase cash flow and strengthen R&D functions
- Continue our TA focus, partnership model
- Extend and elevate our rare disease expertise
- Deliver consistent, breakthrough innovation
- Reinforce patient-centric, science driven culture