RARE DISEASES & GENE THERAPY

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RARE DISEASES: AN OPPORTUNITY TO TRANSFORM TREATMENT

HIGH UNMET NEED

7,000  Distinct rare diseases¹
350 million  Patients worldwide
95%  Diseases have no FDA-approved treatment

SCIENTIFIC AND REGULATORY ADVANCES

80%  Diseases are genetic in origin
Transformative therapies
Recombinant engineering & delivery of proteins and nucleic acids
~90%²  Orphan drug approvals benefited from expedited review
100%³

1. Rare diseases defined by prevalence in line with regulatory agencies (US: <7 in 10,000, EU: < 5 in 10,000 and JPN: <4 in 10,000), Global Genes, NIH National Human Genome Research Institute; 2. Comprises four pathways in US: Accelerated approval, breakthrough therapy designation, fast track designation, priority review designation; 3. Three pathways in JPN: Priority review, Sakigake designation and conditional approval, CIRS R&D Briefing 70, New drug approvals in six major authorities 2009-2018
RARE DISEASE MARKET IS EXPECTED TO DOUBLE IN SIZE

GLOBAL ORPHAN DRUG\(^1\) SALES EXCLUDING ONCOLOGY\(^2\), USD BN

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2018</th>
<th>2024</th>
</tr>
</thead>
<tbody>
<tr>
<td>% share of global, branded Rx sales</td>
<td>7%</td>
<td>11%</td>
<td>17%</td>
</tr>
<tr>
<td>USD BN</td>
<td>37</td>
<td>62</td>
<td>124</td>
</tr>
</tbody>
</table>

- Orphan drugs expected to make up ~17% of global branded Rx sales by 2024
- Growth driven by advances in new modalities and new indications
- Orphan cell and gene therapies estimated at ~$20 bn by 2024, up from ~$2bn in 2018

1. Orphan drugs generally used as synonym for rare disease due to lack of uniform definition, including also non-rare, but neglected diseases lacking therapy (e.g., tropical infectious diseases); 2. EvaluatePharma (03 June 2019)

TAKEDA IS THE LEADER IN RARE DISEASES

**PATIENT IMPACT**

- Foundation of >30 year history of leadership in rare diseases
- Leading portfolio of rare disease therapies: 11 out of 14 global brands spanning Hematology, Metabolic, GI and Immunology

**SCIENCE & INNOVATION**

- Multiple opportunities for transformational therapies across therapeutic areas
- Emerging, cutting edge platforms to drive high-impact pipeline
- Investments in technologies to accelerate diagnosis

**CAPABILITIES AND SCALE**

- Engagement with key stakeholders within the ecosystem e.g. patient groups, regulators
- Pioneering regulatory pathways
- Global footprint
OUR STRATEGY IS TO TRANSFORM AND CURE RARE DISEASES

Transformative

As the global leader in Rare Diseases, we aspire to provide transformative and curative treatments to our patients.

Transformative

Programs with transformative potential in devastating disorders with limited or no treatment options today

Curative

Emerging early pipeline of AAV gene therapies to redefine treatment paradigm in monogenic rare diseases

WE ARE POSITIONED TO DELIVER NEAR-TERM & SUSTAINED GROWTH

1. Projected timing of approvals depending on data read-outs; some of these Wave 1 target approval dates assume accelerated approvals. 2. Some assets in Rare Diseases could be accelerated into Wave 1 if they have breakthrough data. 3. Projected approval date assumes filing on Phase 2 data; 4. TAK-079 to be developed in Rare Diseases indications myasthenia gravis (MG) and immune thrombocytopenic purpura (ITP) (FPI projected in each indication in 2H FY19); 5. Currently in a non-pivotal Phase 2 study; planning underway to include interim stage-gates that can advance the program into a pivotal trial

Estimated dates as of November 14, 2019
### POTENTIAL APPROVALS OF TRANSFORMATIVE THERAPIES

#### WAVE 1

<table>
<thead>
<tr>
<th>Program</th>
<th>Disease Area</th>
<th>Status</th>
<th>Target Approval</th>
<th>Addressable Population in US/WW</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-721</td>
<td>Eosinophilic Esophagitis (EoE)</td>
<td>Phase 3</td>
<td>FY 2020</td>
<td>~150k/Under evaluation</td>
</tr>
<tr>
<td>TAK-620</td>
<td>Cytomegalovirus (CMV) infection in transplant</td>
<td>Phase 3</td>
<td>FY 2021</td>
<td>~7 - 15k/25 - 45k</td>
</tr>
<tr>
<td>TAK-755</td>
<td>Congenital Thrombotic Thrombocytopenic Purpura (cTTP)</td>
<td>Phase 3</td>
<td>FY 2023</td>
<td>~500/2 - 6k</td>
</tr>
<tr>
<td>TAK-611</td>
<td>Metachromatic Leukodystrophy (MLD)</td>
<td>Phase 2</td>
<td>FY 2023</td>
<td>~350/1 - 2k</td>
</tr>
<tr>
<td>TAK-935</td>
<td>Developmental and Epileptic Encephalopathies (DEE)</td>
<td>Phase 1/2</td>
<td>FY 2023</td>
<td>~50k/70 - 90k</td>
</tr>
<tr>
<td>TAK-607</td>
<td>Complications of Prematurity</td>
<td>Phase 2b</td>
<td>FY 2024</td>
<td>70 - 140k/300k – 1.2M</td>
</tr>
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<td>Eosinophilic Esophagitis (EoE)</td>
<td>Phase 3</td>
<td>FY 2023</td>
<td>~25k/80 - 90k</td>
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1. Projected timing of approvals depending on data read-outs; some Wave 1 target approval dates assume accelerated approval
2. Currently in a non-pivotal Phase 2 study; planning underway to include interim stage gates that can advance the program into a pivotal trial
3. Estimated number of patients projected to be eligible for treatment, in markets where the product is anticipated to be commercialized, subject to regulatory approval
4. For TAK-620 and TAK-607, the addressable population represents annual incidence

#### SELECTED TRANSFORMATIVE PROGRAMS

<table>
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<th>Program</th>
<th>Potential Treatment</th>
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<td>TAK-620</td>
<td>Potential first treatment of CMV infection in transplant patients in over 10 years. Inhibitor of protein kinase UL97.</td>
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<td>TAK-607</td>
<td>Potential first pharmacologic therapy in &gt;20 years to prevent complications of prematurity. Recombinant IGF-1 growth factor.</td>
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TAK-620: POTENTIAL BEST IN CLASS TREATMENT FOR POST-TRANSPLANT CMV INFECTION

BURDEN OF CMV INFECTION IN TRANSPLANT RECIPIENTS

CMV infection is the most common post-transplant viral infection.1
Affects >25% of transplants

CMV infection can be fatal2,3
Higher rates of graft failure: 2.3X and mortality: 2.6X

Current therapies have significant toxicities and resistance4,5,6,7
Incidence of neutropenia >20% and renal toxicity >50%

TAK-620: NOVEL MOA TARGETING PROTEIN KINASE UL97

TAK-620 ADDRESSES UNMET NEED IN BOTH FIRST-LINE AND RESISTANT / REFRACTORY SETTING

Transplant treatment CMV Viremia First-Line: Newly diagnosed CMV Failure First-Line Resistant/ Refractory (R/R) CMV

Solid organ transplant (SOT) patients1,2:
~100K

Hematopoietic Stem Cell Transplants (HSCT) patients1,2:
~90K

TAK-620: Ph 3 Study 303
~5K

TAK-620: Ph 3 Study 302
~15K

TAK-620: Ph 3 Study 302
~15K


1. Solid organ and allogeneic HSCT transplants in global major markets: US, Europe, Canada, Japan, China, Australia and Korea
TAK-620 DEMONSTRATED SIMILAR EFFICACY AND BETTER SAFETY VERSUS SOC IN A PHASE 2 STUDY IN FIRST-LINE PATIENTS

**DEMONSTRATED SIMILAR ANTI-VIRAL ACTIVITY TO VALGANCICLOVIR (VGV) ACROSS ALL DOSES**

<table>
<thead>
<tr>
<th>TAK-620: Dose 400, 800 or 1200 mg BID</th>
<th>VGV (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed undetectable plasma CMV DNA within 6 weeks</td>
<td>79%</td>
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**NEUTROPENIA WAS TREATED WITH GROWTH FACTORS MORE OFTEN IN THE VGV ARM (15%) VS. TAK-620 ARM (7%)**

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<th>VGV (N=40)</th>
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<tr>
<td>Neutropenia that occurred or worsened during treatment through week 12</td>
<td>5%</td>
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1. Confirmed undetectable CMV DNA in plasma was defined as two consecutive CMV DNA-polymerase-chain-reaction assay values measured during treatment that were below the level of quantitation (i.e., <200 copies per millimeter according to the central laboratory) separated by at least 5 days. For the primary analyses of confirmed undetectable CMV DNA within 3 weeks and 6 weeks, data were missing for 3 patients: 1 each in the 400-mg TAK-620 group, the 1200-mg TAK-620 group and the valganciclovir group.

2. N Engl J Med 2019; 381:1136-47. Overall risk ratio (95% CI) relative to the Valganciclovir reference was 1.20 (0.95-1.51).

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TAK-620: GRANTED BREAKTHROUGH DESIGNATION IN RESISTANT OR REFRACTORY CMV INFECTION

1. Efficacy in seriously ill R/R CMV in SOT and HSCT recipients with multiple risk factors predictive of poor outcomes

<table>
<thead>
<tr>
<th>TAK-620 Dose: 400 mg, 800 mg, 1200 mg BID</th>
</tr>
</thead>
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<tr>
<td>Primary efficacy endpoint</td>
</tr>
<tr>
<td>Patients with confirmed undetectable plasma CMV DNA within 6 weeks in ITT² population</td>
</tr>
</tbody>
</table>

Historical outcomes: High (~50%) failure rates / relapse rates³,⁴,⁵

Renal impairment is the primary reason for discontinuation with SOC (Foscarnet, Cidovir); nephrotoxicity is > 50%⁶

TAK-620: TWO ONGOING PIVOTAL STUDIES; EXPECT FIRST APPROVAL IN RESISTANT OR REFRACTORY CMV IN 2021

TAK-620 PHASE 3 STUDY 303
Resistant/Refractory CMV Patients with SOT or HSCT

2:1 Randomization

TAK-620 400mg BID (N=234)  
Investigator’s choice (N=117)

Primary Endpoint: Viremia @ 8 wks of Rx

EXPECTED MILESTONES (FY)

2020 2021 2022
2H 2020: Ph 3 Readout  2021: US Approval  2022: EU Approval

TAK-620 PHASE 3 STUDY 302
HSCT Recipients With First CMV Infection

1:1 Randomization

TAK-620 400mg BID (N=275)  
900mg BID VGV (N=275)

Primary Endpoint: Viremia @ 8 wks of Rx

EXPECTED MILESTONES (FY)

2021 2022
1H 2021: US Approval  2022: EU Approval

SELECTED TRANSFORMATIVE PROGRAMS

TAK-620  
Potential first treatment of CMV infection in transplant patients in over 10 years. Inhibitor of protein kinase UL97.

TAK-755  

TAK-607  
Potential first pharmacologic therapy in >20 years to prevent complications of prematurity. Recombinant IGF-1 growth factor.
CONGENITAL AND IMMUNE TTP HAVE SUBSTANTIAL MORTALITY AND MORBIDITY BURDEN DUE TO INADEQUATE SOC

CONGENITAL TTP (cTTP)

- Sub-therapeutic dose with plasma infusions
- Patients still experience ischemic injury of brain, kidneys and heart
- Poor long-term outcomes

IMMUNE TTP (iTTP)

- ~30% relapse rate with plasma exchange (PEX)
- New market entrant reduces relapse rate, but has significant limitations
  - Enhanced risk of bleeding: Gingival bleeding 18% vs. 1% placebo
  - Epistaxis 32% vs. 3% placebo

ADDRESSABLE POPULATION (WW)¹,²

<table>
<thead>
<tr>
<th></th>
<th>cTTP</th>
<th>iTTP</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2,000 – 6,000</td>
<td>5,000 – 18,000</td>
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</table>

TAK-755 DIRECTLY ADDRESSES UNDERLYING CAUSE OF TTP

TAK-755 REPLACES ADAMTS13, DEFICIENCY OF WHICH LEADS TO TTP

ADAMTS13:
Cleaves VWF multimers that mediate platelet aggregation and clotting

ADAMTS13 deficiency:
Formation of microthrombi due to accumulation of large VWF multimers

Normal clotting cascade

Von Willebrand Factor (VWF)
Platelet
Blood vessel

TAK-755: POTENTIAL TRANSFORMATIVE THERAPY FOR TTP

TAK-755 PHASE I, OPEN-LABEL, DOSE ESCALATION STUDY IN cTTP

- Administered as a single dose in 15 cTTP patients
- TAK-755 was well tolerated
- No anti-ADAMTS13 antibodies detected

TAK-755 PK PROFILE AND PD EFFECT ON VWF CLEAVAGE AT 40 IU/KG

Mean FRETS ADAMTS13 Activity
-176 kDa VWF Cleavage Product

TTP diagnosis requires confirmation of ADAMTS13 activity <10%


TAK-755: ONGOING PHASE 3 CONGENITAL TTP STUDY

TAK-755 PHASE 3 PROPHYLAXIS STUDY

- All patients roll over to a 6 month TAK-755 extension
- Phase 3 study has a cohort of acute cTTP patients who receive TAK755. Patients are eligible to enter the prophylaxis study upon completion of acute treatment

**cTTP patients (N = 26 – 42)**

1:1 Randomization

SOC

TAK-755 40 IU/kg

SOC

TAK-755 40 IU/kg

Every other week

Every other week

Primary Endpoint: Incidence of acute TTP episodes

**EXPECTED MILESTONES (FY)**

2019

1H: Ph 3 initiated

2021

2H: Ph 3 Readout

2023

US Approval

2025

EU Approval

1. A single dose modification to 1x/week may be mandated based on clinical outcomes; 2. Plan to seek deferral of pediatric data requirement in EU for initial filing, which would enable possible approval in EU in 2023
TAK-755 IMMUNE TTP PHASE 2 STUDY DESIGN

Primary or relapse acute iTTP episode (N=30)
PEX Day 1

1:1:1 Randomization

Placebo + SOC
TAK-755 Low dose + SOC
TAK-755 High dose + SOC

Remission Phase
Placebo or TAK-755

Primary endpoints: PK/PD

EXPECTED MILESTONES (FY)
2020
2H: Ph2 Readout
2021
2H: Ph3 Start
2023
2H: Ph3 Readout
2025
US/EU Approval

SELECTED TRANSFORMATIVE PROGRAMS

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Potential first treatment of CMV infection in transplant patients in over 10 years. Inhibitor of protein kinase UL97.

TAK-755

TAK-607
Potential first pharmacologic therapy in >20 years to prevent complications of prematurity. Recombinant IGF-1 growth factor.
EXTREMELY PREMATURE INFANTS EXPERIENCE CONSIDERABLE MORBIDITY


Morbidity (%) by birth year, US data

- Bronchopulmonary dysplasia (BPD)
- Severe intraventricular hemorrhage (IVH)

- ~80,000-90,000 Extremely preterm babies (<28 wks gestational age) born WW

- ~40% have lung complications in addition to morbidities in brain, eye that adversely impact development and learning

- ~$200,000 hospitalization costs per infant

TAK-607 REPLENISHES IGF-1, A FETAL GROWTH FACTOR THAT IS DECREASED IN PRETERM INFANTS

TAK-607: IGF-1 / IGFBP-3 COMPLEX

- IGF-1 is an important fetal growth factor supplied by the mother that is involved in the development of multiple organs
- IGF-1 is low or absent in premature infants born before 28 weeks
- TAK-607 demonstrated beneficial effects in lung development and brain vasculature in preclinical models

IGF-1 LEVELS ARE LOW IN PRETERM INFANTS

4. Ley D et al. JINS 2019
TAK-607: PHASE 2 STUDY INFORMED DOSE AND ENDPOINT SELECTION

ROP-2008-01: RANDOMIZED, CONTROLLED PHASE 2 STUDY OF TAK-607

- Pre-term infants with a gestational age (GA) <28 weeks (N = 120)
- Assessed outcomes in ITT and “evaluable” sets (40% patients who achieved target exposure of IGF-1 levels)\(^1\)
  - Primary endpoint: ROP not met
  - Pre-specified secondary endpoints: Bronchopulmonary Dysplasia (BPD) was reduced and Intra-Ventricular Hemorrhage (IVH) showed a positive trend
- Granted FDA fast-track designation

TAK-607 IMPACTED BPD AND IVH\(^2\)

![Graph showing number of infants % (evaluable set) vs. BPD and IVH grades.

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1. Evaluable set: ≥70% IGF-1 measurements within targeted intrauterine range (28–109 µg/L) AND ≥70% intended duration of treatment
2. Levy D, J Pediatrics, 2018
ROP – retinopathy of prematurity

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TAK-607: FOOTPRINTS STUDY DESIGNED TO DEMONSTRATE REDUCTION IN THE COMPLICATIONS OF PREMATURENESS

**Footprints**

- Open label, 1:1:1 Randomization (N = 200/arm)
- Premature infants: <28 weeks GA
- **TAK-607 250 µg/kg/24 h continuous IV**
- **TAK-607 400 µg/kg/24 h continuous IV**
- Standard Neonatal Care

**Treatment**

- (2-7 wks based on GA)
- Rx: Day 1
- Rx End: 29 wk + 6 d PMA

**Post Treatment**

- Follow-up period
- Primary endpoint: 12 months corrected age
- Outpatient: Respiratory morbidity assessments/week

**Primary endpoint:** Duration of supplemental oxygen use through 1 year corrected age\(^3\)

**MILESTONES (FY)**

- 2019: Ph 2b initiated
- 2023: Ph 2b Readout

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1. Supplemental oxygen use defined by one of the following: a) Any fraction of inspired oxygen (FiO\(_2\)) >21%, b) Non-invasive respiratory support delivered via a nasal interface (e.g., continuous positive airway pressure [CPAP], nasal cannula, etc.), c) Invasive respiratory support (mechanical ventilation) via an endotracheal tube or tracheostomy
NME MILESTONES ACHIEVED IN FY19 AND LOOKING AHEAD TO OTHER POTENTIAL MILESTONES\(^1\) THROUGH FY20

**PIVOTAL STUDY STARTS, APPROVALS**

1. Potential key milestone dates as of November 14, 2019. The dates included herein are estimates based on current data and are subject to change.
2. Potentially registration enabling

**KEY DATA READOUTS**

**WE AIM TO PROVIDE CURATIVE THERAPY**

As the global leader in Rare Diseases, we aspire to provide transformative and curative treatments to our patients

**Transformative**

Programs with transformative potential in devastating disorders with limited or no treatment options today

**Curative**

Emerging early pipeline of AAV gene therapies to redefine treatment paradigm in monogenic rare diseases
BUILDING A WORLD CLASS GENE THERAPY ‘ENGINE’

TOP TIER GMP MANUFACTURING

GENE THERAPY AAV² PLATFORM

• Strong capabilities in liver expression
• Emerging capabilities in CNS expression

GENE THERAPY PIPELINE

TAKEDA THERAPEUTIC AREAS

Liver expression

- 3+ Research Candidates
- NextGen Hem A
- TAK-748 Hem B
- TAK-754 Hem A

CNS expression

- StrideBio Research Candidate
- StrideBio Friedreich Ataxia
- TAK-686 Huntington’s Disease

WE WILL APPLY OUR CELL THERAPY PLAYBOOK AND UNIFYING CAPABILITIES TO BUILD A GENE THERAPY PIPELINE

Select Cell Therapy Partnerships/Acquisitions

Cell To Gene Therapy

Unifying Capabilities
- Viral expertise
- Manufacturing

Focus of Future Gene Therapy Partnerships

1. Enable re-dosing
2. Lower dose and enhance biodistribution
3. Develop alternative gene delivery vehicles

Gene Therapy Platform

- Ambys
- Shire Acquisition
- TiGenix Acquisition

Deliver protective or regenerative factors to hepatocytes

AAV tool box and manufacturing platform
SUMMARY

1. Takeda has the capabilities, scale, and innovative platforms to extend our leadership in Rare Diseases

2. We have a leading late stage portfolio of transformative programs that will establish or re-define the standard of care for highly underserved patients

3. We are building cutting-edge capabilities in gene therapy that aim to deliver ‘cures’ in monogenic rare diseases