

RARE DISEASES & GENE THERAPY

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Takeda Pharmaceutical Company Limited

New York, NY

November 14, 2019

Better Health, Brighter Future

RARE DISEASES: AN OPPORTUNITY TO TRANSFORM TREATMENT

HIGH UNMET NEED

7,000	Distinct rare diseases[1]
350 million	Patients worldwide
95%	Diseases have no FDA-approved treatment

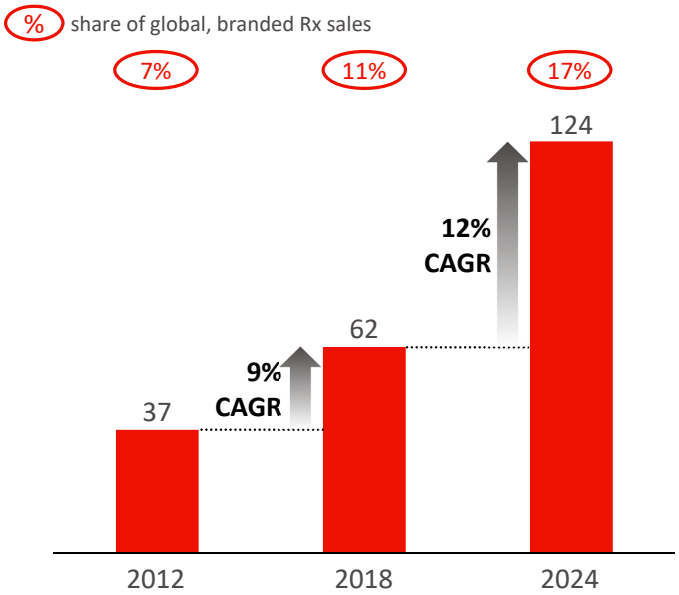
SCIENTIFIC AND REGULATORY ADVANCES

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

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



- 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

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

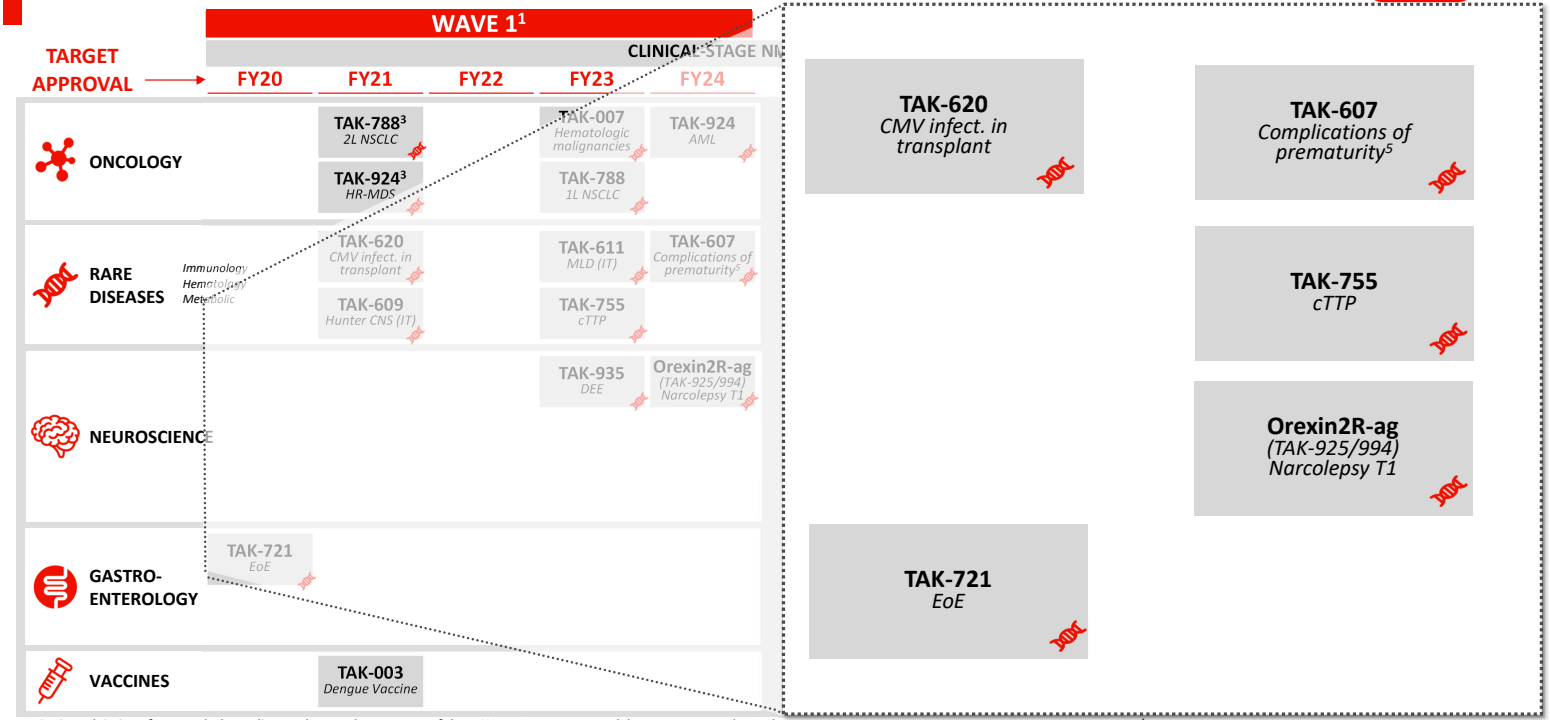
Transformative

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 approval; 2. Some Wave 2 assets 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

Orphan potential in at least one indication
Estimated dates as of November 14, 2019

POTENTIAL APPROVALS OF TRANSFORMATIVE THERAPIES

WAVE 1[1]

Phase 3	Phase 3	Phase 3	Phase 2	Phase 2	Phase 1/2	Phase 2b
TAK-721 Eosinophilic Esophagitis (EoE)	**TAK-620** Cytomegalovirus (CMV) infection in transplant	**TAK-755** Congenital Thrombotic Thrombocytopenic Purpura (cTTP)	**TAK-611** Metachromatic Leukodystrophy (MLD)	**TAK-935** Developmental and Epileptic Encephalopathies (DEE)	**Orexin** Narcolepsy Type 1 (NT1)	**TAK-607** Complications of Prematurity[2]
TARGET APPROVAL						
FY 2020	**FY 2021**	**FY 2023**	**FY 2023**	**FY 2023**	**FY 2024**	**POSSIBLE WAVE 1 APPROVAL[2]**
ADDRESSABLE POPULATION IN US/WW[3,4]						
~150k/Under evaluation	**~7 - 15k/ ~25 - 45k**	**~500/ 2 - 6k**	**~350/ ~1 - 2k**	**~50k/ ~70 - 90k**	**70 - 140k/ 300k – 1.2M**	**~25k/ ~80 - 90k**

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

TAK-620	Potential first treatment of CMV infection in transplant patients in over 10 years. Inhibitor of protein kinase UL97.
TAK-755	Potential best-in-class therapy for Thrombotic Thrombocytopenic Purpura (TTP). Recombinant ADAMTS13.
TAK-607	Potential first pharmacologic therapy in >20 years to prevent complications of prematurity. Recombinant IGF-1 growth factor.

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

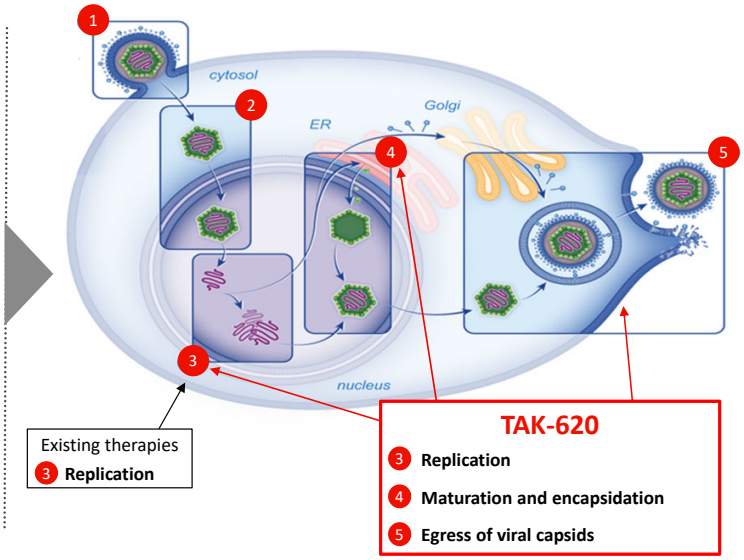
CMV infection can be fatal[2,3]

Higher rates of graft failure: 2.3X and mortality: 2.6X

Current therapies have significant toxicities and resistance[4,5,6,7]

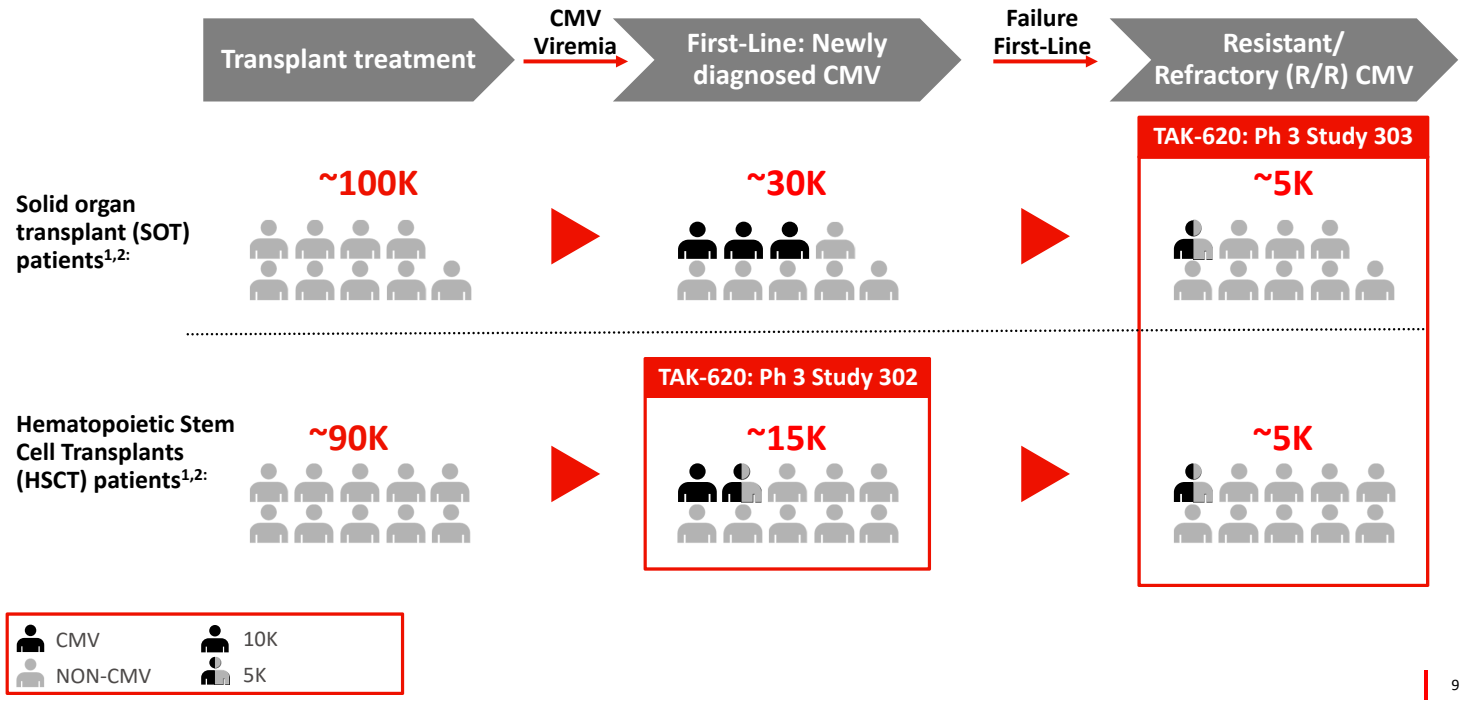
Incidence of neutropenia >20% and renal toxicity >50%

TAK-620: NOVEL MOA TARGETING PROTEIN KINASE UL97



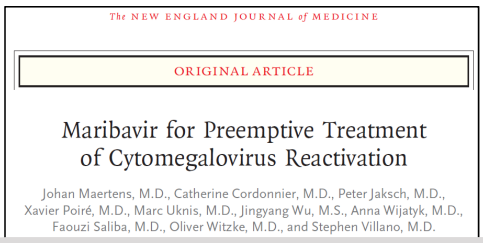
1. Minerva Med. 2009 Dec; 100(6): 479-501; 2. Blood. 2016 May 19;127(20):2427-38; 3. Infect Chemother. 2013 Sep; 45(3): 260–271; 4. Antimicrob Agents Chemother. 2014 Jan; 58(1): 128–135; 5. Transplantation. 2016 Oct;100(10):e74-80;. 6. Clin Microbiol Infect. 2015 Dec;21(12):1121.e9-15; 7. Clin Transplant 2009: 23: 295–304

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



1. Solid organ and allogeneic HSCT transplants in global major markets: US, Europe, Canada, Japan, China , Australia and Korea 2. UNOS Data 2018; CIBMR2017IRODaT Registry 2017, EBMT activity survey 2019 , Shire CMV Epi Study, Feb. 2018

TAK-620 DEMONSTRATED SIMILAR EFFICACY AND BETTER SAFETY VERSUS SOC IN A PHASE 2 STUDY IN FIRST-LINE PATIENTS


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation

Johan Maertens, M.D., Catherine Cordonnier, M.D., Peter Jaksch, M.D., Xavier Poiré, M.D., Marc Uknis, M.D., Jingyang Wu, M.S., Anna Wijatyk, M.D., Faouzi Saliba, M.D., Oliver Witzke, M.D., and Stephen Villano, M.D.

DEMONSTRATED SIMILAR ANTI-VIRAL ACTIVITY TO VALGANCICLOVIR (VGV) ACROSS ALL DOSES[1]

	TAK-620: Dose 400, 800 or 1200 mg BID[2] All Doses (N=119)	VGV (N=40)
Confirmed undetectable plasma CMV DNA within 6 weeks	79%	67%

NEUTROPENIA WAS TREATED WITH GROWTH FACTORS MORE OFTEN IN THE VGV ARM (15%) VS. TAK-620 ARM (7%)[2]

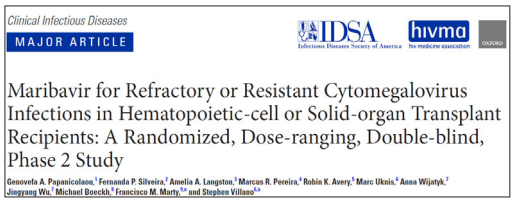
	TAK-620: Dose 400, 800 or 1200 mg BID All Doses (N=119)	VGV (N=40)
Neutropenia that occurred or worsened during treatment through week 12	5%	18%

1. Confirmed undetectable CMV DNA in plasma was defined as two consecutive CMV DNA polymerase-chain-reaction assay values measure 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)

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

TAK-620 Dose: 400 mg, 800 mg, 1200 mg BID[1]	
Primary efficacy endpoint	**All doses (Total N = 120)**
Patients with confirmed undetectable plasma CMV DNA within 6 weeks in ITT[2] population	80 (66.7%)


Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study

Genovefa A. Papanicolaou,[1] Fernanda P. Silveira,[2] Amelia A. Langston,[3] Marcus R. Pereira,[4] Robin K. Avery,[5] Marc Uknis,[6] Anna Wijatyk,[7] Jingyang Wu,[7] Michael Boeckh,[8] Francisco M. Marty,[9,a] and Stephen Villano[7,a]

Historical outcomes: High (~50%) failure rates / relapse rates[3,4,5]

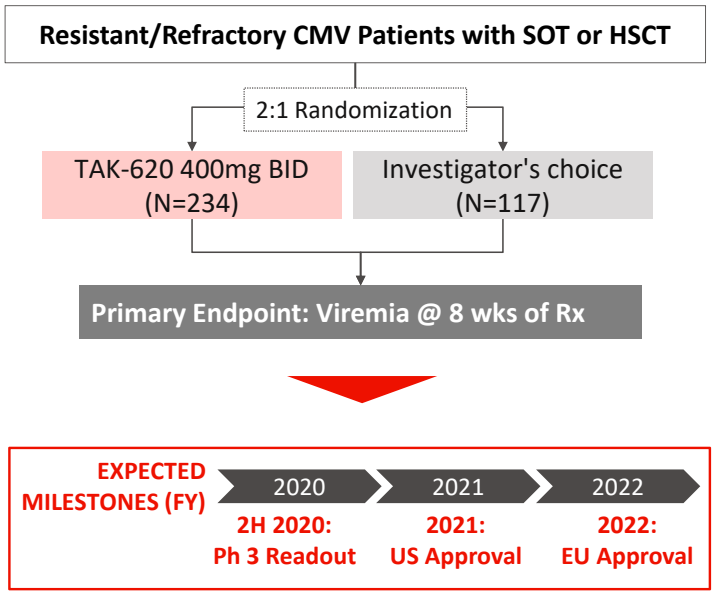
2 Superior renal safety profile - did not result in treatment discontinuations

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

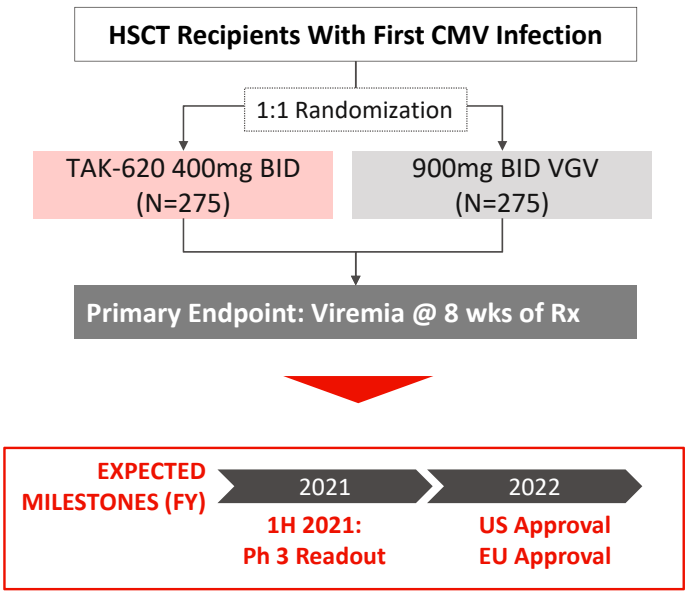
1. Clin Infect Dis. 2019 Apr 8;68(8):1255-1264; 2. ITT - Intent to treat; 3. Antimicrob Agents Chemother, 58, 128-35; 4. Mehta et al, 2016 American Transplant Congress, Meeting abstract C279; 5. J Heart Lung Transplant. 2019 Sep 10; 6. Transplantation. 2016 Oct; 100(10): e74–e80

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

TAK-620 PHASE 3 STUDY 303



TAK-620 PHASE 3 STUDY 302



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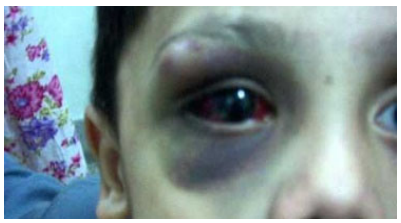
CONGENITAL AND IMMUNE TTP HAVE SUBSTANTIAL MORTALITY AND MORBIDITY BURDEN DUE TO INADEQUATE SOC

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[3,4]
  - Enhanced risk of bleeding:
    Gingival bleeding 18% vs. 1% placebo
    Epistaxis 32% vs. 3% placebo



ADDRESSABLE POPULATION (WW)[1,2]	
cTTP	2,000 – 6,000
iTTP	5,000 – 18,000

1. Global major markets: US, Europe, Canada, JPN, and Global Emerging Markets; 2. Haematologica September 2010 95: 1444-1447; 3. N Engl J Med 2019;380:335-46.; 4. N Engl J Med 2016; 374:511-522

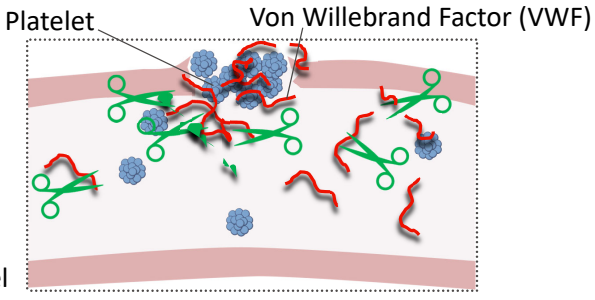
TAK-755 DIRECTLY ADDRESSES UNDERLYING CAUSE OF TTP

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

Normal clotting cascade

ADAMTS13:

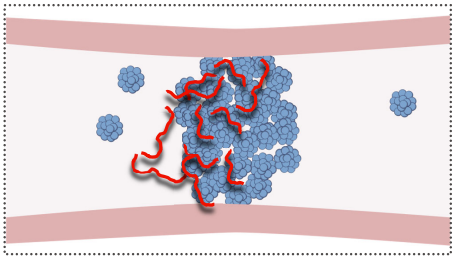
Cleaves VWF multimers that mediate platelet aggregation and clotting



TTP

ADAMTS13 deficiency:

Formation of microthrombi due to accumulation of large VWF multimers

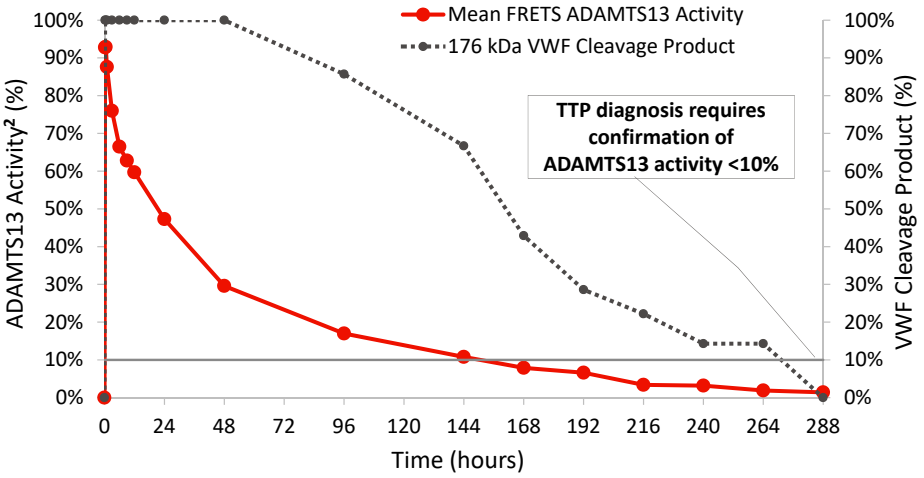


TAK-755: POTENTIAL TRANSFORMATIVE THERAPY FOR TTP

TAK-755 PHASE I, OPEN-LABEL, DOSE ESCALATION STUDY IN cTTP[1]

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

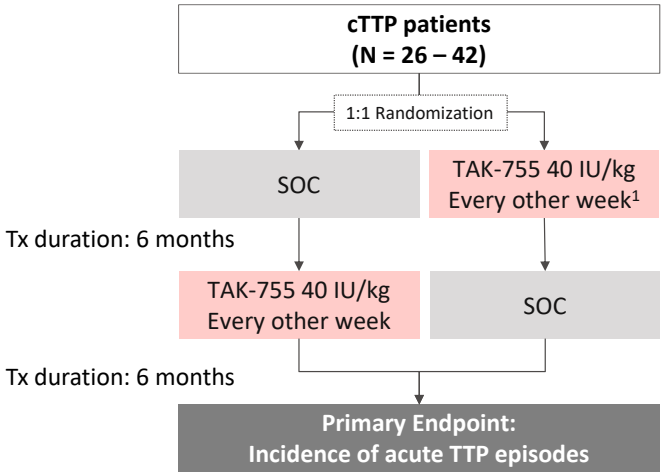
TAK-755 PK PROFILE AND PD EFFECT ON VWF CLEAVAGE AT 40 IU/KG



1. Blood 2017; vol. 130, number 19, 2055-63; 2. Measured using FRETS (fluorescence resonance energy transfer)

TAK-755: ONGOING PHASE 3 CONGENITAL TTP STUDY

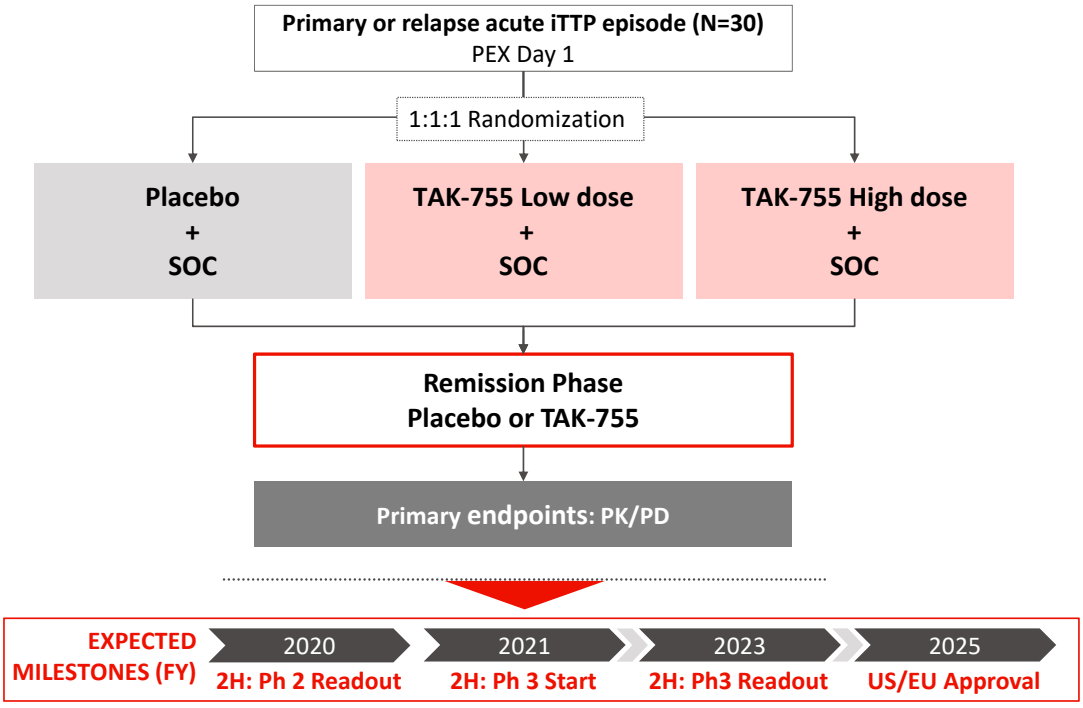
TAK-755 PHASE 3 PROPHYLAXIS STUDY



- 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

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



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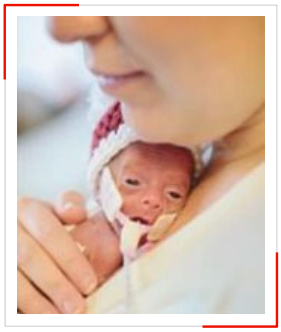
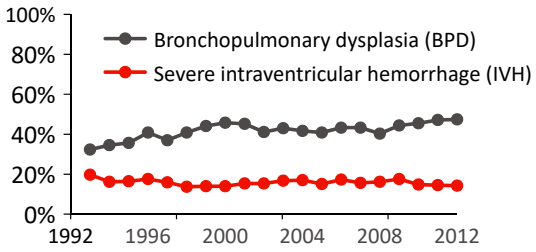
EXTREMELY PREMATURE INFANTS EXPERIENCE CONSIDERABLE MORBIDITY



Morbidity (%) by birth year, US data[1]



~80,000-90,000 Extremely preterm babies (<28 wks gestational age) born WW[2,3]

0 Therapies for prevention of complications of prematurity

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

~$200,000 hospitalization costs per infant [4]

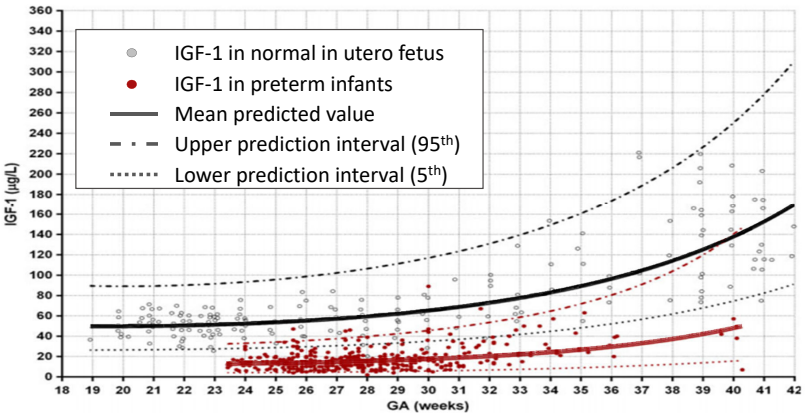
1. Stoll B, JAMA, 2015;314(10): 1039–1051; 2. CDC; 3. UN data and published sources; 4. Mowitz M et al. Co-occurrence and Burden of Complications of Prematurity Among Extremely Preterm Infants in the US AAP 2017 Poster 76

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

TAK-607: IGF-1 / IGFBP-3[1] 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[2]
- TAK-607 demonstrated beneficial effects in lung development and brain vasculature in preclinical models[3,4]

IGF-1 LEVELS ARE LOW IN PRETERM INFANTS[2]



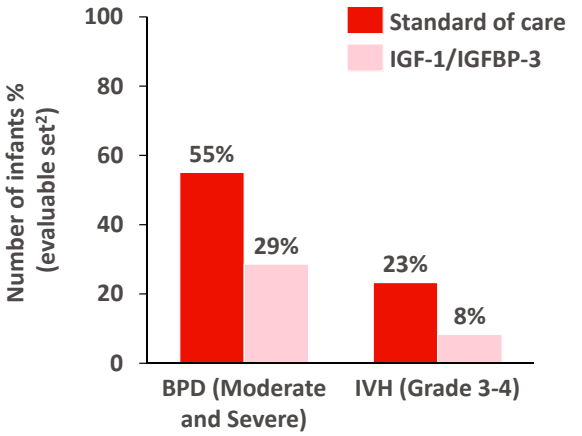
1. Recombinant insulin-like growth factor 1 (rIGF-1), IGFBP-3- IGF binding protein-3; 2. Hellstrom et al., Acta Pædiatrica 2016 105, pp. 576–586; 3. Seedorf G et al. EAPS. Geneva 2016 (manuscript in preparation)
4. Ley D et al. jENS 2019

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

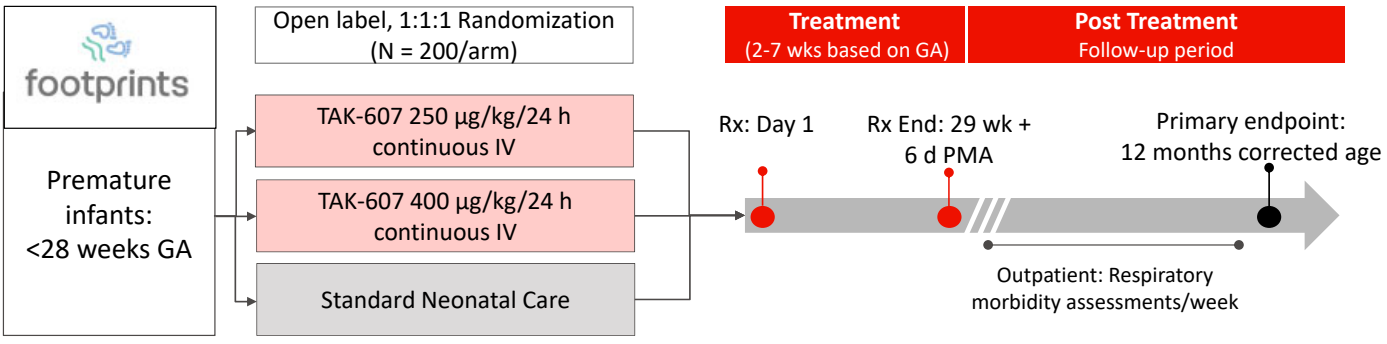
TAK-607 IMPACTED BPD AND IVH[2]



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

ROP – retinopathy of prematurity

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



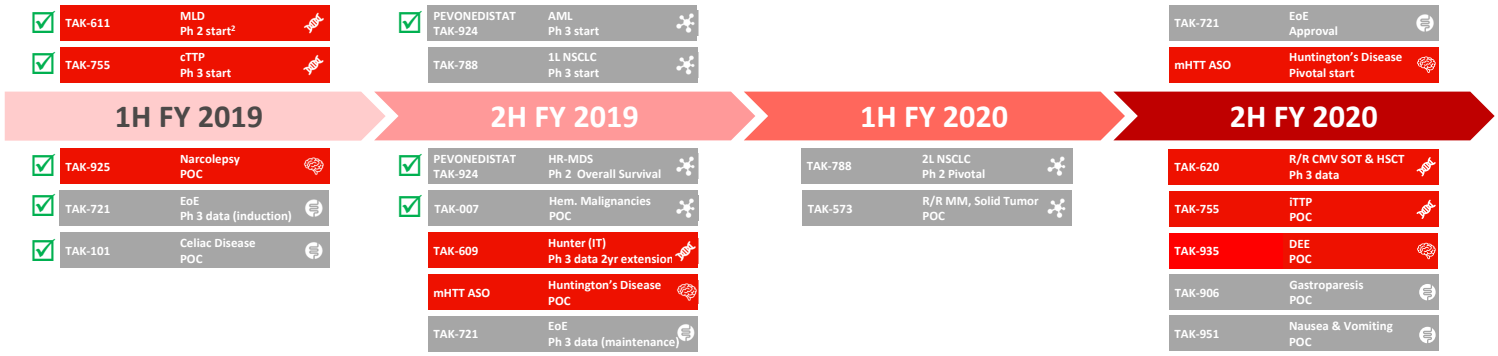
Primary endpoint: Duration of supplemental oxygen use through 1 year corrected age[1]

EXPECTED MILESTONES (FY) 2019 **1H: Ph 2b initiated** 2023 **1H: Ph 2b Readout**

1. Supplemental oxygen use defined by one of the following: a) Any fraction of inspired oxygen (FiO2) >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



☑ Denotes milestones that have been achieved.

KEY DATA READOUTS

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

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 AAV[1] PLATFORM

- Strong capabilities in **liver expression**
- Emerging capabilities in **CNS expression**

GENE THERAPY PIPELINE

TAKEDA THERAPEUTIC AREAS

Preclinical Development → Clinical Development

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

1. Adeno-Associated Virus

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

Select Cell Therapy Partnerships/Acquisitions

7-CiRA · GAMMADELTA THERAPEUTICS · Ambys MEDICINES · MD Anderson Cancer Center · TiGENIX Living Medicines · TiGENIX Acquisition · Memorial Sloan Kettering Cancer Center · 7-CiRA

Cell To Gene Therapy

Unifying Capabilities
- Viral expertise
- Manufacturing

2016 · 2017 · 2018 · 2019 · 2020 · 2021 · 2022+

Gene Therapy Platform

Ambys MEDICINES
Deliver protective or regenerative factors to hepatocytes

stridebio
Capsids to enhance biodistribution in CNS

Shire Acquisition
AAV tool box and manufacturing platform

Focus of Future Gene Therapy Partnerships

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

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

R&D DAY AGENDA – NEW YORK, NOVEMBER 14, 2019

TIME	AGENDA
12:30 – 12:35	**Welcome and Opening Remarks** *Sheelagh Cawley-Knopf, Head R&D Global Portfolio Strategy*
12:35 – 12:45	**Takeda: A Global Values-Based, R&D-Driven Biopharmaceutical Leader** *Christophe Weber, President & CEO Takeda*
12:45 – 13:20	**Translating Science into Highly Innovative, Life-changing Medicines** *Andy Plump, President R&D*
13:20 – 13:45	**Oncology and Cell Therapies with Spotlight on CAR-NK** *Chris Arendt, Head Oncology Drug Discovery Unit*
13:45 – 14:05	**Spotlight on Oncology Opportunities** • **TAK-788** : *Rachael Brake, Global Program Lead* • **Pevonedistat** : *Phil Rowlands, Head Oncology Therapeutic Area Unit*
14:05 – 14:20	**Break**
14:20 – 14:45	**Rare Diseases & Gene Therapy** *Dan Curran, Head Rare Disease Therapeutic Area Unit*
14:45 – 15:00	**Spotlight on Orexin2R agonists** *Deborah Hartman, Global Program Lead*
15:00 – 15:20	**Therapeutic Area Focus in GI with Spotlight on Celiac Disease** *Asit Parikh, Head GI Therapeutic Area Unit*
15:20 – 16:00	**Panel Q&A Session**
16:00	**Drinks reception**