



RARE DISEASES & GENE THERAPY



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Better Health, Brighter Future

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



100%³



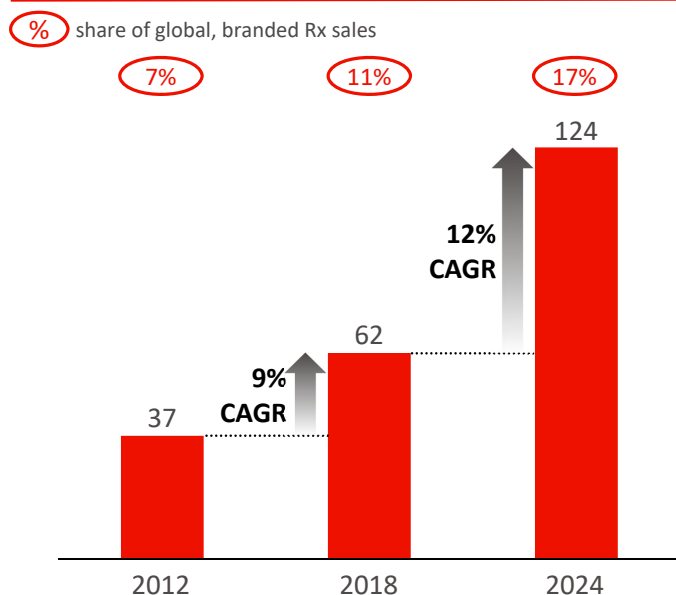
Orphan drug approvals benefited from expedited review

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 DRUG¹ SALES EXCLUDING ONCOLOGY², 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)

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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**

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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

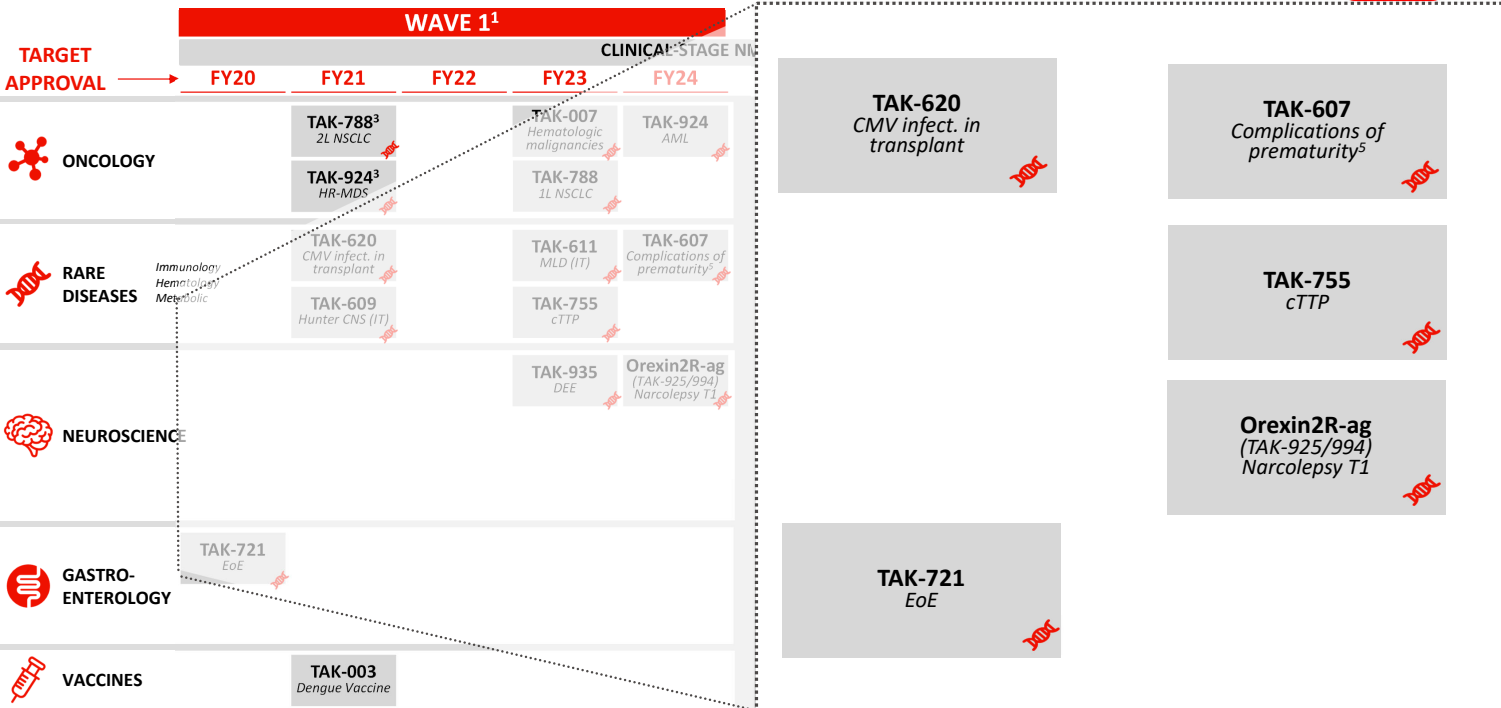
Transformative

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 1¹

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						POSSIBLE WAVE 1 APPROVAL ²
FY 2020	FY 2021	FY 2023	FY 2023	FY 2023	FY 2024	
~150k/Under evaluation	~7 - 15k/ ~25 - 45k	ADDRESSABLE POPULATION IN US/WW ^{3,4}			70 - 140k/ 300k - 1.2M	~25k/ ~80 - 90k
		~500/ 2 - 6k	~350/ ~1 - 2k	~50k/ ~70 - 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

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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.

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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 infection¹

Affects >25% of transplants

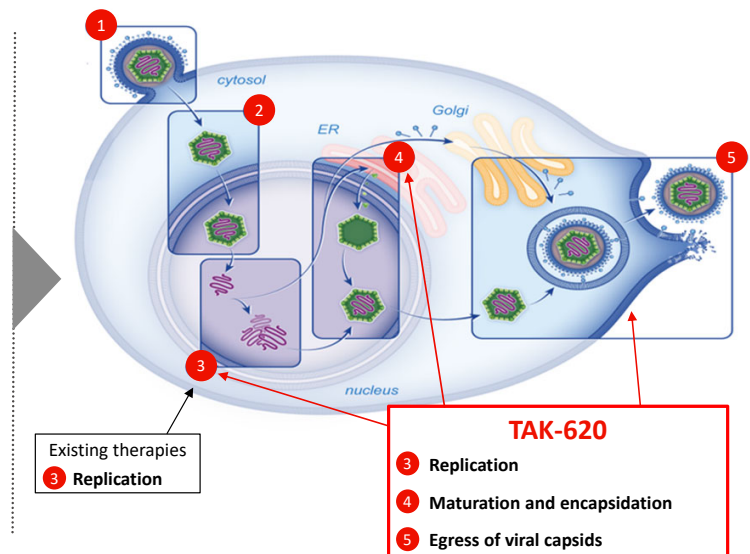
CMV infection can be fatal^{2,3}

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%

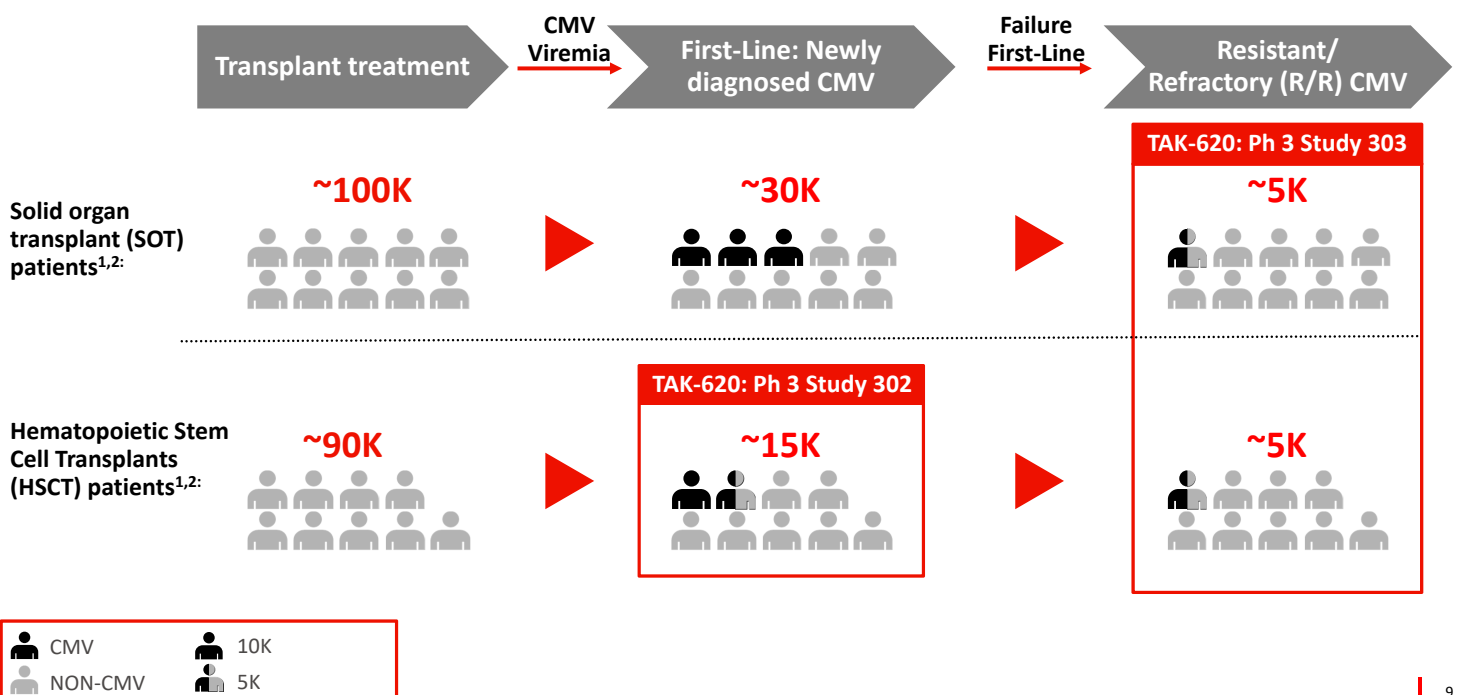
TAK-620: NOVEL MOA TARGETING PROTEIN KINASE UL97



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

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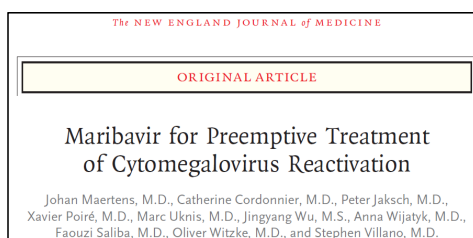
TAK-620 ADDRESSES UNMET NEED IN BOTH FIRST-LINE AND RESISTANT / REFRACTORY SETTING



1. Solid organ and allogeneic HSCT transplants in global major markets: US, Europe, Canada, Japan, China, Australia and Korea 2. UNOS Data 2018; CIBMTR2017/RODaT Registry 2017; EBMT activity survey 2019, Shire CMV Epi Study, Feb. 2018

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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 DOSES¹

	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)

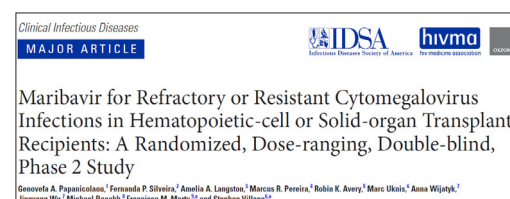
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TAK-620: GRANTED BREAKTHROUGH DESIGNATION IN RESISTANT OR REFRACTORY CMV INFECTION



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

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%)



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, Cidofovir); nephrotoxicity is > 50%⁶

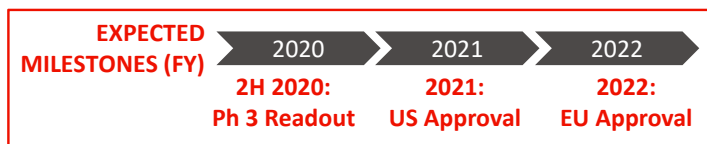
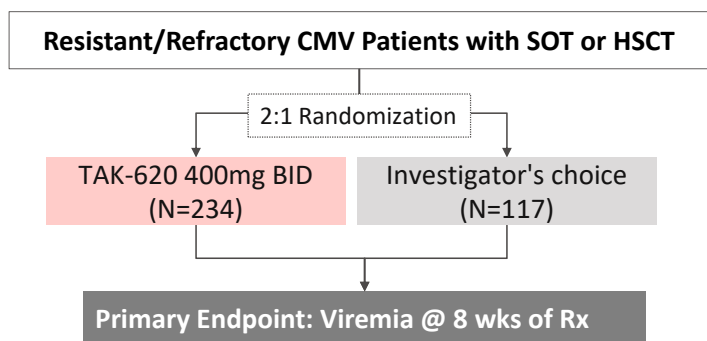
1. Clin Infect Dis. 2019 Apr 8;68(8):1255-1264; 2. ITT - Intent to treat; 3. Antimicrob Agents Chemother, 58, 128-35; 4. Mehta et al, 2016 American Transplant Congress, Meeting abstract C279; 5. J Heart Lung Transplant. 2019 Sep 10; 6. Transplantation. 2016 Oct; 100(10): e74-e80

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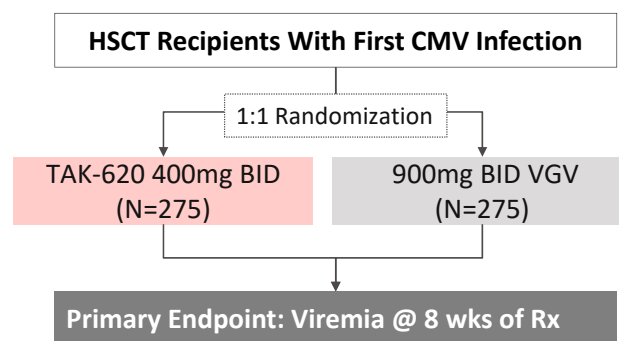
TAK-620: TWO ONGOING PIVOTAL STUDIES; EXPECT FIRST APPROVAL IN RESISTANT OR REFRACTORY CMV IN 2021



TAK-620 PHASE 3 STUDY 303



TAK-620 PHASE 3 STUDY 302



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SELECTED TRANSFORMATIVE PROGRAMS



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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

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TAK-755 DIRECTLY ADDRESSES UNDERLYING CAUSE OF TTP



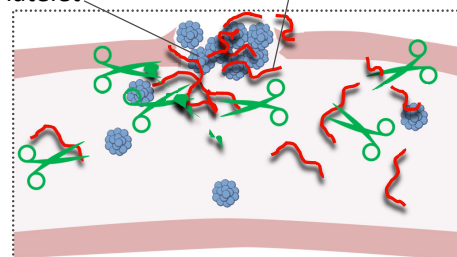
TAK-755 REPLACES ADAMTS13, DEFICIENCY OF WHICH LEADS TO TTP

Normal
clotting
cascade

ADAMTS13:

Cleaves VWF multimers that mediate platelet aggregation and clotting

Platelet Von Willebrand Factor (VWF)

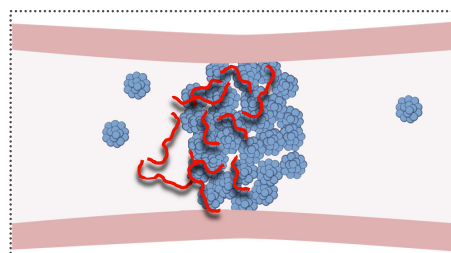


Blood vessel

TTP

ADAMTS13 deficiency:

Formation of microthrombi due to accumulation of large VWF multimers



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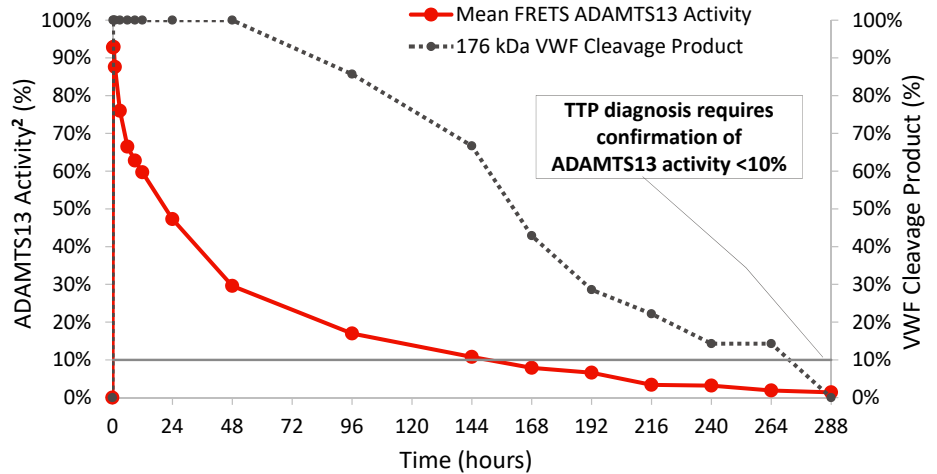
TAK-755: POTENTIAL TRANSFORMATIVE THERAPY FOR TTP



TAK-755 PHASE I, OPEN-LABEL, DOSE ESCALATION STUDY IN cTTP¹

- 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



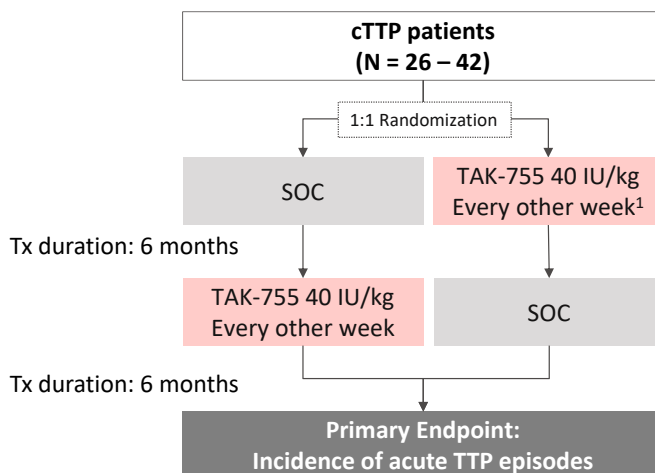
1. Blood 2017; vol. 130, number 19, 2055-63; 2. Measured using FRETs (fluorescence resonance energy transfer)

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TAK-755: ONGOING PHASE 3 CONGENITAL TTP STUDY



TAK-755 PHASE 3 PROPHYLAXIS STUDY



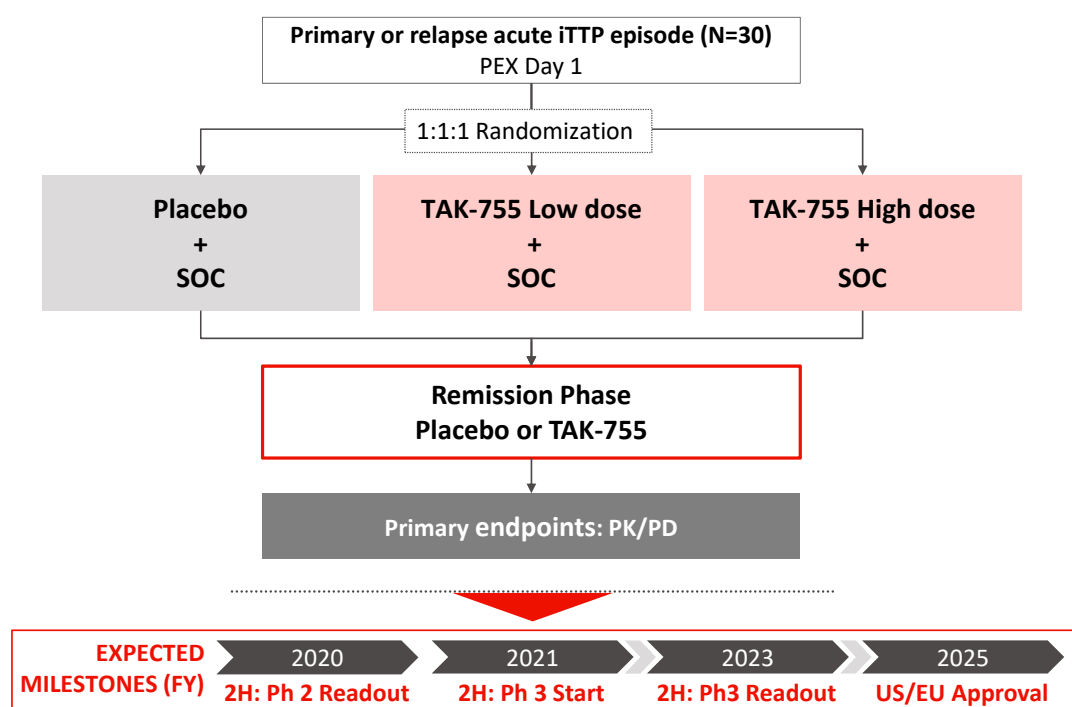
- All patients roll over to a 6 month TAK-755 extension
- Phase 3 study has a cohort of acute cTTP patients who receive TAK755. Patients are eligible to enter the prophylaxis study upon completion of acute treatment



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

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TAK-755 IMMUNE TTP PHASE 2 STUDY DESIGN



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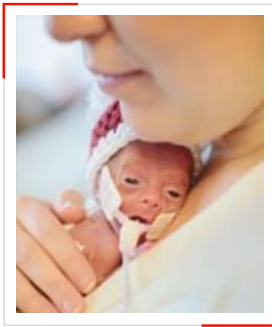
SELECTED TRANSFORMATIVE PROGRAMS



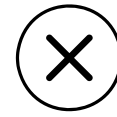
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EXTREMELY PREMATURE INFANTS EXPERIENCE CONSIDERABLE MORBIDITY



**~80,000-90,000
Extremely preterm
babies** (<28 wks
gestational age) born
WW^{2,3}



0 Therapies
for prevention of
complications of
prematurity

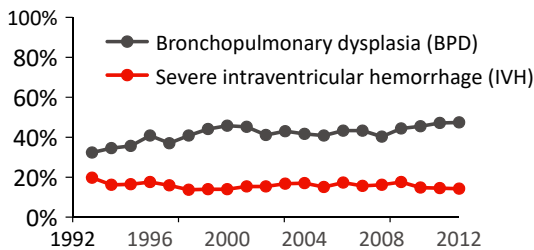


**~40% have lung
complications**
in addition to
morbidity in brain,
eye that adversely impact
development and learning



**~\$200,000
hospitalization
costs** per infant ⁴

Morbidity (%) by birth year, US data¹



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

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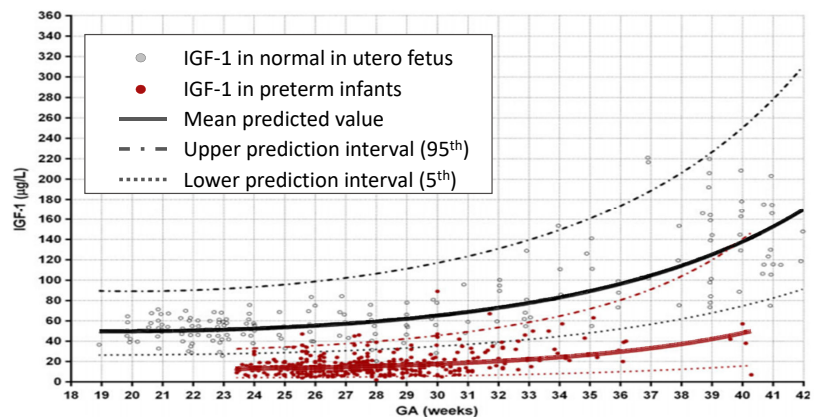
TAK-607 REPLENISHES IGF-1, A FETAL GROWTH FACTOR THAT IS DECREASED IN PRETERM INFANTS



TAK-607: IGF-1 / IGFBP-3¹ 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 weeks²
- TAK-607 demonstrated beneficial effects in lung development and brain vasculature in preclinical models^{3,4}

IGF-1 LEVELS ARE LOW IN PRETERM INFANTS²



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

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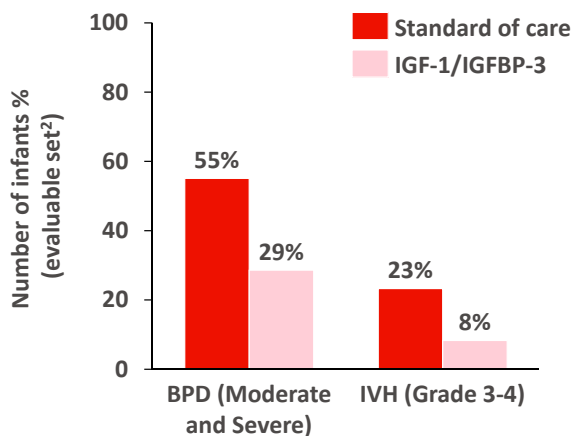
TAK-607: PHASE 2 STUDY INFORMED DOSE AND ENDPOINT SELECTION



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

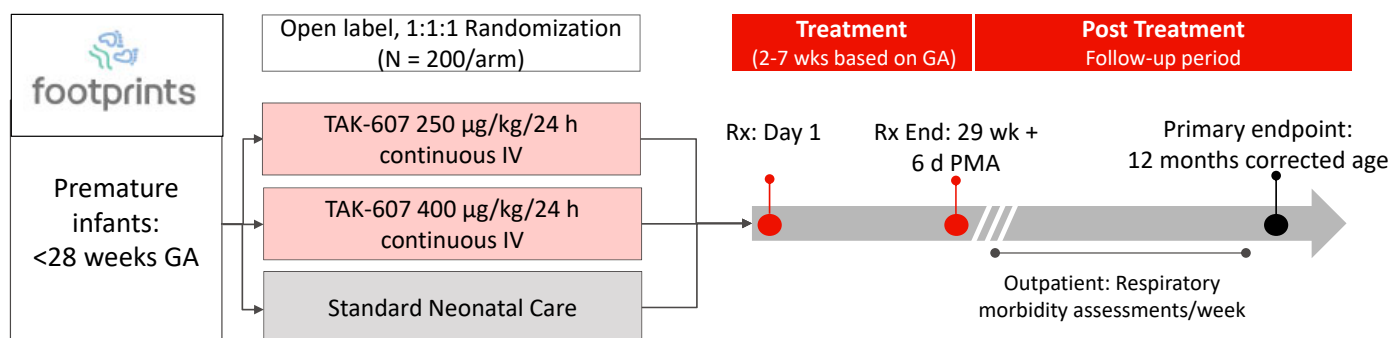
TAK-607 IMPACTED BPD AND IVH²



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

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



Primary endpoint: Duration of supplemental oxygen use through 1 year corrected age¹

EXPECTED MILESTONES (FY)

2019: 1H: Ph 2b initiated

2023: 1H: Ph 2b Readout

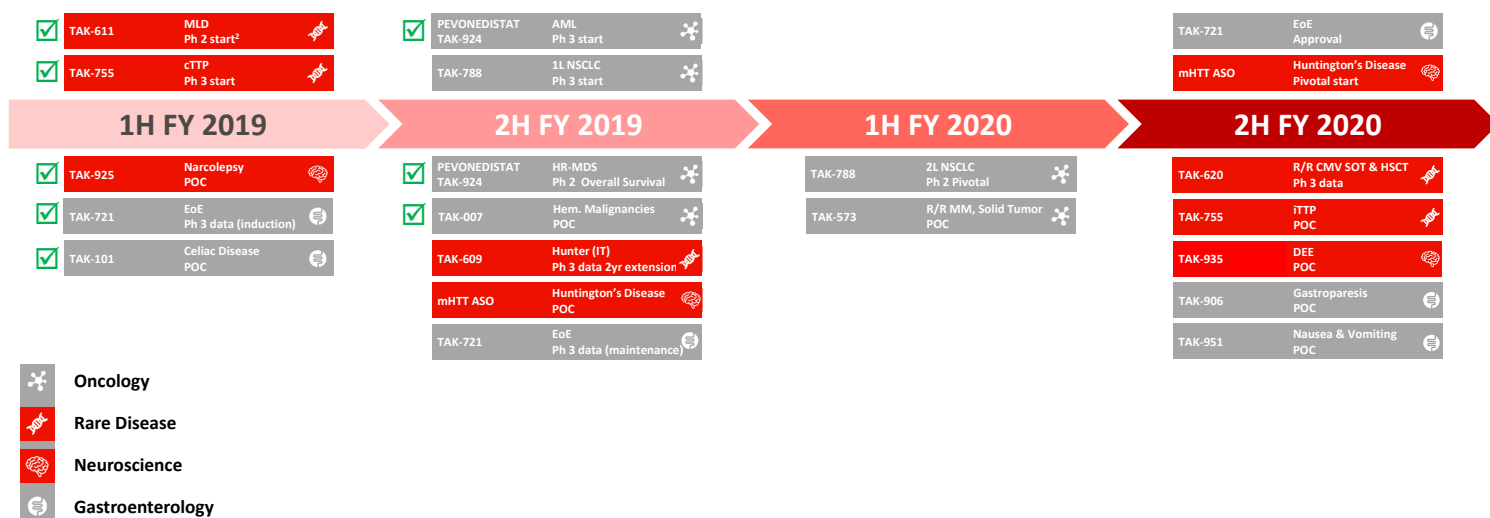
1. Supplemental oxygen use defined by one of the following: a) Any fraction of inspired oxygen (FIO₂) >21%, b) Non-invasive respiratory support delivered via a nasal interface (e.g., continuous positive airway pressure [CPAP], nasal cannula, etc.), c) Invasive respiratory support (mechanical ventilation) via an endotracheal tube or tracheostomy

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NME MILESTONES ACHIEVED IN FY19 AND LOOKING AHEAD TO OTHER POTENTIAL MILESTONES¹ THROUGH FY20



PIVOTAL STUDY STARTS, APPROVALS



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

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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

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BUILDING A WORLD CLASS GENE THERAPY 'ENGINE'



TOP TIER GMP MANUFACTURING



GENE THERAPY AAV¹ 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

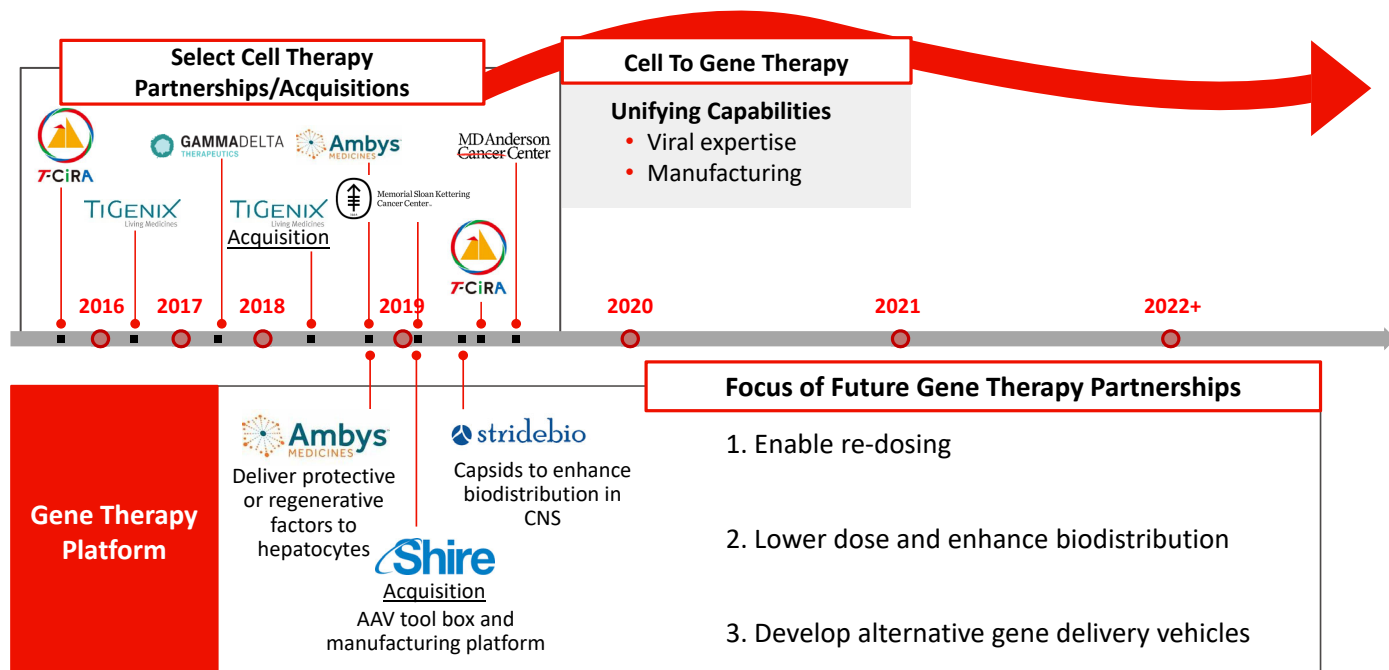
StrideBio
Friedreich
Ataxia

TAK-686
Huntington's
Disease

1. Adeno-Associated Virus

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



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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