



Administration of OTL-101

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Rationale for new ICD-10-PCS code

- Current ICD-10-PCS codes do not adequately describe the Administration of the investigational therapy, OTL-101
- The new gene therapy approach used to design OTL-101 may be more specifically identified with an ICD-10-PCS procedure code that is unique to the product and the method of administration

Introduction of *ex vivo* autologous CD34+ Hematopoietic Stem and Progenitor Cell (HSPC) - based lentiviral vector-mediated gene therapy via intravenous (IV) infusion

- Providers may benefit by having a unique code to assist with tracking outcomes with OTL-101 therapy

Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency (ADA-SCID)

Pathophysiology

Rare inherited metabolic condition¹

- ADA-SCID is inherited in a recessive manner³
- Incidence globally ~ 1:200,000 – 1:1,000,000 births^{2,3}
- Incidence in United States ~ 1:600,000 births⁴

Genetic mutations in the ADA gene⁵⁻⁹

- ADA gene located on chromosome 20 at position 13.12³
- Mutations result in very low levels of ADA enzymatic activity
- Consequent accumulation of toxic levels of purine metabolites,
- Causing severe lymphopenia and immunodeficiency^{1,9,8-10}

Current Management Options

- Enzyme replacement therapy,
- IgRT (immunoglobulin replacement therapy)
- HSCT (hematopoietic stem cell transplant)
- GT (licensed in EU only)
- Supportive care

1. Gaspar HB et al. *Blood* 2009;114:3524–3532. 2. Orphanet. ADA-SCID report. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=277 Accessed October 10, 2018. 3. Hershfield M et al. Gene Reviews - Adenosine Deaminase Deficiency. <https://www.ncbi.nlm.nih.gov/books/NBK1483>. Accessed October 10, 2018. 4. Kwan A et al. *JAMA* 2014;312(7):729-738. 5. Picard C et al. *J Clin Immunol* 2015;35:696–726. 6. Cicalese MP et al. *Hum Gene Ther* 2015;26:210–219. 7. Blackburn MR et al. *Adv Immunol* 2005;86:1–41. 8. Whitmore KV, Gaspar HB. *Front Immunol* 2016;7:314. 9. Bradford KL et al. *J Clin Immunol* 2017;37(7):626-637. 10. Sauer AV et al. *Front Immunol* 2012;3:265. EU, European Union; GT, gene therapy

Severe Immune and Non-Immune Disease Manifestations

Immune system⁴⁻⁶

- Life-threatening opportunistic infections¹⁻³
- Failure to thrive
- Extensive dermatitis
- Absence of lymphoid tissues (tonsils, lymph nodes)
- Persistent respiratory tract infection
- Recurrent pneumonia

Gastrointestinal system⁵

- Gastrointestinal infection and apparent food intolerance

Hepatic and renal dysfunction^{2,6}

Nervous system

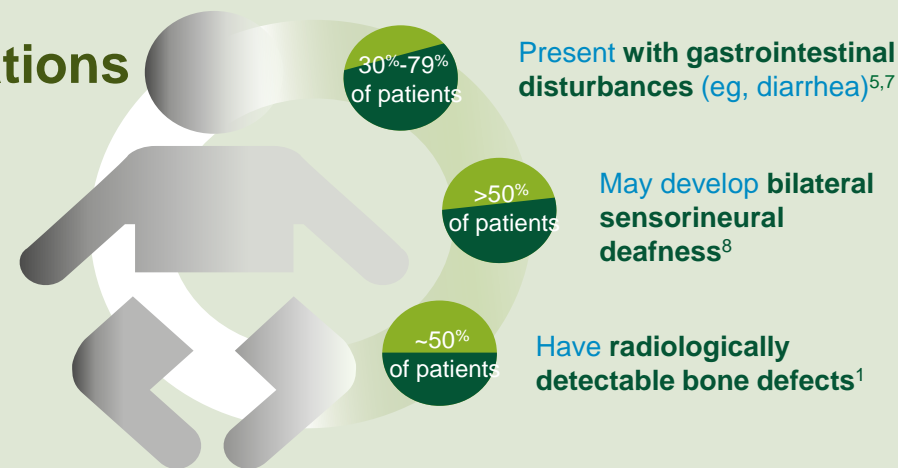
- Neurological deficits that involve motor function^{1,2}
- Bilateral sensorineural deafness^{1,2,4}
- Cognitive and behavioral abnormalities^{2-4,6}

Respiratory system⁴

- Non-infectious pulmonary complications, such as alveolar proteinosis

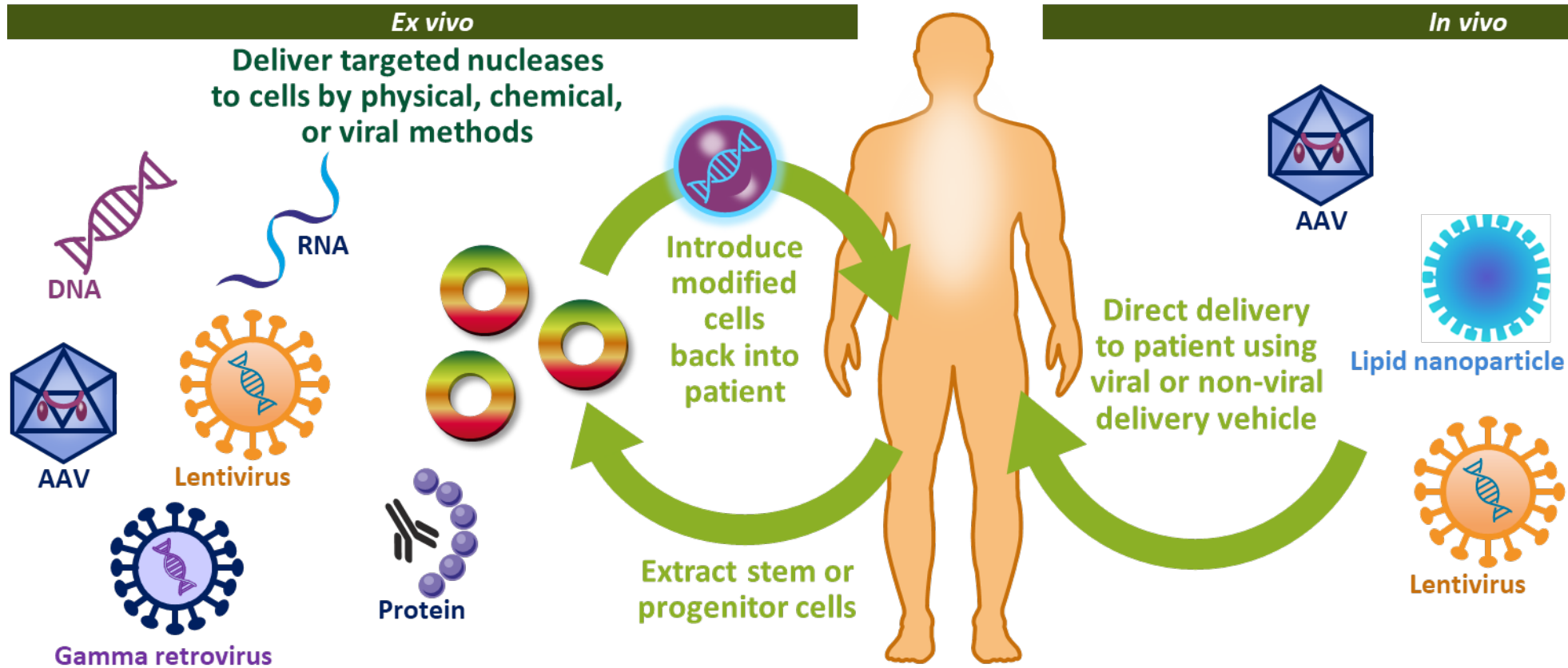
Skeletal system^{2,4}

- Costochondral abnormalities and skeletal dysplasias



1. Whitmore KV, Gaspar HB. *Front Immunol* 2016;7:314. 2. Gaspar HB et al. *Blood* 2009;114:3524–3532. 3. Sauer AV et al. *Front Immunol* 2012;3:265. 4. Flinn AM, Gennery AR. *Orphanet J Rare Dis*. 2018;13(1):65. 5. van der Burg M et al. *Eur J Pediatr*. 2011;170:561–571. 6. Hershfield M et al. Gene Reviews - Adenosine Deaminase Deficiency. <https://www.ncbi.nlm.nih.gov/books/NBK1483/>. 2006. Accessed October 10, 2018. 7. NIH. Adenosine deaminase deficiency. <https://rare diseases.info.nih.gov/diseases/5748/adenosine-deaminase-deficiency>. Accessed October 10, 2018. 8. Alburquerque W et al. *J. Pediatr* 2004; 144(2):278 – 280. ^aCohort of 12 patients treated with HSCT.⁴

Different Gene Therapy Modalities Suited for Different Types of Delivery Requirements and Diseases¹



HSC *ex vivo* viral-mediated gene therapy is an appropriate choice for monogenic disorders historically approached with HSCT²

AAV, adeno-associated virus; DNA, deoxyribonucleic acid; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplant; RNA, ribonucleic acid.

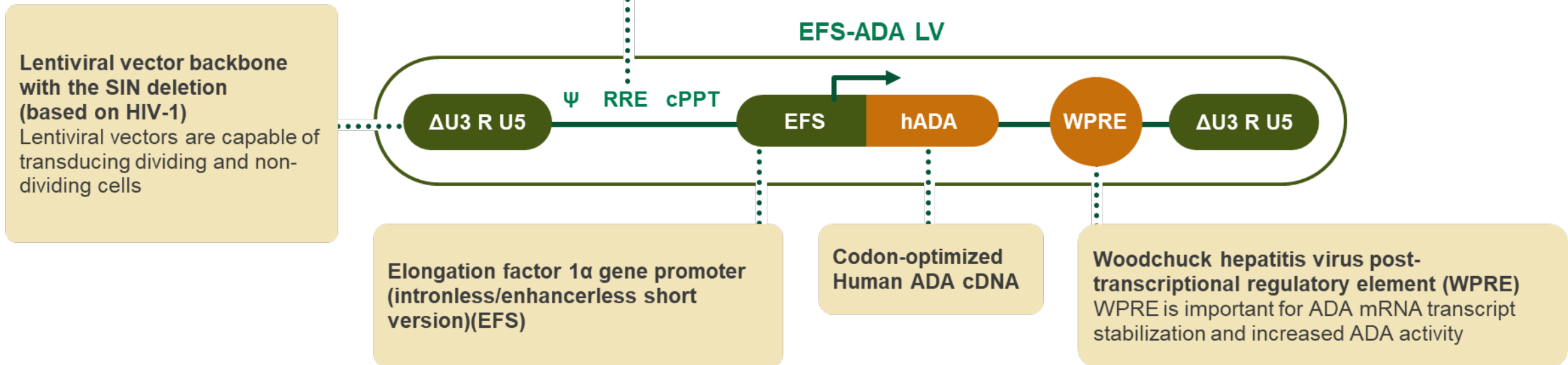
1. Adapted from: FDA website. What is Gene Therapy? Available at: <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm573960.htm>. Accessed February 14, 2019.

2. Kaufmann KB et al. *EMBO Mol Med*. 2013;5:1642–1661.

OTL-101 is an investigational *ex vivo* autologous CD34+ hematopoietic stem and progenitor cell (HSPC)-based gene therapy, produced using the EFS-ADA LV

OTL-101 is a breakthrough therapy composed of an autologous CD34+ cell enriched population, that contains hematopoietic stem and progenitor cells (HSPCs) transduced *ex vivo* using a lentiviral vector (LV) encoding the human adenosine deaminase (ADA) gene. The lentiviral vector used is EFS-ADA LV, which encodes the human ADA cDNA sequence under the regulation of EFS, a shortened, intron-less version of the Elongation Factor 1 alpha gene promoter

Lentiviral vector used in OTL-101



- ADA, adenosine deaminase; cPPT, central polypurine tract; HIV, human immunodeficiency virus; HSC, hematopoietic stem cell; LV, lentiviral vector; mRNA, messenger ribonucleic acid; SIN, self inactivating.
- Carbonaro DA et al. *Mol Ther* 2014;22:607–622

Orchard Therapeutics Autologous ex vivo Gene Therapy Approach

Patient enters outpatient monitoring

Administration Followed by Recovery:

Genetically-modified cells are given back to the patient intravenously

Conditioning:

The patient is given conditioning to “make space” for the genetically-modified cells

Patient returns to center

Cryopreserved genetically modified HSCs:

Drug product is certified that it meets manufacturing standards and sterility

Patient enters center

Blood cell collection:

Blood hematopoietic stem cells (HSCs) and other progenitor cells are taken from the patient via leukapheresis or bone marrow extraction

Patient returns home

HSC selection and purification:

HSCs, identified by the CD34⁺ cell surface marker, are selected and purified by magnetic bead selection

Transduction:

HSCs are genetically-modified outside of the body (“ex vivo”) via exposure to a viral vector carrying a functional copy of the gene

Viral vector carrying a copy of the functional gene

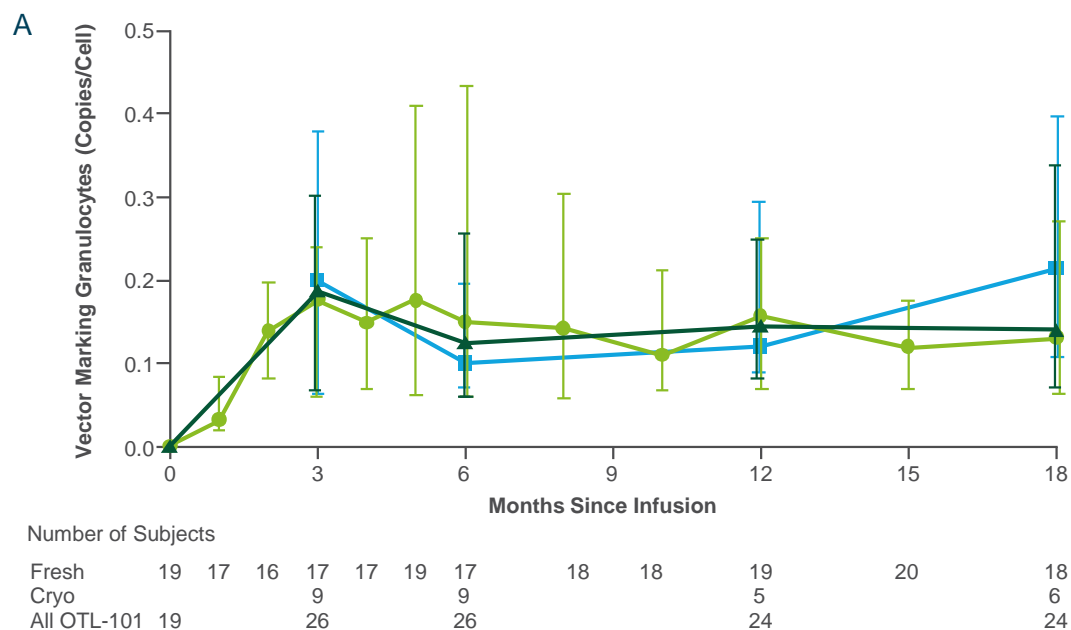
Autologous *ex vivo* Gene Therapy

Anticipated Timeline at Treatment Center

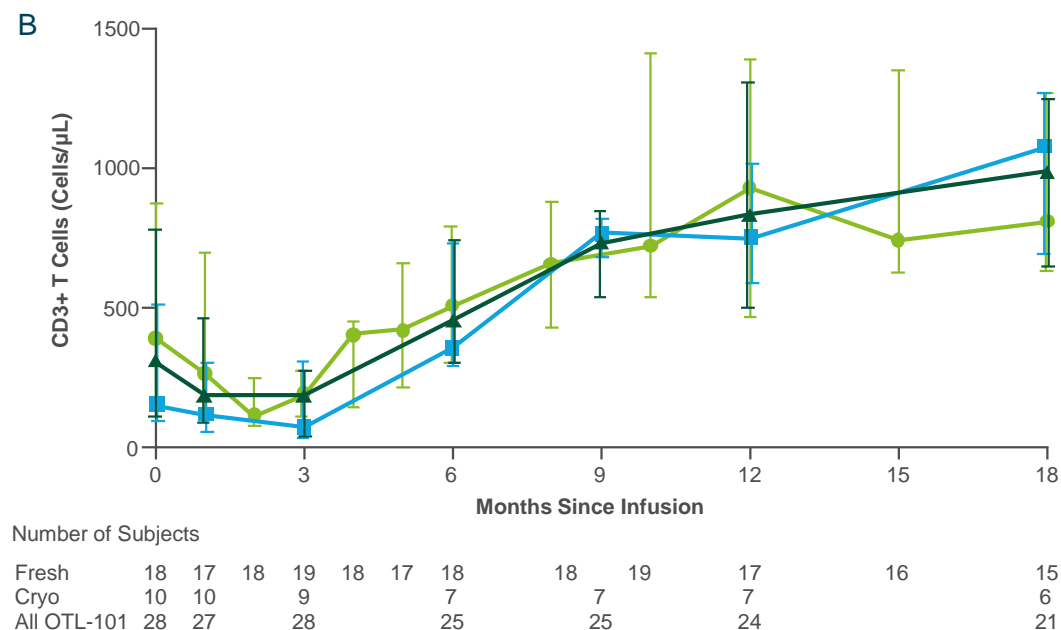
Inpatient Treatment Center Trip 1: Cell Collection [2-3 days or up to 7 days]	
Bone Marrow Harvest [2-3 days]	Mobilized Peripheral Blood Collection (leukapheresis) [up to 7 days]
<ul style="list-style-type: none"> Admit the patient the day before cell harvest Perform the harvest Observe for 24 hours then discharge 	<ul style="list-style-type: none"> Pre-mobilization assessment Pre-treatment with mobilizing agents Possibility of 1-3 leukapheresis
Inpatient Treatment Center Trip 2: Conditioning, Infusion, and Recovery [4–8 weeks]	
Conditioning	
<ul style="list-style-type: none"> Infusion of conditioning regimen [2 days] Day of Rest [1 day] 	
Administration	
<ul style="list-style-type: none"> Infusion of drug product [1 day] 	
Recovery	
<ul style="list-style-type: none"> Inpatient Observation / Monitoring until cell count normalizes (varies by patient) [4-8 weeks] 	
Outpatient Monitoring [4–8 weeks]	
<ul style="list-style-type: none"> Local monitoring following procedure 	

OTL-101 Investigational Therapy for ADA-SCID: Engraftment of Gene Modified Cells and Immune Recovery

Median VCN in Granulocytes



Median Lymphocyte Counts



Data presented at ASH 2019

Cryo, cryopreserved; IQ, interquartile; VCN, vector copy number

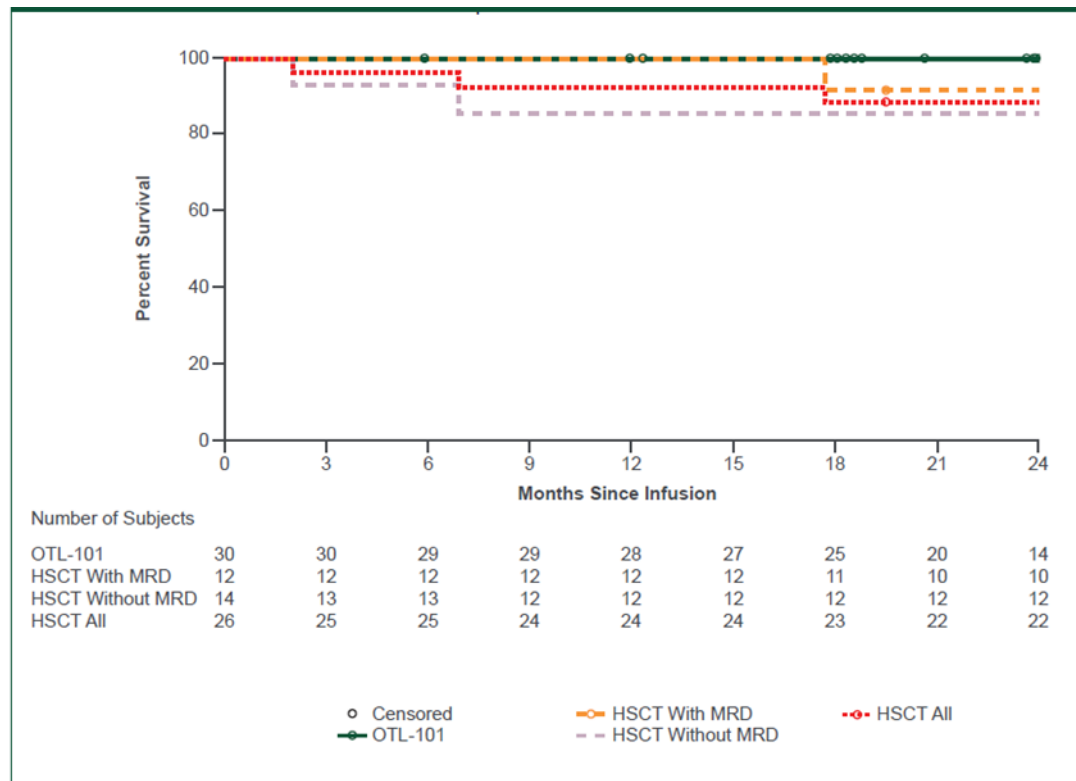
● Fresh

■ Cryo

▲ All OTL-101

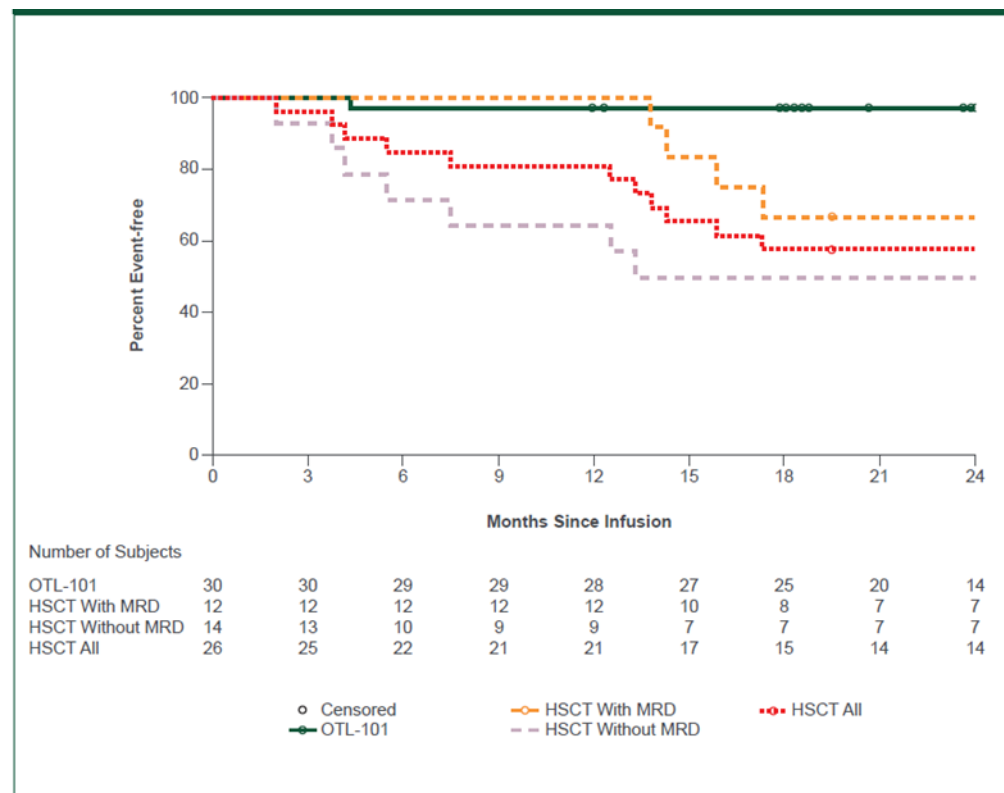
OTL-101 Investigational Therapy for ADA-SCID: Registrational Trials Survival Data

Kaplan-Meier Curve for Overall Survival



100% Overall Survival (n=30)

Kaplan-Meier Curve for Event-Free Survival



97% Event Free Survival (n=30)

OTL-101 Investigational Therapy for ADA-SCID: Summary

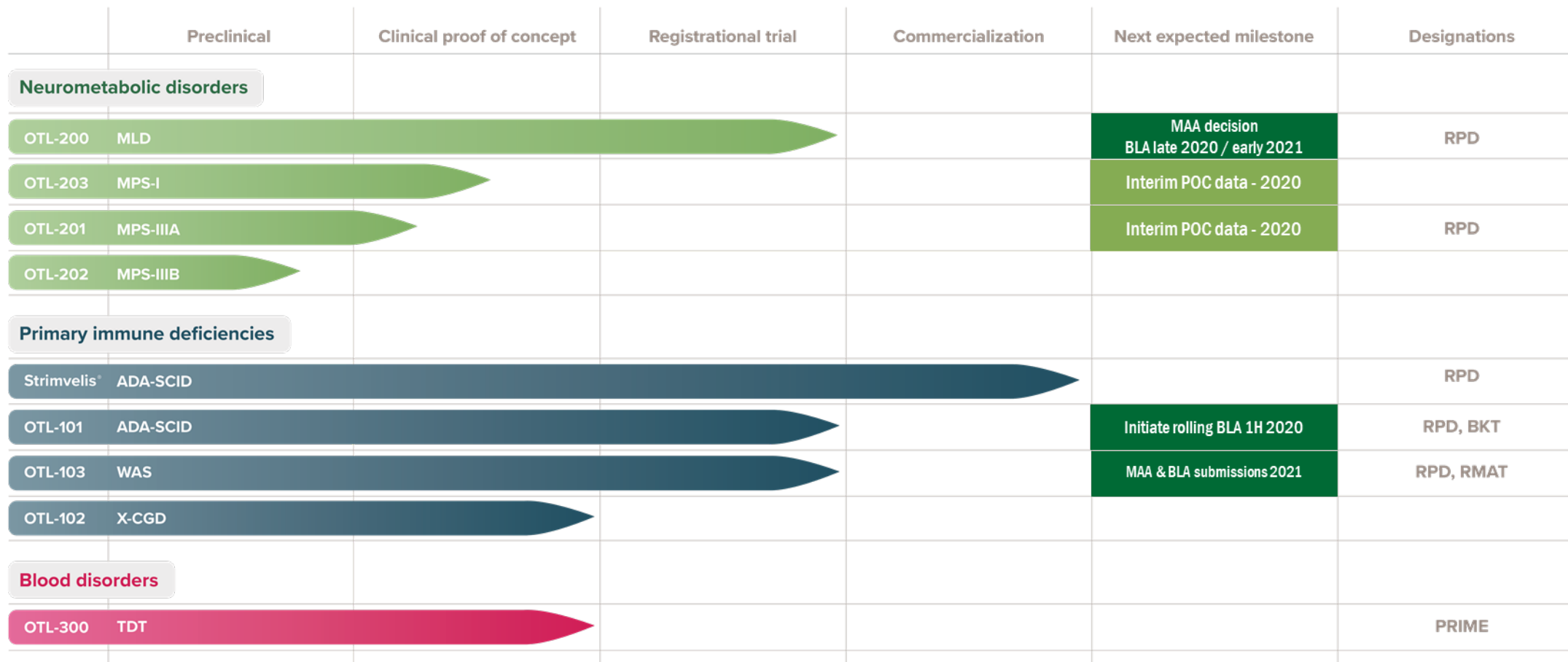
Efficacy Profile

- OTL-101 treatment of Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency (ADA-SCID) results in sustained gene correction and immune function restoration following successful engraftment
- Irrespective of whether fresh or cryopreserved OTL-101 was used, key biological parameters of efficacy, including gene marking, immune reconstitution and ADA enzyme activity were consistent across subjects
- Subjects treated with OTL-101 showed recovery of cellular and humoral immunity, enabling discontinuation of immunoglobulin replacement therapy in 90% of the subjects who had reached 24 months' follow up
- Compared with patients treated with HSCT with or without a matched related donor (MRD), treatment with OTL-101 results in clinically significantly higher rates of overall survival (OS) and clinically and statistically significantly higher rates of event free survival (EvFS)

Safety Profile

- There were no deaths in the OTL-101 group
- In subjects treated with OTL-101 there were no events of autoimmunity, emergence of replication competent lentivirus, or leukoproliferative complications
- Twelve subjects who received OTL-101 experienced one or more serious adverse events (SAEs), most frequently infections and gastrointestinal events.
 - Only one of these events was considered treatment-related (bacteremia due to fresh product contamination, which resolved on Day 3 without sequelae)
 - Two cases of immune reconstitution inflammatory syndrome, assessed as unrelated to OTL-101 by the investigator, which resolved with corticosteroids
- Given the autologous nature of OTL-101, there was no graft-versus host disease (GvHD) in the OTL-101 group. In the HSCT (overall) comparator group, 5 patients experienced acute GvHD and 3 patients experienced chronic GvHD. One HSCT-treated patient with an MRD died due to acute GvHD of the lung

Orchard Therapeutics Gene Therapy Pipeline



Several additional research and preclinical programs under development

RPD Program with Rare Pediatric Disease Designation; eligible for a Priority Review Voucher | BKT Breakthrough Therapy Designation
PRIME Priority Medicine (PRIME) Designation | RMAT Regenerative Medicine Advanced Therapy