INTRODUCTION TO CASGEVY®, THE FIRST CRISPR-Cas9 BASED COMMERCIALLY APPROVED THERAPY FOR SCD AND TDT

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CASSS;

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CONTENT

- Introduction to Vertex
- Overview of CASGEVY process:
  - Challenges of autologous therapies
  - Manufacturing setup and process description
  - Comparability and technical transfer
  - Regulatory challenges

Vertex is a global biotech company investing in scientific innovation to create transformative medicines for people with serious diseases

Quick Facts

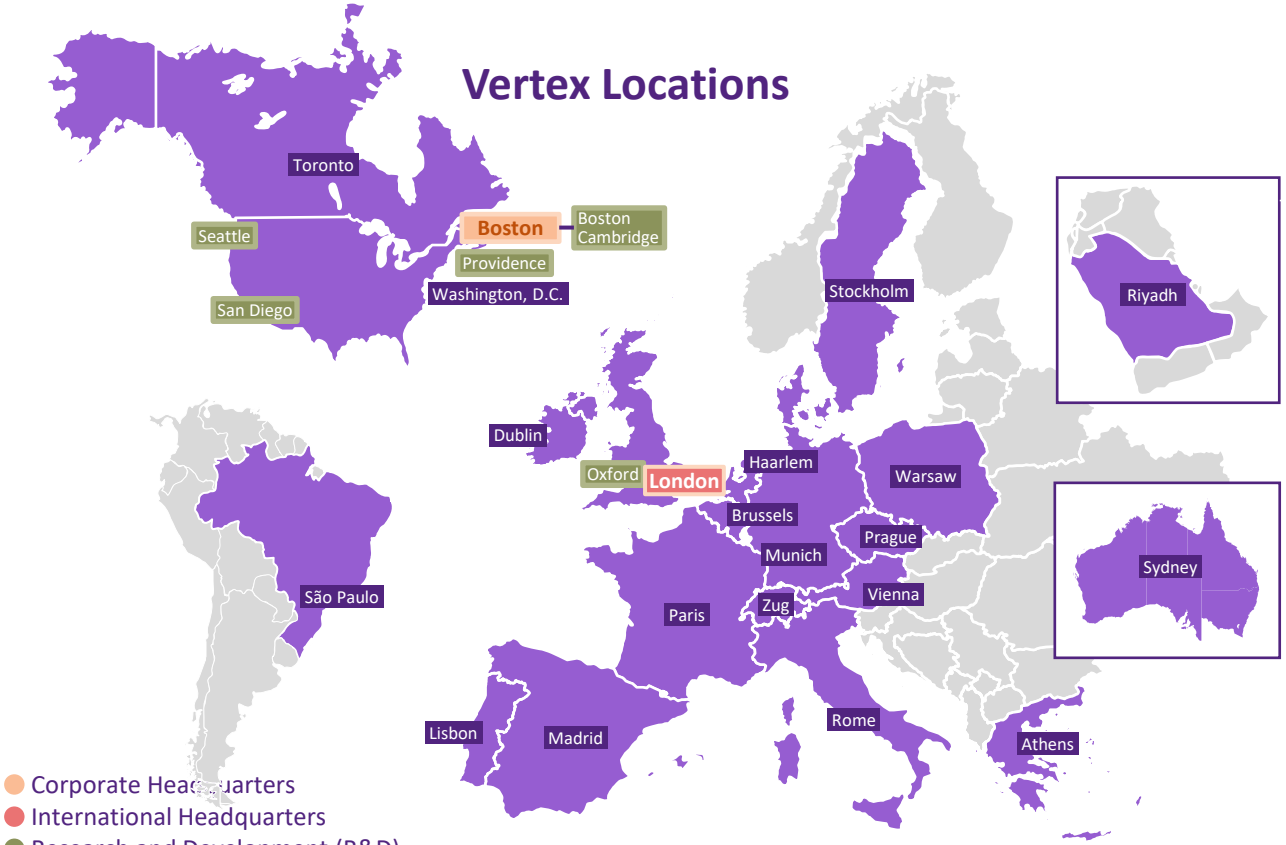
Founded:
1989

Headquarters:
Boston

~6,200
Employees worldwide
(~5,000 in the U.S.)

$>100B
Market cap
(as of April 2025)

$11B
2024 revenue



Our Strategy in Action

Our work is defined by a common strategy that drives a culture of innovation and scientific discovery in multiple serious diseases.

Pioneers in R&D

We discovered, developed and produced the first medicines to target the underlying cause of cystic fibrosis.

We developed and brought to people with sickle cell disease and transfusion-dependent beta thalassemia the first-ever gene-edited therapy.

We developed and brought to patients the first in a new class of medicines for acute pain in more than 20 years.

A Disease-First Approach to Development

When we decide to work on a disease, we investigate it from multiple angles.

We're agnostic to therapeutic area and modality.

Introduction TO CASGEVY

- Vertex received approval for manufacturing CASGEVY across the globe for the first cell gene therapy utilizing CRISPR/Cas9 technology:
  - It increases production of fetal hemoglobin, HbF, to improve production and function of red blood cells
- CASGEVY is a one-time therapy to treat people aged 12 years and older with
  - Sickle Cell Disease (SCD)
  - Beta-Thalassemia (TDT, transfusion dependent thalassemia)

casgevy®
(exagamglogene autotemcel)
suspension for IV infusion

CASGEVY MOA: Beta thalassemia & Sickle cell disease are Caused by Mutations in the Beta-Globin Gene

CRISPR-based Gene editing precisely targets and corrects the defective BCL11A locus

Sickle Cell Disease [1,2]

MUTATION IN THE BETA-GLOBIN GENE

Leads to hemoglobin polymerization

Polymerized hemoglobin deforms red blood cells into their characteristic sickled shape

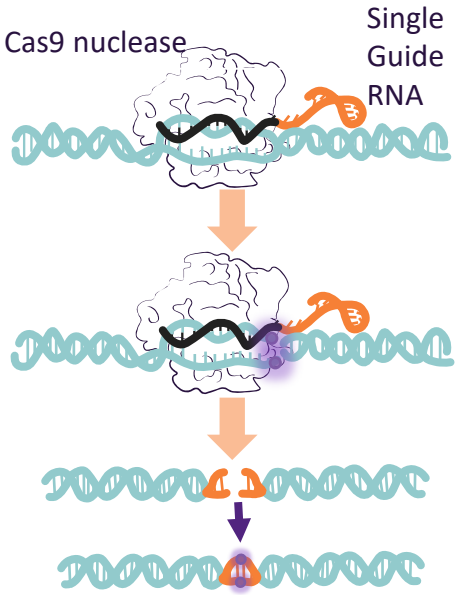
Beta Thalassemia [1,2]

MUTATION IN THE BETA-GLOBIN GENE

Leads to reduced or **no** beta-globin

Loss of beta-globin prevents red blood cell development, reducing number and function of red blood cells

Cas9 and the single guide RNA complex edit the target DNA at Target Locus[3,4]



1. Galanello R, Origo R. *Orphanet J Rare Dis*. 2010;5:11. 2. Kato GJ, et al. *Nat Rev Dis Primers*. 2018;4:18010.

3. CRISPR, clustered regularly interspaced short palindromic repeats; DNA, deoxyribonucleic acid; RNA, ribonucleic acid. Adli M. *Nat Commun*. 2018;9:1911. 4. Barman NC, et al. *Neurol Ther*. 2020;9:419-434.

Challenges OF Autologous Therapies

- CASGEVY is an autologous treatment:
  - Autologous cell therapies are derived from the patient's stem cells.
  - Cells are processed and modified outside the body using gene editing or other techniques to correct or enhance their function and address underlying medical conditions.
  - Goal is to maximize return of cells back to patient

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The technologies & Quality/ Regulatory Considerations for CGT Manufacturing are in an Early Stage of Maturity

Autologous ATMP

- Scale-out/ small batches
- Variable starting material
- Manual/ Bespoke
- Open systems/Small Cleanrooms

- COI/COC and supply chain logistics
- Complex testing requirements (potency/sterility)
- Aseptic and particulate controls
- Complex materials (critical components)
- Vein-to-vein turnaround time
- Sheer number of batches!

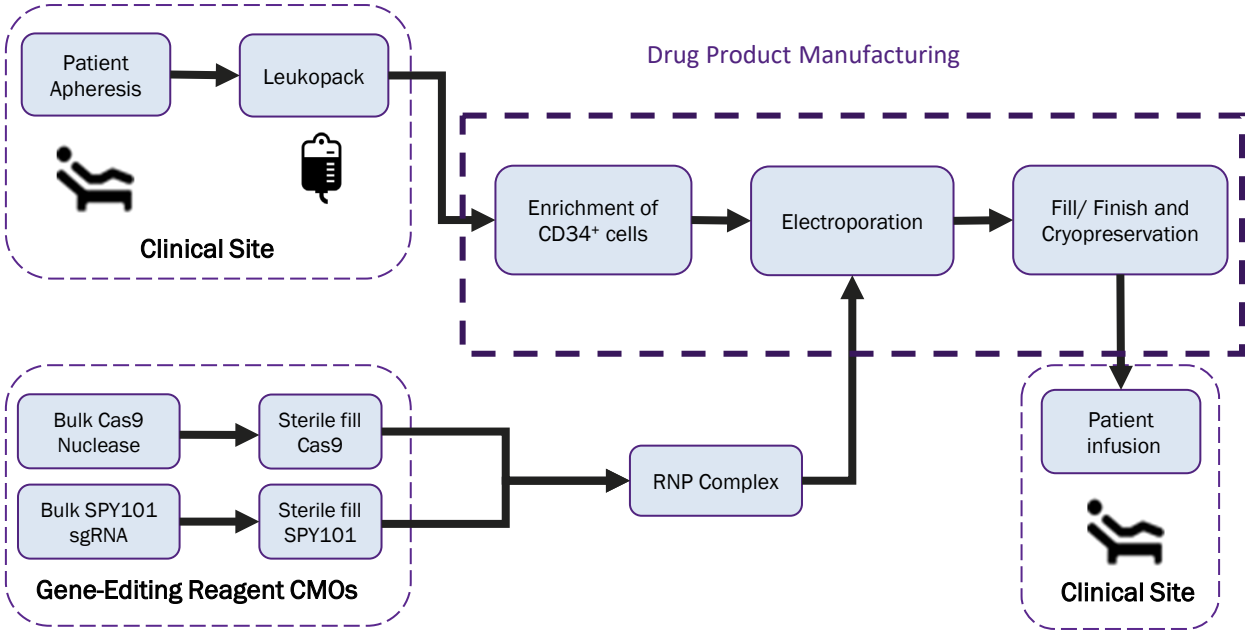
VERSUS

Traditional Biologics

- Scale-up/ large batches
- Cell banks
- Automated/ Platforms
- Closed systems/ ballrooms

* Content from Ken Green: Building the Capabilities for Success in Cell Therapy Commercialization; Wednesday Keynote Session

CASGEVY Process



Exagamglogene autotemcel (exa-cel) is an Advanced Therapy Medicinal Product (ATMP) consisting of autologous CD34+ human hematopoietic stem and progenitor cells (hHSPCs) modified by CRISPR-Cas9-mediated gene editing. The goal of exa-cel is to induce the expression of γ-globin leading to an increase in hemoglobin F (HbF; fetal hemoglobin (Hb)) levels in adult erythroid cells to treat sickle cell disease and transfusion-dependent β-thalassemia patients.

Comparability considerations

Risk Assessment

Phase-appropriate

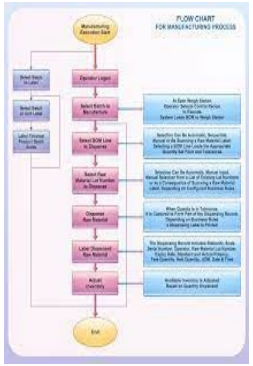
Identify product quality and safety attributes most likely to be affected by the change

Like-for-like supports lower risk of facility change

Analytical Comparability

Leverage Tech Transfer and/or Engineering runs, together with Analytical Tech Transfer outcomes

Comparison against Reference Site (release and stability)



Process Comparability

Assess sources of variability - donor, process, materials, analytical, facility

Limit and justify differences

Facility - suite size, layout, EM controls, operating model (operators, shifts), equipment type and qualification, QMS

Process fit - buffers/media solutions preparation/storage, hold times, etc

Analytical - equipment, methods, QC capabilities, sample plan and storage conditions, contract test labs

Process materials - MoC, vendor, sterility certification, etc

Objective:
Prove product from new site is comparable to reference site

Process Comparability

Sources of variability:

Donor, process, materials, analytical, facility

Historical ranges reflect actual experience, but limited and confounded by donor-to-donor variability

Split runs minimize donor and analytical variability

Challenges with logistics, coordination of donor materials

Cross-testing at both sites

Pre-established acceptance criteria:

In-process, release and characterization test data, residuals, process-related impurities (incl forced degradation), stability (long-term and accelerated; n=3)

CQA's (e.g. viability, potency, purity) subject to greater scrutiny

Initial (Reference) Site

- Data Sources - Process establishment runs, Tech Transfer / Engineering runs, Clinical runs

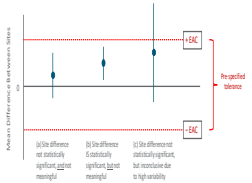
New Site

- Data Sources - Process establishment runs, Tech transfer / Engineering runs (min n=3)
- Analytical comparability: new site data set vs total data set from reference site

Process Comparability

Comparison against reference site

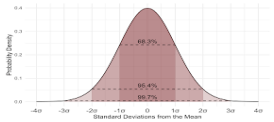
- Use of reference standards, assay controls (where possible and appropriate)
- Pre-defined acceptance criteria (protocol)
  - Narrower tolerances make it easier to assess comparability; higher risk of not meeting
  - Wide tolerances: difficult to justify release specifications are sufficient to show consistency and comparability
  - Characterization: justify against historical ranges and using SME judgement



Statistical tools for acceptance criteria: challenges with limited data sets

EACs* are favored by FDA: may be wide due to low 'n' and high %CV with biological assays

If EAC's do not provide a meaningful assessment of product comparability, propose alternate measure of comparability based on data with justification



- T-tests, TOST, Confidence Intervals
- Low-level impurities may have high variability but extremely low levels; EAC's may not be meaningful. Consider proposing upper limit based on historical experience
- Agency may be open to different statistical approaches for different data sets within the same study

Differences in regulatory perspectives/experience – EMA vs FDA

Zhong, Yi and CMC Analytical Biosimilar Team (Meiyu Shen, Cassie Xiaoyu Dong). *Development of Statistical Approaches for Analytical Biosimilarity Evaluation* [Powerpoint]. DIA/FDA Statistics Forum 2015

Statistical Analyses of Process and Product Performance

	Comparability section (site-dependent)
Considered approaches	EACs, p-value, ranges with CIs, t-test
Proposed approaches	Graphs, and tables with ranges
Comparison for groups	Available datasets
Attributes	Quantifiable release attributes In addition, monitor process performance and characterization attributes

Casgevy Regulatory Journey and LifeCycle Management Strategy

Key Learnings and Focus Areas

- Cas9 and gRNA are considered drug substances
- Major focus on contamination control strategy and particulate controls
- MOA / Phenotypic Potency Assay required
- Process Validation: Patient and Healthy Donors
- COI/ COC and segregation controls
- Data Integrity/ Part 11 compliance

Lifecycle management

1. Add Capacity through highly flexible network of global suppliers and Process Intensification
2. Maximize and Improve Yields: starting material and cell transfection technology optimization
3. Optimize batch turnaround times through digital capabilities
4. Migrate to high level of automation

Critical Success Factors

Highly collaborative and transparent interactions with Regulators

Strong partnerships with critical suppliers

An amazing cross-functional team!

Advancing Multiple Programs in Sickle Cell Disease and Beta Thalassemia

"It's not just the hospitalizations or the crises, but just the daily aspects of living with sickle cell disease that can be extremely challenging if you don't balance it very well."

– 39-year-old mother, wife and advocate living with sickle cell disease

Next steps:

- Approved gene-edited therapy
- Conditioning regimens (investigational)
- Small molecules (investigational)
- *In vivo* gene editing (investigational)