Where are we with gene therapy?

Session 9: Gene Based Therapies

Professor Alan Boyd PFPM

7th February 2018

Faculty of Pharmaceutical Medicine, Royal Colleges of Physicians, UK

Topics to be covered

- Gene Therapy
  - Development of Gene Therapies
    - Delivery using vectors
    - How gene therapy works
    - Use in Clinical Indications
    - Development Process
      - Barriers to Successful Development
- Examples of Specific Gene Based Therapeutics
- Gene Therapies – Regulatory Approvals to Date

Development of Gene Therapies

Gene Therapy - Definition

Gene Therapy is the use of DNA/RNA as a pharmaceutical agent to treat disease.

Gene therapy can involve the use of DNA/RNA that encodes a functional, therapeutic gene to replace a mutated gene

OR

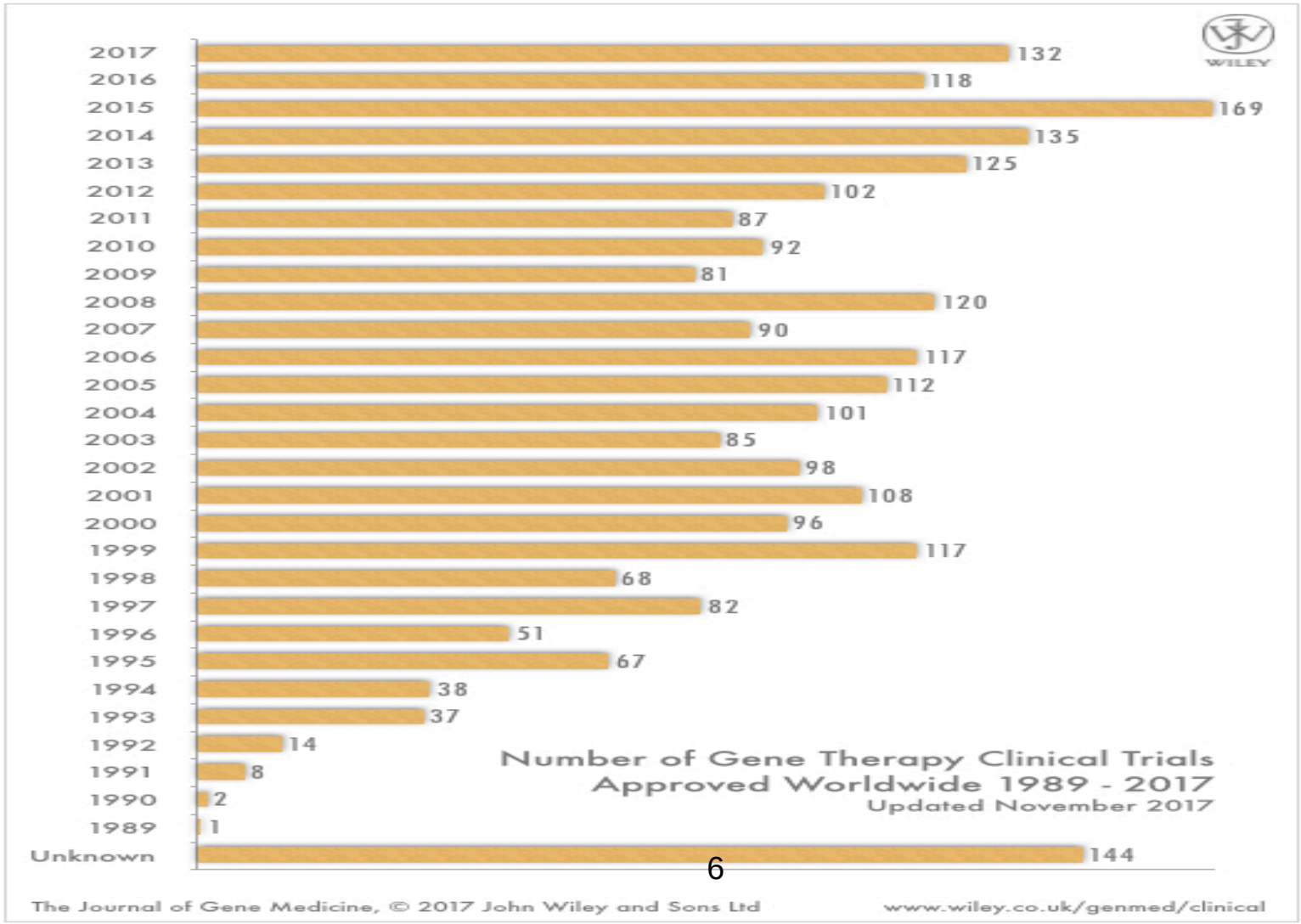
Gene therapy can involve the use of DNA/RNA that encodes a therapeutic protein drug (rather than a natural human gene) to provide treatment.

Origins of GENE THERAPY

- Background
  - 1972 Friedmann and Roblin authored a paper in Science titled *'Gene therapy for human genetic disease?'*
    - Proposed "that exogenous 'good'" DNA could be used to replace the defective DNA in those who suffer from genetic defects.
  - The first gene therapy clinical study was in the United States and took place on September 14, 1990, at the National Institute of Health, Washington DC.
    - It was performed on a four year old girl named Ashanti DeSilva. as a treatment for a genetic defect that caused her to have an immune system deficiency (SCID). The treatment effects were only temporary, but successful.
  - Since then, over 2,500 clinical trials have been conducted using a number of techniques for gene therapy.

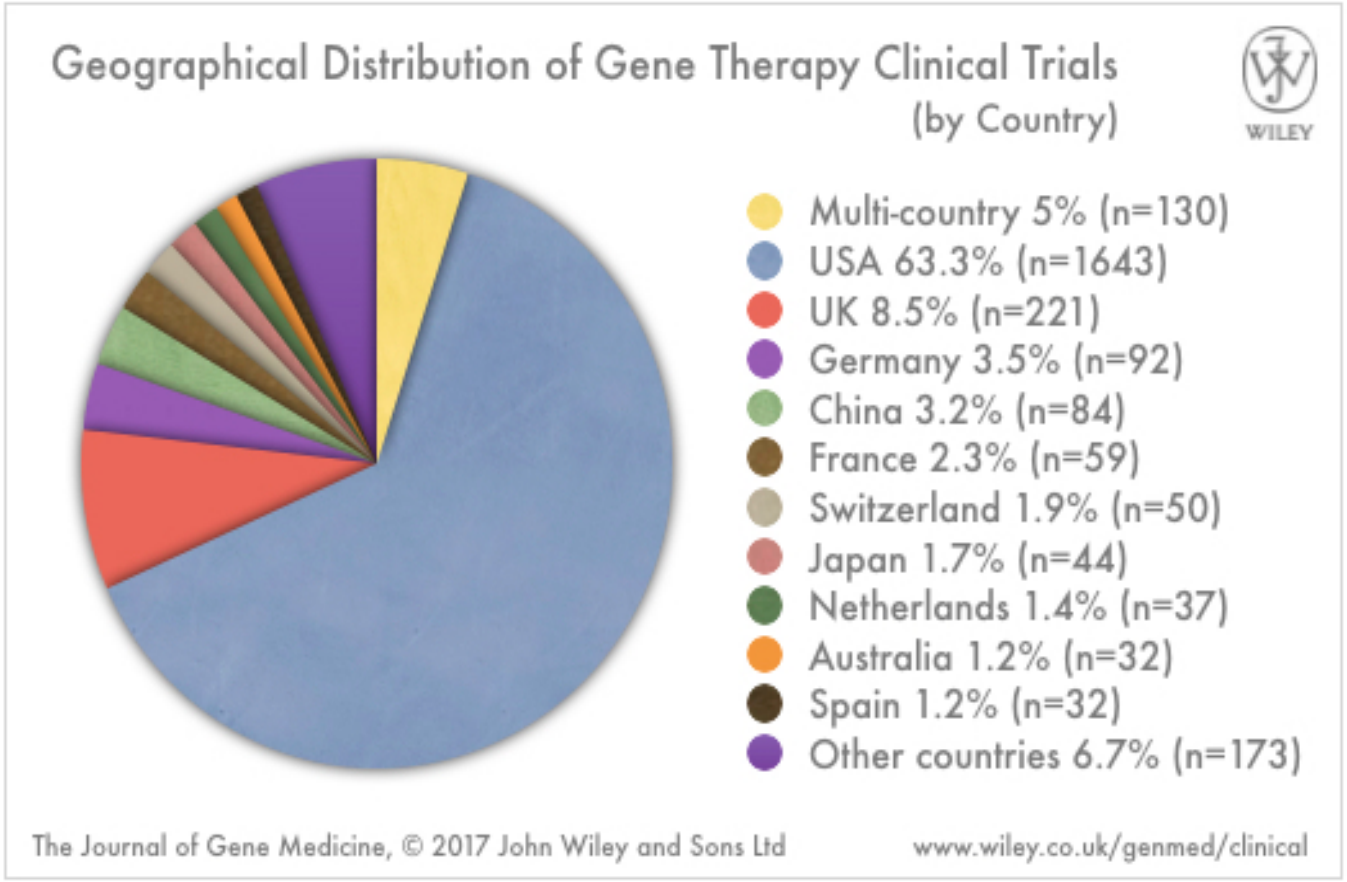
GENE THERAPY – Clinical Trials Worldwide

Number of Clinical Studies Approved – to November 2017



GENE THERAPY – Clinical Trials Worldwide

Geographical Distribution

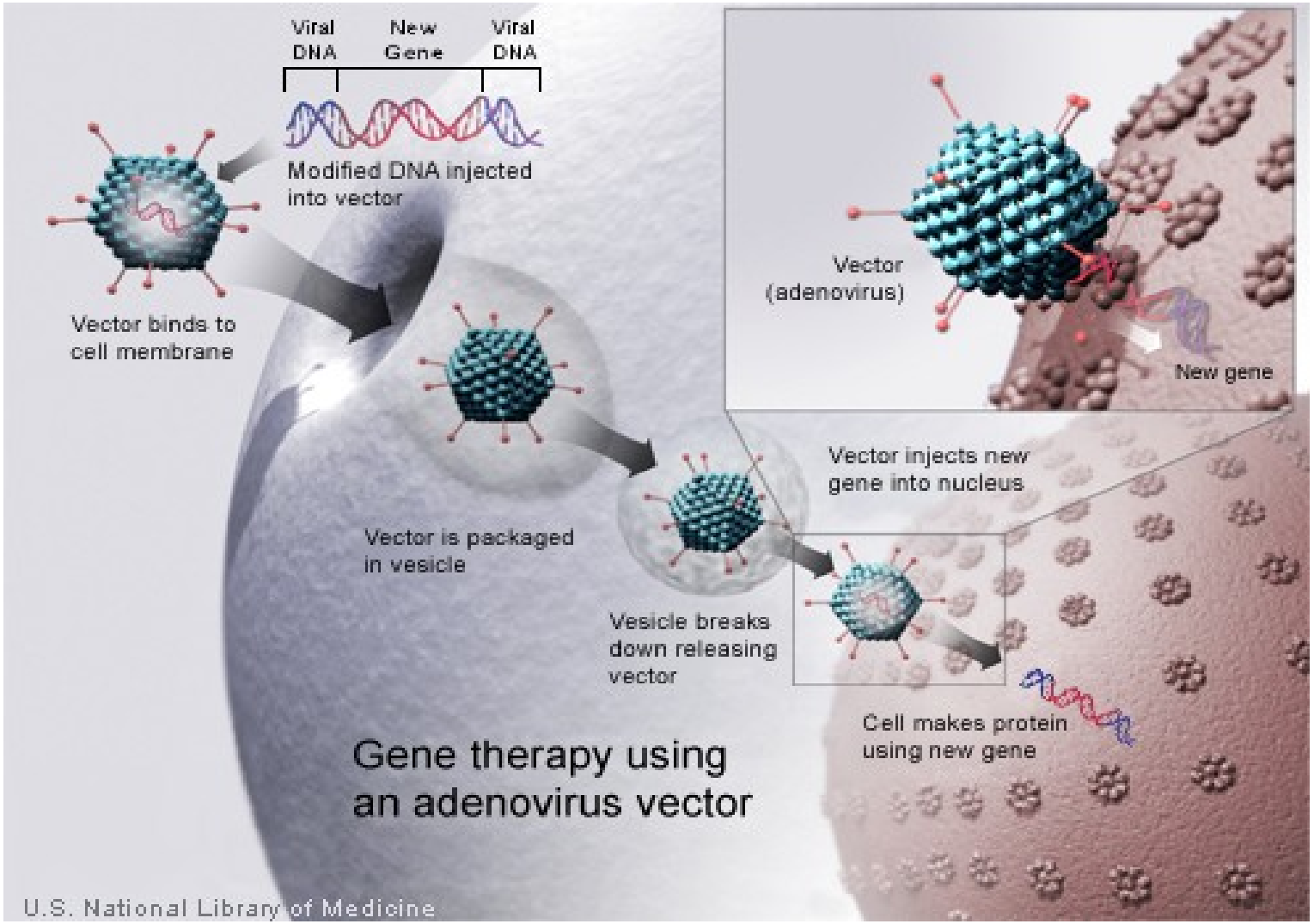


Total = 2597 Clinical Trials

How does Gene Therapy work?

- A ‘carrier vector’ is typically used to deliver the therapeutic gene to the patient's target cells.
- Majority of vectors are viruses that has been genetically altered to carry normal human DNA.
- Viruses have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner.
- Vectors are utilised to take advantage of this capability and the virus genome is manipulated to remove disease-causing genes and insert therapeutic genes.
- Target cells in the patient are infected with the viral vector.
- The vector then unloads its genetic material containing the therapeutic human gene into the target cell.
- The generation of a functional protein product from the therapeutic gene restores the target cell to a normal state.

How does Gene Therapy work?



Types of Viral Vectors - Most Frequently Used

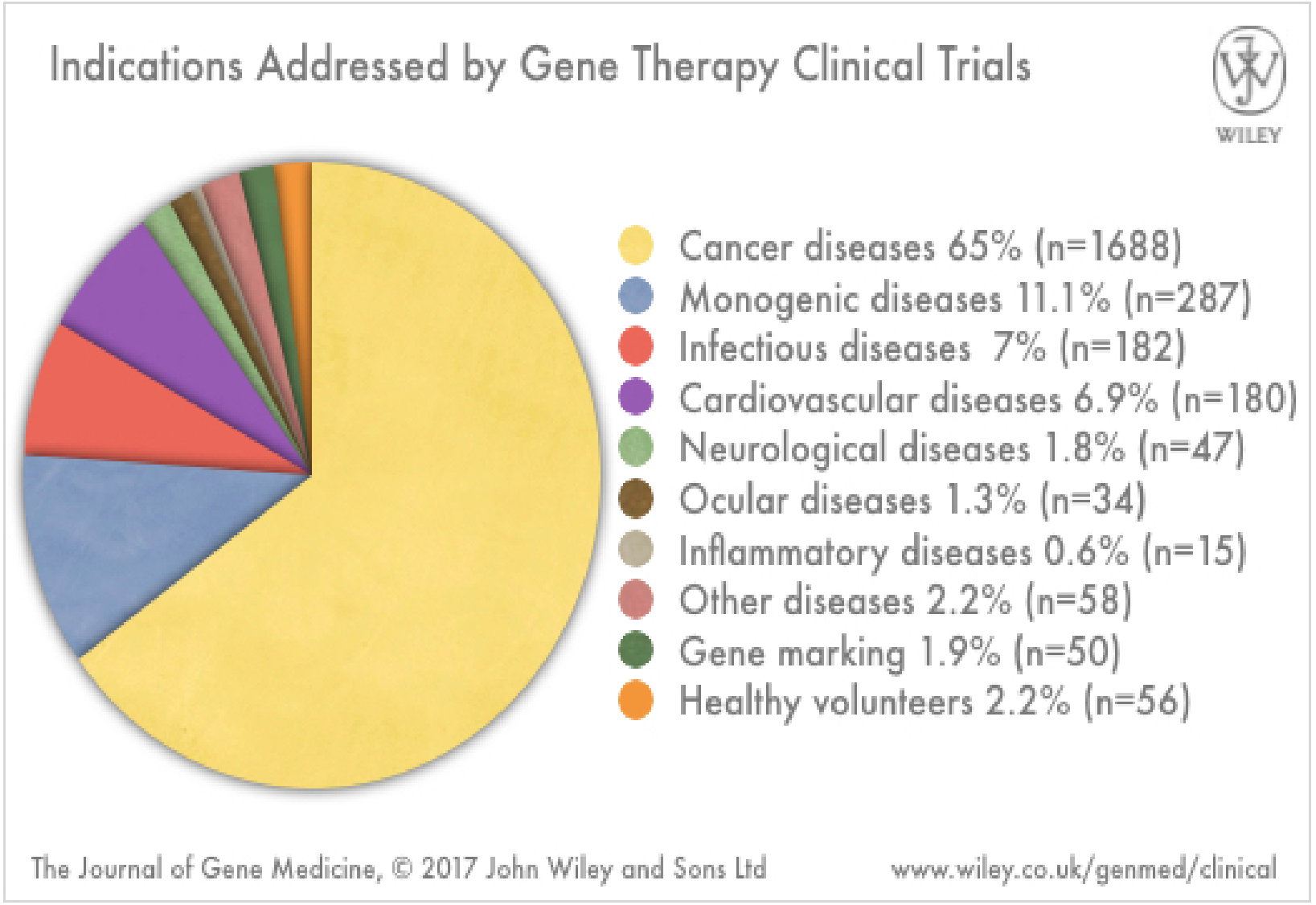
- **Adenoviruses** - A class of viruses with double-stranded DNA genomes that cause respiratory, intestinal, and eye infections in humans. The virus that causes the common cold is an adenovirus. Their DNA does not integrate into the host cell genome

- **Adeno-associated viruses** - A class of small, single-stranded DNA viruses that are not pathogenic to humans. The DNA does not integrate into the genome of the host cell.

- **Retroviruses** - A class of viruses that can create double-stranded DNA copies of their RNA genomes. These copies of its genome can be integrated into the chromosomes of host cells. They can only infect dividing cells. Human immunodeficiency virus (HIV) is a retrovirus.

- **Lentiviruses** – A sub-species of Retroviruses that can deliver a significant amount of viral RNA into the DNA of the host cell and have the unique ability among retroviruses of being able to infect non-dividing cells, so they are one of the most efficient methods of a gene delivery vector

GENE THERAPY – Clinical Indications

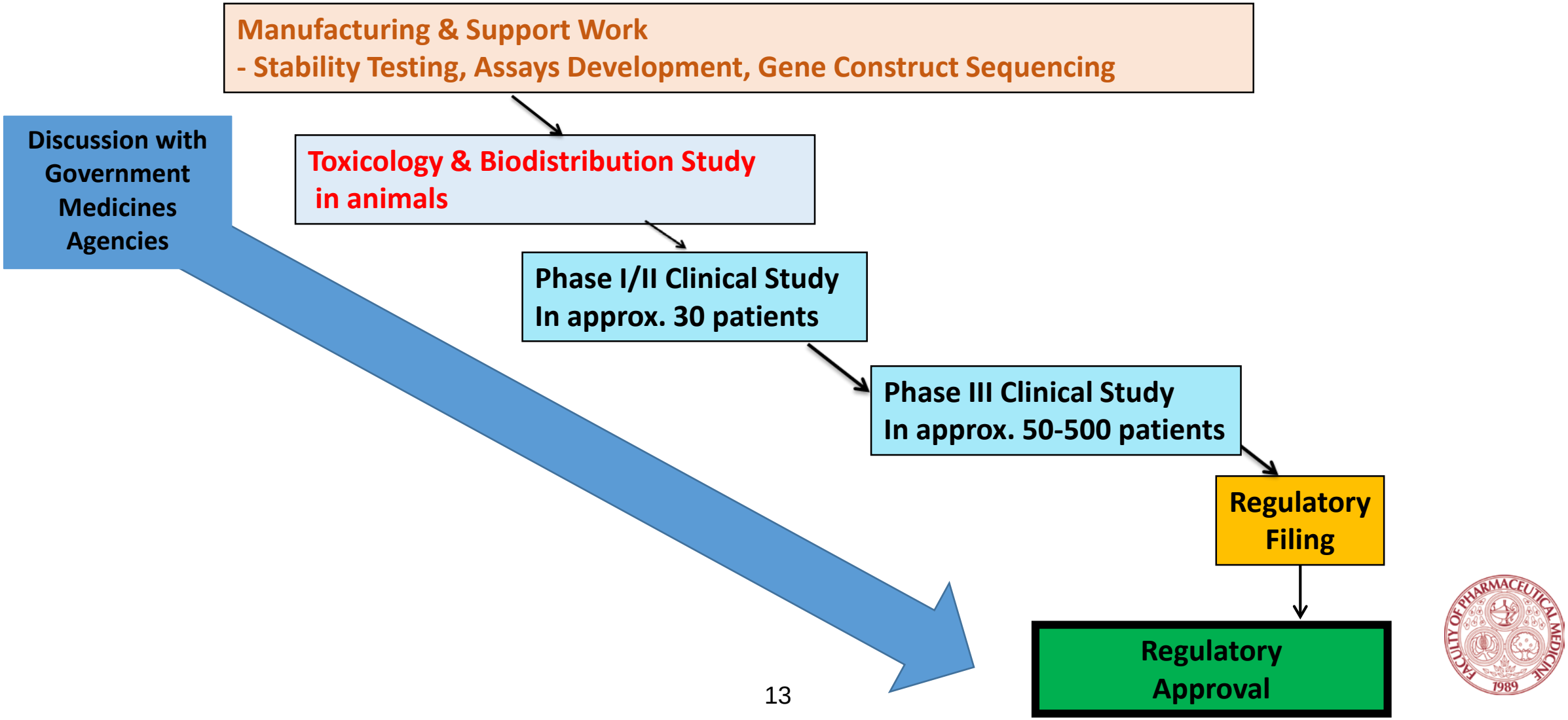


GENE THERAPY – Clinical Indications

Clinical Indications & Use of Vectors

- Oncology – Adenoviruses & Retroviruses
- Cardiovascular - Adenoviruses
- CNS and Eye & Muscle Diseases – AAV
- Inherited Genetic Diseases – Lentiviruses & Retroviruses

Gene Therapy – Overall Development Process



Gene Therapies – Barriers to Development

- Route of administration to site of action
- Immune Response

Location,

Location,

Location !!!

Examples of Specific Gene Based Therapeutics

An example of an Ex-Vivo Gene Therapy Administration

ADA-SCID - Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency

- ADA-SCID - a rare disorder occurring in approximately 15 patients per year in Europe.
- Caused by a gene mutation that results in the absence of an essential protein called adenosine deaminase (ADA), which is required for the production of lymphocytes.
- Children born with ADA-SCID do not develop a healthy immune system so cannot fight off everyday infections, which results in severe and life-threatening illness.
- Without prompt treatment, the disorder often proves fatal within the child's first year of life.

ADA-SCID - Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency

- The main symptoms of ADA deficiency are pneumonia, chronic diarrhoea, and widespread skin rashes.
- Affected children also grow much more slowly than healthy children and some have developmental delay.
- Most individuals with ADA deficiency are diagnosed with SCID in the first 6 months of life.

ADA-SCID - Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency

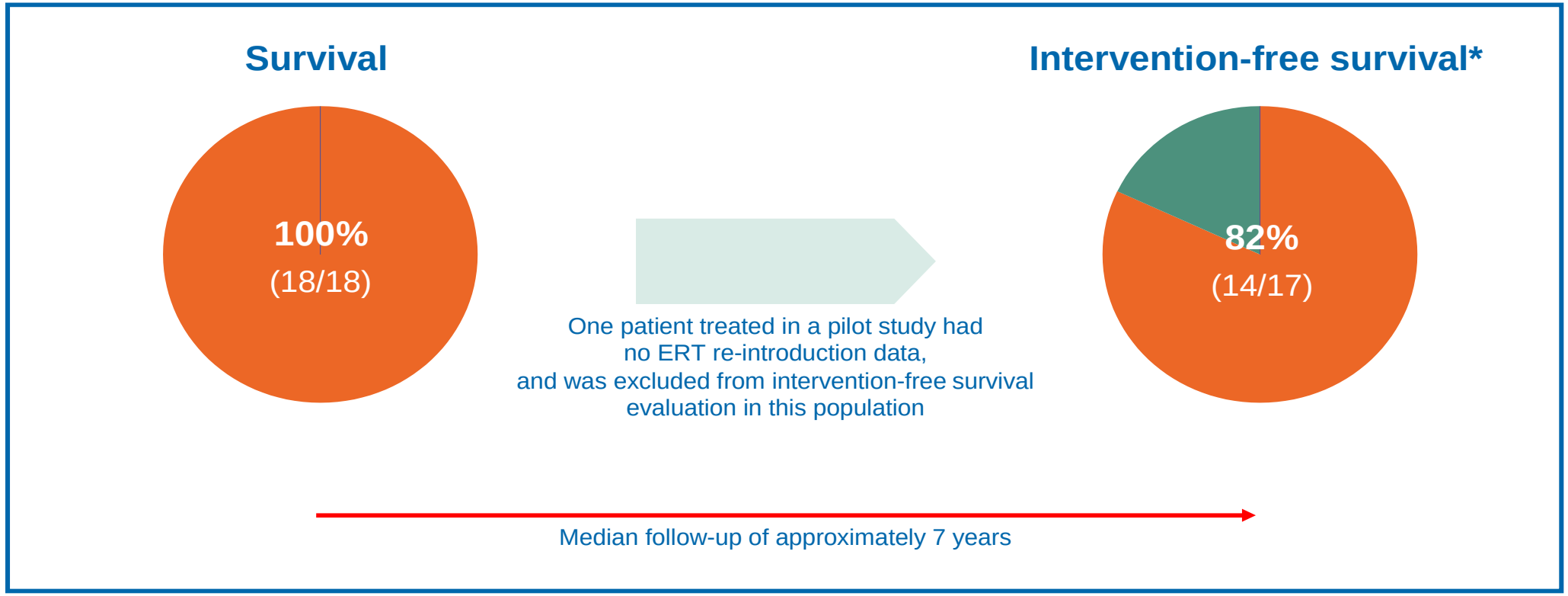
- Treatment of ADA-SCID
  - Matched Related Bone Marrow Transplant (BMT) Or Matched Unrelated BMT
  - Enzyme Replacement Therapy – Weekly injections with PEG-ADA Enzyme
- In April 2016 the Committee for Medicinal Products for Human Use of the European Medicines Agency endorsed and recommended for approval a stem cell gene therapy called Strimvelis, for children with ADA-SCID for whom no matched related bone marrow donor is available

Clinical Experience with Strimvelis (GSK2696273)

Patients treated with GSK2696273 (n=18 integrated population)	
Median age at gene therapy[1]	1.7 years (range 0.5-6.1)
Gender[1]	11 (61%) male
Ethnicity[1]	• White: 15 (83%) • African American/African: 2 (11%) • Asian: 1 (6%)
Previous treatment[1]	• Unsuccessful HSCT (n=4) from haploidentical donor • PEG-ADA (n=15) o PEG-ADA was withdrawn 10-22 days before GSK2696273 treatment

HSCT, hematopoietic stem cell transplantation; PEG-ADA, polyethylene glycol-conjugated adenosine deaminase.
Strimvelis Summary of Product Characteristics. June 2016; 2. Aiuti A, et al. N Engl J Med 2009; **360**: 447-58.

100% survival in the integrated population[1]



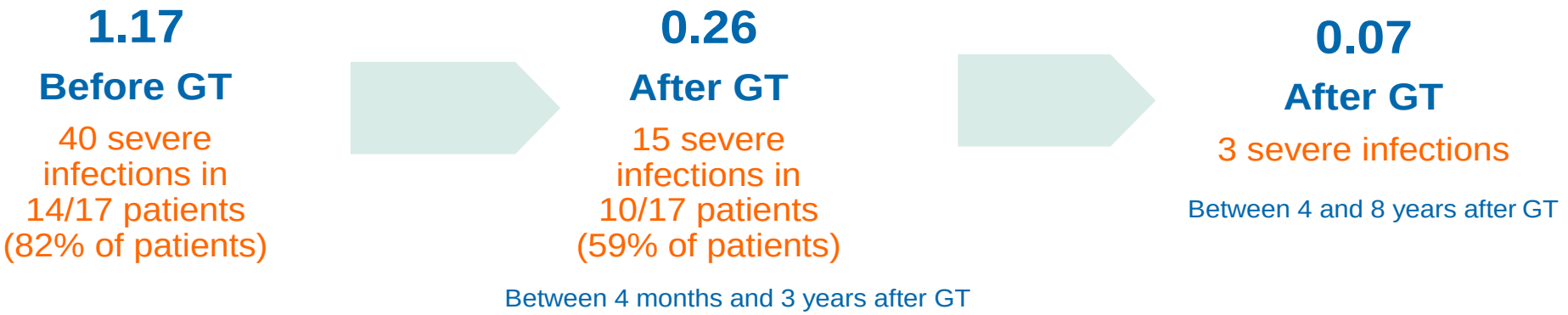
- Three patients received long-term ERT (>3 months' continuous use)
  - Two of these subsequently received successful sibling-matched HSCTs and one remained on long-term ERT

- *Survival without the need for long-term (≥3 months) re-introduction of ERT with PEG-ADA, or HSCT.

1. Strimvelis Summary of Product Characteristics. June 2016.

Long-term decrease in the rate of severe infections* in the integrated population

Rate of severe infections* per person-year before and after gene therapy in the integrated population[1]



- After GT, 80% of severe infections occurred between 4 months and 3 years after GT (12 of 15 severe infections)[1]
- Rate of severe infections decreased rapidly during the first year after treatment, and remained low during long-term follow-up[2]

*Severe infections were those that required hospitalization or prolonged an existing hospitalization.

1. Cicalese MP, et al. Blood 2016; **128**: 45-54.
2. Strimvelis Summary of Product Characteristics.

Summary of GSK2696273 safety

Most adverse reactions were related to busulfan conditioning or immune reconstitution[1]

To date, no cases of leukaemia or myelodysplasia have been reported following treatment with GSK2696273 [1]

Currently, GSK2696273 treatment is only available at Ospedale San Raffaele and is prepared and administered as per protocol[1]

A long-term registry has been established to monitor the long-term safety and efficacy of GSK2696273 for at least 15 years

- OSR, Ospedale San Raffaele.

1. Strimvelis Summary of Product Characteristics. June 2016.

Summary of clinical experience with GSK2696273[1]

- The totality of the efficacy and safety data have been reviewed and granted marketing authorisation by European Commission in May 2016.

- Approved indication:

  GSK2696273 is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available

1. Strimvelis Summary of Product Characteristics

Investigational Gene Therapy: Voretigene Neparvovec for Biallelic *RPE65* Mutation-Associated Retinal Dystrophy

An example of an In-Vivo Gene Therapy Administration

The Eye as a Target for Gene Therapy

- The eye is a small, enclosed compartment, which accommodates small amounts of a gene therapy to act and also keep side effects to a minimum.
- The eye's structure allows for non-invasive assessment via direct observation of the retina with an ophthalmoscope and imaging techniques
- In addition, because the eye is a self-contained, immune-privileged organ, the potential for the gene therapy to disseminate outside of the eye is minimised and the risk of an immune response is reduced.[2]

Inherited Retinal Dystrophy – RPE65 Mutation - Clinical Manifestations

- The RPE65 enzyme is encoded by the *RPE65* gene and is an important part of the 'visual cycle'.
- Mutations in the *RPE65* gene lead to partial or total loss of RPE65 enzyme function and eventually causes the accumulation of toxic byproducts in the retina.
- This leads to a range of visual impairments such as:
  - Night blindness
  - Reduced visual fields
  - Reduced visual acuity

  Which all progress with age
- Currently no approved treatments are available for these conditions

A Novel Solution – Gene Therapy to target the specific RPE65 Gene Mutation - Voretigene Neparvovec gene therapy

Delivering Genes to the Eye using Adeno-associated Virus (AAV)

- Non-pathogenic
- Ability to penetrate photoreceptor cells
- Long-term gene transfer
- Low immunogenicity
- 170 plus human clinical trials with AAV worldwide

Delivered by Subretinal injection

Assessment of Gene Therapy Effectiveness in Inherited Eye Diseases

- Because the eye disease affects functional vision including the ability to navigate, a novel test of functional vision was needed to quantify change during treatmentgene therapy clinical trials.
- The Multi-Luminance Mobility Test (MLMT) has been developed to assess ambulatory vision at light levels encountered during activities of daily living.
- A mobility course was designed to be navigable by children as young as age 3 & subjects were evaluated for accuracy and speed on the MLMT at 7 standardized light levels, ranging from 1 to 400 lux.

Assessment of Gene Therapy Effectiveness in Inherited Eye Diseases - Results

- The main clinical study enrolled 31 subjects aged ≥4 years with confirmed *RPE65* gene mutations and sufficient viable retinal cells– 2 subjects withdrew prior to treatment – Total Patients =29
- Subjects randomized 2:1 to the treatment or control groups
- Subjects in the treatment group received the gene therapy in each eye, with the second eye being injected within 6 to 18 days after the first
- The control group subjects had the option to cross over to receive the gene therapy following 1 year from baseline evaluation.

- Mean ages - 14.7 years for the treatment group vs 15.9 years for the control group
- Age distribution - 43% of the treatment group were under 10 years of age vs 40% of the control group
- Main endpoint of the clinical study was the mean change in the Mobility Test from baseline to 1 year compared between the treatment and control groups.

Assessment of Gene Therapy Effectiveness in Inherited Eye Diseases – Results – Control Group after Cross-Over

Mean mobility test change score (primary endpoint) at year 1 and year 2 (mITT population). P=0.004 at 1 year; difference (95% CI)
Intervention
− Control: 1.6 (0.76, 2.50).
Intervals are ± 1 standard error. BL, injection baseline; CI, confidence interval; D, day; mITT, modified intent-to-treat; Y, year.

Investigational Gene Therapy: Voretigene Neparvovec for Biallelic *RPE65* Mutation-Associated Retinal Dystrophy

Gene Therapy Products – Regulatory Approvals to Date

UniQure's Glybera®(alipogene tiparvovec) - First Gene Therapy Approved by European Commission

First Gene Therapy Approved by European Commission

Amsterdam, The Netherlands – November 2, 2012 – uniQure announced today it has received approval from the European Commission for the gene therapy Glybera® (alipogene tiparvovec), a treatment for patients with lipoprotein lipase deficiency (LPLD, also called familial hyperchylomicronemia) suffering from recurring acute pancreatitis. Patients with LPLD, a very rare, inherited disease, are unable to metabolize the fat particles carried in their blood, which leads to inflammation of the pancreas (pancreatitis), an extremely serious, painful, and potentially lethal condition.

The approval makes Glybera the first gene therapy approved by regulatory authorities in the Western world.

Approved November 2012

T-Vec *(Talimogene laherparepvec, Imlygic®)* from Amgen Approved by FDA & EU

Approved April 2015

Strimvelis®** from GSK Approved in EU

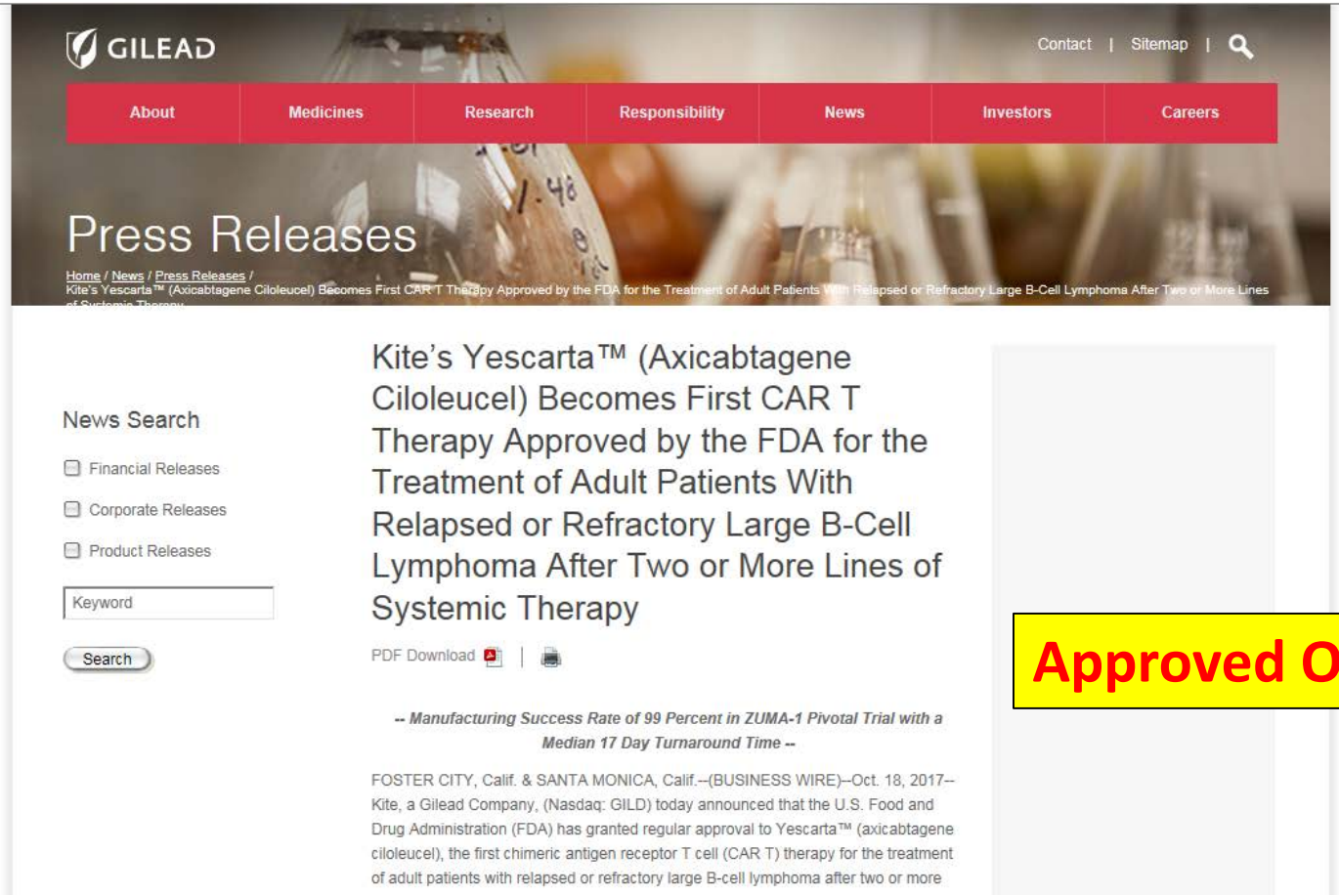
Approved May 2016

***autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence*

Kymriah® (tisagenlecleucel) from Novartis Approved by FDA and EU

Approved August 2017

Yescarta™ (axicabtagene ciloleucel) - from Kite/Gilead Approved by FDA



Approved October 2017

FDA approves Spark's Luxturna® (Voretigene Neparvovec)

CBS NEWS NEWS SHOWS VIDEO CBSN MORE

CBS/AP / *December 20, 2017, 9:55 AM*

FDA approves gene therapy for rare form of blindness

ISTOCKPHOTO

Share / Tweet / Reddit / Flipboard / Email

Last Updated Dec 20, 2017 9:55 AM EST

WASHINGTON — U.S. health officials on Tuesday approved the nation's first gene therapy for an inherited disease, a treatment that improves the sight of patients with a rare form of blindness. It marks another major advance for the emerging field of genetic medicine.

The approval for Spark Therapeutics offers a life-changing intervention for a small group of patients with a vision-destroying genetic mutation and hope for many

Approved December 2017

Future Developments

Where are we with gene therapy?

Acknowledgments:
The information provided by GSK plc and Spark Therapeutics Inc in the preparation of this presentation is appreciated

Faculty of Pharmaceutical Medicine

19 Angel Gate, 326a City Road, London EC1V 2PT, United Kingdom

Company No: 6870644 | Registered Charity No: 1130573

Telephone: +44 (0) 20 3696 9040

Email: fpm@fpm.org.uk

Website: www.fpm.org.uk

Follow us on Twitter @FacultyPharmMed