CBG MEB
MEDICINES EVALUATION BOARD

Trends and challenges in ATMP assessment

ISPE CGT SIG monthly meeting
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GOOD MEDICINES USED BETTER

Disclaimer

The views expressed in this presentation are my personal views, and may not be understood or quoted as being made on behalf of the MEB/EMA or reflecting the position of the MEB/EMA

Contents

- ATMP classification
- Current trends in ATMP
- RWE as external control arm in ATMP trials
- Post-marketing data collection
- EMA vs HTA
- Patient perspective

Definitions

ATMP:

- gene therapy,
- somatic cell therapy,
- tissue-engineered therapies,
- combined advanced therapies

A **GTMP** should have the following characteristics:

*a) it contains an active substance which contains or consists of a **recombinant nucleic acid used** in or administered to human beings with a view to **regulating, repairing, replacing, adding or deleting a genetic sequence;***

*b) its therapeutic, prophylactic or diagnostic **effect relates directly** to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.*

Part IV of Annex I to Directive 2001/83/EC

Definitions

a **CTMP** should have the following characteristics:

*a) contains or consists of cells or tissues that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, **or** of cells or tissues that are **not intended to be used for the same essential function**(s) in the recipient and the donor; and*

*b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through **the pharmacological, immunological or metabolic action** of its cells or tissues.*

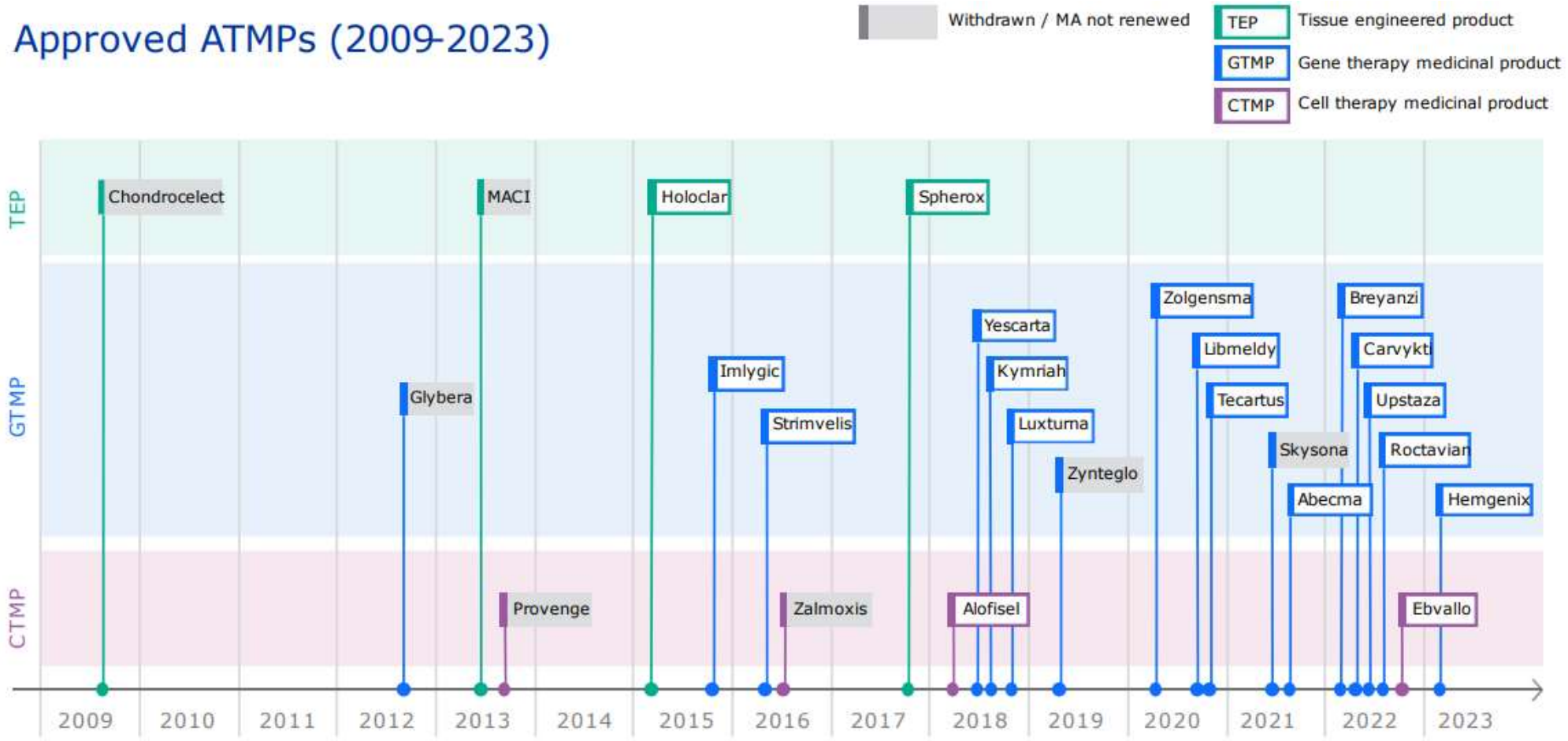
Part IV of Annex I to Directive 2001/83/EC

a **TEP** is a product that:

- *contains or consists of engineered cells or tissues, and*
- *is presented as having properties for, or is used in or administered to human beings with a view to **regenerating, repairing or replacing a human tissue**.*

Article 2(1)(b) of Regulation (EC) No. 1394/2007

Current status (25 authorised products)



Trends

- **Increase in number of marketing authorization applications**
  → 579 Scientific Advices (2009-April 2023)!
- **Increased experience**
- **Learning from post-marketing longer follow-up**
- **Often substantial benefit** (disease modifiers, cure)

Most promising products

- CAR-T cells
- Gene therapy for monogenetic disorders

What makes ATMP different from other products?

- Often developed in academia, SME

Manufacturing

- Complex manufacturing process
- Big impact manufacturing process on the product
- Small batches (up to 1 batch for each patient)
- Variability

Clinical development

- Small patient populations
- Large treatment effect (expected)
- Duration of treatment effect (life-long? irreversible?)

External control arm in ATMP trials

- Conditions
  - Rare diseases
  - Randomisation is not possible
  - Effect size is large
  - High unmet medical need

- Data sources
  - **Medical records**
  - **Registries**
  - Literature (natural disease course)
  - Compassionate Use Program

- Comparison to available therapies is of particular importance to HTA

Real world evidence in regulatory decision making

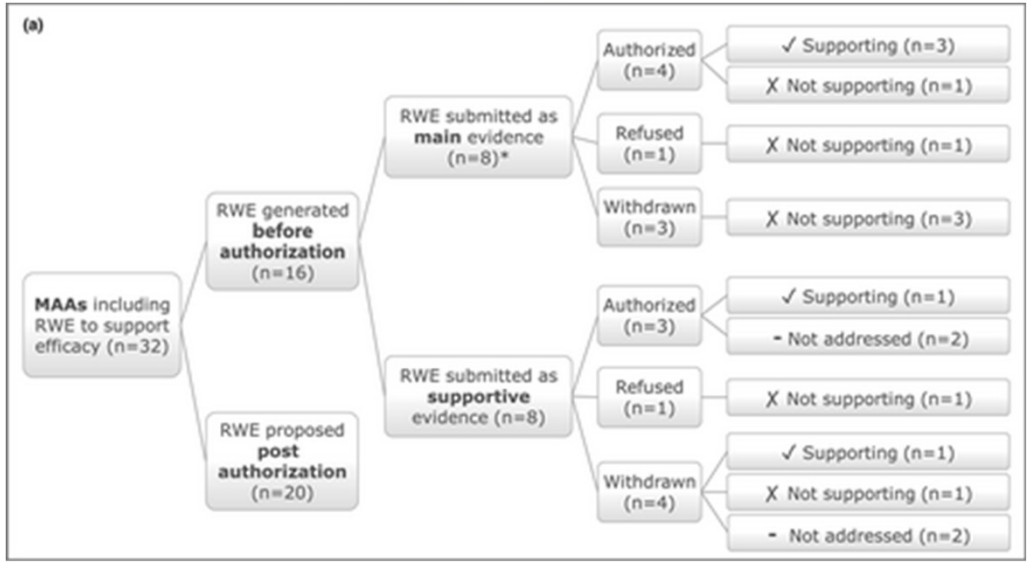
Clinical Pharmacology & Therapeutics

Article | Open Access

Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making

Elisabeth Bakker, Kelly Plueschke, Carla J. Jonker, Xavier Kurz, Viktoriia Starokozhko, Peter G. M. Mol

First published: 17 October 2022 | https://doi.org/10.1002/cpt.2766 | Citations: 4



- Often used, but not widely accepted as main evidence
- Often used in post-marketing settings

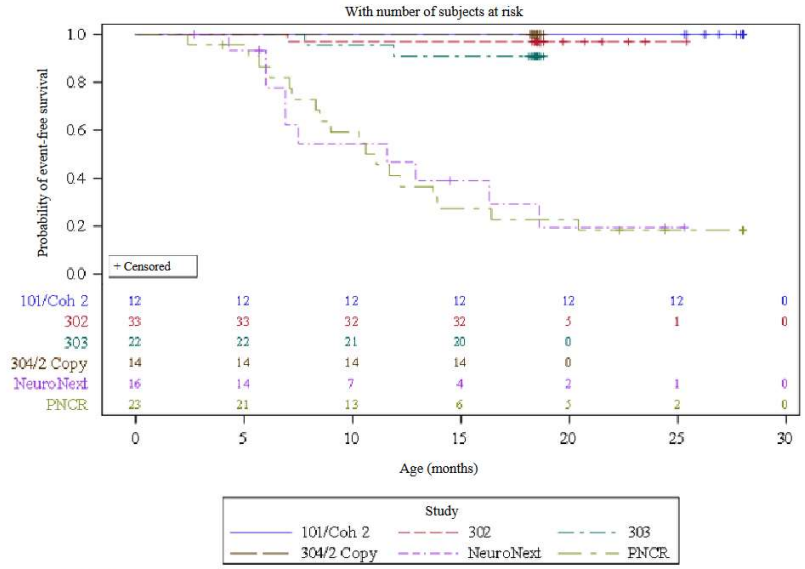
Real world evidence in regulatory decision making

Zolgensma

External comparator arm was accepted as main evidence:

- The potential bias created by a difference in populations is not in favor of the drug
- Historical controls considered adequate for comparison with the study population since this group is relatively homogeneous
- Timepoints for efficacy analysis of supportive single-arm trial matched with major efficacy end points in natural history study
- The use of RWE external arm was agreed in Scientific Advice
- Data on the external control included in SmPC

Figure 1 **Time (months) to death or permanent ventilation pooled from onasemnogene abeparvovec IV studies (CL-101, CL-302, CL-303, CL-304-2 copy cohort)**



PNCR = Pediatric Neuromuscular Clinical Research natural history cohort
NeuroNext = Network for Excellence in Neuroscience Clinical Trials natural history cohort

Real world evidence in regulatory decision making

Challenges & Important points to consider:

- Comparability of trial population and an external control group (heterogeneity of diseases)
- Matching methods
- Missing data
- Selection bias
- Prespecified analysis plan

Post-marketing data collection

Registries for gene therapies is a pré!

Clin Ther. 2018 May;40(5):768-773. doi: 10.1016/j.clinthera.2018.04.005. Epub 2018 Apr 27.

Drug Registries and Approval of Drugs: Promises, Placebo, or a Real Success?

Carla J Jonker [1], Marcel S G Kwa [2], H Marijke van den Berg [3], Arno W Hoes [4], Peter G M Mol [5]

Affiliations + expand

PMID: 29709456 DOI: 10.1016/j.clinthera.2018.04.005

Free article

Challenges of the registries:

- enrollment feasibility

  - poor enrollment (the median enrollment in the 41 registry studies was 31% ([IQR], 6–104) of the required sample size.

"Registries have had only a limited impact on resolving gaps in the knowledge of a drug's benefits and risks at the time of marketing authorization. It is important to be careful with broadening the use of postmarketing studies as a means of resolving uncertainties about benefits and risks after marketing authorization."

Post-marketing data collection

Registries for gene therapies is a pré!

22 October 2021
EMA/426390/2021
Committee for Human Medicinal Products (CHMP)

Guideline on registry-based studies

Challenges of the registries:

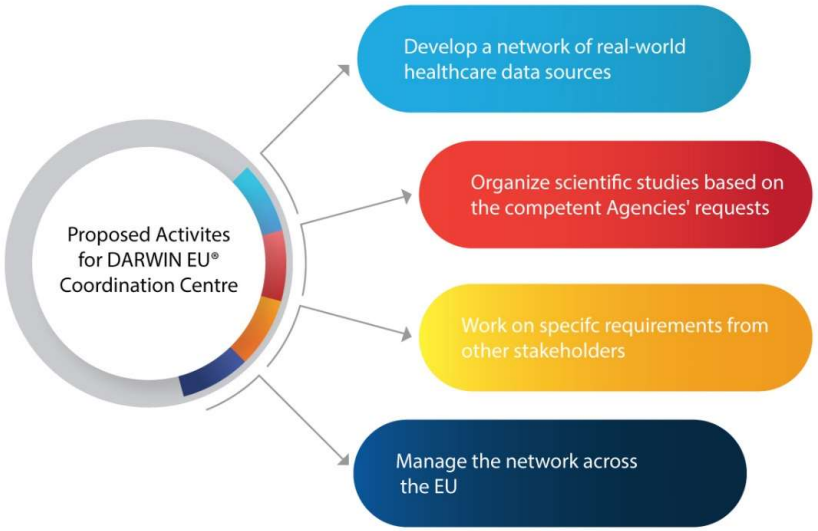
- Possible poor enrolment due to the limited patient access
- Data are spread through different registries (disease, procedure, product registries etc)
  - EMA encourages to work with existing disease registries when collecting data
- Non-observational versus observational study
  - different regulations in different countries complicates data collection

DARWIN-EU

DARWIN EU® is a platform to generate real-world evidence (RWE) to support the decision-making of EMA scientific committees and national competent authorities in EU Member States throughout regulatory processes.

The protocols and results of these studies are publicly available in the EU PAS Register:

- DARWIN EU®'s first disease epidemiology study investigated the prevalence of rare blood cancers in five European countries.
- The second study focused on the use of medicines containing valproate and alternative therapies among girls and women between 12 and 55 years of age, in light of the potential of these types of medicines to cause harm to unborn babies.
- The third study aimed to characterise prescription patterns for 141 antibiotics from the Watch list of the WHO AWaRe classification. The results will serve as additional evidence in the monitoring of antibiotic use as part of the work on antimicrobial resistance and help to guide product information and guideline review.
- The fourth study is on severe asthma and its final results are expected in spring 2023. The study will inform the safety assessment of all products authorised or under development for the treatment of severe asthma in adolescents and adults.



Patient access and HTA assessment

Registration ≠ Reimbursement

MEB/EMA	Zorginstituut Nederland/HTA
Benefit/Risk balance	State of science and practice
Efficacy	Cost-effectiveness
Safety	Budget impact
Quality	Public/societal considerations

ATMP considerations:
- Single-arm, observational studies
- Heterogenous small populations
- (Often) ambiguous natural history data
- Uncertainty about long-term efficacy and safety

Cost-effectivness:
- Life-long effect?
- No additional therapies needed? (*Nusinersen®* / *Zolgensma®*)
- Quality of Life measurements

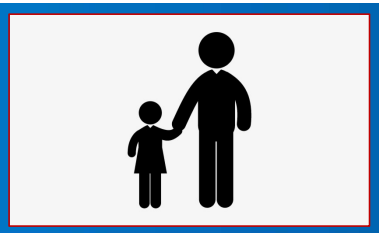
ATMP reimbursement

Follow-up reseach is needed to collect more data on long-term efficacy and safety

High prices: the risks should be shared with the Marketing Authorisation Holder – e.g. pay for performance concept

In the Netherlands so far 3 ATMP products are included in the basic insurance policy (Zolgensma, Yescarta and Kymriah)

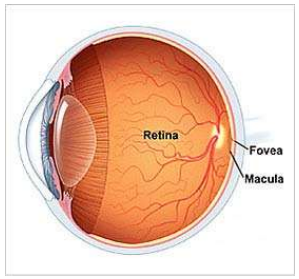
How long is the effect?



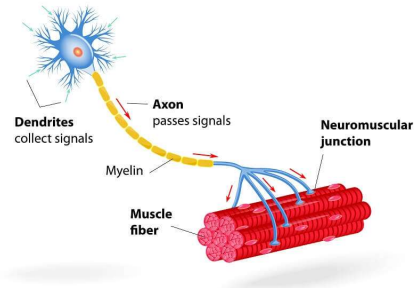
Target organ

Cell turn-over

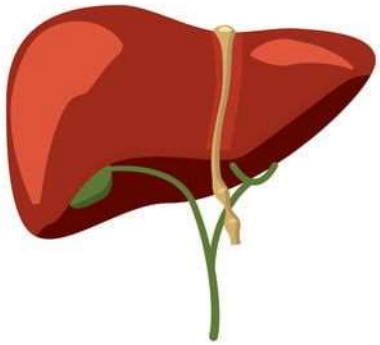
Integrating vs nonintegrating vectors



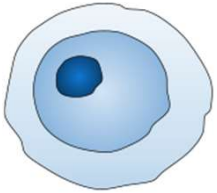
negligible cell turnover of retinal pigment epithelium



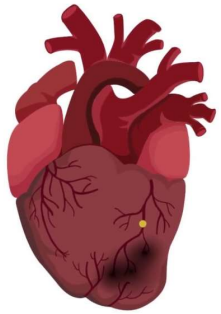
slow renewal



hepatocyte lifespan 200 to 300 days



stem-cells



less than 50% of the cardiomyocytes are replaced during life

Patient's perspective

Example: Haemophilia

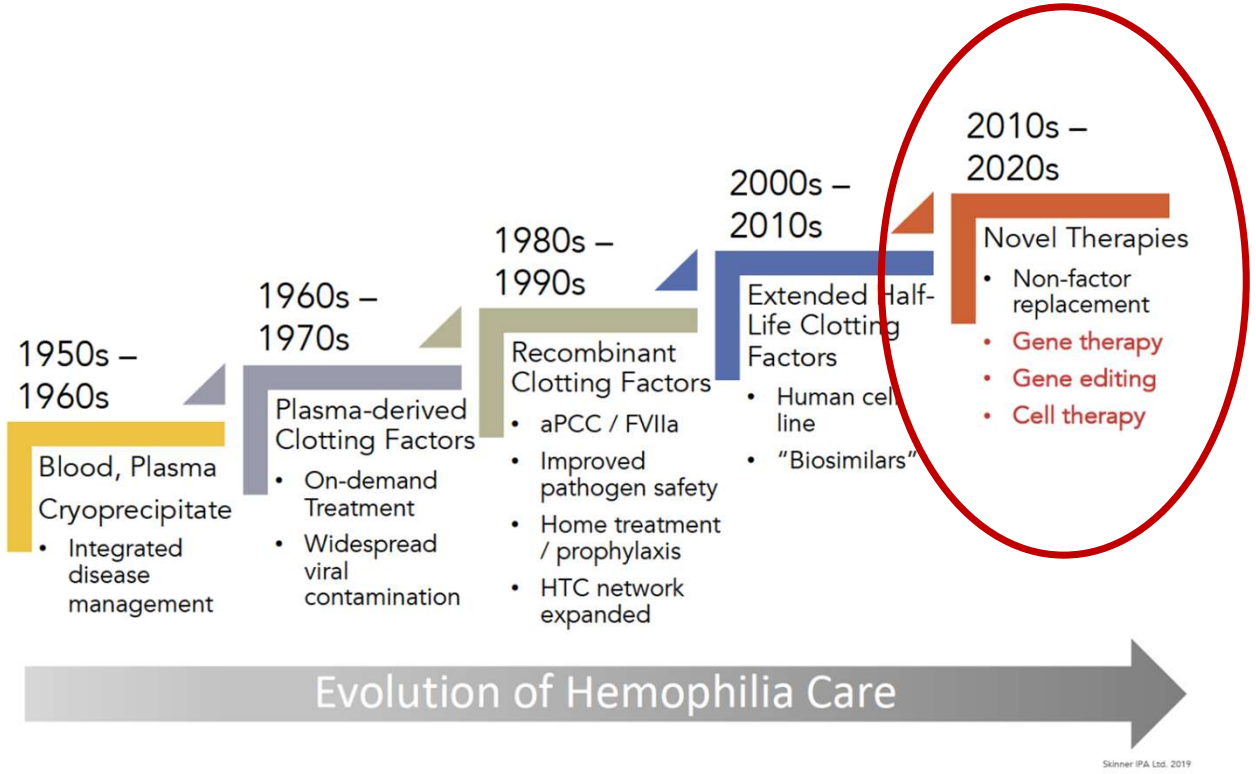
Hemophilia A and B are X-linked disorders that predominantly affect males

lack of factor VIII (FVIII) in the case of hemophilia A and factor IX (FIX) in the case of hemophilia B that are necessary for coagulation cascade

Severity	Factor VIII or IX Level	Type of Bleeding
Severe	Less than 1% of normal	Spontaneous bleeding into joints or muscles, usually without any apparent cause.
Moderate	1% – 5% of normal	Occasional spontaneous bleeding; longer-lasting bleeding with minor trauma or surgery.
Mild	5% – <40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

Haemophilia treatment

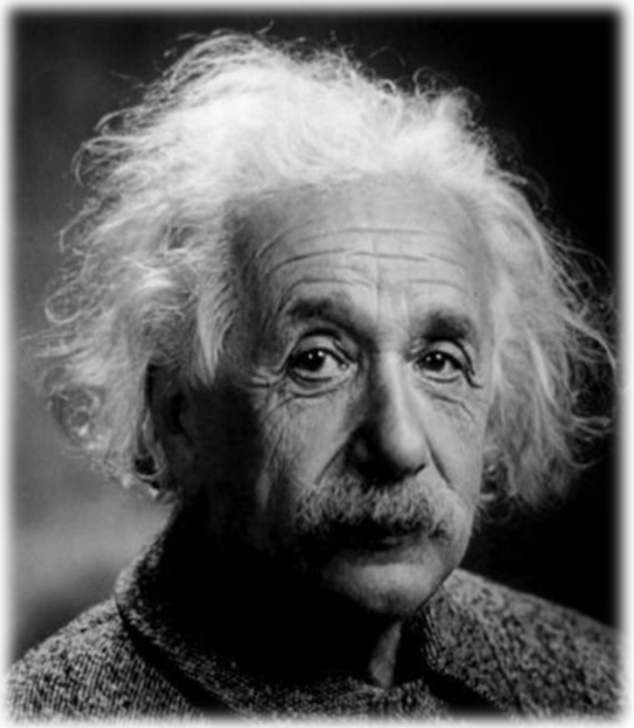
- Gene therapy - “one-and-done” treatment?



Value to the patient

'**Not everything that can be counted counts** and **not everything** that **counts can be counted**'

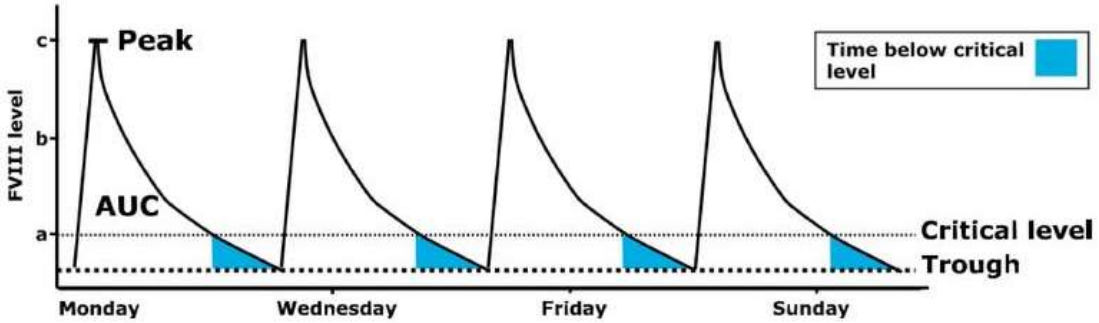
(attributed to Albert Einstein)



Factor replacement therapy vs gene therapy

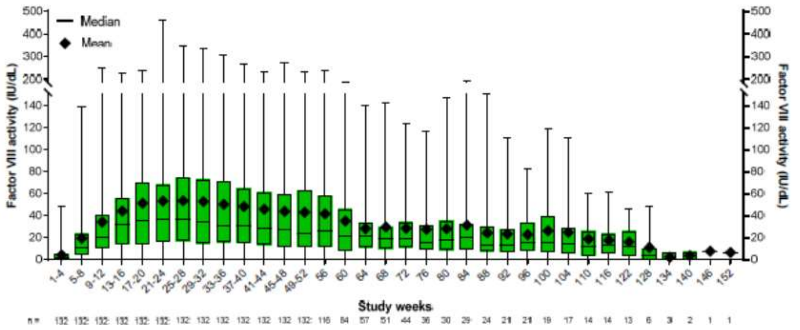
Which therapy gives more control & confidence?

FVIII replacement therapies



AAV-based gene therapy

Figure 8 Box Plot for Median Factor VIII Activity Level Using Chromogenic Substrate Assay by 4-Week and 6-Week Windows (mITT Population)



Roctavian EPAR

Patient perspective

Regulator

HTA

Value – A Matter of Perspective

Patients have a unique perspective and will consider issues differently than regulators, manufacturers, scientists, clinicians and payers.

Patient

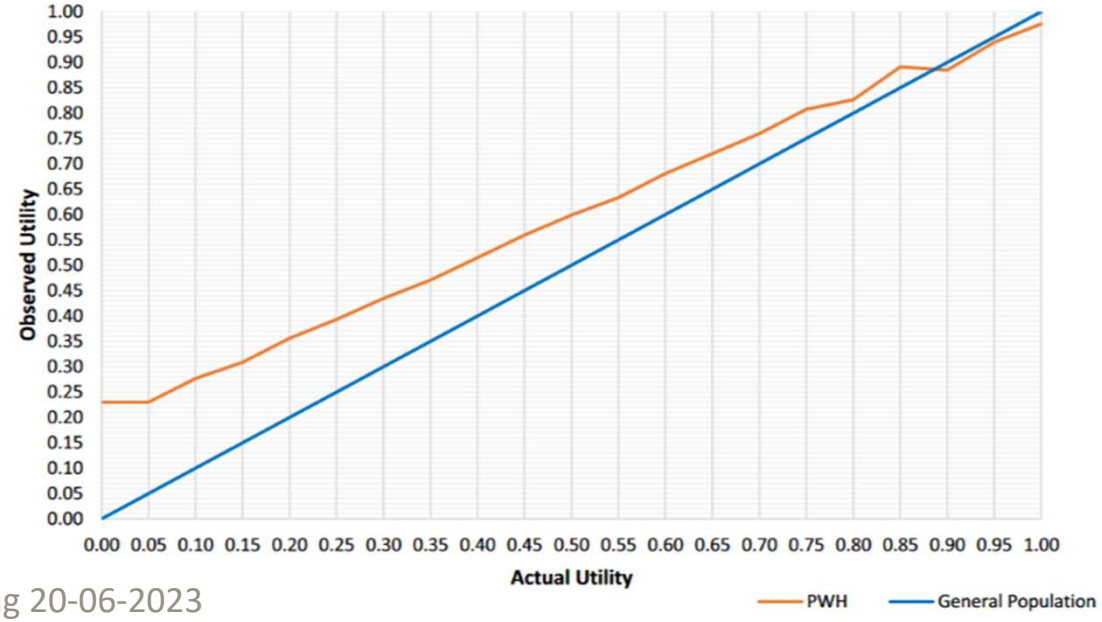
Doctors

MAH

Disability paradox

- People with inherited and long-term conditions have been shown to adapt to their levels of disability, often reporting better quality of life than expected from the general population

- Impact of haemophilia may be underestimated if general population value sets are used



O'Hara, 2021

Durability of effect – what are we ready to accept?

How Long Is “Lifelong?”

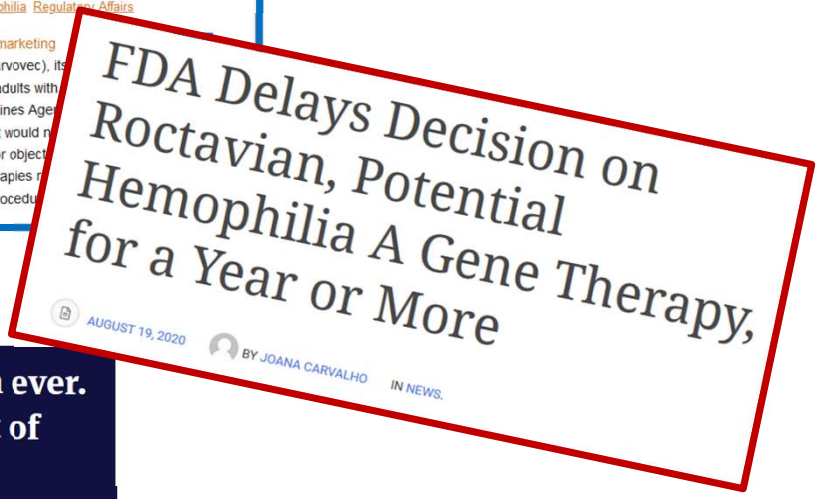
- What is “cure”?
- Duration of the expression of the factor genes encoded by the vectors
- Cell turnover

long-lasting therapy


BioMarin pulls EU filing for haemophilia A gene therapy Roctavian

(Ref: EMA)
November 13th, 2020
By: Anna Bratulic
Tags: Top Story Roctavian BioMarin EMA Haemophilia Regulatory Affairs

BioMarin Pharmaceutical has withdrawn the EU marketing application for Roctavian (valoctocogene roxaparvovec), its experimental gene therapy for the treatment of adults with haemophilia A. In a letter to the European Medicines Agency (EMA) dated November 4, BioMarin stated that it would not to provide the data requested to resolve a "major objection" by the regulator's Committee for Advanced Therapies results from clinical studies "within the current procedu


FDA Delays Decision on Roctavian, Potential Hemophilia A Gene Therapy, for a Year or More

AUGUST 19, 2020 BY JOANA CARVALHO IN NEWS.

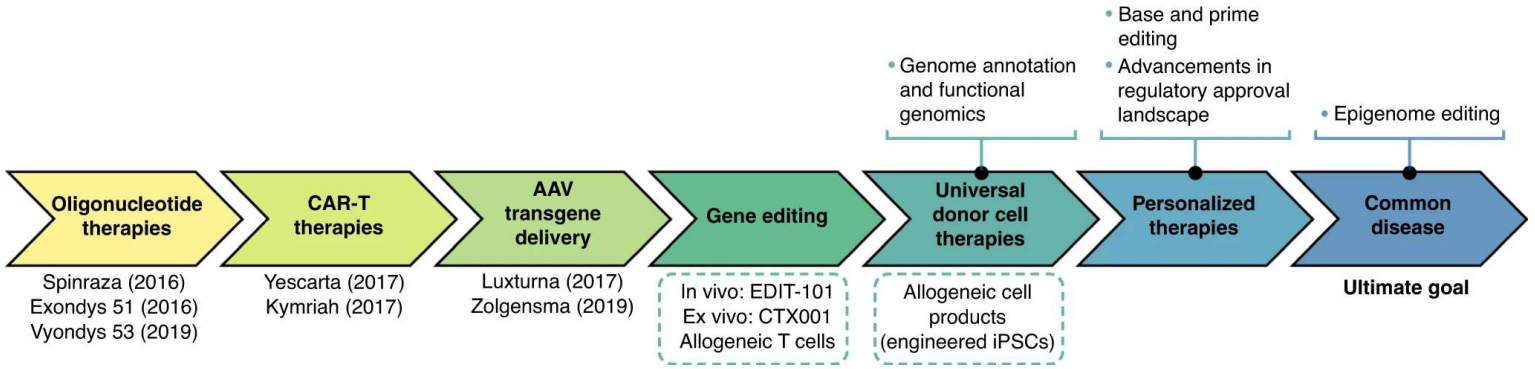

A cure for hemophilia seemed closer than ever. For many patients, it's now further out of reach.

The surprise rejection of BioMarin's hemophilia A gene therapy delays a decades-long mission to fix the rare bleeding disorder.

August 18, 2020 • By Jacob Bell

Gene therapies in development

- Oncology
- Haematology (sickle-cell disease, thalassemia, haemophilia etc)
- Immunodeficiencies
- Cystic fibrosis
- Spinal muscular atrophy
- Cardiac disease (cardiomyopathy, heart failure, transthyretin amyloidosis etc)
- Diabetes (painful diabetic peripheral neuropathy , critical limb ischemia)
- etc



Bulaklak & Gersbach, 2020

Current status

- Increasing experince in regulatory ATMP assessment
- Better involvement of all steakholders
- Post-marketing data collection remains challenging, but…
- …Trends for streamlining post-marketing data collection are seen
- Patient access to ATMPs is not optimal

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Questions?