From research to market approved ATMPs and patient access – the regulatory perspective

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From research to market approved ATMPs and patient access

- What we hear
- What we know
- What we expect

ATMPs – what we hear

- ATMPs and specifically gene therapies deliver, with a one-time administration, a causative treatment with long-term efficacy and potential for cure to patients in need

- ATMPs are (among) the most expensive treatments
  - Hemgenix $3.5 million, haemophilia B.
    - Cost savings for the overall healthcare system by generating factor XVIII levels for years?
  - Skysona $3 million, cerebral adrenoleukodystrophy, expected to treat 10 US patients/year, withdrawn from EU market
  - Zolgensma € 2,26 million (Germany 7.2020), spinal muscular atrophy, single i.v. administration
    - Spinraza, range € 260.000 – 523.000/year, repeated intrathecal administration
    - Erysdi, € 100.000 – 260.000/year, daily oral administration
- Innovative payment models are needed to address the value of ATMPs
- Patients in the EU have differing levels of access to innovative therapies

Sources
www.pharmamanufacturing.com; www.iqwig.de; www.g-ba.de;
EFPIA White Paper ATMPs Jan.2022
COM(2023) 193 final (EC proposal for revision of pharmaceutical legislation April 2023)

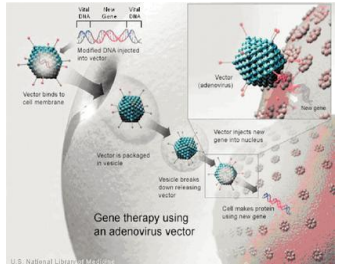
ATMPs – what we know

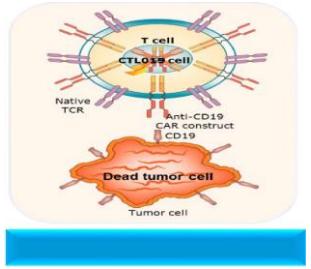
- Marketing authorisations
- Clinical evidence at marketing authorisation
- Scientific considerations
- Patient access to ATMPs

ATMPs are regulated since 2009 according to the EU ATMP Regulation (EC) No1394/2007

- Stipulates EU authorization via the centralized procedure, coordinated by European Medicines Agency (EMA)
- Principles of existing legislation apply: quality, safety, efficacy, pharmacovigilance, post-authorisation patient follow-up, GMP, GCP
- Marketing authorisation assessment by EMA Committee for Advanced Therapies

Gene therapy



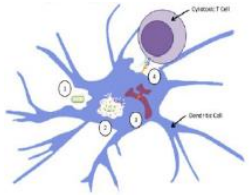


➔ **Recombinant nucleic acid**

Rek. AAV vectors

Genetically modified cells

Somatic cell therapy



➔ **Pharmaco-immunological…**

Expanded allogeneic MSC, complex anal fistula

Tissue engineered product

➔ **Regeneration, repair**

Cultured chondrocytes, Regeneration knee cartilage

Exemption from centralized marketing authorisation

- Empowers EU Member States to authorize the manufacturing and administration to patients of ATMPs under **certain conditions**, subject to national legislation, implemented at the national level

An ATMP

- which is prepared on a non-routine basis according to specific quality standards (equivalent to other ATMPs),
- and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner,
- in order to comply with an individual medical prescription
- for a custom-made product for an individual patient

...can be applied, based on national implementation rules and oversight, under the so-called Hospital Exemption. Article 28(2) ATMP Regulation

The medicine / ATMP life cycle

ATMP DEVELOPMENT

MARKETING AUTHORISATION
COORDINATED BY EMA

POST-APPROVAL LIFE CYCLE MANAGEMENT, PHARMACOVIGILANCE

Discovery

Pre-clinical

Clinical Evaluation

Clinical Trial Authorisation

CAT*

PRAC*

CHMP*

COMP*

Benefit-risk assessment / opinion

European Commission (conditional) **approval**

Post approval obligations
Indication extension

Medicine is reimbursed and available/patient access

National Scientific Advice

Simultaneous NSA

EMA scientific advice

National HTA advice

EMA/HTA parallel advice

Scientific assessments and authorisations by experts from NCAs throughout life cycle

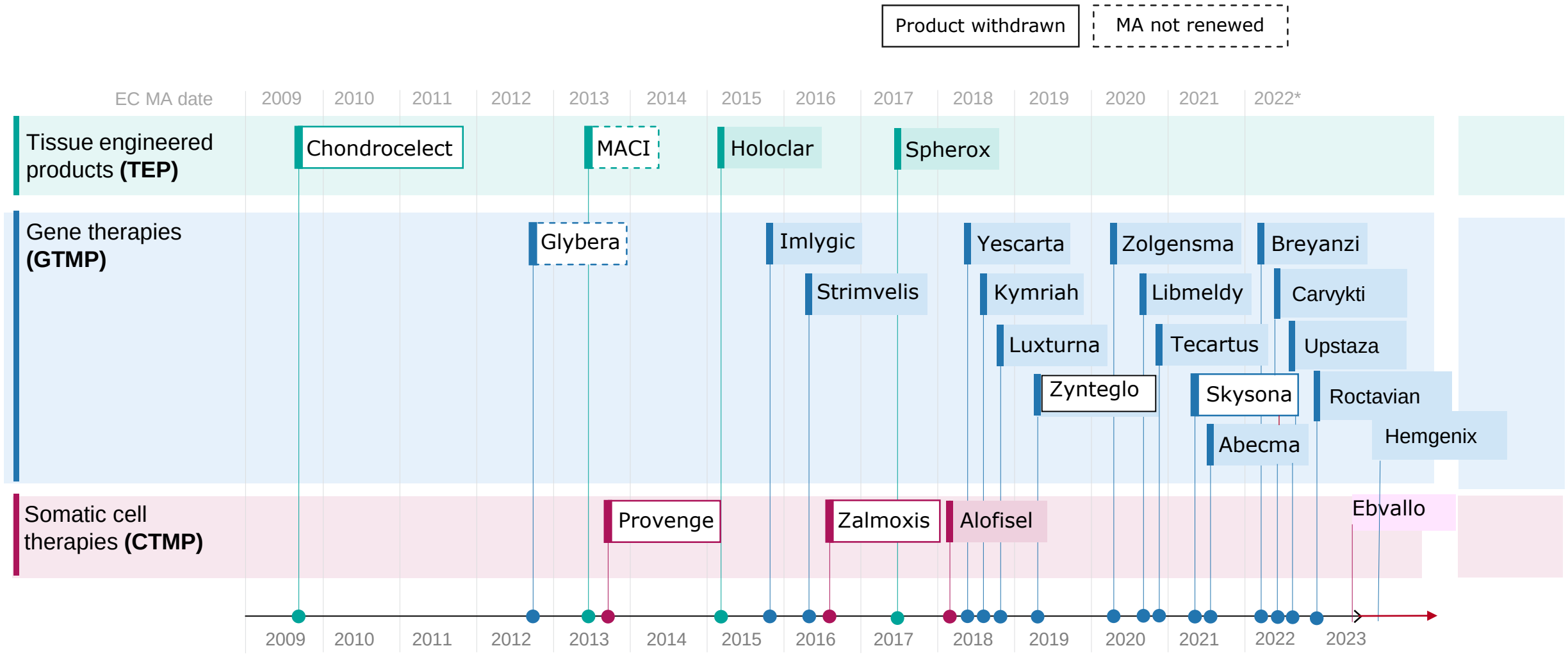
*Committee for Advanced Therapies
*Committee for Medicinal Products for Human use
*Pharmacovigilance Risk Assessment Committee
•Committee for Orphan Medicinal Products

Robust evidence at marketing authorisation
Regulatory considerations

- Clinical evidence: the totality of clinical data about the use, benefits and risks of a medicinal product across the development program.
  - Clinical trial data, data from hospital exemption, early access programs, real world data
- Randomized controlled trials (RCTs) as standard for providing robust and confirmatory evidence.
- Statistically compelling, clinically relevant data, substantial evidence with one instead of two RCTs.
- Same principles for ATMPs
  - randomized controlled design
  - also in late stage refractory disease
  - randomize to best supportive care, investigator`s choice
  - Adhere to intention-to-treat (ITT) principle,
  - EMA/CAT/GTWP/671639/2008 Rev. 1 – corr, EMA/CAT guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. Annex CART-cells

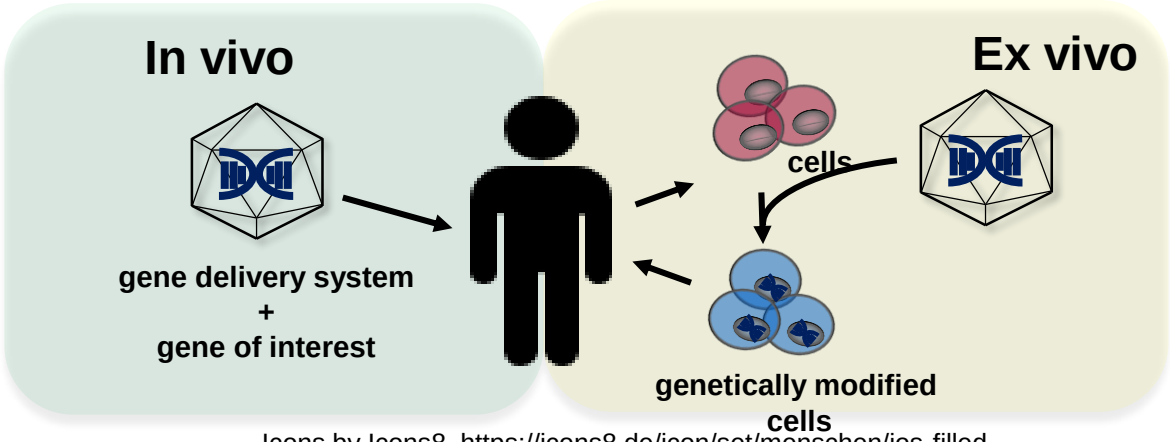
Sources:
ICH E8,9,10. EMA PtC single pivotal study CPMP/EWP/2330/99, FDA substantial evidence one well-controlled clinical investigation 44625092draft

EU approved ATMPs, 11/2023



https://www.EMA+ATMP+quaterly+report

The principles of gene transfer



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Off the shelf gene therapies, e.g.

- recombinant adeno-associated viral vectors (rAAVs)

➢ genetic correction of spinal muscular atrophy, haemophilia….

Ex vivo genetically modified or gene edited cellls, e.g.

- CD34+ haematopoietic stem cells (HSC)

➢ genetic correction of severe combined immunodeficiency ADA-SCID

- CART cells: adaptive immunotherapy

Approved *ex vivo* modified cell-based gene therapies since 2018

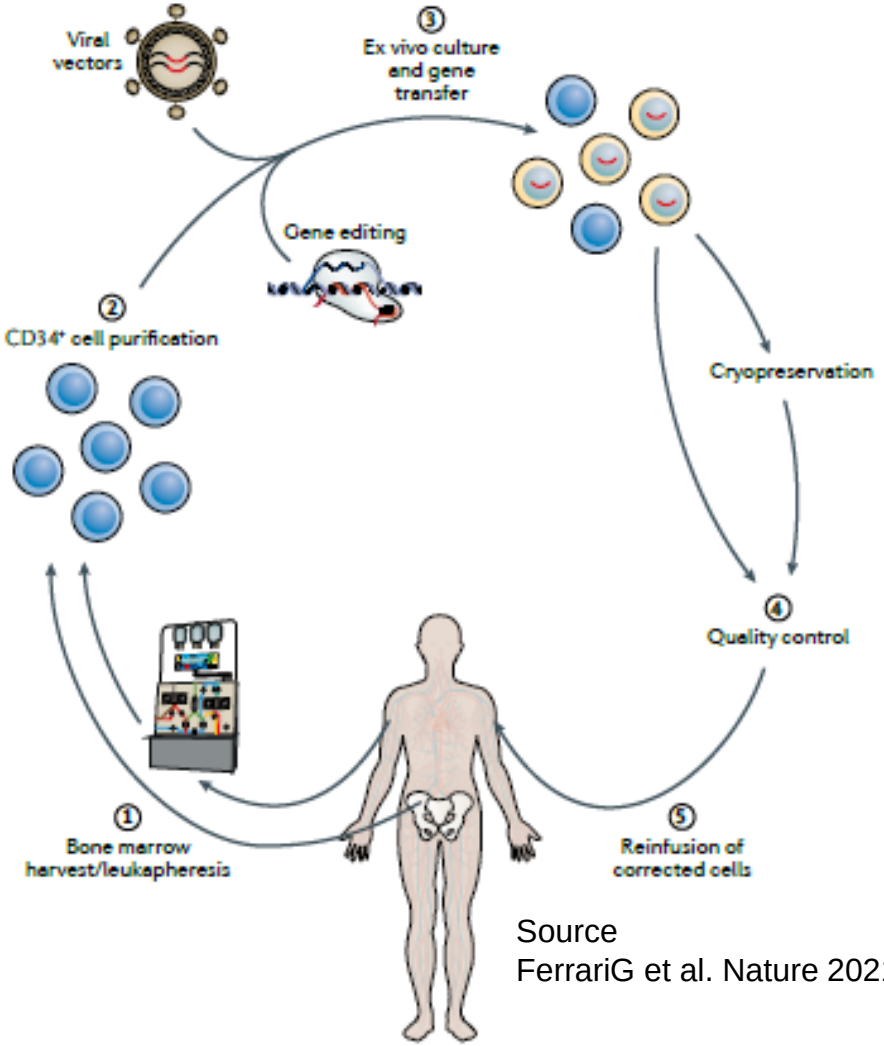
T-cells	**Indication (shortened)**
Yescarta®	B-cell-lymphoma (DLBCL und PMBCL), follicular lymphoma (FL)
Kymriah®	Acute lymphocytic leukemia, DLBCL and FL
Tecartus®	Mantle cell lymphoma
Abecma®	Multiple myeloma
Breyanzi®	DLBLCL, PMBCL, FL3B
Carvykti®	Multiple myeloma
CD34+ cells	**Indication / Genetic disorder**
Zynteglo®	Transfusion dependent β-thalassaemia
Skysona®	Adrenoleukodystrophy, genetic mutation inABCD1 gene
Libmeldy®	Metachromatic leukodystrophy, mutation in arylsulfatase A gene

Ex-vivo genetically modified cells
CD34+ haematopoietic stem cells

<u>What it requires to treat patients</u>

- Diagnose genetic disorder, neonatal screening
- Identify patient population
  - HLA-matched stem cell donor yes/no
- Identify qualified treatment center -> transplant center
  - HSC mobilisation, apheresis
  - Myeloablative conditioning
- Infrastructure for acute and long-term monitoring, data collection, reporting (registry-based)
- Logistics for ATMP handling, freeze, thaw…

- ➢ Authorisations
  - ➢ Manufacturing
  - ➢ Clinical trial, hospital exemption
  - ➢ Placing on the market
  - ➢ HTA value assessment
  - ➢ Reimbursement



Source
FerrariG et al. Nature 2021

6-Safety and efficacy follow-up

7- Clonal tracking of vector insertions

Ex-vivo CD34+ genetically modified HSCs

Scientific and regulatory considerations related to efficacy and potential for cure

Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)

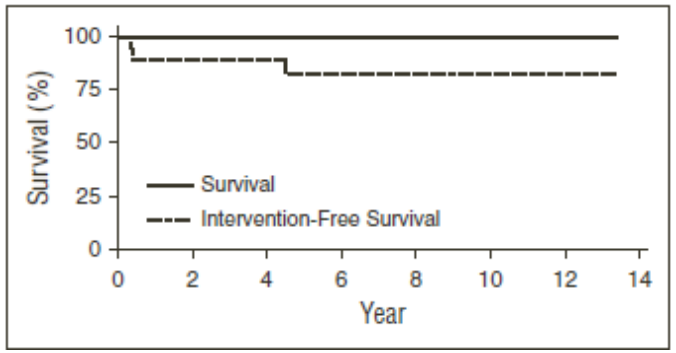
- < 50 children/year US and EU
- < 2 year survival without treatment
- <25% suitable for HLA-matched SCT

Therapeutic principle

- Bone marrow engraftment, repopulation of genetically modified HSC
- Polyclonal differentiation, haematopoietic and immune reconstitution

Pivotal efficacy data, Strimvelis 2016

- Open label single-arm trial
- N=18 children, median age 1.54 years at transplantation
- Immune reconstitution in all subjects, 7y median follow-up, external control group
- Condition imposed at MA to follow-up all trial subjects and newly treated patients
- Current - 100% survival confirmed in n= 35 subjects



Source: Cicalese et al, Blood, 2016

Approved *in vivo* gene therapies since 2018
Adeno-associated viral vectors

AAV-based	Indication / Genetic disorder (shortened)	Administration
Glybera 2012	lipoprotein lipase deficiency (LPLD)	i.m. injections leg, single treatment
Luxturna 2018	Vision loss due to inherited retinal dystrophy, bi-allelic RPE65-mutation	Subretinal injection, single treatment
Zolgensma 2020	Spinal muscular atrophy caused by bi-allelic mutation in SMN1-gene	Intravenous injection Single treatment
Upstaza 2022	Aromatic-L-aminoacid-decarboxylase (AADC)-deficiency > 18 m of age	Intraputaminal infusion Single treatment
Roctavian 2022	Adult patients with severe haemophilia A	Intravenous injection Single treatment
Hemgenix 2023	Adult patients with severe and moderately severe haemophilia B	Intravenous injection Single treatment

In-vivo rAAV-based gene therapies

Scientific and regulatory considerations related to efficacy and potential for cure

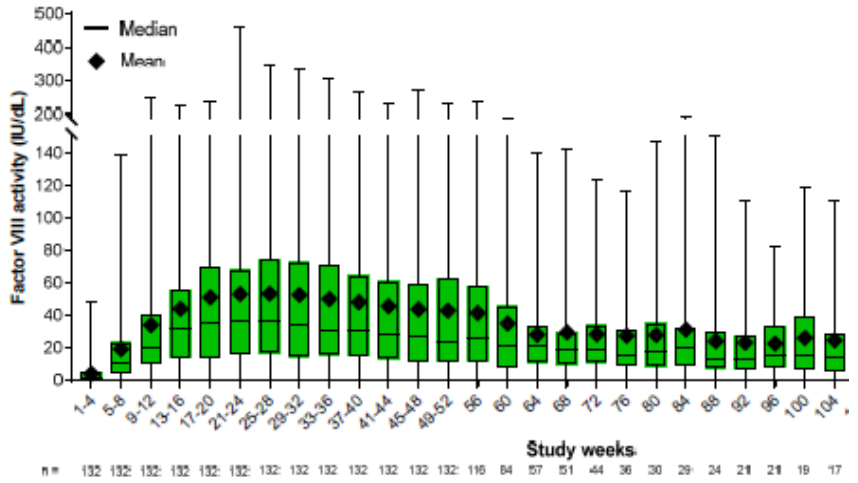
Haemophilia A

- X-linked factor FVIII deficiency
- Various treatment options

Therapeutic principle

- non-pathogenic, replication-defective virus
- transgene of interest is carried to target tissue
- Duration of effect is related to maintenance/loss of transgene expression (episomal, non-integrated)
  - Function of target organ growth/turn-over, age, immunological, non-immunological factors

- Pivotal efficacy data, Roctavian 2022, conditional MA
- N= 134 adults, mean 122 weeks follow-up
- ≥ 6 months run-in phase, intra-individual comparison
- FVIII activity level, bleeding rates at week 104



Source: EPAR Roctavian, EMA

Patient and physician involvement in ATMP benefit-risk assessment

Ad-hoc expert group (AHEG) for haemophilia gene therapy

Rationale for involvement

- First gene therapy for haemophilia
- Potential paradigm shift in therapeutic management of patients with severe haemophilia A
- Considering already available treatment modalities
  - Contribution to current armentarium
  - Uncertainties regarding long-term data
  - Managing risk of hepatotoxicity
  - Impact on patient`s quality of life

Composition

- Haematologists, hepatologists, haemophilia patient representatives

➢ Agreement that benefits outweigh risks

➢ On relevance for specific patients and specific situations, where factor VIII substitution is avoided for a number of years.

Gene therapy marketing authorisations by MA type, 2018-2023

Ex vivo modified cells			
T-cells	**(Shortened) Indication**	**Approval**	**Orphan**
Kymriah®	B-ALL, NHL subtype	MA	✓
Yescarta®	NHL subtype	MA	✓
Tecartus®	B-ALL, NHL subtype	cMA	✓
Abecma®	NHL multiple myeloma	cMA	✓
Breyanzi®	NHL subtypes	MA	✓
Carvykti®	NHL multiple myeloma	cMA	✓
CD34+ cells			
Zynteglo®	β-thalassaemia	cMA	✓
Skysona®	Adrenoleukodystrophy	MA	✓
Libmeldy®	Metachromatic LD	MA	✓

In vivo gene therapies			
AAV-based	**(Shortened) Indication**	**Approval**	**Orphan**
Luxturna®	Retinal dystrophy	MA	✓
Zolgensma®	Spinal muscular atrophy	cMA	✓
Upstaza®	AADC deficiency	Exceptional	✓
Roctavian®	Haemophilia A	cMA	✓
Hemgenix®	Haemophilia B	cMA	✓

Marketing authorisations	n=14
Orphan designations	n=14,
Conditional MA (cMA)	n=7
Full MA	n=6
exceptional circumstance	n=1

Gene therapies – benefit-risk assessment at marketing authorisation
Summary

- Follows specific regulatory rules and guidelines
- Takes into account the specificities of ATMPs
- Requires robust clinical evidence - case-by case, disease and stage, medical need, treatment options
- May be based on non-randomized single arm trials
- Involves views of patient and physician organisations
- Requires always post-authorisation data to expand the understanding of ATMP safety and efficacy (Real World Data)
- ..which is only possible if ATMP is reimbursed and used
- Is the first step towards patient access

From market approved ATMPs to patient access

- Orphan availability 2018-2021
  - EU average 39%
  - Time to availability: range 55 – 1031 days from EU authorisation to entry in national reimbursement list

Source
EFPIA Patients W.A.I.T. Indicator 2022 Survey

From market approved ATMPs to patient access

- CART cell availability
  - Highly variable in EU member states

Availability & reimbursement

Country	Kymriah	Yescarta	Tecartus	First use	Centres	Pts treated*	NHL	p ALL
Bulgaria				--	--	--	--	--
Croatia				2020	1	28	24	4
Czech R.				2019	7	128	118	10
Estonia				--	--	--	--	--
Hungary				2023	2	1	0	1
Latvia				--	--	--	--	--
Lithuania				--	--	--	--	--
Poland				2021	6	82	57	25
Romania				2022	1	15	10	5
Slovakia				2023	3	0	0	0
Slovenia				2021	1	9	7	2

*By December 2022

Hajek. Presented at EHA-EBMT CART-cell meeting. Rotterdam. February 2023

Source
5th EU CART cell meeting, 2023 Rotterdam, R. Hajek, CZ

From market approved ATMPs to patient access
Different tasks and responsibilities

Benefit-risk assessment at marketing authorisation

- Follows specific regulatory considerations and rules
- Takes into account the specificities of ATMPs
- Requires robust clinical evidence - case-by case, disease and stage, medical need, treatment options
- May be based on non-randomized single arm trials
- Involves views of patient and physician organisations
- Requires always **post-authorisation data to expand the understanding of ATMP safety and efficacy (Real World Data)**
- ..which is only possible if ATMP is reimbursed and used

Added value and cost-effectiveness of ATMPs - national HTA, pricing and reimbursement bodies

- Relies on comparative clinical data
- Follows specific HTA models that may not be suitable to appraise the value (clinical, economic, social, mental) of ATMPs
- Requires often **post-authorisation data to support cost-effectiveness, alternative payment models**

From research to market approved ATMPs and patient access

What we expect

- A favorable EU environment for research and innovation that supports ATMP development.
- A favorable EU environment and infrastructure „..for patients to benefit from equal access to safe, modern and affordable medicines ……*EC Pharmaceutical Strategy for Europe*
- Improving pre-planning of post-authorisation evidence generation, needed by regulators, HTA bodies and pricing authorities to reduce evidence gaps and foster timely patient access.
- Reducing administrative burden for companies and strengthen HTA capacity building and joint clinical assessment across member states……*EC HTA Regulation*

THANK YOU VERY MUCH

FOR YOUR ATTENTION