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# Timely patient access to Advanced Therapy Medicinal Products (ATMPs)

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# Advanced therapy medicinal products (ATMPs)
# New treatment options for patients with rare diseases

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## New gene therapy to treat spinal muscular atrophy

EMA has recommended granting a conditional marketing authorisation in the European Union for the gene therapy Zolgensma (onasemnogene abeparvovec) to treat babies and young children with spinal muscular atrophy (SMA), a rare and often fatal genetic disease that causes muscle weakness and progressive loss of movement.

Gemeinsamer Bundesausschuss

gen und insbesondere auch der SMA belegen muss. Diese Erfahrungswerte können beispielsweise über die Meldung der Behandlungen an das Register für Patienten mit spinaler Muskelatrophie, dem SMArt-CARE-Register, dokumentiert werden.

20/11/2020 Quality assurance, data generation, German HTA

**How will we pay for the coming generation of potentially curative gene therapies?**


STAT Opinion June, 2019

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## Advanced Therapy Medicinal Products (ATMPs) Regulation (EC) No1394/2007

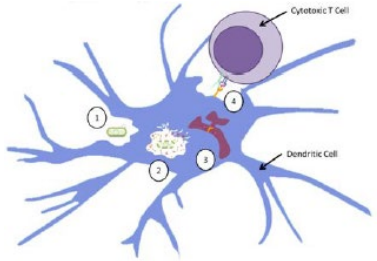
- ATMPs are medicinal products
- Are authorized in EU via the centralized procedure
- Post-authorisation safety and efficacy follow up, risk management
- Are assessed by the Committee for Advanced Therapies

**Gene therapy**

e.g.CAR T cells, rAAVs

➔ **Recombinant nucleic acid**

**Somatic cell therapy**




➔ **Pharmaco-immunological…**

**Tissue engineered product**

➔ **Regeneration, repair….**

# EMA Committee for Advanced Therapies (CAT)

## Quality, safety, efficacy -> benefit-risk assessment

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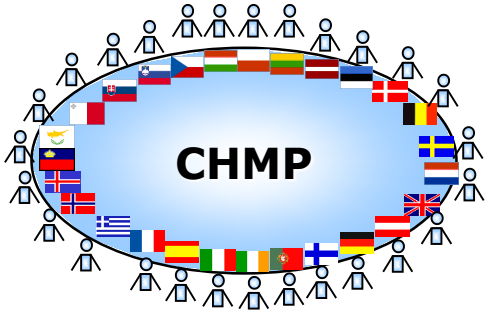
Draft opinion → Final opinion → European Commission


CAT rapporteurs




CHMP coordinators

Authorisation for placing ATMPs on the market in the European Union





*2 patient and phycisian rep. plus alternates

# EU ATMP Marketing Authorisations and the ATMP pipeline

## Authorised ATMPs

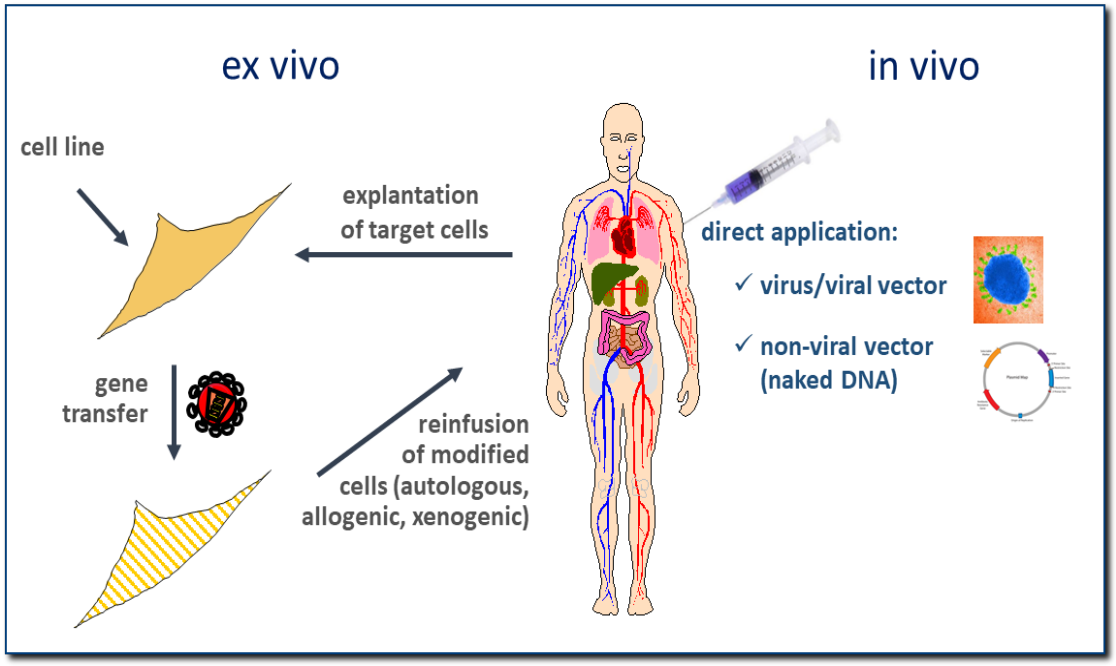
- 4 Tissue engineered products, e.g. cultured autologous chondrocytes for knee cartilage repair
- 3 Somatic cell therapies, e.g. allogeneic mesenchymal stem cells for anal fistula treatment
- 10 Gene therapies, e.g. CAR T cells for treatment of CD19 positive Non-Hodgkin Lymphoma subtypes

## ATMP pipeline

- Ten marketing authorisation submissions/year expected
- Mostly gene therapies, e.g. for monogenic disease including haemophilia A/B

# The principles of gene transfer

Autologous products e.g. CART cells




Off the shelf products e.g. gene therapies for haemophilia



Slide Dr. Renner, PEI

# In vivo and ex vivo gene transfer

## In vivo gene transfer

- Luxturna – recombinant adeno-associated viral vector (rAAV) – inherited retinopathy
- Zolgensma – rAAV - spinal muscular atrophy

## Ex vivo gene transfer

- Kymriah, Yescarta, Tecartus – autologous CAR T cells – CD19 targeting haematological maligancies
- Strimvelis - genetically modified autologous CD34+ cell enriched population – ADA-SCID
- Zynteglo - genetically modified autologous CD34+ cell enriched population - β-thalassaemia
- Libmeldy - genetically modified autologous CD34+ cell enriched population – Metachromatic leukodystrophy

# CAR T cells - from apheresis to infusion

EU hospital/trial site → EU preselection site → US manufacturing site → EU hospital/trial site

Freeze -> thaw

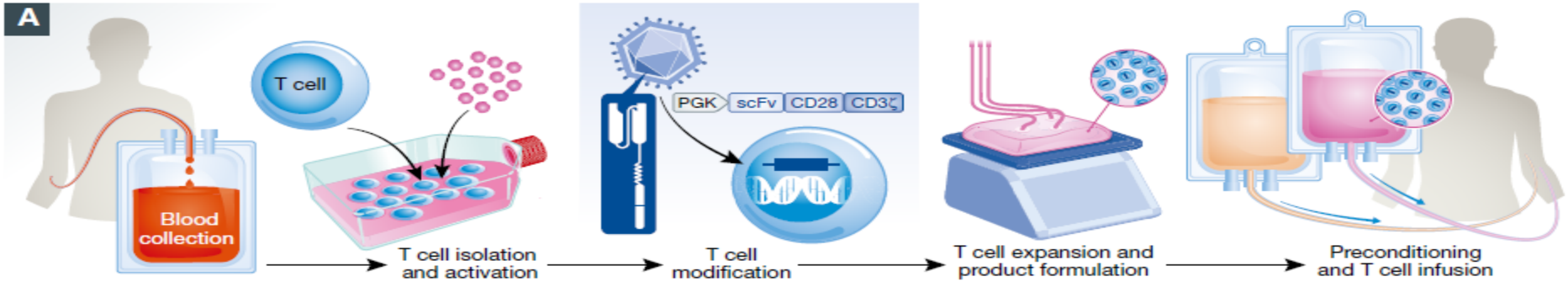
EU manufacturing site

Freeze -> thaw

Apheresis PBL

Lymphodepletion/ Conditioning

Infusion



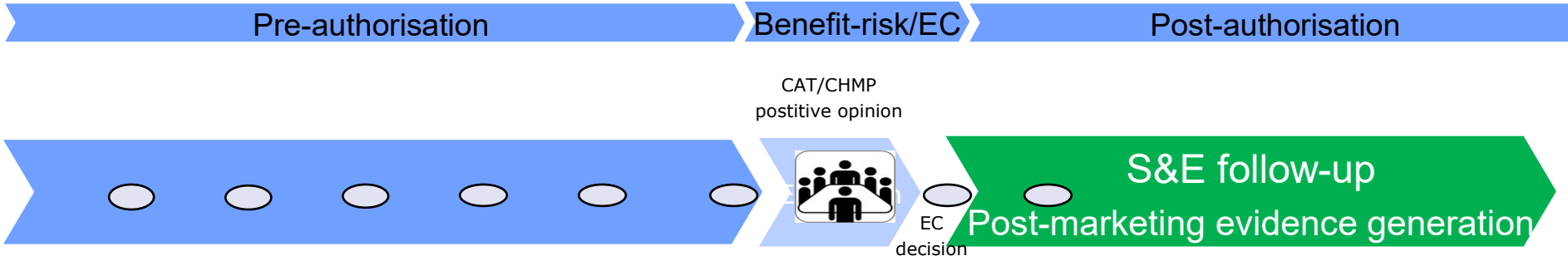

**Hartmann J**, **Schüßler-Lenz M**, Bondanza A, **Buchholz CJ,** *EMBO Mol Med* , 8 2017.

# ATMPs and innovation

## New treatment modalities for patients with limited or no treatment options

- Exhausted all available treatments in relapsed/refractory heamatological malignancies, e.g. CAR T cells
- Practice changing treatments in haemophilia A/B
- Curative potential in children with monogenic disease

# ATMP life cycle - Regulatory challenges – Real World Data




## Clinical trials - safety, efficacy, benefit/risk

- Single arm trials in orphan indications
- ATMP administered by single administration
- Limited patient numbers
- Limited follow-up time

## Real World Data – incremental knowledge gain

- Long-term safety&efficacy follow-up (15 y)
- Risk management/mitigation/monitoring
- Adverse event reporting
- Comparative effectiveness

# Registry-based studies for authorised ATMPs

## CAR T cells – lymphoma, leukaemia

- Post-authorisation (PA) safety and efficacy follow-up - agreed protocol - EU wide disease registry (EBMT)

## Zynteglo - β-Thalassaemia

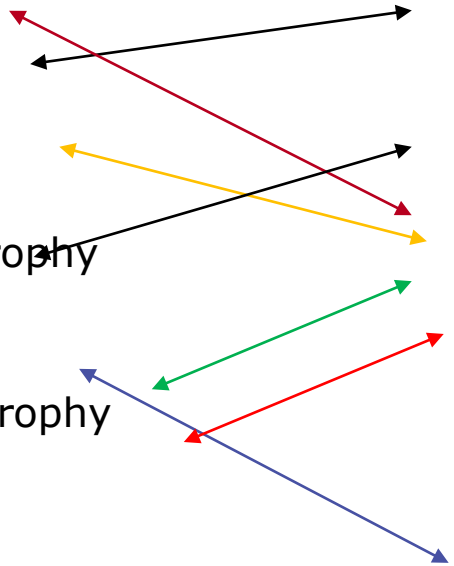
- PA safety and efficacy follow-up - agreed protocol - product registry and data from EU registry as comparator

## Zolgensma – Spinal muscular atrophy

- PA efficacy and safety follow-up – agreed protocol - SMA registry (Restore).

# Disease registries for registry-based studies of ATMPs

- Non-Hodgkin lymphoma
- Beta-thalassemia
- Spinal muscular atrophy
- Metachromatic leukodystrophy
- Haemophilia A/B
- Cerebral adrenoleukodystrophy



- National registry
- Multinational registry
- Data ownership
- Data systems
- Patient consent
- Health care professional engagement
- Data quality
- Incentives

# Disease registries for registry-based studies of ATMPs

## CAT experience

### Gaps

- Availability/potential of disease registries in a fragmented EU landscape
- Companies` (often US based/Biotech) engagement with registry holders
- Post-authorisation safety and efficacy study protocol finalisation
- Patient enrolment, coverage and monitoring (treated vs reported, efficacy outcome, adverse events)
- Data collection, extraction, reporting to marketing authorisation holder -> EMA

# Patient access* to ATMPs

## Roadmap

- Pre-authorisation phase
- Marketing authorisation
- Post-authorisation data generation
- Infrastructure for diagnosis, patient identification, genetic screening
- Health technology assessment
- Pricing and reimbursement
- Center qualification (genetically modified cells)
- Vein-to-vein time and supply management
- Cross border travel (e.g. Strimvelis)





Access: ATMP is available and reimbursed

# Patient access to ATMPs

## Health technology assessment - pricing and reimbursement

### General issues

- National pricing and reimbursement frameworks vs. Central Marketing authorisation
- Average time to reimbursement of innovative treatments across EU/EEA countries differs by factor of 7 (127 – 823 days, average 504 days*)

### ATMP-specific issues

- Limited patient numbers, lack of comparator, uncertainty regarding duration of response, survival, cure, long-term toxicities, high treatment costs

### Result

- Uncertainty in the HTA value** assessment at time of launch
- Outcomes-based reimbursement models for ATMPs, payment linked to response assessment





*Root cause unavailability innovative medicines EU (EFPIA), 7.2020

# Patient access to ATMPs

## Health technology assessment - pricing and reimbursement Germany

ATMPs which qualify as orphan drugs are reimbursed with entry into market/launch

BUT

New HTA quality assurance directive for ATMPs*

- Treatment center and HCP qualification, structure, processes
- Reimbursement linked to post-authorisation data generation (orphans, conditional MA, MA exceptional circumstances)
- Disease registries are scrutinized for their performance and data quality

ATMP-Qualitätssicherungsrichtlinie § 136a Absatz 5 SGB V

Anwendungsbegleitende Datenerhebung § 35a SGB V

# Timely patient access to ATMPs

## Summary and outlook

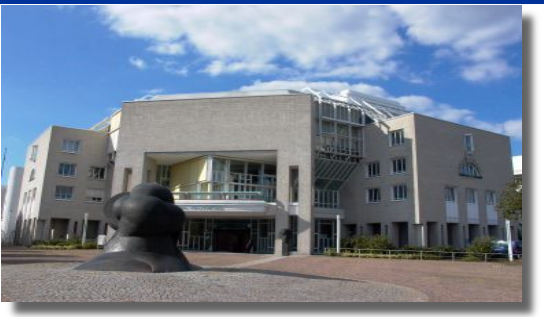
- ATMPs have enormous potential
- Safety and efficacy follow-up of patients treated with authorized ATMPs is mandatory
- Alignment of post-authorisation evidence generation between regulators, HTAs, pricing and reimbursement bodies is key to ensure timely patient access
- CAT/EMA has identified gaps in the implementation of registry-based studies and is taking actions in PRIME, scientific advice, interaction with downstream decision makers (CAT work plan)

# Timely patient access to ATMPs

## Summary and outlook

### We need your support

- ✓ CAT – patient and HCP´s expertise, input, weight highly appreciated
- ➢ PASS/PAES protocols – input regarding patient relevant outcomes (Zolgensma)
- ➢ Disease registries – exchange knowledge and information
- ➢ Registry-based ATMP studies - advocate for acceptance by patients and physicians, national decision makers
- ➢ Scientific advisory groups (SAGs) – contribute with knowledge and expertise
- ➢ EMA/CAT based outputs – communicate and close information gaps



Thank you for your attention

# EU ATMP Marketing Authorisations 2009 – 2021

| Medicine | Indication |
|---|---|
| Chondrocelect®* | Cultured chondrocytes for repair of knee cartilage defects (2009) |
| MACI®* | Cultured chondrocytes for repair of knee cartilage defects |
| Spherox® | Cultured chondrocytes for repair of knee cartilage defects |
| Holoclar® | Cultured corneal epithelial cells, limbal stem cell deficiency |
| Provenge®* | Metastatic prostate cancer |
| Zalmoxis®* | Stem cell transplantation, adjunctive treatment |
| Alofisel® | Crohn`s disease, complex anal fistula |

* Marketing authorisation withdrawn

Tissue engineered products Somatic cell therapies Gene therapies

# EU ATMP Marketing Authorisations (MA) 2009 – 20201

| Medicine | Indication |
|---|---|
| Glybera®* | Familial lipoproteinase deficiency |
| Imlygic® | Injectable melanoma |
| Strimvelis® | Severe combined immunodeficiency ADA-SCID |
| Yescarta® | B-cell Lymphoma (DLBCL) |
| Kymriah® | B-cell Lymphoma (DLBCL), B-cell acute lymphoblastic leukemia |
| Luxturna® | Vision loss, inherited retinal dystrophy, RPE65 mutation |
| Zynteglo® | Transfusion-dependent β-thalassaemia, not β0/β0 |
| Zolgensma® | Spinal muscular atrophy, bi-allelic mutation SMN1, 3 SMN2 copies |

Tissue engineered products Somatic cell therapies Gene therapies

*Marketing authorisation withdrawn

# EU ATMP Marketing Authorisations (MA) 2009 – 20201

| Medicine | Indication |
|---|---|
| Tecartus® | Mantle cell lymphoma (12.2020) |
| Libmeldy® | Metachromatic leukodystrophy (12.2020) |
| | |
| | |

Tissue engineered products Somatic cell therapies Gene therapies