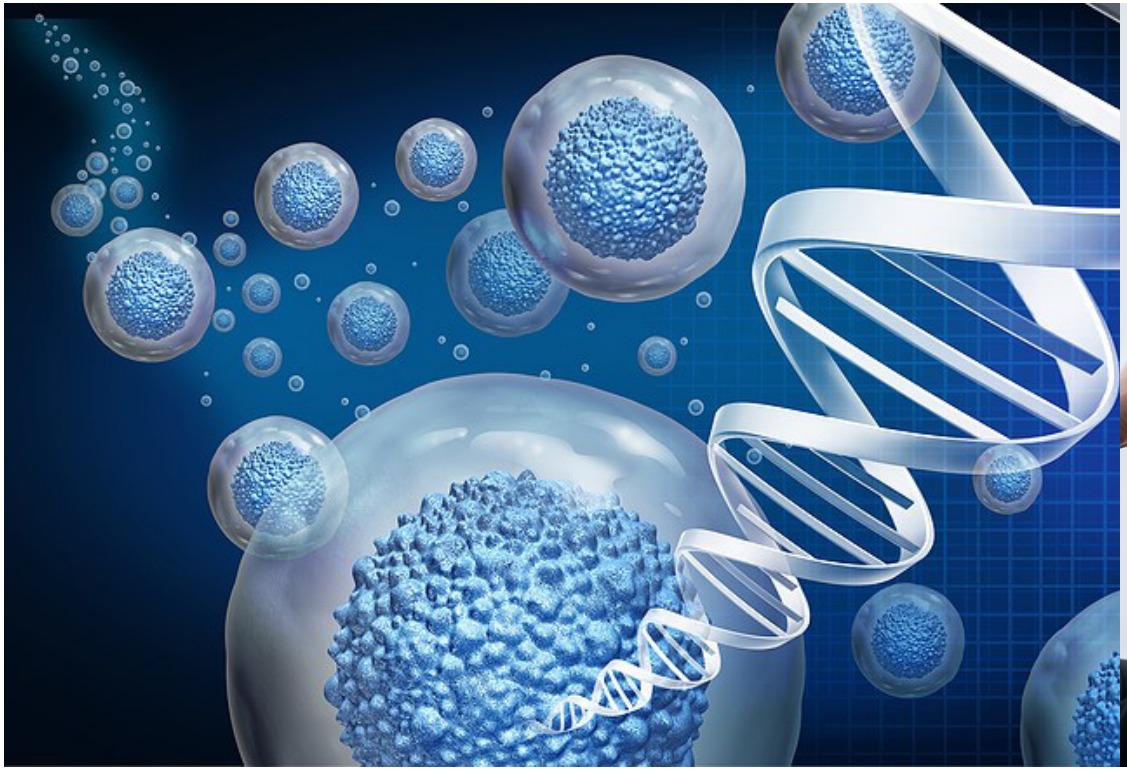
KCE REPORT 396

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

ACADEMIC DEVELOPMENT OF ATMPS IN BELGIUM

AN EXPLORATORY STUDY OF THE LEGAL & STRATEGIC OPTIONS



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KCE REPORT 396
HEALTH SERVICES RESEARCH

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AN EXPLORATORY STUDY OF THE LEGAL AND STRATEGIC OPTIONS

CÉLINE POUPPEZ, JOLYCE BOURGEOIS, FRANK HULSTAERT, IMGARD VINCK

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ATMP	Advanced Therapy Medicinal Product
BTC	Blood Tissues & cells
CAT	Committee for Advanced Therapies (within the EMA)
CDMO	Contract Development and Manufacturing Organisation
CJEU	Court of Justice of the European Union
CMO	Contract Manufacturing Organisation
CRO	Contract Research Organisation
CTC	Clinical Trial Centre
CTU	Clinical Trial Unit
CU	Compassionate use
EMA	European Medicines Agency
FAMHP	Federal Agency for Medicines and Health products (= in Belgium)
GBER	General Block Exemption Regulation
GMP	Good Manufacturing practice
HE	Hospital Exemption
HTA	Health and Technology Assessment
IND	Investigational New Drug (in the United States)
IP	Intellectual property
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
NPU	Named Patient use
SoHO	Substances of Human Origin
TEP	Tissue engineered products

SPV	Special Purpose Vehicle
SGEI	Service of general economic interest
TTO	Technology transfer office

SCIENTIFIC REPORT

GLOSSARY

In the context of this report, the following concepts are defined as follow:

- **Academia**: in this report, “Academia” refers to any non-profit organisation engaged in education and research (usually linked to universities and scholarly institutions) involved in the development of Advanced Therapy Medicinal Products (ATMPs). This includes hospitals, scientific institutes or universities but does not cover for profit entities such as private clinics.
- **ATMPs**: Advanced Therapy Medicinal Products are innovative medical products that, under the European regulatory framework, include gene therapies as well as cell therapies, and tissue-engineered products. They aim to treat, prevent, or diagnose diseases.
- **Bed-side manufacturing** (also called *point-of-care* manufacturing): in the context of ATMPs this concept generally refers to the process of producing personalised medical treatments directly at or near the patient’s location, such as in a hospital or clinic. It is the most decentralised model for ATMPs production. It is very often used in relation to CAR-Ts production.
- **CAR-T therapy**: immunotherapy primarily used for (blood) cancer, where immune cells (T-cells) from a patient or a donor are modified in the lab to better recognise and attack cancer cells. “CAR” stands for chimeric antigen receptor, which is a protein added to the T cells to help them target specific cancer cells.
- **Clinical Trial Units (CTUs)**: specialised units within hospitals, research institutions, or universities that manage and conduct clinical trials to test new medical treatments, drugs, or therapies.
- **Decentralised manufacturing**: in the context of ATMPs generally refers to the production of these therapies at multiple, smaller, and often local facilities rather than at a single, central location. This also includes point-of-care manufacturing where the location is near the patient/hospital.

- **Hospital Exemption (HE)**: EU regulatory pathway allowing Member States to authorise the use of custom-made ATMPs prepared on non-routine basis without a marketing authorisation, provided that the product is used for individual patients in a hospital and under the professional responsibility of a medical practitioner. The so-called hospital exemption requires the application of national requirements on quality, traceability, and pharmacovigilance equivalent to those required for authorised medicinal products.
- **Market failure**: situation, used in State aid assessment (in the European Union), where the free market does not efficiently allocate resources or provide optimal outcomes due to various factors such as externalities, information asymmetry, or monopolies.
- **Orphan drug:**
  - Generally: drug to prevent or treat (rare) diseases with no existing treatment options.
  - Legally in the EU: drug intended for the treatment, prevention or diagnosis of life-threatening or chronically debilitating disease with a prevalence of less than 1/2000 ***or*** for which it is unlikely that marketing of the medicine would '*generate sufficient returns'* to justify the investment needed for its development (this criteria has only been used once "*due to the difficulty of estimating future investments and returns on that investment a priori, before the therapeutic indications for which the product may be used or the price at which it will be sold are clear* [1]); *and* for which no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition
- **Orphan status**: set of advantages and incentives granted to developers of drugs meeting the criteria of the EU Orphan legislation (see above Orphan drugs).
- **Out-licensing:** when an entity grants permission to another entity to use (and generally develop) its patented technology, research, or products, (often towards commercialisaton) usually in exchange for royalties or milestone payment.
- **Public - Private Partnerships**: broad concept covering different types of collaborations between governement entities or Academia and private companies to advance research, development and commercialisation of new treatments.
- **Rare disease:** generally, cover life-threatening or chronically debilitating diseases that affect a small percentage of the population the percentage of which depends on the framework using this concept (orphan designation, pharmaceutical incentives, flexibilities or support mechanisms). Under the EU Orphan legislation, rare diseases are severe, debilitating and often life-threatening diseases affecting no more than one person in 2000 in the Union.
- **Special needs**: a concept referenced in the case law of the Court of Justice of the European Union (CJEU) in the *Commission vs. Poland* case, related to Article 5 of Directive 2001/83/EC. This concept allows Member States to waive certain provisions of the EU Directive on (a priori industrial) medicinal products when there is a specific medical need for an individual patient and no authorised treatment is available. Economic motives are strictly inadmissible for invoking this specific waiver [a].
- **Special Purpose Vehicle**: refers to a legal entity that could be created by Academia for the development and commercialisation of an ATMPs. It could be seen as a specific type of (light) spin-off created to separate certain activities from the core activities of the Academia and to

[a] CJEU, C-619/18, Judgment of 24.06.2019, *European Commission v Republic of Poland*.

circumvent restrictions under existing regulations (e.g. national hospital legislation), but is fully controlled by the Academia ensuring that the incentive for its activities is not profit maximisation. The SPV would still need to comply with state aid and will generally need to compensate the institution for the aquisition and commercialisation of the intellectual property (by hypothesis, publicly funded).

- **Spin-out / Spin-off:** terms often used interchangeably to cover the process of creating a new, independent company based on technology, research, or products originally developed within a larger organisation, typically a university or research institution. An academic spin-off usually entails shareholdership of the original technology owner (e.g. principal investigator) while a spin-out does not entail such academic involvement.
- **Technology Transfer Office** (TTO): university or research institution department that helps transferring scientific findings from research labs to the commercial sector, facilitating the development and commercialisation of new technologies.
- **TILs therapy**: treatment that uses a patient's own immune (T) cells to fight cancer (incl. advanced melanoma) without genetic modification.
- **Ultra-rare diseases**: concept used in the EU Clinical Trials Regulation, referring to severe, debilitating, and often life-threatening diseases that affect no more than one person in 50,000 within the Union.
- **Unmet medical needs:** general concept that is frequently used to describe therapeutic areas that require additional attention, where current therapeutic possibilities are not yet available or not satisfactory. Although this concept is sometimes linked to regulatory procedures, assessment of medicines or public intervention to re-direct investments in neglected areas, there is no universal definition of UMN, allowing different interpretations by the various stakeholders (patients, industry, regulators, HTA bodies and payers), depending on the context. In the context of the revision of the EU pharmaceutical legislation (see Box 1) (article 83 of the proposed Directive), this concept is still highly debatted as it shapes eligibility conditions for regulatory data protection, conditional marketing authorisations, and enhanced regulatory and scientific support. At the time of writing (October 2024) the concept was defined as a life threatening or severely debilitating condition for which there is no treatment (or there is a treatment with a high remaining mortality or morbidity).
- **High unmet medical need**: undefined concept allowing different interpretations by the various constituents (patients, industry, regulators, HTA bodies and payers), depending on the context. In the context of the revision of the EU pharmaceutical legislation (see Box 1), this concept would cover a rare disease for which no treatment exists or is considered an “exceptional therapeutic advancement” but is still higly debatted at the time of writing (September 2024). This concept would shape the eligibility conditions for market exclusivity, regulatory data protection, conditional marketing authorisations, and enhanced regulatory and scientific support.
- **Unmet health related needs:** concept covering health, healthcare, and social needs at both the patient and societal level, developed in the context of the NEED study (Needs Examination, Evaluation, and Dissemination). The NEED assessment framework outlines criteria for assessing unmet needs across various health conditions. The objective of the NEED initiative is to create a publicly accessible database containing scientific data on unmet health-related needs, enabling stakeholders to identify and address the most critical health-related needs of patients and society.[2]

1 INTRODUCTION

CÉLINE POUPPEZ (KCE), FRANK HULSTAERT (KCE), JOLYCE BOURGEOIS (KCE), IMGARD VINCK (KCE)

1.1 Complex medicinal products

Advanced Therapy Medicinal Products (ATMPs) are complex medicinal products that now encompass, under the European product rules, significantly modified cells or tissues, as well as gene therapies. Their development, manufacturing, and use often involve sophisticated study designs, advanced and rapidly evolving techniques as well as highly specialised facilities and professionals. This complexity necessarily creates a challenging environment to navigate, not only for the Academia but also for the industry.

1.2 High hopes and scientific uncertainties

ATMPs offer groundbreaking new opportunities for the treatment of diseases and injuries in many areas from very rare diseases including very rare forms of cancers to much more common diseases such as Parkinson's or diabetes.

However, generating appropriate pre-clinical and clinical data for ATMPs remains an important challenge not only for the Academia but also for the industry, especially when ATMPs are targeting very rare disease for which there is no treatment options. An important part of ATMPs currently authorised by the EMA, were authorised on the basis of single-arm trials, involving a limited number of patients, using surrogate endpoints and including limited follow-up data.[3, 4] Additionally, some products have been withdrawn from the EU market following disappointing results[b].[4, 5] In the United States, the Food & Drugs Administration has recently announced investigations into the long-term safety of 6 authorised cell-based immunotherapies after the reporting of a number of newly developed cancers.[6]

These remaining uncertainties and challenges to produce scientific evidence may partly explain the limited number of ATMPs accessible to patients, either via the commercial route (marketing authorisation) or via alternative pathways (such as hospital exemption).

In September 2024, 27 ATMPs have been approved for the European market by the EMA (see full overview in Appendix 1.1). In 7 cases (out of 27), authorised products were withdrawn from the market or did not have their marketing authorisation renewed by the marketing authorisation holder for commercial reasons (see Figure 1).

1.3 Costly medicines and limited access

The prices of most ATMPs are also extremely high. This is due to several factors, such as high development costs, manufacturing complexities, significant investments to meet stringent regulatory requirements, challenging distribution conditions, and often a limited market size (small population) coupled with high expected profit margins.[7]

In a context where healthcare expenses are under significant pressure, payers would like to see rigorous and reliable data (usually more robust than what is available at market entry) to assess the cost-effectiveness and budget impact of these new therapies.[8, 9] This evidence-based decision-making process often results in limited patient access (no reimbursement or limited reimbursement under Managed entry agreements or *ad hoc* interventions).[10, 11]

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[b] Alofisel® a cell based ATMP approved by the EMA since 2017. In November 2023 disappointing phase III clinical study results showed the ATMP did not attain the efficacy outcome. Consequently, they decided not to file for regulatory approval in the US. Zalmoxis® a gene therapy approved by EMA since 2016 had unfavourable results from the post-approval phase III clinical trial and was consequently withdrawn in October 2019.

The recently adopted EU Health Technology Assessment Regulation is expected to improve the clarity of the European reimbursement landscape for ATMPs by enforcing mandatory Joint Clinical Assessments (relatively harmonised HTA assessment) and proposing enhanced Joint Scientific Consultations to developers (including Academia). Joint Clinical Assessments (JCAs) will be mandatory for all new ATMPs from January 2025. (see sections 6.2.1 and 5.1.1 of this report).

In parallel, one of the work packages of the JOIN4ATMP initiative launched in 2024[c] aims to propose how ATMP developers can improve their interactions with HTA bodies throughout the ATMP development process, improve the usability of real-world data for HTA evaluation, and propose alternative pricing and reimbursement schemes. Although no HTA bodies are involved as partner at the moment, they are planned to be actively engaged as stakeholders in this project.

1.4 Challenging legal environment

Since the early 80's clinicians have explored cell-based therapeutic options (at first mainly tissue engineered products) for their patients. In Europe, these products were initially regulated under the European and national rules on blood, tissues and cells. In 2007, therapies based on cells and tissues that have been subject to substantial manipulation and gene therapies became centrally regulated in all EU countries as a medicinal product, and in particular as an advanced therapy medicinal product (ATMPs) based on Regulation 1394/2007 and Directive 2001/83/EC.[12, 13]

Under these rules, the specific nature of ATMPs has justified their specific status (such as specific MA dossier requirements, specific evidence requirements, early access authorisations, enhanced regulatory support, …), but also the recognition of a specific pathway for ATMPs prepared on a non-routine basis and used within an hospital (hospital exemption).

Despite these specific rules, a number of legal issues still affect the development of ATMPs by Academia but also by the Industry, and both plead[d] for further adaptations and flexibilities for ATMPs e.g. with regard to (see more detail in sections 3.3 and 5.3 of the Supplement):

- clearer classification rules between ATMPs and other regulated product including blood, tissues and cells that are not a medicinal product)
- clearer autorisation pathways (in particular with regard to hospital exemption)
- more flexible (limited) pre-clinical/ non-clinical dossiers;
- more flexible market access criteria including lower level of / different type of evidence (single arm trials, RWD, registries etc.), adapted quality rules;
- more flexible rules regarding GMOs (exemption);
- more flexible GMP standards, including specific manufacturing rules adapted to bed-side/decentralised production;
- more flexible or adapted distribution rules;

In the meantime, these aspects are currently being discussed as part of the EU Pharma Revision and could evolve in the coming years (see Box 1).

[c] JOIN4ATMP involves Academia, industry and patient representatives and aims to accelerate and de-risk European ATMP development and ensure wide-spread access of ATMPs, through the mapping of obstacles to such development, the audit of real-world-based solutions and the definition of new paths forward. https://www.join4atmp.eu/

[d] Including initiatives such as JOIN4ATMPs, European Alliance for Transformative Therapies (TRANSFORM) funded by industry, and public private partnership T2EVOLVE consortium coordinated by the Universitätsklinikum Würzburg and Servier.

1.5 Difficult translation to the patient

The early development of ATMPs often takes place in an academic setting, while bringing the product to the market is taken up by industry (see Appendix 1.3). Based on a positive proof of concept, Academia will usually create a spin-off and try to attract private investors or sell or out-license the intellectual property to industry in exchange for royalties or other rewards. For ATMPs, industry and investors see results of the first clinical trial as a necessary part of this proof of concept.

ATMP clinical development has specific challenges for Academia for example when compared with small molecule development.

First, ATMPs that can be used in a clinical trial are often difficult and expensive to produce. However, Academia does not necessarily study and develop ATMPs with a specific regulatory goal in mind. Therefore, the initial choices made for the qualification of starting materials and the manufacturing processes used for pre-clinical studies may not meet the GMP demands for clinical trial use or marketing authorisation. This not only leads to a repetition of these experiments and a waste of resources but also lengthens the time to reach the patient. [14] (see section 6.2.1 of this report).

Second, ATMPs often target very rare patient populations, which may reduce the interest of industry.[15]

Finally, fragmented funding opportunities and potentially lower or more complex intellectual property protection make it more complex for Academia to set up a valorisation and implementation strategy.

To improve this situation, ATMP-focused public-private partnerships are being tried across Europe, including in Belgium, with significant public support. The EMA also offers enhanced regulatory support to Academia in this area. To improve their manufacturing expertise, some academic institutions are also developing pre-GMP training facilities or specialised CMOs and CDMOs working both for Academia and Industry (see section 8.5.4.2 of this report).

1.6 Emerging funding and business models

Despite these efforts, the challenges faced by Academia in developing ATMPs remain important. As mentioned above, the business model for certain niche areas is extremely complex; for some ATMPs, especially those targeting rare and ultra-rare diseases (see Glossary), commercial deployment and marketing authorisation is not obvious. As a result, some ATMPs, even those with positive clinical results, are at risk of becoming stuck in early clinical development or disappearing because Academia does not have the capacity, funding or ambition to take them forward.

Reports from both the WHO [16] and a special research group commissioned by the European Parliament[17] have highlighted the scarcity of real innovation and the need, in certain areas, to propose additional drug development models to ensure that real innovation occurs and is accessible.

Various proposals have been put forward. For example, in the field of vaccine, proposals have been made to establish a European R&D infrastructure to address issues such as public health preparedness, vaccine development and cross-border scientific collaboration.[18]

At the same time, especially since COVID, there has been a significant increase in awareness of the need to improve public financing policies in the pharmaceutical sector to ensure better access to medicines. Concentration of efforts and better monitoring, transparency and authorisation mechanisms are advocated in the EU[19], [20] but also the US[21]

A possible new role for Academia in drug development is being explored in the ATMP field, with recent cases in Spain, the Netherlands and Denmark showing academic institutions, public funders and charities working together to lead advanced ATMP development and preparing market authorisation (see section 7 of this report).

These case studies clearly illustrate the need to combine the expertise of the different stakeholders, as well as the need for considerable public and charity funding. The question explored in this report is: "***What are the legal and strategic tools*** *to support academically developed ATMPs* ?"

The question of "***Why***" is more complex to answer and involves ethical, philosophical and political issues that are beyond the scope of this report. What are the public health needs that society must address in priority? What are the cases of market failure? And how to balance the health-related needs and economic considerations? These are questions that this report does not seek to answer. It does, however, seek to explore the tools for creating alternative development pathways that complement existing approaches.

2 AIM, SCOPE & LIMITATIONS

CÉLINE POUPPEZ (KCE), FRANK HULSTAERT (KCE), JOLYCE BOURGEOIS (KCE), IMGARD VINCK (KCE)

To improve accessibility and affordability of ATMPs in Europe, several charities, academic institutions, or public authorities advocate for academic, non-commercial, development pathways for ATMPs to complement the standard commercial road, particularly in the areas with high unmet medical needs where industrial development efforts are lacking, or where resulting commercial treatments are too expensive to ensure equitable patient access.[22-25]

Charities funding ATMP trials in oncology in Belgium had observed that the therapies funded by charities failed to reach the patients. After a large consultation of the Belgian stakeholders involved in ATMPs research for cancer treatments, the three main cancer charities and the cabinet of the Minister of Health have requested the KCE to prepare a roadmap for the development of academic cell therapies in Belgium, with a focus on legal aspects.[23]

Based on emerging examples of academic development in other European countries, and additional interviews with academics, clinicians, and translational experts, it was confirmed that several general legal and strategic issues needed to be clarified before implementing a concrete roadmap for Academia. It was also confirmed that these issues were not affecting cell therapies only.

This report focusses on these ‘pre-conditions’ towards a roadmap and explores the legal and organisational strategy for the academic development of ATMPs in Belgium.

Four research questions were identified:

1. What are the current landscape and the current manufacturing capacities for ATMPs in Belgium? (see Chapter 1 & 2 of this report)

2. What are the authorisation routes for ATMPs, and what legal challenges and potential improvements exist for Academia? (see Chapter 3 of this report)
3. What are the emerging examples of academic, non-profit, or socially responsible pathways for ATMPs, and what are the key drivers and lessons learned from these case studies? (see Chapter 4 of this report)
4. Which legal and strategic options can be explored to support academically developed ATMPs in Belgium, with the goal to promote patient access to safe, high-quality therapies with a clear clinical benefit? (see Chapters 5 and 6 of this report)

This exploratory study focuses on the 'business-related' legal aspects relevant to the academic development of ATMPs.

However, it is important to note that some of the 'product-related' legal issues affecting the ATMP development process (academic and industry driven) may also see improvements in the coming years with the revision of the EU pharmaceutical legislation (see Box 1); although not necessarily the main focus of the study, these aspects are briefly described in the report and further detailed in the Supplement.

Furthermore, concerns were raised in Europe about clinics or physicians offering unregulated cell therapy products or using grey zones in the legislation which can pose significant risks to patients (see an EMA communication in 2020,[26] and in 2024 an international consortium of journalists highlighted the illegal use of advanced therapy drugs by a company Immucura[27]).[28]

Our report does not cover such products or abuse; it explores the business case to support academic development, assuming that the developed products are compliant within the existing regulatory pathways.

3 METHODOLOGY

CÉLINE POUPPEZ (KCE), FRANK HULSTAERT (KCE), JOLYCE BOURGEOIS (KCE), IMGARD VINCK (KCE)

The research methodology used for this report is combined, on the one hand, classical legal methodology and, on the other hand, literature review, experts interviews and stakeholders consultations and data collection from official databases.

Legal methodology entails a systematic collection and analysis of the national and European law applicable to the subject (including existing law and currently proposed changes provided that these have been officially presented in a legislative process), parliamentary discussions leading to their adoption, case-law and policy documents (such as official guidelines from the national and European competent authorities). To collect the legislation and case-law, the official legislation and case-law databases (Eurlex, Curia, Belgian Official journal, …) were used.

Targeted literature review was also performed to identify the relevant legal and non-legal literature (e.g. handbooks and papers, legal/social sciences/scientific journals, policy reports, working papers, position papers from the various stakeholders). To collect literature, various databases and search tools, including LexisNexis, Kluwer Competition, Concurrences, HeinOnline, JSTOR, SSRN, Jura, Stradalex and ScienceDirect, Google Scholar, Pubmed were used with relatively simple search strings based on combinations of keywords, including for instance hospital exemption, ATMPs, cell/gene therapy, Clinical Trials, academic development, Marketing Authorisation holder, non-for-profit/public manufacturing, point-of-care/ bed-side manufacturing, socially responsible licensing clauses, etc. After collecting and analysing key sources, the so-called “snowball method” was used, checking for additional essential references in the footnotes of those key sources.

The literature was discussed within a (multidisciplinary) research team (8 lawyers, one physician and one pharmacist) and with experts in the field (national competent authorities, European Commission, national public

funding agencies, charities, academic clinicians, academic TTOs and CTUs, etc.) to analyse the existing hurdles and area for improvements/

The data related to the ATMP landscape in Belgium (Chapter 2 of this report) (including reimbursement) were either based on official databases (Eudragmdp), or direct input from the Belgian competent authorities (FAMHP and NIHDI) and discussed with them.

Case studies in different jurisdictions were identified and investigated via interviews and contact with experts directly involved in the implementation of those cases.

In total, during the project the research team interviewed and contacted more than 40 experts (from 17 different Belgian and European institutions[e]) to help prioritising the subjects for this report and obtain insight on the cases and examples studied in the report.

In addition, possible improvements identified in the report were discussed during three discussion meetings three discussion meetings with stakeholders familiar with the Belgian context (with prior sending of the key questions):

- With CTUs, TTOs and clinicians of the Belgian academic hospitals and universities involved in ATMPs projects to refine the scope et discuss the main issues in Belgium;
- With Belgian and EU public funders to discuss criteria to fund ATMPs projects;
- With a broader group Belgian stakeholders (incl. Academia, charities, Belgian reimbursmeent authorities, National competent authority in Belgium, industry and patient associations) together to discuss the key findings of the report and to examine the recommendations.

[e] KOTK, ACF, STK, Genethon & Telethon France, UZ Ghent and University of Ghent, Public hospital of Barcelona, Biowin, Euro CTG, European Alliance of Academic hospitals, FAMHP, RegMed XB, Inovigate, UZ Brussel, LRD (KU Leuven) European Commission (DG Santé), Cabinet of the Belgian Federal Minister of Health, ZonMw, Dutch ministry of Health care and Sport.

4 CHAPTER 1 - LEGAL FRAMEWORK FOR ATMPS IN EUROPE

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Key points

In Europe, ATMPs are mainly regulated at EU level. However, several aspects of ATMPs are in the hands of the national Members States.

EU harmonised fields include:

- Clinical trials (frameworks)
- Hospital Exemption (definition and basic requirements)
- Central marketing authorisation
- Quality, Safety, and Efficacy Standards
- Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP)
- GMOs (marketing and importing of GMOs are regulated at the EU level. However, the cultivation of GMOs is left to individual EU Member States, which can prohibit or restrict cultivation based on health and environmental concerns)
- Post-Authorisation Pharmacovigilance

National competencies include:

- Clinical trials: implementation of EU framework, authorisation and oversight of clinical trials

- Hospital Exemption: implementation of the EU definition, national authorisation and oversight
- Concrete interpretation, certification and control of GMP and GCP compliance
- Pricing and reimbursement
- Healthcare delivery
- GMOs: EU member states have the right to prohibit or restrict the sale or cultivation of approved GMOs based on adverse effects on health and the environment.
- The SoHO classification

4.1 Definition and applicable legal framework

ATMPs are subject to a complex legal framework, which is not always easily delineated from other frameworks.

Taking into account that ATMPs are often based on substances of human origin, other connected legal frameworks include the Directives regarding human body materials (blood, cells and tissue (BTC legislation[f]) and their national implementations.

Some substances of human origin are used practically unaltered from the form in which they have been procured from the donor, other substances of human origin are subject to extensive further manipulation prior to use in patients.[29] In Europe, the applicable legal framework will primarily differ depending on the level of manipulation that has been executed.

The core legal instrument governing ATMPs is the Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 ("**ATMP Regulation No 1394/2007**"). The ATMP Regulation No 1394/2007 supplements the general requirements under the central European legal instrument governing authorisation of pharmaceutical products in the European Union, the Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

The ATMP Regulation No 1394/2007 is applicable to medicinal products which are qualified as gene therapy medicinal product, as a somatic cell therapy medicinal product, or as a tissue engineered product. According to the ATMP Regulation No 1394/2007

- A gene therapy medicinal product is a biological medicinal product which has the following characteristics:
  - 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; and
  - 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. Gene therapy medicinal products do not include vaccines against infectious diseases.

[f] Note that a new SoHO Regulation will apply as from 7 August 2027, 3 years after its publication and entry into force, with an extra year for certain provisions (see infra Box 2).

- a somatic cell therapy medicinal product is a biological medicinal product which has the following characteristics:
  - it 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[g]; and
  - it 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.
- a tissue engineered product is a medicinal product which has the following characteristics:
  - It 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. A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, biomolecules, biomaterials, chemical substances, scaffolds or matrices. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues, and which do not act principally by pharmacological, immunological or metabolic action, are excluded from this definition
  - it 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.

Cells or tissues are considered 'engineered' if (i) the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved (note that the Regulation includes a list (Annex I) of manipulations which are not considered as substantial manipulations), or (ii) the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Additionally, the ATMP Regulation No 1394/2007 is applicable to combined advanced therapy medicinal products, which are advanced therapy medicinal products incorporating medical devices with viable cells or tissues, or with non-viable cells or tissues that can act upon the human body with action that can be considered as primary to that of the device.

The EU ATMP definition entails several aspects that can be subject to interpretations and discussions. To identify whether their product is an ATMP, developers have the possibility (not the obligation) to request the advice of the EMA or of their national competent authority (Article 17 of the ATMP regulation). At EU level, the European Committee for Advanced Therapies (CAT) has provided a guidance on ATMPs classification (under the form of a reflection paper).[30] In addition, the CAT can also provide a free scientific recommendation on an ATMP classification upon request (within maximum 60 days). This advice is available to the industry and to Academia and does not require the product to be already in the non-clinical or clinical development phase. Any EMA classification advice is published on quarterly basis on the EMA website.[31] The advice provided by the CAT on the classification of a product as an ATMP is not legally binding. However, it is highly influential and typically followed by the European Commission when making the final decision on classification (in the context of a marketing authorisation).

[g] The manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification

In Belgium, several advices are available. The fees for Academia are reduced (in 2024, fees could vary between 660,91€ for simple advice and 5.287,30 € for more complex scientific assessment).[32]

Box 1 – The Pharma Revision

The European Commission proposed a major revision of the EU pharmaceutical legislation in April 2023 ('the EC Pharma Proposal'). The proposal adopted by the Commission propose a revision of the existing general pharmaceutical legislation (Regulation 726/2004 and Directive 2001/83/EC) and the legislation on medicines for children and for rare diseases (Regulation 1901/2006 and Regulation 141/2000/EC, respectively).

Some of the proposed changes could potentially impact selected issues addressed by this report. For instance, the proposal alleviates in part the requirements for the decentralised manufacturing of ATMPs (see article 142 of the current EC Pharma Directive proposal).[33] It is also revising the rules governing hospital exemption with the aim to make the use of this exemption more transparent and to harmonise certain aspects. In the recitals, the Commission also proposes to charge EMA to examine whether an adapted framework should be established for certain less complex ATMPs that have been developed and used under the hospital exemption. A new definition of ATMPs is also being discussed at the time of writing.

As of April 2024, the European Parliament has adopted its position, and the next steps involve trialogue negotiations with the Council.

The proposed revision is unprecedented and this negotiation process can take some time and no timetable for adoption has been announced at the time of writing.

4.2 Differentiation with regulations on human tissues and cells

As indicated above, the ATMP Regulation No 1394/2007 applies to human bodily materials such as cells or tissue that have been subject to a substantial manipulation, or which are not intended to be used for the same essential function or functions in the recipient as in the donor.

However, in many instances, cells and/or tissue will be used in therapies without such substantial manipulation, in particular in cell or tissue transplant therapies.[h] [34] For such types of cell and tissue therapies, in which these human biological materials are not used as medicinal product, the ATMP Regulation No 1394/2007 does not apply, but the general regulations on human tissue and samples apply. These distinctions are not always easily determined, or consistent; there are examples of ATMPs that have been classified as medicinal products in one Member State, but not in another (in which case they remain subject to BTC legislation), leading to uncertainties on the applicable legal framework and regulatory requirements. [35, 36 37]

The key EU legal instruments under the BTC Legislation are Directive 2002/98/EC on safety and quality of human blood and blood components and Directive 2004/23/EC on safety and quality of human tissues and cells, soon to be replaced by the Regulation of the European Parliament and of the Council on Standards of Quality and Safety for Substances of Human Origin Intended for Human Application and Repealing Directives 2002/98/EC and 2004/23/EC.

[h] A Belgian example where classification differs based on manufacturing process: when cells can be extracted directly from the blood with improved purification techniques – myeloid dendritic cells - it is not considered a substantial manipulation, therefore not classified as an ATMP. In contrast, *ex vivo* cultured monocyte-derived dendritic cells are classified as ATMPs.

Box 2 – The SoHO legislation (Substance of Human Origin)

In April 2024, the European Parliament has approved the new Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application.[38, 39]

These substances were previously regulated by the blood, tissues and cells EU Directives[40, 41]

1. Scope:
    - The SoHO Regulation applies to any substance collected from the human body in whatever manner, whether it contains cells or not and whether those cells are living or not, including blood, blood components, tissues, cells (including haematopoietic peripheral blood, umbilical-cord blood and bone-marrow stem cells, reproductive cells and tissues, foetal tissues and cells and adult and embryonic stem cells) and any substance of human origin such as human breast milk, intestinal microbiota, blood preparations not used for transfusion, and any other SoHO that may be applied to patients in the future. Organs are not covered by the SoHO Regulation.
    - The SoHO Regulation applies to the registration, evaluation and testing of SoHO donors, as well as to SoHO collection and release, as well as the storage, import and export of SoHO up to and including their distribution to a manufacturer regulated by other Union legislation (such as ATMP Regulation).
2. Purpose of the new Regulation:
    - Ensure high safety and quality standards for substances of human origin (SoHOs).
    - Protect SoHO donors and recipients.
    - Improve harmonisation across EU, facilitation cross-border exchange of SoHo and improving patient access to therapies.
    - Monitor and support the sufficiency of SoHO supply critical for patient health.
3. Changes introduced:
    - Annual collation, reporting, and reviewing of data by national authorities.
    - Publication of data by the European Medicines Agency (EMA) in a central repository.
    - Improved crisis preparedness and resilience to safeguard access to therapies.
    - Creation of a SoHO Coordination Board to improve regulatory qualification of substances, product or activity at hand.
4. Next Steps:
    - The Regulation will apply from mid-2027, three years after publication and entry into force, with an extra year for certain provisions.

The SoHO Regulation also seeks to facilitate the consistency of classifying SoHO and ATMPs respectively. As such, it specifically states that where there is doubt about the regulatory status of a particular substance, product or activity under the SoHO Regulation, SoHO competent authorities should consult the relevant authorities responsible for other relevant regulatory frameworks, namely medicinal products, advanced therapy medicinal products, medical devices or organs, and the SoHO Coordination Board (SCB) established by the SoHO Regulation, with the aim of ensuring coherent procedures for the application of the SoHO Regulation and other relevant EU

legislation.[i] The SCB must be informed on the outcome of the national consultations and give its opinion on the regulatory status of the substance, product or activity. In order to ensure consistent decisions across all Member States with regard to borderline cases, where SoHO competent authorities decide not to follow the SCB's opinions, they must justify their decisions, and the European Commission can decide on the regulatory status of a particular substance, product or activity under the SoHO Regulation.

When SoHO or SoHO preparations are used to manufacture products regulated by other EU legislation (such as ATMPs), SoHO competent authorities are required to cooperate with the relevant authorities responsible for the products regulated by other EU legislation on their territory. That cooperation should aim to reach an agreed approach for any subsequent communications between the SoHO competent authorities and those relevant authorities responsible for the other relevant sectors, as needed, regarding authorisation and monitoring of the SoHO or the product manufactured from SoHO.

Cell gene and tissue therapies which do not qualify as ATMP do not need to follow the clinical trial trajectory up to marketing authorisation (or follow other alternative pathways, such as the hospital exemption), to use them in clinical practice. In addition, manufacturing requirements (referred to as Good Manufacturing Practice) differ depending on the use case of the human bodily materials, as transplant materials, or as medicinal products.[42] While many healthcare organisations are GMP-accredited for handling human bodily materials, they are not accredited for the further complex steps required for ATMP manufacturing.

In cases of borderline classification between SoHOs and ATMPs, the national SoHO competent authorities (in Belgium the FAMHP also competent for medicines) are in principle competent to decide case by case. However, they must consult other relevant regulatory authorities (e.g., medicinal products, ATMPs, medical devices) and inform the SoHO Coordination Board (SCB). The board's advice can help clarify classification issues (even if its recommendations are not legally binding). In case of disagreement of the national authorities with the advice of the SCB, the Commission may conduct its own assessment and issue a binding decision to resolve the issue. This ensures that the regulations are applied consistently across all Member States and that any disputes are settled effectively (recital 40 and Article 69 of the SoHO Regulation) Legislation on genetically modified organisms.

Drug developers of ATMPs should also take into account the legislation on genetically modified organisms ("**GMOs**") as they are strictly regulated within the European Union, under Directive 2001/18 (the "GMO-Directive").[43] If an ATMP qualifies as a GMO, additional requirements must be met before the ATMP may be used or released in the environment (e.g. via a clinical trial). Since the GMO-legislation is laid down in a Directive, variability between the Member States is still possible since Member States have some freedom in how to transpose the GMO-Directive into national laws. Navigating GMO legislation is essential for obtaining regulatory approval. Without compliance, academic developers may face significant delays or rejections in their research and clinical trials. Compliance with GMO legislation is also often a prerequisite for bringing ATMPs to market. This ensures that the products can be safely and legally distributed to patients. The main regulatory requirements in Belgium are summarised in the Supplement (see section 2.3.4.2 in the Supplement).

[i] Article 69 of the SoHO Regulation.

5 CHAPTER 2 - ATMP LANDSCAPE IN BELGIUM

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Key points

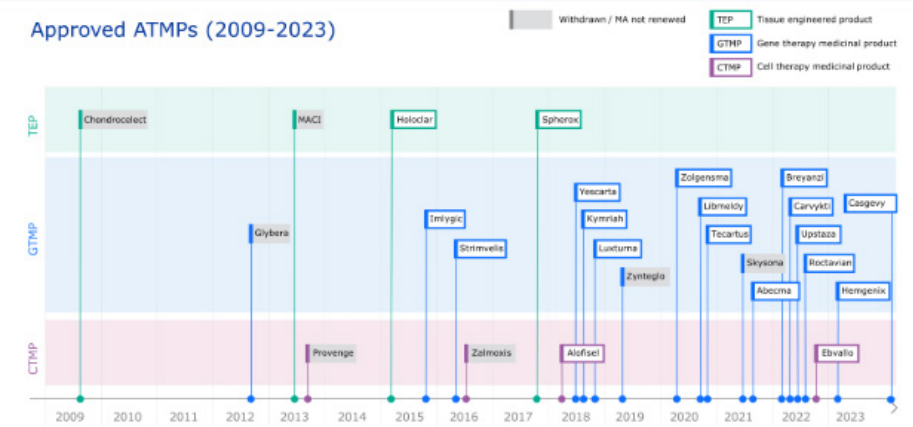
- Of the 20 ATMPs with a license to be marketed, only 8 are effectively commercialised in Belgium and all are reimbursed via a confidential managed entry agreement (Sept '24).
- Other access pathways are emerging such as cross-border initiatives to receive reimbursement for ATMPs not commercialised in Belgium and administered abroad in specialised centres (for very rare diseases). Additionally, initiatives are underway to explore new reimbursement pathways adapted to the specificities of ATMPs.
- Current access to ATMPs via clinical trials is common in Belgium. There are many clinical trials started in Belgium. The vast majority of the trials have a commercial sponsor.
- The academically led ATMP clinical trials in Belgium are focused on cell therapy, and mainly involve the use of autologous dendritic cells (UZGent/VUB/UZA) or allogeneic mesenchymal stem cells (CHU Liège). The academically led trials are early phase, i.e. phase I/II (see Table 2)
- Access to ATMPs via Hospital exemption (HE) is currently non existing in Belgium. Academia perceives the eligibility criteria for HE and the unclarity on the reimbursement possibilities in the Belgian legislation a major hurdle (see section 6).
- Belgium has a rich field of ATMP players, from facilities producing parts of the ATMP (biological starting material such as viral vectors), to facilities certified for manufacturing cell and gene therapy for clinical use (e.g. CDMOs). The majority have a licence for investigational medicinal products (meaning for clinical trials).
- However, it is a dynamic field with a lot of takeovers and cases of bankruptcy, due to high cost of keeping a manufacturing facility running, which requires structural financing.
- The creation of spinoffs and public-private partnerships in the ATMP field are fostered by regional public authorities in charge of research, innovation and economy and their innovation clusters (BioWin and MEDVIA see sections 8.2.1.). The primary aim of such financing by the regions is to create innovation and employment.
- There are three academic institutions with a manufacturing authorisation for ATMPs (only for clinical trials), of which two have in-house GMP facilities to manufacture. These academic facilities also act as a CDMO for private players (diversification of projects to secure financing)
- The manufacturing landscape for ATMPs in Belgium is highly dynamic and is expected to evolve further with ongoing discussions, interest, and testing of point-of-care manufacturing.

5.1 Access to ATMPs

5.1.1 Via (reimbursed) centrally authorised ATMPs

ATMPs obtain market authorisation via the central procedure at EMA which grants them a licence for the EU, thus including Belgium. However, this does not guarantee their availability on the Belgian market. Sometimes a pharmaceutical firm does not commercialise it in a given country because the market is considered too small or because of the low probability to obtain reimbursement by the health insurance for a high-priced ATMP with a lot of uncertainty concerning the beneficial effect.[9] Figure 1 entails the general EU picture and shows which ATMP products have received market approval from 2009 till April 2024. In July 2024 another ATMP *Durveqtix*® (now *Beqvez*®) has received authorisation. Of the in total 27 approved ATMPs, already seven have been withdrawn, most of the time for commercial reasons.[44] Of these 20 remaining ATMPs, only 8 are effectively commercialised in Belgium (September 2024). Table 1 informs which ATMPs authorised in Europe are accessible for Belgian patients: commercialisation and reimbursement status.

Figure 1 – ATMPs approved by the European Medicines Agency from 2009 till 2024



Medicinal products with grey background indicate the ones removed from the market. Note that in July 2024 another ATMP Durveqtix® has received authorisation (not shown on figure) Source: CAT quarterly highlights[45]

In Belgium, several reimbursement pathways exist, and initiatives are underway to explore pathways adapted to the specificities of ATMPs.

The primary route for authorised ATMPs is via **reimbursement by the Belgian National Health and Disability insurance (RIZIV-INAMI**). However, the prices are high and for a lot of those ATMPs the added value compared to the cost is highly uncertain, making them less suited for a standard reimbursement procedure. **Managed entry agreements – MEA** ("article 81/111") between market authorisation holder and Belgian authorities (RIZIV-INAMI) are now very common to grant patients access to innovative treatments (including ATMPs), while allowing the industry to collect additional evidence on value. Eight ATMPs are effectively commercialised and reimbursed in Belgium[j], all of them via a MEA (see Table 1). The price-volume details of these managed entry agreements are confidential. Most of them have a time span of 3 years but are often renewed.[46, 47]

In some cases, **collaboration between multiple countries** is necessary to secure financial access. In March 2024 the BeNeLuxA initiative enabled the reimbursement of the gene product Libmeldy®, which is not commercialised in Belgium.[48] In this cross border type of reimbursement the patient needs to go to the specific treatment centre (five in Europe: Utrecht, Paris, Tubingen, Milan and Manchester, all accredited by the concerned company) to get the treatment reimbursed via RIZIV-INAMI.

Box 3 – BeNeLuxA – collaboration on pharmaceutical policy

The BeNeLuxA initiative aims to ensure patient's access to expensive medicines.[48] Anno 2024, it is a collaboration between five EU countries: Belgium, The Netherlands, Luxemburg, Austria and Ireland. They work together in different areas: horizon scanning to find out which innovative medicines are about to become available in the near future, Health Technology Assessment, information sharing, and negotiating together on prices with industry. In March 2024 the joint HTA and price negotiation between Ireland, Belgium and the Netherlands on the one hand and the pharmaceutical firm lead to the reimbursement of the gene product Libmeldy®.

j Alofisel not included as commercialisation has been interrupted from March 2024 onwards

In the near future, the implementation of the **Regulation on Health Technology Assessment** (HTA Regulation) will introduce a permanent framework for joint European collaboration on, amongst other things, HTA, to improve and facilitate access on to innovative health technologies in the EU.[49] From January 2025 onwards, ATMPs will be required to undergo joint clinical assessments. The relative efficacy of the ATMP will from then on, be assessed centrally in Europe with the intent to reduce duplication of HTA activities and improve patient access. Although Member States will be able to use common HTA tools, methodologies and procedures across the EU, they remain responsible for assessing a medicine's non-clinical elements, including economic, social and ethical ones, and making decisions on pricing and reimbursement. It remains to be seen whether a common HTA assessment will also lead to more alignment in pricing and reimbursement policies amongst EU Member States. The methods and procedures for the joint clinical assessment and for an early dialogue with industry (joint scientific consultation) under the HTA regulation are currently being developed and can be found on the EU website.[50]

In May 2024, **renewed procedures** were introduced in Belgium to enable **early and/or fast access** to innovative drugs with potential added therapeutic value for patients.[51] The existing 'early temporary reimbursement' procedure did not work in practice and was therefore made more attractive, procedurally, administratively and financially. Since March 2023 there has been only one compassionate use program for the somatic cell therapy *Ebvallo*®. During the program the product was provided for free by the company. However, from July 2024 onwards *Ebvallo*® has been included in the reimbursement system by the National Health insurance via a MEA

Under the early and fast access procedures, companies can receive a lump-sum contribution from the NIHDI if they make innovative drugs with potential added therapeutic value available. Implementing decrees (including details on the lump sum) are not yet available.

Early access relates to the pre- MA period, is limited to medicines covered by a compassionate use or medical need programme (see Appendix 3.1.2), included in the list of unmet medical needs established by the NIHDI General Council.

Fast access refers to the period between the positive advice for approval of the medicine by the Committee for Medicinal Products for Human Use (CHMP) and the introduction and the result of a reimbursement dossier at the Commission for the reimbursement of pharmaceuticals (Commissie Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments, CTG-CRM) for a pharmaceutical that has been granted early access, for pharmaceuticals granted PRIME status[52] by the European Medicines Agency (EMA) and for pharmaceuticals that are the subject of accelerated assessment procedure undergone by the EMA[53] (see sections 3.3.6.1. and 3.3.7.3 in the Supplement). In this sense, fast access already allows compensation when negotiating pricing and when going through the HTA process. The collection of data has been integrated in the early and fast access procedures. As the fast access programme could help to reduce or respond to certain uncertainties through the collection of real world data, this may help to reduce the number of MEA negotiations.

For both the early access program and the fast access program, there will be lump sums per patient that will vary depending on the type and complexity of the molecule. In both cases, the amount will be fixed for a certain period of time (per month, per year or only once for gene therapies, for example). For the early access program, in addition to this lump sum per patient, there will be a lump sum per dossier, which will be paid only once. This lump sum is intended to cover the additional costs associated with setting up a compassionate use or medical need programme.

At the time of the writing of the report, the amounts of the lump sums are not defined yet. In the proposals of a 2023 Roadmap related to the revision of early and fast access procedures that came about after a consultation process with stakeholders, a lump sum of 25.000 euro/dossier to cover the costs for setting up a compassionate use or medical need programme and a lump sum per patient of 60.000 euro for cell- and gene therapy was proposed.[54]

It can be questioned whether Academia can apply for early and fast access programs if they comply with the conditions and obligations.[k] Compassionate use programs can be an option for Academia developing ATMPs and having the intention to obtain a MA. The person requesting for a compassionate use program can be a sponsor in the comprehension of the law of 7 May 2004 regarding experiments on humans.[l] This can be a person, an enterprise, an institution or an organism responsible for the launch, management and/or financing of an experiment with the concerned medicinal product.[m] As such, not only pharmaceutical companies but also Academia can apply for a compassionate use program. In order to apply for a compassionate use program, an application for marketing authorisation must have been submitted or clinical trials must still be ongoing.[n] However, the legislation does not specify which stage of clinical trials this concerns. According to personal communication by the FAMHP, for ATMPs, phase 2 study data can be accepted as sufficient clinical data if they are convincing.

As Academia can apply for a compassionate use program, the possibility to get a financial compensation via the early and fast access programmes is relevant. According to the law related to the early and fast access procedures, “enterprises” can apply for early or fast access. However, the notion of “enterprise” is not defined in this law. According to the personal communication by the NIDHI, this notion must be understood as the party responsible for the drug in question to the competent Belgian authorities (i.e. either the pharmaceutical company that produced the drug and conducted all the studies, or any other company that is recognised as the parent company's legal representative to the Belgian authorities, thereby signing a commitment on behalf of the parent company). Academia can thus probably not qualify as enterprise in the existing legislation. The respective legislation should be amended (or at least clarified) to allow the application for early and fast access procedures by Academia. Yet, as mentioned in section 5.4 of the Supplement of the report, Belgian laws may restrict the potential for Academia to establish commercial activities, such as progressing to marketing authorisation. Establishing a separate legal entity (i.e. a special purpose vehicle) which takes on the development activities, in cooperation with the hospital, and which takes on the further commercialisation of the resulting ATMP could be a solution.

Specifically for the context of ATMPs, a patient access/funding procedure for early and fast access and for outcomes-based market entry agreements with integrated real-world evidence (RWE) was developed in a **project** led by **Inovigate**.[55] The French model partly served as source of inspiration.[o]

Another route for financing is via the **Special Solidarity Fund**, which grants or refuses **individual** requests for financial compensation for diseases affecting vital signs. A small number of ATMPs have been granted financial compensation on a per patient basis via this route (see Table 1): Strimvelis® and Zolgensma®).

Despite some discussions on the experimental nature of Hospital exemption, there is, in theory, no prohibition to cover ATPMs authorised under hospital exemption via the Special Solidarity Fund (see Box 4). So far, however, the Special Solidarity Fund has not received any applications for reimbursement of an ATMP under hospital exemption (see section 6.4.2.5 of this report).

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k Note that an application for early access is linked to a number of obligations and commitments, including the successful completion of ongoing trials and the submission of a MA application for the indications covered by the application within six months of the date of application for the early access program.

l See art.106 § 1 Royal Decree of 14 December 2006 on medicinal products for human use*, B.S./M.B.* 22 December 2006

m Art. 2, 21° Law of 7 May 2004 regarding experiments on humans, *B.S./M.B.* 18 May 2004.

n Art. 6 quarter, § 1, 2° Law of 5 March 1964 on medicinal products for human use, *B.S./M.B.* 17 April 1964

o For more information on the French model see : Autorisation d’accès précoce, autorisation d’accès compassionnel et cadre de prescription compassionnelle - Ministère de la santé et de l'accès aux soins (sante.gouv.fr)

Box 4 – Special Solidarity Fund

The Special Solidarity Fund within the RIZIV-INAMI gives patients with a very serious condition a financial compensation for certain medical services, for which no reimbursement is provided, and which are particularly expensive. To qualify, some specific conditions must be met, such as rare conditions that threaten vital functions and for which no reimbursed therapy is available. Medicines that are still in clinical trial stage are not allowed. The conditions are specified on the RIZIV-INAMI website. The decisions of the BSF are taken by the College of Physician Directors on a case-by-case basis. An application can be submitted up to 3 years after delivery of the medicine. An application should be submitted via the patient's health insurance fund to the RIZIV-INAMI which then provides a response after about 15 days. Ideally, one already has an agreement from the BSF before the treatment is administered (prior agreements in principle are possible). If the request is refused, the patient or (often) the hospital will have to bear the costs.

Table 1 – Overview of ATMPs on the Belgian market (September 2024)

ATMP with EMA authorisation	Commercialised in Belgium (FAGG website)	Reimbursed in Belgium by the National Health insurance (RIZIV-INAMI website)	Medical need/compassionate use Program in Belgium (FAGG)	Special Solidarity Fund (RIZIV-INAMI) (on an individual basis)
Holoclar®	Yes	Under temporary confidential contract since 2017 Official price 91 644 euro (for 3,8 cm² cells) (one treatment dose per patient and per procedure) • For adults with limbic stem cell deficiency resulting in cornea and vision loss as a consequence of chemical or physical burning of the eye		
Spherox ®	No (commercialisation stopped in 2024)*	Reimbursement since March 2022 10 046 euro per injection (one treatment dose per patient and per procedure) • For adults under 50y with severe cartilage lesion of the knee and no arthrosis or joint infection		
Imlygic®	not commercialised	no		
Strimvelis®	not commercialised	no		Has been allowed for treatment of ADA-SCID in Milan expert centre in 2022
Yescarta®	yes	Under temporary confidential contract since 2021 296 807 + extra budget if data-collection is foreseen at 6-12 and 20 months (21 207 euro + 21 207 euro) per IV bag of cells (single treatment for single use) • Adults with refractory/recurrent B cell lymphoma (different forms)		
Kymriah®	yes	Under temporary confidential contract since 2019 Official price 296 807 + extra budget if data-collection is foreseen at 6-12 and 20 months (21 207 euro + 21 207 euro) per IV bag of cells. • Adults with refractory/recurrent DLBCL • Children (<25y) with refractory Bcell ALL		
Luxturna®	yes	Under temporary confidential contract since 2021 Official price 351 079 euro per injection		

ATMP with EMA authorisation	Commercialised in Belgium (FAGG website)	Reimbursed in Belgium by the National Health insurance (RIZIV-INAMI website)	Medical need/compassionate use Program in Belgium (FAGG)	Special Solidarity Fund (RIZIV-INAMI) (on an individual basis)
Zolgensma®	Yes	Under temporary confidential contract since December 2021 Official price 2 061 707 euro per patient • Children younger than 2 year Genetic disorder spinal muscular atrophy and permanent invasive breathing support		Has been allowed for treatment Type 1 spinal muscular atrophy in 2021. (1 patient refused in 2019 as the clinical trial stage was not completed)
Libmeldy®	not commercialised (cross border)	Under temporary confidential contract since March 2024 Official price 3 047 507 euro per patient • Children congenital hereditary metabolic disease metachromatic leukodystrophy (with no symptoms yet)		
Tecartus®	yes	Under temporary confidential contract since 2022 Official price 346 627 euro per IV bag of cells • Adults with refractory/recurrent mantel cell lymphoma		
Abecma®	not commercialised	no		
Breyanzi®	not commercialised	no		
Carvykti®	not commercialised	no		
Upstaza®	yes	Under temporary confidential contract since November 2023 Official price 3 710 000 euro per patient • > 18months old with clinical and genetic confirmed AADC deficiency		1 refused in 2022 (as the clinical trial stage was not completed)
Roctavian®	not commercialised	no		
Hemgenix®	not commercialised	no		
Casgevy®	Not commercialised	no		
Alofisel®	No (commercialisation stopped in 2024)**	no		

ATMP with EMA authorisation	Commercialised in Belgium (FAGG website)	Reimbursed in Belgium by the National Health insurance (RIZIV-INAMI website)	Medical need/compassionate use Program in Belgium (FAGG)	Special Solidarity Fund (RIZIV-INAMI) (on an individual basis)
Ebvallo®	Yes	Under temporary confidential contract since July 2024 Official price 79 500 euro for 1 treatment cyclus. It is foreseen that a patient needs two cycli and a maximum of four cycli is reimbursable. • > 2 years and adult transplant patients with recurrent/refractory Epstein bar virus positive post-transplant lymphoproliferative disease	Compassionate use program since 28/03/2023 till July 2024	
Durveqtix®* **	Not commercialised	no		

*Source: RIZIV-INAMI-Note: * Market authorisation holder filed for bankruptcy in 2022. **in October 2023 Phase 3 study did not meet primary endpoint of combined remission at 24 weeks.*** Durveqtix® has received EMA authorisation in July 2024 – and changed its name to the one on the USA market: Beqvez®*

5.1.2 Via clinical trials

Prior to an ATMP obtaining market approval, it undergoes a clinical development process, during which its efficacy and safety must be demonstrated through different phases of clinical trials (see section 2 in the Supplement).

To analyse the field of clinical trials on ATMPs in Belgium and the role of Belgian Academia in ATMP clinical development, an analysis of recent clinical trial applications to the FAMHP was performed together with a search in clincialtrials.gov and grey literature.

Clinical trials on ATMPs taking place in Belgium need to be approved by the FAMHP and the relevant Ethics Committees. FAMPH reported there were 67 trials with ATMPs introduced over the timespan 2021 – 2023, of which 6 were already withdrawn, and some (>10) stopped (due to disappointing results, bankruptcy, recruitment focus outside of EU (see table on clinical trials with ATMPs in Belgium in Appendix 1.2).

The majority of the clinical trials with ATMPs **introduced** since 2021 had a **commercial sponsor** (see table on clinical trials with ATMPs in Belgium in in Appendix 1.2). Only seven were non-commercial of which five were academically led. Of the other two non-commercial trial applications, one was sponsored by the European Myeloma Network and another via a public-private partnership *Persomed* (see further).

The sponsor is not always equivalent to the entity that finances a clinical trial. Most of the time a specific grant or charity involvement makes the academically led clinical trial financially possible (charities such as Kom op tegen Kanker, Stichting tegen Kanker, public grants from authorities).

Table 2 provides an overview of the academically led ATMP clinical trials in Belgium and shows a focus on cell therapy. These trials primarily involve the

use of autologous dendritic cells (UZGent/VUB/UZA) or allogeneic mesenchymal stem cells (CHULiège)[p].[34, 56, 57]

The academically led trials are all early phase, i.e. phase I/II. They manufacture their ATMP products according to GMP standards either in their own facility (CellGenTherapies for UZGent, Laboratory of Hematology for Cell and Gene Therapy CHU Liège) or via a spinoff/CDMO facility (e.g. Anicells for UZA and EtheRNA for UZBrussel).

Note that also other academic hospitals and research groups are involved in ATMP research but do not have clinical trials running: Cellular Therapy Research Laboratory ULB- Institute Jules Bordet (mesenchymal stem cells)-UCLouvain -Cell and Tissue Therapy Center - Hepatic Cell Therapy Unit isolation, expansion and cryopreservation of hepatic stellate cells (HSCs), The Prometheus platform at KULeuven (skeletal tissue engineering). The Antwerp Research Group for Ocular Science.(AGROS) on tissue engineering in ophthalmology. The KULeuven research group Trellis on advancing adeno-associated viral vectors for gene therapy.

In addition to academic institutions being the sponsor of a clinical study, academic hospitals and their facilities often collaborate with the private sector to conduct clinical trials and recruit patients (clinical trial centres/units). Even earlier, at the pre-clinical stage, there is close collaboration between the academics and spinoffs and other private partners.

[p] Note that there were also clinical trials with cells/tissue but that were not classified as ATMP: for example, dendritic cells (VUB/UZBrussel) with no substantial manipulation (NCT03707808, NCT04571632, NCT03747744). Another example is stromal vascular fraction from adipose tissue (UZGent) (NCT06171204)

Table 2 – ATMP clinical trials with a Belgian academic sponsor

Study identification	Sponsor	ATMP	Indication	Study details
CLINICAL TRIALS introduced to FAMPH since 2021 till 2023*				
ADDICT-pedGLIO Eudract 2020-004125-23 NCT04911621	Antwerp University Hospital (UZA)	Autologous Wilms' tumor 1 (WT1) mRNA-electroporated **dendritic cells** Somatic cell therapy	brain (stem) tumors (High-grade Glioma or Diffuse Intrinsic Pontine Glioma)	Two arms single centre **phase I/II study** in 10 pediatric patients – arm A with newly diagnosed and arm B with pre-treated patients
PERSOMED *Eudract 2021-003303-17*		*Autologous monocytic derived **dendritic cells** electroporated with two types of mRNA (Tetramix via plasmid DNA and Neoantigen via a synthetic DNA)*	*metastatic microsatellite stable colorectal cancer*	*Phase I* *Did not start -Persomed consortium did not secure investment*
Immuno-MESODEC Eudract 2021-003229-31 NCT05765084	Antwerp University Hospital (UZA)	Autologous WT1 mRNA loaded **dendritic cells** Somatic cell therapy	Pulmonary membrane cancer - Malignant pleural mesothelioma	multicenter single arm **phase I/II t**rial in 15 adult patients in addition to first line therapy 3 sites(UZ, AZ St Niklaas, AZ MariaMiddelares) in Belgian hospitals are recruiting
MS-tolDC_Phase2-RESTORE Eudract - 2022-003465-38	Antwerp University Hospital (UZA) Hospital Universitari Germans Trias I Pujol (horizon 2020)	Autologous myelin peptide-loaded tolerogenic **dendritic cells** Somatic cell therapy	Multiple sclerosis	phase II study in 72 patients is to determine whether intradermal (in Belgium) or intranodal (in Spain) injection of tolDC is effective and safe
Eudract 2022-003833-21 NCT03901235	CHU of Liège	Allogenic bone-marrow derived **mesenchymal stromal cells** Somatic cell therapy	Crohn's Disease	Single centre, single arm, **phase I/II** in 50 adult patients
IL15-TransDC Eudract : 2020-004124-42 **NCT05964361**	Antwerp University Hospital (UZA)	Autologous **dendritic cells** electroporated with mRNA encoding WT1, IL15 and IL15 receptor alpha subunit Somatic cell therapy	refractory or advanced solid tumors of the esophagus, liver, pancreas and ovaries	Single centre, First-in-human – phase I in 10 patients
CLINICAL TRIALs (studies introduced before 2021)*				
MIDRIXNEO Eudract 2018-004666-34 NCT04078269	University Hospital Gent (UZGent)	Autologous Dendritic Cells loaded with tumor-specific antigens (neoantigens)	Non-small Cell Lung Cancer	Phase I first in human trial in 6 patients (single arm, open label, UZGentl)

Study identification	Sponsor	ATMP	Indication	Study details
				Results published Ingels et al 2024[58]
MIDRIX4LUNG Eudract 2018-004665-14 NCT04082182	University Hospital Gent (UZGent)	Autologous Dendritic cells loaded with 4 antigens	Non-small Cell Lung Cancer	Phase I fist in human in 7 patients (single arm, single centre, open label, UZgent)
MESODEC Eudract 2014-001099-75 NCT02649829	Antwerp University Hospital (UZA)	Autologous WT1 mRNA loaded **dendritic cells** Somatic cell therapy	Pulmonary membrane cancer - Malignant pleural mesothelioma	Multicenter single arm phase I/II trial in 20 adult patients with newly diagnosed as a first line therapy 3 BE sites AZ MariaMiddelares, AZNikolaas, UZA (active, not recruiting - anticipated completion March 2025)
WIDEA Eudract:2012-001494-91 NCT01686334	Antwerp University Hospital	Autologous WT1 mRNA loaded **dendritic cell**s Somatic cell therapy	Acute Myeloid Leukemia	multicenter randomised open-label **phase II** clinical study in 130 adult patients Recruit 8 sites in Belgian hospitals (active not recruiting, expected completion December 2027)
ADDIT-GLIO NCT02649582 EudraCT: 2014-001098-15	Antwerp University Hospital	Autologous WT1 mRNA loaded **dendritic cells** Somatic cell therapy	Brain tumour (glioblastoma multiforme	single arm single centre phase I/II trial on 20 adult patients with newly diagnosed, histologically verified glioblastoma who have received a total or subtotal resection of the tumor (active not recruiting - anticipated completion dec 2025)
NCT04445454 EudraCT: 2020-002102-58	CHU de Liège	Allogeneic bone-marrow derived **mesenchymal stromal cells** Somatic cell therapy	severe to critical COVID-19 pneumonia	Single centre, single arm phase I/II clinical trial in 20 patients with severe to critical COVID-19 pneumonia (preliminary resulted published Grégoire 2022[59])

Study identification	Sponsor	ATMP	Indication	Study details
NCT00603330 EudraCT: 2007-004310-14	University of Liège	Allogeneic mesenchymal stromal cells Somatic cell therapy	Steroid resistant Graft versus host disease	Multicenter Phase II: single arm 100 patients 11 BE recruiting BE locations (results published Servais et al 2023[60])
TriMix-Breast Eudract 2017-002711-34 NCT03788083	UZ Brussel	TriMix mRNA solution (intratumoral injection)	Early breast cancer	Phase I on 36 patients preliminary results[61]

*Source: *FAMHP referred to the public data of the clinical trial applications on ATMPs between 2021 and 2023 inclusive. However, there are also trials introduced outside this timeframe of which some ongoing. Those were identified based on own search in clinicaltrials.gov and relevant websites.*

5.1.3 Via Hospital Exemption

While there is an EU framework, it is the Member State that defines the criteria for granting access through the hospital exemption route. In Belgium, the FAMPH determines whether a hospital exemption is possible. This route has been seldom tried and used, with only one ATMP product (an autologous cell-based therapy for bone reconstruction) approved by the Belgian FAMPH. Furthermore, this hospital exemption was granted in 2019 to a private company but was retracted in 2024 when a clinical trial with the ATMP began. This suggests that the hospital exemption route is not easily accessible in Belgium, especially for the academic sector (see section 6.4.2 of this report).

5.2 GMP manufacturing capacity in Belgium

In the EU, all manufacturers of finished, intermediate, experimental or commercial medicinal products must hold a manufacturing authorisation and requires that the product is developed under GMP. The national competent authority in Belgium, the FAMHP, manages the inspections and issues the certificates (which can be consulted in the EudraGMDP database[62]).

Table 3 shows the capacity to produce ATMPs for clinical use according to GMP requirements (clinical trials and authorised ATMPs) in Belgium. Most facilities are private, and some have an academic origin (spinoffs). However, it is important to note that the Belgian **ATMP production is volatile,** and that manufacturers and licences/certificates are often adjusted because of discontinuation of activities (bankruptcy, disappointing trial results), mergers, changes in the nature of ATMPs produced, establishment of spin-offs. The GMP certificate and the manufacturing authorisation discriminates between whether it is for cell therapy, tissue engineered or for gene therapy, whether it is for an investigational product in trial setting or not, and which manufacturing actions are GMP approved. The majority of GMP certificates in Belgium is for investigational medicinal products. Moreover, Belgium also has a rich network of firms specialised in biological equipment, biological starting material.

There are three academic hospitals that hold a manufacturing authorisation for investigational cell and/or gene medicinal products. Of those, two have **in-house GMP certified facilities** for the manufacturing of **cell and gene investigational medicinal products** (CellGenTherapies at UZGent and Cell&Gene therapy Lab at CHULiège)**.** The UZA Centre for Cell Therapy and Regenerative Medicine has clinical trials running with mRNA loaded dendritic cells and contracts the manufacturing of the cell therapy to the CDMO Anicells, which was once a spinoff of the University. Similarly, the VUB Laboratory for Molecular and Cellular Therapy contracted specific manufacturing steps for their (former) clinical trials to a CDMO eTheRNA which was a spinoff of the University. In addition, the **academic GMP facilities act as a CDMO for other (private) players.**

There are also many more academic research groups active in the field of ATMPs but who are e either focussing on specific parts of the production process (e.g. viral vectors or mRNA) and not on production of GMP products for clinical use).

In addition to the in Table 3 listed facilities, extra GMP compliant facilities for different ATMP products are being built in Belgium, both in the private sector (Janssen Pharmaceutical on CAR-T cell therapy in Ghent) as well as in the academic sector (CellGentTherapies of UZGent, and CHULiège and as well as KULeuven/ and UZLeuven plan to open a GMP approved facility for ATMPs) indicating the capacity will increase.[63] The impact of closed automatic systems and point-of-care manufacturing on production capacity is also to be evaluated (Anicells 2.0, Point of Care project ROTEA-DC)[q], Galapagos clinical trials, see 8.5.2 on decentralised manufacturing).

Table 3 – Facilities with a GMP certificate for ATMPs (as identified in the EudraGMP databank in May 2024)

GMP facility for ATMPs	info
ACADEMIC	
UZGent – CellGenTherapies	• Investigational Cell and Gene therapy: Dendritic cells, in vitro RNA technology, lipid nanoparticles, stromal vascular fraction, multivirus-specific T cells, CAR-T • CDMO activity for academics and industry • New facility expected in 2025
CHULiège – Cell & Gene Therapy Lab	• Investigational Cell and Gene therapy: mesenchymal stem cells cultured in vitro, Regulator T cells, point of care CAR-T • CDMO activity for academics and industry • New facility built
NON-ACADEMIC	
Anicells	• Investigational Cell and Gene therapy: Dendritic cells, CAR-T • Spinoff of UZA • CDMO activity for academics and industry • Produces the cell therapy for the UZA Centre for Cell Therapy and Regenerative Medicine
Cellaïon	• Investigational Cell therapy: allogeneic liver-derived progenitor cells (HepaStem®) • Spinoff of UClouvain (Promethera Biosciences) • Filed bankruptcy in Juin'24 due to disappointing results of the phase IIb study with Hepastem®
Catalent	• Investigational Cell and Gene therapy: autologous and allogeneic platforms (CAR-T, TIL, NKs, MDcs) + plasmid DNA (viral vector) • Three facilities • CDMO • Catalent acquired Masthercell in 2020, and in 2024 Novo Holding acquires Catalent

[q] VUB - PoC project ROTEA-DC Implementing the RoteaTM technology in dendritic cell manufacturing.

Cellistic (former Celyad Oncology facility)	• Investigational Cell and Gene therapy: allogenic CAR-Ts • The facility was formerly owned by Celyad Oncology which made the CAR-T products for several clinical studies. The facility is now being prepared for manufacturing induced pluripotent stem cells
Kaneka Eurogentec	• Investigational Gene therapy : plasmid DNA, recombinant proteins, antibody fragments • Focus on GMP production of starting materials and active pharmaceutical ingredients • CDMO • Once spinoff of UCLiège
Exothera	• Investigational Gene therapy: viral vector and nucleic acid manufacture; Establishment of virus and cell banks(en) • CDMO • Part of Univercells
Etherna Immunotherapies	• Investigational Gene therapy: RNA technology and lipid nanoparticle formulation • CDMO • spinoff of VUB
Henogen (Thermofisher)	• Investigational Gene therapy: Viral vector, starting material • human medicinal product gene therapy (e.g. manufacturing of COVID vaccin) • Henogen has been acquired by Thermo Fisher in 2021
Janssen Pharmaceutica	• Investigational Gene therapy • human medical product (live cells)
Novadip Biosciences	• Investigational Tissue engineered product: autologous and allogenic stem cells for bone reconstruction • Clinical trials running with own product • Spinoff of UClouvain

*Source: EudraGMDP: Note that the selection in the database is based on GMP for manufacturing operations for cell therapy or gene therapy for human use (veterinary products excluded). There are other facilities/sites that have a GMP certificate for batch certification (PDC*line pharma, BioGenCell Europe, BioSenic, Precigen etc) Some of the facilities are focused on starting material*

6 CHAPTER 3 - AUTHORISATION ROUTES FOR ATMPS

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Key points

Several authorisation routes are, in theory, available to Academia to bring ATMPs to patients in Europe, each with its own purposes, conditions, and challenges.

Clinical trial (CT)

- Clinical trials aim to discover or verify the effects, to identify adverse reactions or to study how the human body process one or more medicinal products.
- Although Academia plays a prominent role in conducting early stages clinical trials with ATMPs, regulatory barriers, manufacturing requirements, difficulties in finding the appropriate trial design, and the lack or insufficiency of structural funding make it difficult for Academia to independently pursue later stage clinical trials in the field of ATMPs.
- Increased knowledge sharing and facility sharing between Academia, coupled with structural investments to support long-term resources (including low hurdle regulatory support) may help in improving this late-stage clinical trials capacity within Academia.

Centralised Marketing authorisation (MA)

- Centralised MAs are mandatorily required for all ATMPs that are industrially produced and that are intended to be placed on the market in Europe.
- MAs entail that regulatory authorities have evaluated the clinical evidence of ATMPs, confirming that they are deemed (sufficiently) safe and effective. However, due to the specifics of ATMPs and difficulties in gathering clinical evidence, ATMP MAs are often based on less data, (often Phase I/II or small phase III, non-randomised, non-controlled clinical trials using intermediate endpoints) and subject to additional conditions (conditional market authorisation).
- There exist multiple support schemes to help ATMP developers, including Academia (i) in the regulatory process, including scientific advice, (ii) budget-wise, with fee waivers and discounts for Academia, and (iii) with additional incentives in the valorisation, including orphan designation.
- There is no prohibition in European pharmaceutical legislation that prevents Academia from holding a MA and there are several support mechanisms available to this specific actor (scientific advice, reduction fees, etc. see section 4 of the Supplement)
- However, despite these support mechanisms, this route to approval remains extremely difficult for Academia, as it involves high costs and responsibilities that are generally not part of their core business and are prohibitively difficult to overcome. With a single exception (Fondazione Telethon Italy) *all* marketing authorisations for ATMPs approved in the EU are held by commercial actors.
- If public funding is provided, this (theoretical) possibility for Academia to hold MAs for ATMPs might furthermore be constrained by state aid restrictions. Since the development of academic ATMPs towards an MA will likely rely on funding by public authorities, there is a significant risk that such funding could be classified as state aid requiring notification to the European Commission before being granted. The European Commission must then decide on the aid's compatibility. The notification creates additional administrative uncertainty and burden.
- As analysed in Chapter 5 and developed in the Supplement, in most cases where academic ATMP development is government-funded, these ATMPs will, in practice, only be commercially exploited under an MA once they have been out-licensed or transferred by Academia to a dedicated entity.

Hospital Exemption (HE)

- HE allows certain ATMPs to be excluded from the scope of the EU Directive on medicinal products for human use (and exempted from the requirement to obtain a centralised MA) provided they are authorised and used within the same Member State, non-routinely used in a hospital and that their preparation comply with specific (nationally defined) quality standards equivalent to the ones necessary for MAs.
- The current EU legislation defines the general concepts of HE but further national interpretation of those criteria has led to considerable differences in implementation across the EU. While in some countries HE is used as a rather experimental framework (for instance for patients that are not eligible for CT), in other countries it is considered as clinical practice.
- At the time of writing, the European Commission is mapping HE products and use across EU and has proposed, in the context of EC Pharma Proposal (see Box 1) to revise certain aspect of HE (see section 6.4.3 of this report).
- In contrast with other countries (Spain, Germany, the Netherlands, France), HE is almost never used in Belgium, mainly because the conditions are perceived by Academia to be overly restrictive.

None of these routes can necessarily guarantee effective patient access. CTs are limited in scope and population and require substantial funding. MAs often lead to high prices for which reimbursement is difficult to obtain. HEs are only available nationally and are not necessarily paid for by public payers.

6.1 Introduction

Authorisation routes available to Academia for ATMPs generally include CTs, MAs and HEs

Regarding CTs and MAs, this section will only focus on the specific challenges that Academia faces, compared to industry players and the possible solutions to overcome these challenges. A more complete description of the legal framework and requirements is available in the Supplement as background information.

This section will mainly focus on the case of hospital exemption because it is frequently presented[64, 65] and was sometimes effectively used (see section 7 of this report) as a pathway that can help bridge the gap between research and patient access, enabling academic researchers to translate their innovations into clinical practice more quickly and cost-effectively.[66]

For the completeness, it should be mentioned that in several EU countries, various national exceptional regimes such as compassionate use programmes or 'special needs schemes' are also occasionally used to grant access to academically prepared ATMPs (see Appendix 3). These frameworks are not always transparent and are sometimes misused to cover the use of unauthorised products. In Germany, for instance, non-transparent and non-controlled use of the "Individueller Heilversuch" has raised concerns on potential safety issues.[67] It is a procedure that may be carried out by a physician without prior regulatory approval (in contrast to the hospital exemption) for the benefit of an individual patient if other treatment methods have been exhausted or at an earlier stage at the patient's request

6.2 Clinical trials

The EU clinical trials regulation (Regulation No 536/2014 – CTR)[68] defines a clinical trial as any investigation in relation to humans that goes beyond the normal clinical practice and is intended to (i) discover or verify the clinical, pharmacological or other pharmacodynamic effects, (ii) to identify any adverse reactions or (iii) to study the absorption, distribution, metabolism and excretion of one or more medicinal products, in each case, with the objective of ascertaining the safety and/or efficacy of those medicinal products. An

investigation goes beyond the normal clinical practice if either (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.[r]

Clinical trials are often categorised in four temporal phases (see more details in section 2 of the Supplement). However, categorising clinical studies in phases is a description and not a requirement, as the phases of drug development may overlap or be combined.[s] Notably, this is often the case for clinical studies involving ATMPs, where smaller, open-label, non-randomised and single arm studies are more prevalent, either without control or by using historical controls.[3] Unlike the traditional drugs, ATMPs are frequently not or cannot be tested in healthy human volunteers as is the case in the classical phase I study. Most of the time the first-in-human studies are combined as phase I/IIa and directly enrol ill patients[65.] It should of course be acknowledged that for some of the ultrarare diseases it may be impossible to recruit a minimum number of patients in an RCT. However, the single arm design should not be misused to evaluate treatments for which a sufficient number of eligible patients are available to conduct a well powered RCT. Even in patients who have exhausted the existing treatment options, a randomised comparison versus best supportive treatment is possible[69]

6.2.1 Challenges and consequences

Academia generally has ample experience in experimental (pre-clinical) and early phase clinical research (first-in-human) but less experience in the specific pre-clinical studies (toxicity, pharmacokinetics, pharmacodynamics, etc.) required by regulators. Approximately 25% of the currently approved ATMPs originated in an academic environment (e.g. Kymriah® at the University of Pennsylvania., Holoclar® at the University of Modena and Reggio Emilia).[70] (See also table Clinical trial pathway of authorised ATMPs in Appendix 1.3)

However, the process of taking a cell or gene therapy to the market, as well as phase III clinical studies with testing on a larger population (often several hundreds) is labour and resource intensive and usually taken up by the industry.[71, 72]

Indeed, in the current ATMP landscape, Academia is facing several challenges to establish a clear access strategy for their investigational medicinal product.[73]

6.2.1.1 Regulatory barriers

Knowledge of the regulatory framework, including knowledge of the specific requirements for ATMP manufacturing, GMO legislation, the correct classification of a product as ATMP or BTC product and knowledge necessary to build a full product dossier towards obtaining a marketing authorisation for ATMPs has been identified by Academia as an important hurdle in ATMP development.[36]

While academic institutions and investigators have considerable expertise in certain aspects of the clinical trial set-up, such as drafting the protocol or patient information, the same cannot necessarily be said about certain aspects of the investigational medicinal product dossier, considering the confidentiality of such files that are submitted in commercial trials.[70]

The current GMO-legislations can further complicate the start-up of ATMP clinical trials for Academia and cause delays. As long as the drug developer aims to have a single-site study, in a facility which already has the required environmental permit, this effect should be limited. A cross-border, multi-site

[r] Art. 2.2(1) and (2) of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.68. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 2014. Available from: https://eur-lex.europa.eu/eli/reg/2014/536/2022-12-05

[s] EMA, ICH guideline E8 (R1) on general considerations for clinical studies, Step 5, version 1 December 2022, 11-14 p.

study, however, will require significant planning and preparation. Once the development phase is completed, the application for a marketing authorisation can continue at a centralised, EU-level, although an elaborate ERA is needed.

6.2.1.2 GMP manufacturing

The conduct of clinical trials requires adequate GMP manufacturing and distribution capabilities and capacity, including access to sufficient qualitative starting materials. This is specifically relevant for later stage clinical trials, where production needs to be scaled up to supply a broader patient population and possibly multiple sites. This may require considerable investments and costs related to infrastructure, training of personnel, logistics and regulatory requirements for Academia,[11, 36, 74] which could be high-risk, especially without a resilient strategy for the future. The specific GMP manufacturing requirements are described section 7 of the Supplement.

6.2.1.3 Clinical trial design

Academic trials face similar challenges in establishing an appropriate clinical trial design. To add to this, limited resources might impact the robustness of the clinical trial that can be conducted by non-commercial actors. For instance, although the data that could be gathered from multicentre trials may be more representative, such trials require considerably more resources than a single-site trial.[75] As stated above, if the primary objective of a clinical trial is primarily to provide access to an ATMP, rather than to collect data to contribute to long-term development goals of an investigational medicinal product, it might also be of less importance to Academia to conduct qualitative research that ensures comprehensive clinical evidence towards the latter goal.

While such single arm design can be used as pivotal trial to obtain regulatory approval, it will likely be insufficient to inform the HTA bodies and payers on the relative effectiveness (joint clinical assessment).[50]

The methodological guidelines for JCA mention: "*For some interventions, single-arm or non- randomised evidence may be the only evidence available for consideration. However, it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA*." [50]

6.2.1.4 Funding

A general lack of resources is often considered the reason why Academic sponsors in later stage clinical trials are scarce. Academia generally lacks the funding, the personnel and the manufacturing capabilities to direct later stage clinical trials.[36] ATMP clinical development demands a systematic and interdisciplinary approach. Academia has historical difficulties in shouldering the high-risk investments and the associated costs required to establish and - perhaps more importantly - maintain such infrastructure.[74]

6.2.1.5 Use of Clinical trials as an access pathway

Where clinical trials are generally a tool for ATMPs developer to generate evidence to substantiate a potential marketing authorisation application or to fulfil the conditions imposed by a conditional marketing authorisation (i.e. a means to an end), Academia sometimes conduct clinical trials as an end goal in itself (i.e. as a means to provide access to patients) or at least without clear intent to progress the investigational approach to marketing authorisation or even hospital exemption.[t 36]

A clinical trial nevertheless presents a number of potential shortcomings as an access strategy. For one, strict eligibility and protocol requirements usually apply, which limits the number of patients that can be given access to the investigational ATMP and, for instance, restricts therapeutic freedom (e.g.

[t] de Wilde et al. (in the Netherlands) noted that only 16% of principal investigators had a plan to implement the ATMP investigated in clinical trials into regular clinical care in the future.

dosage requirements). In addition, clinical trials place a high burden on sponsors, as the investigational medicinal product and any other protocol required drugs must be provided to the patient free-of-charge[u], the sponsor is even without fault liable for any adverse events relating directly or indirectly to the clinical trial[v] and comprehensive data record and retention requirements need to be respected.

In addition, this mindset may impact certain aspects of the manufacturing and clinical development by Academia, as there may be less incentive to develop the upscaling of the production or to collect reliable and robust data to support a marketing authorisation application and more incentive to collect data necessary to make relevant publications and to generally provide access to an investigational medicinal product to patients in their care.

6.2.2 Existing support mechanisms and possible improvements

Clinical development of ATMPs is very complex and resource intensive. While Academia has ample experience in conducting clinical trials, the complexities in relation to ATMPs, including pre-clinical work, study design, and GMP requirements, and, very importantly, related costs, remain a key hurdle for Academia to engage in broad clinical trials for ATMPs.

To help overcome these hurdles, several key improvements can be considered:

- **Enhanced dialogue between the stakeholders:**

Knowledge sharing between academic institutions, regulatory authorities and industry stakeholders should be further facilitated and encouraged. Early dialogue between regulatory authorities and non-commercial investigators is particularly important, as this might aid organisations in gathering sufficient pre-clinical evidence to support clinical trial applications and to conduct studies that generate robust clinical data, which is crucial for preparing a comprehensive marketing authorisation application or reimbursement dossier.[70]

- **Funding for infrastructure improvements:**

Structural investments into academic development units, (pre-)clinical research infrastructure and (clinical) manufacturing infrastructure to improve capabilities of Academia in ATMP development is a key prerequisite for accelerating clinical development at Academia (see section 8.4).

- **Innovative approaches to clinical trial design:**

Shortcomings in clinical trial designs with ATMPs may also be surpassed by approaching such design in an innovative way, for instance, by making use of platform trials see Box 5 (e.g. registry-based for rare diseases) or by relying on historical data from patient registries.[3]

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[u] Art. 92 of the Regulation (EU) No 536/201468. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 2014. Available from: https://eur-lex.europa.eu/eli/reg/2014/536/2022-12-05

[v] Art. 12 of the law of 7 May 2017 on clinical trials of drugs for human use [76]. Law of 7 May 2017 on clinical trials of drugs for human use, 2017. Available from: https://www.ejustice.just.fgov.be/cgi_wet/article.pl?language=nl&sum_date=&pd_search=2017-05-22&numac_search=2017012146&page=1&lg_txt=N&caller=list&2017012146=2&trier=afkondiging&dt=WET&ddd=2017-05-07&nl=n&choix1=en&choix2=en

Box 5 – Registry-based RCTs and Platform Trials

A registry-based randomised controlled trial makes optimal use of the standard data collection that exists for the registry. The only additional element is the informed consent process and the use of a randomisation module. While registry-based clinical trials can be run at a small fraction of a typical RCT, the pre-condition is a high-quality registry. This takes time and money to set up and maintain. For rare diseases, a high-quality international disease registry would greatly lower the hurdle for the evaluation of new treatment options. When multiple treatment options are to be evaluated, a platform trial within the registry might be considered.

A platform trial is a type of clinical trial that allows for the simultaneous investigation of multiple treatments for a single disease within the same overarching trial structure and 'master protocol'. During the covid pandemic platform trials have proven their value to rapidly assess new treatment options.

They are open ended, meaning new interventions can be added, assessed, and removed as time goes on, without having to specify what they might be at the start. This innovative approach is designed to improve the efficiency and flexibility of clinical research.

Platform trials offer several benefits compared to traditional trials:[77]

- establishing an infrastructure including a master protocol, a single sponsor, a stable network of investigator sites with trained teams, a data safety monitoring board (DSMB), a common data processing and pharmacovigilance system, resulting in profitable standardisation and economies of scale after an initial investment in the infrastructure;
- the possibility of a shared control arm, which avoids the repeated creation of identical control groups (standard of care) in independent trials, decreasing the number of patients to be enrolled, the costs, and the time limits;
- the possibility of considering the platform trial as a single trial, and of activating each new intervention arm with a simple amendment, which also reduces time limits (and potentially costs).

- **Regulatory clarity and streamlining for ATMP clinical trials:**

From a regulatory perspective, clarity and early-stage guidance on study requirements is needed. In addition, at the EU level, the legal framework for GMOs could benefit from further harmonisation and simplification. For instance, it may be worthwhile to explore the possibility of exempting ATMPs from certain GMO regulations, simplifying the environmental assessment for clinical trials with ATMPs and streamlining the assessment procedures for clinical trials by linking the CTIS to the GMO-assessment portal so that all submissions and applications can be handled through a single platform.

The above suggestions could help Academia (and SMEs) in conducting high-quality research that ensures the safety of clinical trial participants and guarantees the reliability and robustness of the generated data. This data can serve as a foundation for other pathways aimed at effectively delivering care to patients.

6.3 Centralised Marketing authorisation

A central marketing authorisation ensures that a drug is approved throughout the EU and in line with standard requirements and generally with broader data than under exceptional regimes such as hospital exemption.

Some argue that Academia should focus only on those niche development trajectories that are not commercially viable and that a specific development trajectory should be established for these products. .[25] Until such alternative development route exists (e.g. through certain flexibilities or alternative standards that could be tried under the regulatory sandbox that is being considered under the EC Pharma Proposal (see Box 1 and Box 6) Academia

could consider the current commercial pathway as a viable option to bring academically developed ATMPs to the patients, next to the hospital exemption (and clinical trials).

Holding a marketing authorisation in principle means that the safety, quality and efficacy of the relevant ATMP has been sufficiently demonstrated and is authorised (in case of a centralised procedure, throughout the EU). It also facilitates a possible reimbursement, is not subject to strict eligibility criteria (as is the case under the clinical trial pathways) and enhances transparency (through the availability of an approved SmPC). It is sometimes argued that a marketing authorisation therefore should be the preferred method of providing access to patients, since it ensures control on the safety and efficacy of the product and allows for a more equitable access. That being said, specifically for ATMPs, considering the often limited clinical evidence caused by the flexibilities and the constraints discussed under section 0 of this report and detailed in the Supplement, a marketing authorisation does not necessarily guarantee long-term safety of the treatment (see also Section 1.2 of this report). Moreover, patient access is often limited, considering that ATMPs are often not effectively commercialised and reimbursed throughout all of the EU.

6.3.1 Challenges and consequences

Under current European and Belgian law, no specific legal provision expressly prohibits academic institutions from applying for and holding MAs. Moreover, current regulatory support and interaction initiatives affirm the right of academic institutions to apply for and hold MAs, particularly in the context of ATMPs (see Box 13).

Obtaining a MA is expensive, with initial MA applications costing 357,600 EUR, and recurrent fees significantly increasing such number. Future fees might even be more expensive (note that for SMEs and Academia reductions apply in relation to many steps under a MA procedure)[78w]. In addition, due to the difficulties (not specific for Academia) to generate the appropriate evidence, a significant number of ATMP MAs are only conditional, or granted under exceptional circumstances, requiring annual extensions, important post- authorisation obligations (e.g. complete ongoing or conduct new studies or collect additional data to confirm, within the agreed timeframe, that the medicine's benefit-risk balance remains favourable).

Financial, commercial, legal and operational expertise and resources are indispensable to successfully complete the regulatory process.[79] Without additional support measures some of these requirements are likely too burdensome and costly for Academia.

The (theoretical) possibility for academia to hold MAs for ATMPs is, therefore, likely to be constrained by state aid restrictions outlined in Chapter 4 of the Supplement. Since the development of academic ATMPs towards an MA will likely rely on funding by public authorities, there is a significant risk that such funding could be classified as state aid requiring notification to the European Commission before being granted. The European Commission must then decide on the aid's potential compatibility. The notification creates additional administrative uncertainty and burden. As a result, in most cases where academic ATMP development is funded by public authorities, these ATMPs will, in practice, only be commercially exploited under an MA once they have been out-licensed by Academia to a separate entity.

In addition, other legal provision may restrict certain academic institutions from engaging in the commercial activities associated with such MAs. We have provided in the Supplement our analysis on the feasibility of academic institutions holding MAs, in particular with regard incompatibles activities and the burden of product liability. (Section 5.4.4.1 in Supplement)

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w It should be noted that Academia has its own definition under the decision, which is not identical to the definition used in the present report

6.3.2 *Existing support mechanisms and possible improvements*

Important support measures exist for facilitating and incentivising the development process and MA application process, including

1. the EMA's Innovation Task Force to establish a discussion platform for free early dialogue with applicants, in particular SMEs and Academia, to proactively identify scientific, legal and regulatory issues arising from innovative medicines development, emerging therapies, new technologies and borderline products.
2. the provision of a free advice by the CAT on ATMP classification (available to everyone)
3. a certification by the CAT of early experimental data (available to micro, small- and medium-sized enterprises).
4. early PRIME designation granting an enhanced support (including a free scientific advice) for medicines that target unmet medical needs based on a proof of concept (this early PRIME status is only available to small and medium-sized enterprises and applicants from the academic sector)
5. an Academic Pilot, aimed at specifically supporting academic drug developers, by providing free scientific advice and enhanced regulatory support throughout the entire development and market access process, starting from best practice principles for manufacturing to planning clinical development that meets regulatory standards (see Box 13).
6. Orphan designation, after which protocol assistance in the form of a broadened possibility to request scientific advice from the EMA regarding the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy, at a reduced fee, reduced fees for regulatory activities, and market exclusivity become available. (designation available to everyone but certain incentives are limited to SME's)

Notwithstanding the existence of these support measures, additional low hurdle support at EMA and national level should be considered, e.g. broadening the Academic Pilot, further reducing fees and encouraging early dialogue, ensuring that ATMP development efforts are aimed, to the extent possible, at obtaining a marketing authorisation.

Box 6 – The concept of regulatory sandbox

Regulatory sandbox: a regulatory framework during which it is possible to develop, validate and test in a controlled environment innovative or adapted regulatory solutions that facilitate the development and authorisation of innovative products which are likely to fall in the scope of the EU pharmaceutical legislation, pursuant to a specific plan and for a limited time under regulatory supervision.

Under the proposed legislation under the Pharma Reform,[x] a regulatory sandbox will only be possible if (i) the product-related characteristics or methods mean it is not possible to develop the medicinal product or category of products in compliance with existing medicines rules; and (ii) the product-related characteristics or methods are likely to contribute positively and distinctively to the quality, safety or efficacy of the product(s) or provide a major advantage in terms of patient access.

To overcome these challenges and incentivise Academia to consider MA pathways, additional national (financial or other) support measures could be needed (besides the abovementioned currently available support measures provided within the EU). The compatibility of the national measures (notably under applicable state aid principles) will be further addressed under Chapter 5. State aid rules should indeed be carefully considered when providing support by public authorities for academic ATMP development,

[x] See in particular Article 112 – 114 of the Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

particularly if the support aims to result in an academic ATMP Marketing Authorisation (MA).

6.4 Hospital exemption

6.4.1 EU framework

The ATMPs EU Regulation[13] harmonises the rules related to the authorisation, supervision and pharmacovigilance of all ATMPs across the EU. The aim of this Regulation is to enact robust standards to protect human health, and to harmonise market access to ATMPs in the European Union. In essence, the Regulation is a *lex specialis* that introduces more specific requirements for ATMPs. However, the general scope of the Directive 2001/83/EC as well as the scope of the ATMP Regulation apply only to products that are '*intended to be placed on the market*' in the Member States and are '*either industrially prepared or manufactured using a method that involved an industrial process'*. As developed in the Supplement (section 1), the definitions of these two concepts have never been straightforward and has extensively been discussed by the Court of Justice of the European Union[y].

Yet, with regard to ATMPs the Regulation acknowledges that there should be some flexibility for small scale operators including hospitals in this area[z].

A. EU definition

The provision known as the 'hospital exemption' raised extensive debates during the legislative process that led to its adoption. Debates concerned the definition of industrial *vs.* non industrial preparations, the concept of 'in-house use' *vs*. broad distribution[aa].

The final provision adopted in 2007 exempts certain ATMPs from the scope of the Directive 2001/83/EC[bb] -and thus from the associated obligations- under specific, cumulative, conditions[cc]:

1. The product **qualifies as an ATMP**, as defined in the ATMP Regulation
2. The ATMP is **prepared** on a **non-routine** basis according to **specific quality standards (equivalent to the one required for an MA)**
3. The ATMP is **used within the same Member State**
4. The ATMP is **used in a hospital** only under the exclusive professional responsibility of a **medical practitioner.**
5. The ATMP complies with an **individual medical prescription** and is **custom-made** for an individual patient[dd].

The EU legislation does not define the above mentioned concepts or restrict the general purpose of HE. In essence, it allows Member States to tailor the implementation of HE to their specific legal and healthcare contexts and to further interpret the HE criteria and conditions.

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y See, for instance CJEU *Octapharma France*, C-512/12, EU:C:2014:149, para. 38.

z Use by commercial players is not mentioned in the impact assessment reports.

aa Impact assessment report annexed to the Proposal for a Regulation on ATMPs (2005) https://data.consilium.europa.eu/doc/document/ST-15023-2005-ADD-1/en/pdf.

bb Article 3 of the Directive 2001/83/EC contain a complete list of products that are out of scope of this Directive: magistral formulas, officinal formulas, Investigational Medicinal Products (for clinical trials), intermediate products, radionuclides in the form of sealed sources, blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process and ATMPs prepared under hospital exemption.

cc Article 28 of the ATMP Regulation, inserting § 7 in article 3 of the Directive 2001/83/EC.

dd Article 3 of the Directive 2001/83/EC. See also article 6 quarter § 3 of the Belgian law of 25 March1964 and Royal Decree of 08 January 2017.

In the interest of patient safety, Member States are however required to **authorise HE products** and to impose pharmacovigilance, traceability and **manufacturing/quality standards** 'equivalent' to the ones applied to products centrally authorised by the EMA).

B. National authorisations, interpretations and use of HE in Europe

While important differences exist regarding the scope, eligibility criteria, data collection and manufacturing requirements,[80, 81]. However, it should also be underlined that where HE exists in national frameworks, a risk-benefit analysis is always performed by the national competent authority before granting HE. Additionally, some countries require the control of an ethics committee (e.g., required in Belgium). Safety reporting to the national competent authority and follow up are also required.[81] These boundaries differentiate HE from unregulated, unproven and unethical interventions that are directly marketed to consumers by certain private clinics.[82]

Different purpose of HE

While some Member States see HE as a form of experimental use in the early clinical phase of development, others see it as small-scale clinical practice or as a bridge to ensure patient access to treatment between two phases of clinical trials. Still other countries allow HE during the transition period from one-time production to routine production (MA). In some countries, these different objectives may be combined. [83] [81]

When the aim of using an intervention on a human person is to test a treatment, a clinical trial must, ethically[ee] and legally[ff] be conducted. However, the situation is not as clear-cut in some countries, where HE is sometimes used for early clinical development before formal clinical trials

It should be noted that products under HE are nationally authorised and can be considered under the CTR as investigational medicinal product (IMP). The regulatory status of the product under the pharmaceutical legislation is irrelevant for the CTR application[gg].

[ee] Article 1 of the Declaration of Helsinki.84. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[ff] Article 1 of the Clinical Trials Regulation.68. Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 2014. Available from: https://eur-lex.europa.eu/eli/reg/2014/536/2022-12-05

[gg] See Q&A documents on the application of Clinical Trials Regulation Regulation (EU) No 536/2014.

Competition with licensed products

Today, several countries have legislation that prohibits HE when an identical authorised alternative is available (Belgium, Spain, Netherland). Other countries do not (UK, Germany), or impose such limitation only when the HE is requested without clinical data available to support the use (e.g. France)[hh].

However, there is no clear definition of what constitutes an 'identical' and 'available' alternative For example, the use of a different manufacturing process may mean that an ATMP is not considered 'identical'. With regard to availability, it is also unclear whether this concept refers to the physical presence of the product on the market or the existence of a reimbursement. As demonstrated in Spain, if the patient cannot be treated with a commercially available product (even though this product might be similar to the HE-product), a HE would be permissible.

These discussions on the coexistence of 'identical' commercial alternatives and preparations also exist in relation to magistral preparations.

Different interpretations of 'non routine'

Although several EU Member States have implemented HE rule into their national legislation, the majority of national competent authorities (NCAs) offer no clarity as to the definition of non-routine. In the UK (before Brexit)[85], the authorities underlined the impossibility to provide a simple numerical formula that would delineate the boundary between routine and non-routine production and the need to assess this situation case by case (taking into account i.e. the *scale,* the *lapse of time* between the preparations, their *increase over time* etc.).

In the Netherlands, the Health Care Inspectorate (competent administration) considers that the following preparation are non-routinely prepared[86]:

- ATMP prepared from autologous cells.
- ATMP prepared from non-autologous cells but specific to one patient.
- ATMP prepared on a small scale.

The German Medicinal Products Act defined ATMPs prepared on a non-routine basis as those "*medicines which are manufactured and used on such a small scale that it is not to be expected that sufficient clinical experience can be gained to fully evaluate the medicinal product, or which have not yet been produced and applied in sufficient numbers so that the necessary knowledge for their comprehensive evaluation has not yet been obtained*"[ii]. This includes products which are manufactured on a small scale by hospitals for a very small number of patients without a commercial sponsor and where it is not expected that products will ever achieve a central MA. It could also cover products under development but who do not have enough evidence for a central Marketing Authorisation yet.

ii https://www.pei.de/EN/regulation/approvals/authorisation-atmp/authorisation-atmp-node.html.

ii https://www.pei.de/EN/regulation/approvals/authorisation-atmp/authorisation-atmp-node.html.

Different interpretation of "custom made".

Custom usually refers to a prescription for a specific patient. However, this does not exclude groups of patients. In most countries, there are no provisions for any specific quantity but this criterion is assessed on a case by case basis[87].

In the Netherlands, a preparation performed for up to 10 patients/ year is considered 'custom made for a particular patient but this number has evolved over time and deviations (up to 50) were granted on an exceptional basis[jj].

Different data requirements and level of evidence

In some EU countries, HE is granted for ATMPs that have not yet demonstrated safety and efficacy and hence are equivalent to investigational drugs (Austria, Finland, France and Italy). In other countries (Belgium and Spain), HE cannot be granted for firs-in-human studies.

In Finland, quality (but not non-clinical) data are required, allowing small-scale clinical use while non-clinical studies are carried out to facilitate a later CT. In Germany HE may be applicable to facilitate or accompany a CT (not as an alternative) but also for conveying products in a preliminary "non-routine status" on their way to a centralised MA.

This is evaluated on a case by case basis and will often be based on the available data. If the available data is limited, additional conditions might be imposed.

Different "equivalent" quality standards

While the legislation requires HE products to be prepared in compliance with equivalent GMP quality standards, there are some different interpretations and adaptations. For instance, in the United Kingdom, a qualified person is not required. Although GMP is required in the Netherlands, France and Spain, there is some degree of flexibility (specific *ad hoc* adapted GMP rules).

Different possible holders for HE

Eligible organisations are also not explicitly limited by the European legislation, which lead certain countries (i.e., Germany and Belgium) to grant HE authorisations to commercial entities.

HE clause does not limit the type of manufacturer either[82] which means that, under current European law, the product does not need to be prepared within the hospital by the hospital itself (it should just be used in an hospital). Manufacturing can be delegated to a manufacturer (not necessarily the hospital) and the EU legislation does not limit the number of hospitals where the product can be used within the same Member State (provided that this preparation is made non-routinely and that it is used in the same Member State).

jj https://www.igj.nl/publicaties/vragen-en-antwoorden/vragen-en-antwoorden-over-de-hospital-exemption-voor-atmp%E2%80%99s; Deviation for 50 patient /y granted for the TILs.

The current use of HE in Europe is very complex to estimate because the number of HEs granted (and a fortiori the number of patients treated under this exemption) is not systematically recorded and published in an EU registry. Numbers in the literature and published reports considerably vary depending on the sources.

In 2014, the data provided by the Member States to the European Commission announced that approximately 60 derogations (not only HE) from the obligation to obtain a marketing authorisation prior to the marketing of advanced therapies had been granted until April 2012. Derogations were granted under Article 3(7) of Directive 2001/83 (so-called "hospital exemption") as well as under other provisions of the Directive, notably Article 5 (see the 'special needs' regime in Appendix 3). [88]

At the time of writing, the European Commission is mapping these products. This analysis is expected in early 2025 and should provide a more accurate picture of the number of HE in Europe (in countries where this option exists). A stakeholders discussion took place on 21.11.2024 and confirmed that this scheme was being used with quite different objectives from one country to another.

6.4.2 Challenges and consequences (BE)

In Belgium, specific requirements permitting the use of the HE are outlined in the Royal Decree of 08.01.2017 on the hospital exemption for advanced therapy medicinal products (hereafter referred to as RD 2017).[89] This Royal Decree provides for the implementation of Article 6quater, §3, Alinea 1, 6° of the Law of 25 March 1964 on medicines[kk].

6.4.2.1 Criteria for HE in Belgium: specific requirements for use and interpretation

Authorisation of the Agency for Medicines and Health products

According to the Belgian legislation, ATMPs can be prepared and supplied under HE following a **prior authorisation** by the Federal Agency for Medicines and Health Products (FAMHP).[ll]

Those seeking a HE submit to the FAMHP a **dossier including** administrative data and all available scientific documentation supporting the quality, safety and efficacy of the product. According to personal communication of the FAMHP, approximately the same level of information as for a phase II clinical trial is required. The Royal Decree 2017 lists in detail the elements to be included in the dossier.[mm] The FAMHP has provided specific guidance for applicants regarding applications for HE.[90] This guidance primarily covers technical aspects related to ATMP-HE including initial applications and substantial modifications and scientific guidance on the content. The dossier needs to be complemented with a positive advice of an ethics committee which mainly focusses on the informed consent procedure. Admissible dossiers go to the Commission for Medicinal Products for Human Use for an opinion.[nn] This Commission considers two issues: whether the conditions for a hospital exemption are met and whether the benefit-risk ratio of the risks of the product is positive. The final decision on the hospital exemption rests with the Minister of Health or his delegate, the administrator-general of the FAMHP.[oo] They may attach additional conditions to the exemption in order to protect public health or protect the health of the patient. The hospital exemption is granted to a specific entity. It needs to be adjusted if the activity

[kk] This article is the transposition in internal law of § 7 in article 3 of the Directive on medicinal products for human use, inserted by Article 28 of the ATMP Regulation

[ll] Art. 2, 1° RD 2017

[mm] Art. 7 RD 2017

[nn] Art. 9 RD 2017

[oo] Art. 10 RD 2017

is transferred. When substantial changes are made to the hospital exemption, a new dossier must be submitted to the FAMHP.[pp]

Prepared in Belgium

ATMPs under HE for use in Belgium need to be prepared **in Belgium**. The RD 2017 does not restrict the preparation of ATMPs to hospitals, which means that the preparation can be done in an external preparation facility (with a manufacturing or preparation authorisation). Moreover, the **entity holding the HE** can (in theory) be a natural or legal person, without any specification with regard to the commercial or non-commercial nature.[qq] The HE can thus be issued to a(n academic) hospital for the preparation and administration to the patient in that hospital or distribution of the authorised product to other hospitals in Belgium as long as the non-routine character was respected. However, hospital exemptions can also be granted to a spin-off or an industrial manufacturer who is then allowed to manufacture and distribute the authorised product to different hospitals (in Belgium).

Preparation in **Belgium** includes that *the preparation steps determining classification as an advanced therapy medicinal product* are carried out in Belgium.[rr] This implies that it is not allowed to collect biopsies from patients in Belgium, export it for processing in another country and import it back to Belgium for clinical use. However, import of raw materials intended for manipulation in Belgium (for instance stem cells or viral vectors) for allogenic therapeutics is allowed.[91]

According to an individual medical prescription and custom-made for an individual patient

Preparation of ATMPs under HE needs to take place according to an individual medical prescription. The individuality of the medical prescription lies in the specific order, for that particular patient, as prescribed by the physician. However, the HE 'in se' can be requested for a certain product, for a specific pathology, but that does not mean that one has to know in advance all the patients who could be treated with it.

Used in Belgium, in a hospital under the exclusive responsibility of a physician

These provisions are taken verbatim from the European regulations.[ss] The fact that ATMPs under the Hospital Exemption may only be **used** in the Member State of manufacture leaves no room for interpretation and implies that import and export of ATMPs under the HE is not possible (although this is currently under discussion in the scope of the revision of the EU pharmaceutical legislation) (see Box 1 and section 6.4.3).

On a non-routine basis.

Although there is no definition of the notion 'non- routine basis' in the Belgian legislation, some guidance is provided on the parameters representing the non-routine character.[tt] In order to ensure compliance with the "non-routine" criterion for the manufacture of ATMPs under HE, the FAMHP monitors on a case-by-case basis in particular the **number of patients treated, the number of batches of the medicinal product released and the frequency of their manufacture.** Unlike in the Netherlands (cfr. supra), no exact number of patients was defined as a cut-off for the notion 'small number'. However, a number similar to the number of subjects enrolled in the first phase of a clinical

pp Art. 11 RD 2017

qq Art. 2, § 1, 1° RD 2017

rr Art. 5, §1, 5°, 2nd al. RD 2017

ss Article 28 of the ATMP Regulation, inserting a § 7 in article 3 of the Directive on medicinal product for human use.

tt Art. 2. N. 2. Annex 2 RD 08.07.2017

trial is referred to as guidance for the order of magnitude. According to personal communication of the FAMHP, a phase I study includes on average 30 patients. However, this is not used as an official cut-off for the notion "non-routine". The overall number of patients treated is evaluated per HE, per year and not per hospital (in case the product would be manufactured in a separate entity and transferred to several hospitals). In addition, long-term use is not necessarily considered to be routine use. Nor is the fact that the ATMPs is allogenic (indeed an allogenic product can still be personalised at some point of the process.

All parameters, representing the non-routine character are assessed by the FAMHP both during the initial application[uu] and during a yearly follow-up.[vv]

Restrictions: the HE is refused under certain conditions

According to Belgian legislation, the use of the hospital exemption is prohibited if other treatment options with the **same** pharmaceutical are available to patients. To determine what constitutes the same pharmaceutical, the FAMHP will take into account, amongst other things, the mode of action and intended use of the product (indication, method of administration, presentation i.e. liquid, pre-filled syringe, etc.), the production process used to generate the finished product, and any intermediate or product-specific raw material. Thus, different autologous medicinal products for which the intended use, production process and presentation of the final product are the same, are not necessarily different medicinal products.[ww]

The hospital exemption is refused if there is:

- A MA or existing HE for the same product

While this is not an explicit requirement under European law, the Belgian regulations impose that an authorisation for HE is refused if a **MA was delivered for the same product or if a HE was already granted to another applicant**, provided that this product is '***available for the patients'***. According to personal communication of the FAMHP, this does not mean that co-existence of an ATMP under HE with an authorised alternative is excluded. The interpretation of what is an identical product is flexible: if other viral vectors are used, certain process steps are different or a different indication is targeted,…products can be considered as non-identical. However, it is important that the element that distinguishes the ATMP under HE from the authorised alternative provides an advantage for the patient over the authorised alternative.

With regard to the notion of 'availability for the patient', it is not clear whether this refers to the 'physical and commercial' availability (i.e. available on the Belgian market, independently of its reimbursement status) of the product or accessibility for the patient in terms of price (i.e. reimbursed). The text of the Belgian regulations does not explicitly exclude an ATMP preparation under HE in cases where there is a product authorised (and commercialised in Belgium), but this alternative is unavailable for the patients due to an excessive price (and lack of reimbursement).

- A clinical trial with the same product (and the patient is eligible)

A hospital exemption is also refused if patients can be enrolled in a clinical trial where the same product is tested. This was the case for NVD-003, which is a single treatment for critical size bone reconstruction.[92] A clinical trial with the NVD-003, applied for by the hospital exemption holder (Novadip), was approved by the FAMHP and after assessing the inclusion and exclusion criteria, it was concluded that patients who could be treated under the hospital exemption could be included in the clinical trial. Therefore, the hospital exemption was stopped. Nevertheless, the HE holder must continue to meet the regulatory pharmacovigilance requirements associated with the hospital exemption. Hence, in this case the holder must monitor the clinical evolution of each patient for (at least) a period of 5 years after the implantation of NVD-003.

[uu] Art. 7, § 1, 14° RD 2017

[vv] Art. 21, § 1, 3° RD 2017

[ww] Art.N1 Annex 1 RD 2017

- No possibility to be included in a compassionate use program or a medical need program.

Hospital exemption is refused if patients can be enrolled in a compassionate use or medical need program with the same product (see Appendix 3) .

- The ATMP was never administered to humans

Although this is not a requirement under European law, Belgian legislation prohibits the use of an ATMP under HE if it was never administered to humans before. The rationale is probably driven by the desire to protect patients by avoiding any risk if the product has not previously been tested by human beings.[93] Some experts from the international and Belgian academic field and governments argued that this limitation is problematic for (rapid) patient access to innovative potentially lifesaving therapies.[93] Furthermore, it was stated that Belgium's position as an international player in clinical research could possibly be affected compared to other Member States where this requirement does not apply. Yet, even though some eligibility criteria in other Member States seem to be less stringent than the Belgian ones, the number of the authorised HE in these countries remains limited.

Evidence requirements

All available data regarding pre-clinical tests or clinical trials conducted, but at least the results of the primary pharmacodynamic data supporting the rationale for the proposed therapeutic use, safety studies, toxicology studies and, where relevant, pharmacokinetic biodistribution data should be provided. In addition, pertinent clinical experience and pertinent clinical data regarding the medicinal product, possibly in other indications, should also be included in the application dossier.[xx] For products under development, preliminary safety data collected at least during phase I clinical trials are necessary. As such, the hospital exemption cannot be granted if the same ATMP has not been previously administered to humans. More details on the specific evidence requirements can be found in the FAMHP guidance.[90]

Prepared in a GMP conform unit

Belgium requires the conformity of the preparation with Good Manufacturing Practices (GMP). GMP are indeed the highest quality standard for the manufacturing of medicines. They are also mandatory for the manufacturing of all industrial medicinal products in Europe. GMP includes amongst others the construction of specialised facilities for product development, product manufacture, quality control testing, and the establishment of a pharmaceutical quality system that is compliant with applicable laws and regulations, all to guarantee the consistent manufacture of high-quality ATMPs for its patients.[yy] Before starting the preparation of the ATMP, the holder of the hospital exemption must have a certificate of good manufacturing practice, which can be obtained from the FAMHP following a positive inspection. The inspection is carried out at the request of the holder. The holder must also comply with good distribution practices for medicinal products.[zz]

Pharmacovigilance

The holder of the hospital exemption authorisation must implement a pharmacovigilance system. This allows him to scientifically assess the information on risks of the product (such as side effects) and to investigate how it can be avoided or contained. In the case of a significant risk to public health or patient health, the applicant may be required to establish a Risk Management System. This should allow to determine, characterize and avoid or reduce the risks. The fact that the holder of the hospital exemption must comply with pharmacovigilance obligations does not necessarily mean that he is liable for any harm caused to the patient by the ATMP. Legal liability may be distributed among several parties involved in the process of an ATMP

[xx] art. 7 §, 6 and 7 RD 2017

[zz] Art. 14. §1. 1° of RD 2017

procedure. In the EU definitions of the hospital exemption, the treating physician is responsible for the (choice of the) treatment. In particular, if there is an authorised alternative, the physician's liability could be at stake if the choice of the ATMP under hospital exemption could not be justified. The liability of the manufacturer(s), service providers or other intervenants could be involved in the case of production errors that cause harm to the patient. Furthermore, pharmacists are also responsible for the conformity of what they dispense.[aaa]

Traceability

The hospital exemption holder sets up a traceability system. Each individual ATMP and its starting materials and raw materials - including those that come into contact with tissues and cells – must be traceable. And this throughout the entire process from source selection, manufacturing, packaging, storage, transport and delivery to the hospital. Comprehensive documentation includes batch records (including information on raw materials, manufacturing steps and quality control tests), certificates of analysis and patient-specific information. The holder retains the data for at least 30 years from the expiry date of use of the product. The FAMHP may also impose a longer period. Under no circumstances may the data be kept for longer than 50 years. After that, they are destroyed or anonymized. The hospital pharmacist ensures patient and drug traceability using the serial number and medical prescription.

Follow-up of the patient

The patient must have follow-up consultations with the physician for a minimum period and at a minimum frequency as defined in the HE decision.

6.4.2.2 Use of data collected from use under HE

The Belgian HE is currently seen as an early access clinical practice model (and exception to the obligation to get a MA before placing the product on the market) where the scope of use allowed is similar to a phase I trial. As such, it is not considered as an alternative to a MA or an alternative or precursor to clinical trials but as a last resort mechanism. However, the use of ATMPs under the HE in clinical practice, and in particular the clinical data collected prospectively, could support a marketing authorisation dossier and also the design of CTs. Even if the HE is not intended or set up as a clinical trial (e.g. in terms of follow-up), the information obtained from the HE can be added to the MA dossier and serve as scientifically relevant and informative data with a lower scientific value than randomised clinical trials.[bbb]. It should also be noted that in the proposal for a Regulation to revise the EU's pharmaceutical legislation, it is foreseen that real world data can be used by the EMA in the assessment process for marketing authorisation. [ccc]

6.4.2.3 Evaluation of the hospital exemption

Each year the FAMHP evaluates the hospital exemption based on the holder's activity report. The report includes the number of doses prepared and the number of patients treated, the pertinent clinical experience and the pertinent clinical data on the drug, the data resulting from the pharmacovigilance system and the data on the trade-off between benefits and risks. A statement showing that the conditions for granting the HE are still met is also part of the report.

[aaa] Article 2 Royal Decree of 21 January 2009 containing instructions for pharmacists, *B.S./ M.B.* 30 January 2009

[bbb] Personal communication FAMHP.

[ccc] Art. 166 Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

6.4.2.4 HE (potential) authorisations

Since the entry into force of the ATMP Regulation in 2017 and its implementation in 2017 (RD 2017), as already mentioned, only one hospital exemption has been granted in Belgium in 2019, more in particular to Novadip Biosciences, a pharma company (spin-off of the UCL and Cliniques universitaires St Luc) specialised in bone and tissue regenerative medicine. The HE authorisation was granted for a medicine called NVD-003, an autologous cell therapy indicated in congenital pseudarthrosis of the tibia (or CPT), a rare pediatric orthopaedic condition in which the tibia of a young child breaks due to bowing and does not heal. The authorisation was granted with a minimum of 5-year long term follow up. The number of patients treated under this exemption has however not been disclosed publicly.

This authorisation was then abrogated in 2024 following the authorisation of a clinical trial in Europe with the same medicine. The FAMHP examined the inclusion and exclusion criteria for the trial and concluded that the patient that could be treated under the HE could be included in the clinical trial.

The company Novadip has announced that they obtained an orphan designation for this product in the United States and have plan to develop their activities there.

A HE was considered and discussed for the preparation and use of allogenic keratinocytes within the Queen Astrid Military Hospital. However, there was no application for a HE due to a lack of funding to comply with the conditions of HE and the risk of seeing the investment lost if the same medicinal product would become available commercially. The QAMH reported that the move to an industrial step would, according to their estimations, increase the price of their product 10X. No equivalent commercial keratinocyte product is currently available across the EU. [37] In Sweden the product is prepared and used under hospital exemption[ddd].

The ATMP Regulation was already applicable since December 2008. However, a relatively long transitional period was foreseen for ATMPs that were already in the EU market when the Regulation was adopted. The last products were expected to be compliant for December 2012.

In 2015, the Belgian Superior Health Council was requested to issue an opinion on the future RD on hospital exemption; in this context, the Council estimated that there were around 20 products qualifying as ATMPs[93] produced by cell and tissue banks in Belgian hospitals (non for profit in BE) and that would be eligible for the Belgian hospital exemption regime [94],[37] Table 2). The Superior Health Council also underlined that the requirement of the RD should not be foreseen without a corresponding funding.

Today, there is only one HE in Belgium and the reason why none of the potentially eligible products applied for a HE in Belgium is unknown. Some products might still exist under the BTC legislation, other might be under clinical trials and other might have stopped (such as the keratinocytes prepared by the QAMH)

6.4.2.5 Reimbursement options of ATMPs under HE

In Belgium, there is no structural reimbursement of ATMPs used under the hospital exemption. The standard procedure via the Drug Reimbursement Committee of the NIHDI (see 5.1.1) is not applicable for products without marketing authorisation. The costs associated with the hospital stay, however (e.g. the costs of stay, the fees of the physicians,...), are (partly) covered by the national health insurance.

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ddd https://www.akademiska.se/en/departments/specialist-healthcare/atmp-center/past-and-ongoing-atmp-projects/transplantation-of-keratinocytes-skin-cells-for-severe-burn-injuries/ According to Eder and Wild (2019), chondrocytes, mesenchymal stem and stromal cells, foetal stem cells and keratinocytes are approved.

Possible financial compensation for an ATMP under hospital exemption could be granted by the Special Solidarity Fund (SSF), installed within the NIHDI (see 5.1.1).

The main categories for which the SSF can intervene are the medical treatment costs related to rare indications, rare diseases, medical devices and/or interventions that are innovative medical techniques, chronically ill children and medical treatment abroad.[eee]

In each of these categories, several eligibility criteria have to be met. Although eligibility criteria are specific per category and need to be applied cumulatively, the following criteria show up in most of the categories:

- The intervention is expensive
- The disorder threatens the vital functions of the patient.
- The scientific value and effectiveness of this provision is well established and widely recognised by the relevant medical authorities. This criterion implies that the experimental stage should be exceeded.
- There is no alternative available within the compulsory health system.
- Prescription made by a medical doctor, specialized in the treatment of the related disease.

The decisions of the SSF are taken by the College of Physicians Directors on a case-by-case basis. An application for reimbursement must be submitted via the patient's health insurance fund to the NIHDI, which then provides a response after about 15 days. In principle, it is possible to obtain approval from the BSF before the medical intervention is carried out.

At the time of the writing of the report, the SFF has never received a request for reimbursement of an ATMP under hospital exemption. In theory, ATMPs could be eligible for reimbursement by the SSF under several reimbursement categories. As ATMPs under hospital exemption are most often used to treat rare diseases, this reimbursement category is probably the most likely. For ATMPs under HE for the treatment of a rare condition, consideration will be given to whether this treatment is identified by the authoritative medical bodies as the specific approach for the condition in question.[fff]In general, the College of Physicians Directors expects at least one phase III trial to have taken place. However, each request is analysed individually and deviations are possible for rare diseases and indications where it is inherently difficult to conduct large-scale trials. It is not uncommon for the College of Physicians-Directors to intervene for treatments for which fewer studies have been conducted but based on a level of expertise recognised by "relevant medical authorities".

For treatments that are not reimbursed in another indication, the reimbursement amount is usually 100% of the billed amount for children and 75% for adults (with a personal share for the patient of up to €1,250 on an annual basis). There may be exceptions to this rule. Budget wise, the SSF can ask for extra budget (on top of the closed yearly budget) to allow exceptional expenses related to very expensive innovative treatments. This was the case for Zolgensma, where one million Euros was granted for the treatment of one patient.

[eee] Art. 25 and following Law on compulsory health insurance, coordinated on 14 Juli 1994, *B.S./M.B.* 27 August 1994

[fff] Art. 25ter (rare diseases) does not explicitly include the requirement that the intervention needs to have exceeded the experimental stage. Yet section b) of this article, i.e. “the intervention has been endorsed by the relevant medical authorities as being the specific physio-pathological treatment for the rare disease in question” can be used as a ground for refusal if the treatment for the rare condition is still at the experimental stage. The College will generally give the following justification: ‘The treatment cannot be considered to have a widely recognised scientific value and efficacy and, as the experimental stage has not been exceeded, the treatment cannot be designated by the relevant medical authorities as a specific pathophysiological approach to the rare condition’. (personal communication SSF)

The financing of ATMPs under development in an academic setting may, according to art. 56 of the law on compulsory health insurance, be set within the framework of an agreement between the NIHDI and the respective specialized academic centre.[ggg] In this way, compensation can be provided for a group of patients and specific conditions can be imposed regarding scientific reporting and evaluation.

Examples of reimbursement (options) of ATMPs under HE exist in **other countries**, although most of them have no formal reimbursement schemes, specific to ATMPs manufactured under HE.

In February 2021, the ATMP ARI-0001 (CART19-BE-01), developed at Hospital Clínic de **Barcelona (Spain)**, received authorisation from the Spanish Agency of Medicines and Medical Devices (AEMPS) under the hospital exemption approval pathway for the treatment of patients aged >25 years with relapsed/refractory acute lymphoblastic leukemia (cfr. 7.3). All products approved by the AEMPS, including those under HE are eligible for incorporation in the national health system after a negotiation with the Ministries of Health and Finance of the Government of Spain (which also needs the approval of the autonomous communities). The negotiation for CART19-BE-01 (similar to what is done for commercial drugs) was carried out based on the data of the production costs and the Health Ministry and the regional health councils established the price of reimbursement.[hhh]

Another example is the reimbursement in **the Netherlands** of TIL therapy for patients with metastatic melanoma who cannot have surgery and who did not respond to immunotherapy (cfr. 7.2). TIL therapy was developed by several academic hospitals led by the Netherlands Cancer Institute (Nederlands Kanker Instituut – NKI). The Health and Youth Care Inspectorate (Inspectie Gezondheidszorg en Jeugd) approved the hospital exemption for TIL treatment as long as the drug is produced in the Netherlands by the NKI or Sanquin. The exemption came into effect as of 15 January 2023 for one year and has been renewed in 2024. The Dutch National Health Care Institute (Zorginstituut Nederland) decided that TIL therapy is as effective and not more expensive as the standard treatment and thus can be covered by the basic health insurance package.[95]

In **France**, a route for reimbursement, specific to ATMPs under HE ("médicaments de thérapie innovante préparés ponctuellement" or MTI-PP), was introduced in 2021.[iii] MTI-PPs that are granted authorisation by the Agence nationale de sécurité du medicament et des produits de santé (ANSM) are eligible for a lump sum reimbursement. The level of clinical data expected by the ANSM is equivalent to that required for a MA application, except in cases where no alternative treatment exists at the time of application and the treatment represents the only option for the patient to avoid a fatal outcome in the short term. The reimbursement is based on an annual lump sum per patient, determined by decree of the ministers of health and social security in accordance with the conditions specified by a decree in the Council of State. An impact study preceding the introduction of this route estimated the costs of the system at 3 million Euros for 2022, 4 million euro in 2023, 12 million euro in 2024 and 17 million euro in 2025, based on the assumption that 5 patients were treated per ATMP under HE (in 2022) and 6 additionally in the following years.[jjj] At the time of the writing of the report, however, there is still no implementing decree in place. It seems difficult to make the system of a lump sum operational for ATMPs for which the costs may vary to a large extent per product. It is also unclear whether the political will exists to make this system fully operational.

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ggg Art. 56 Law on compulsory health insurance, coordinated on 14 Juli 1994, *B.S./M.B.* 27 August 1994.

hhh More information on the price regulation: Ministry of Health - Areas - Interministerial Price Commission (sanidad.gob.es)

iii Article L162-16-5-5 Code de la Sécurité Sociale, Art. L162-16-5-5, Code de la sécurité sociale | Lexbase

jjj Sénat France, Projet de loi de financement de la sécurité sociale pour 2022 : Examen des articles, available from : https://www.senat.fr/rap/l21-130-2/l21-130-29.html#:~:text=L'article%2033%20du%20PLFSS,'op%C3%A9rationnalit%C3%A9%20et%20l'efficacit%C3%A9

6.4.3 Existing support mechanisms and possible improvements

At the time of writing, Europe is discussing a major revision of EU pharmaceutical legislation (see Box 1). As part of this revision process, EU lawmakers are actively discussing how to improve standards for hospital exemption.

Regarding the general scope of the legislation, the European Commission, and the European Parliament both suggest moving away from the industrial criteria, without completely being able to depart from this concept[kkk]. Without a more precise definition or guideline definition the placing of the market, this amendment may not resolve all the grey areas.

With regard to hospital exemption in particular, the European Commission's proposal maintains the principle of a national authorisation for the manufacturing and use of ATMPs within hospitals. The proposal also keeps unchanged the definition of HE and the concepts of "prepared on a non-routine basis," "used in a hospital," and "custom-made" products which remain at the discretion of individual Member States.

The focus of the European Commission's proposal lies mainly in the following points:

- **Data collection, reporting and review:**

  The proposal introduces measures for collecting and reporting of data related to the use, safety and efficacy of HE. National competent authorities will review this data annually, and the EMA will publish it in a repository.

- **Assessing Hospital Exemption implementation:**

  The EMA will compile a report on the implementation of hospital exemption based on contributions from Member States. This assessment will aim to determine whether an adapted framework should be established for certain less complex ATMPs developed and used under hospital exemption.

- **Safety concerns and authorisation revocations:**

  If safety concerns arise, leading to the revocation of authorisation for manufacturing and using an ATMP under hospital exemption, the relevant competent authorities will promptly inform the EMA and their counterparts in other Member States.

The proposal also entails certain clarifications:

- Specific quality requirements should be *adopted* by the national competent authorities (thus clearly implemented not just applied by analogy or referred to) and be equivalent to GMP for ATMPs
- The application must be submitted to the competent authority of the Member State in which the hospital where the ATMPS is used is located.

On several aspects, the European Parliament has proposed a different approach:

- **Shared Responsibility:**

  The hospital pharmacist shares responsibility alongside the medical practitioner, when relevant.

- **Criteria for non-routine basis:**

  For the Parliament, hospital exemption should apply only **to meet the *'special needs'*** of an individual patient. It is however unclear whether this refers to the framework foreseen in article 5 of the Directive 2001/83/EC (see infra section 6.5)

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kkk The European Parliament proposal states that : (12) *The definitions and scope of Directive 2001/83/EC should be clarified in order to achieve high standards for the quality, safety and efficacy of medicinal products and to address potential regulatory gaps, without changing the overall scope or affecting national competences in that regard, due to scientific and technological developments, e.g. low-volume products, bedside-manufacturing or personalised medicinal products that do not involve an industrial manufacturing process.*

The EU Parliament also wants the application dossier to contain evidence on quality, safety and ***expected efficacy*** of the advanced therapy medicinal products prepared under hospital exemption while the European Commission was planning to define the requirements on quality, safety and efficacy in delegated acts.

- **Manufacturing requirements:**

  The European Parliament calls for clearer expectations regarding manufacturing practices. These practices should, according to the European Parliament, align with national good pharmacy preparation standards adapted for hospital processes while maintaining equivalence to GMP for ATMPs.

- **Patient follow-Up data:**

  Relevant patient follow-up data should be collected over a sufficient period after administering the advanced therapy medicinal product. The European Parliament also insists on the need to structure standardise data collection way that enables robust, reliable and comparable results and conclusions.

- **Cross-border exchange:**

  For the European Parliament, in exceptional cases of medical need and when no other solutions exist, Member States may authorise cross-border exchange of advanced therapy medicinal products prepared under hospital exemption. A second medical practitioner and a hospital pharmacist in the receiving Member State would assume exclusive professional responsibility for using and collecting follow-up data.

The proposal also suggested initially an adapted framework for less complex ATMPs, which would still ensure safety and quality but with potentially less stringent requirements compared to more complex ATMPs. This is intended to facilitate easier access to these therapies while maintaining high standards of patient care (recital 18 of the proposed Directive). At the time of writing no details were available on this proposed framework.

If most stakeholders, including Academia and industry, welcomed the joint introduction of provisions to ensure more data collection, transparency, patient risks reduction and increased efficiency, certain changes are more controversial issues[lll], in particular the introduction of a prohibition to grant HE when there is a commercial alternative for the same indication. The industry strongly supports this amendment of the European Parliament.

The industry is insisting that future European legislation on medicinal products should stipulate that HA is prohibited if there is a possible alternative via an ATMP with marketing authorisation. However, several stakeholders (academics, patient associations, etc.) point out that not all medicines with marketing authorisation are actually available on the market in question, and even less (financially) accessible in all countries[mmm].

It should be emphasised here that, although its basic conditions are defined at EU level, EH remains a national authorisation issued in a national context on the basis of unmet needs.

Another problem in this discussion is that the notions of 'unmet needs', 'unmet medical needs' and 'special needs' remain ill-defined and are used differently depending on the context. In this respect, the EU authorities have also recognised the importance of consistent identification and analysis of the notion of need (which is used in different ways in different parts of current EU

lll As illustrated by the important number of contributions introduced by interested stakeholders mentioning hospital exemption. (add links to EU public consultation, in particular the contributions of Europabio, LERU, EAHP, Sanchez-Guije et. al 2023).

https://www.eahp.eu/sites/default/files/he_atmp_position_eptri_eahp_eueye_july2023_final_c.pdf

mmm https://europeanbloodalliance.eu/resources/eba-opposes-restriction-of-hospital-exemption-of-atmps/

legislation) (see Council conclusions on the Future of the European Health Union: A Europe that cares, prepares and protects[nnn]).

6.5 Difference with other exceptions

For the sake of completeness, it should be noted that some Member States use other regulatory derogations or therapeutic freedom and the obligation to assist a person in danger[ooo] to authorise or tolerate the use of certain academic ATMPs.

However, magistral preparations cannot be used for ATMPs in the EU framework due to the specific nature of the ATMP legislation. As a *lex specialis*, ATMP legislation imposes more stringent requirements (including 'equivalent' (to industrial) GMP, traceability and pharmacovigilance standards) than those applied to magistral preparations.

For the same reasons, the application of the "special needs" framework (article 5 of Directive 2001/83/EC) may be questioned (as it covers in principle only products falling within the scope of Directive 2001/83/EC, i.e. "industrial" and "placed on the market").

Compassionate use programmes, as provided for in Article 83 of Regulation (EC) No 726/2004, could be applied to ATMPs in a development pathway (provided that they fulfil the conditions set out in Annex 1.6).

7 CHAPTER 4 - EMERGING CASES OF ACADEMIC DEVELOPMENT PATHWAYS IN EUROPE

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Key points

- Traditionally, advanced ATMP clinical development steps (late-stage clinical trials and market authorisations) are sponsored and driven by the industry.
- Exceptions are emerging with recent cases in Spain, the Netherlands, and Denmark showing academic institutions, public funders and charities leading together an advanced ATMP development and anticipating market authorisation (via a separate legal entity) .
- Common features:
  - The products in question are highly personalised autologous therapies utilising the patient's own T cells. For these therapies, manufacturing closer to the patient was clinically relevant, ensuring timely and effective treatment.
  - Various charity and public funding schemes were combined to support the final stages of clinical development and the translational phase.
  - Academic GMP manufacturing units were employed, staffed with highly skilled personnel and guided by strong academic leadership.

nnn https://data.consilium.europa.eu/doc/document/ST-9900-2024-INIT/en/pdf

ooo In Germany, this possibility called *Individuelle Heilversuche* using nonstandard therapeutic approaches finds its roots in article 37 of the Declaration of Helsinki and is allowed, within the remit of the physicians therapeutic freedom (and limited by section 34 of the German criminal code regarding 'justifiable emergency").

- Regulatory advice is crucial to navigate the regulatory landscape and provide the necessary high-quality pre-clinical and clinical evidence: ideally via direct contact with regulators (Barcelona case) or building the regulatory expertise inhouse (Fondazione Telethon).
- The hospital exemption was used (and reimbursed) as an access pathway, following sufficient evidence from studies (e.g., for TILs, a randomised phase IIb/III study in 168 patients; for ARI, a single arm phase I/II study with 47 patients).

- Traditionally, all ATMP marketing authorisations in the EU are held by commercial entities. There is currently a single exception: the MA for the gene therapy Strimvelis® was transferred from the pharmaceutical company to the charity Fondazione Telethon ETS in Italy because the product was no longer considered commercially viable by the industry. In this case a possible success factor is that the product itself is reimbursed in Italy (and in other EU countries).

7.1 Introduction

Till recently, all marketing authorisations for ATMPs approved in the EU were held by commercial actors. In 2023, an exception to the rule emerged, when industry no longer wanted to commercialise a specific ATMP for a very rare disease and transferred the license to a large charity (Fondazione Telethon Italy). The involvement of Academia as a sponsor of late-stage clinical trials is usually scarce. However , there are two recent cases (one in Spain and the other in the Netherlands and Denmark) where academic leadership has decided to go as far as possible in the development and translation pathways to bring their ATMP to the patients via an academic route.[66]

These three examples provide information on both the challenges and the solutions for Academic/non-for profit pathways.

The first two case studies presented, TIL therapy and CAR T therapy, are both forms of autologous cell-based medical treatment that enhance the body's immune system to fight specific cancers. Whereas CAR T is categorised as a gene therapy (according to EMA), TIL therapy does not use genetic modification and is therefore categorised as a somatic cell therapy. The processes of production differ significantly.[96] However both are highly personalised therapies prepared specifically for one patient by using his own T cells. In both instances, academic institutions successfully advanced the development process to the final stages. As of the writing of this report, they are establishing a separate private entity to handle the final commercialisation steps while remaining committed to promote accessibility and affordability of those therapies.

The third case concerns a gene therapy for a very rare genetic disorder that affects the immune system called ADA-SCID (Adenosine Deaminase Severe Combined Immunodeficiency).This gene therapy, known as Strimvelis, was originally developed by researchers at the San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) in Milan, a joint venture between Fondazione Telethon and Ospedale San Raffaele. The development was later advanced through a strategic collaboration with GlaxoSmithKline (GSK).

7.2 Tumor infiltrating lymphocytes (TILs) in advanced melanoma – The Netherlands (and Denmark)

The research on use of TIL in melanoma patients was published already in the 90's by Steven Rosenberg.[97] However, progress in the field proved difficult. The "concept" was thus, already largely disseminated in the scientific community. Many clinical trials were and are still being conducted with TILs to fight different types of solid cancer by both Academia and the industry. In addition, several companies and research institutions have filed patents for specific methods of isolating, expanding, and administering TILs. These patents cover various aspects of the therapy, including the processes used to enhance the effectiveness of TILs and the specific conditions under which they are cultured.[98]

At the Netherlands Cancer Institute (NKI) - Antoni van Leeuwenhoek hospital, TIL-therapy has been offered as an experimental treatment in patients with advanced melanoma since 2011. This has been financially supported by charitable and institutional funding from NKI to create the manufacturing facility and to start a pilot study on 10 patients.[99]

Between 2014 and 2022 a comparative phase IIb/III study was conducted at the Netherlands Cancer Institute (NKI-AVL, Amsterdam, The Netherlands) and the Centre for Cancer Immune Therapy (CCIT, Herlev, Denmark). It was a 1:1 randomised phase III trial (NCT02278887) in 168 patients comparing TILs with ipilimumab in stage IIIC and IV melanoma.

The vast majority of patients enrolled had progressed on anti-PD-1 treatment. Evidence was found that progression-free survival after TIL therapy was significantly prolonged compared with anti-CTLA-4 (ipilimumab) for patients with advanced melanoma (7.2 months compared to 3.1 months).

This project was funded to the amount of € 8,634,000 (partially thanks to donations and to a budget of € 6.2 million granted by the Zorginstituut Nederland (ZIN) under the *Veelbelovende zorg* programme (conditionnally reimbursing the treatment while evidence was being collected)[ppp].[100] In addition, the ZonMw (The Netherlands Organisation for Health Research and Development) (Doelmatigheid) Efficiency programme provided a grant of around 550 000 euros for this trial.[101]

Based on the longer progression free survival, the Netherlands Cancer Institute (NKI) obtained a hospital exemption early 2023 for the use of TIL produced by NKI or by Sanguin. The HE was valid for one year but could be renewed. As the cost-effectiveness study concluded that TIL is equally effective and not more expensive,[102] it led the healthcare payer Zorginstituut Nederland (ZIN) to decide in 2023 that TIL treatment can be reimbursed from the basic package.[95] Zorginstituut Nederland (ZIN) still includes this hospital exemption treatment (considered as existing care) for advanced melanoma patients under the Basic Package under certain conditions.[103]

The production cost per (academically prepared) TIL treatment has been reported to be € 67 547 (min € 45 031 and max € 101 320) depending on the number of patients that should be receiving TIL therapy.[99, 102] When also considering the cost of the patient's hospital care, the total could amount to 125 000€ per patient.[100]

In addition, the Foundation KWF Kankerbestrijding (charity) has provided a grant of 3,86M euros to NKI-AVL **to prepare the EMA registration and to investigate options for marketing** at a fair price.[104] Filing for a market authorisation requires specific expertise. This grant covers the appointment of consultants experienced in introducing an EMA application. To facilitate this process and because the involved academic institutes do not want to take the liability and bear the burden of being a market authorisation holder (including having a dedicate and ultra specialised staff for this activity), a not-for-profit license holder company entity is planned to be created and the Marketing Authorisation would be transferred to this separate legal entity if and when the EMA would grant such MA. At the time of writing this report this legal entity was not yet created. The MA holding entity will not itself produce TILs, but will ensure data oversight, comply with pharmacovigilance obligations and fulfill any other responsibilities of a MA holder towards EMA. It will grant licenses for TIL production and arrange tech transfer to qualified academic hospitals following a '*point-of-care production'* model.

The overall strategy involves creating a sustainable infrastructure for TIL therapy, involving multiple disciplines such as medical, production, quality of life, health technology assessment, data management, financing, and business development.

Multiple clinical trials worldwide are currently being performed with TIL therapy in melanoma and other tumors, also investigating improvements in the process.[96] The US company Iovance has obtained FDA approval (under accelerated approval pathway) on 16/2/2024 for TIL (lifileucel – Amtagvi® in advanced melanoma) and has submitted an EMA marketing authorisation application in advanced melanoma in June 2024 .

Iovance is also sponsoring an ongoing international phase III trial (NCT05727904). This multicentre, open label, 1:1 randomised, parallel group trial is testing lifileucel in combination with pembrolizumab compared with

ppp https://www.zorginstituutnederland.nl/publicaties/standpunten/2022/12/13/standpunt-tumorinfiltrerende-lymfocyten-til.

pembrolizumab alone in 670 participants with untreated, unresectable or metastatic melanoma.

If a marketing authorisation is obtained by a company for TILs and becomes available in the Netherlands, the hospital exemption may have to be discontinued in The Netherlands. The price quoted in the US for a lifileucel treatment is 515.000 USD.[96] Contrary to the academic production of TIL in the Netherland and Denmark, production of this commercial treatment is currently centralised in Philadelphia.[105]

7.3 CAR-T cells for ALL - Spain

ARI-0001 (varnimcabtagene autoleucel) was developed at Hospital Clínic de Barcelona, Spain and was named after Ari Benedé, a girl diagnosed with ALL who passed away on 2 September 2016. It is a second-generation CAR, built upon a new construct based on A3B1, a monoclonal antibody developed by the Hospital Clínic de Barcelona in **1990**. Despite multiple preclinical and clinical CAR-T projects that were ongoing and the difficult road to commercialisation, the hospital clinic de Barcelona decided to develop their own CAR-T to ensure access for their patients.[106]

In **1996**, the August Pi Sunyer Biomedical Research Institute (IDIBAPS) was founded, as a public consortium comprising the Hospital Clínic de Barcelona, the University of Barcelona, and the Government of Catalonia, with the CSIC Institute of Biomedical Research in Barcelona later joining as an associated centre.

In **2013**, the specific CAR19 construct was developed based on in-house availability of the anti-CD19 monoclonal antibody (generated since 1990 in the immunology department) and was successfully transferred in a viral vector (lentivirus).[106]

After obtaining positive results in preclinical experiments and demonstrating robust and reproducible lentivirus and ARI-0001 cell production, its safety and efficacy were assessed in a phase 1 study conducted together with the paediatric hospital Sant Joan de Déu (Barcelona). This **CART19-BE-01** phase 1 trial (NCT03144583) was approved in May **2017** by the Spanish Agency for Medicines and Health Products (AEMPS). This trial funded by a crowdfunding recruited 47 patients with resistant/refractory (R/R) lymphoproliferative B disorders, with a median age of 47.5 years (range 3–67), of which ALL accounted for 80% of patients. The efficacy outcomes achieved were reportedly similar to those of other academic and commercial products, including tisagenlecleucel (Kymriah®, Novartis), while safety was improved with the fractionated administration of the cells (split in three fractions: 10%, 30% and 60%) to reduce the cytokine storm. ARI was produced via a closed semi-automatic bioreactor CliniMACS Prodigy® which provides a logistical advantage compared to the centralised production model used so far by industry.[107]

This phase 1 study was the basis for the hospital exemption dossier submitted in February 2020 and obtained in February **2021** for CAR T ARI-0001 used in treatment-resistant ALL in >25y (based on 38 cases >25y). Pricing and reimbursement were agreed with the Ministry of Health in June 2021 at €89 270. Around 40 patients are treated per year. A pharmacovigilance programme was created.[107] The product is reimbursed and for patients that do not meet the HE eligibility criteria, a compassionate use programme can be used (case by case) in Spain. In 2018 a specific plan was adopted by the Spanish authorities to ensure CAR T accessibility. [108]

The overall development costs for the ARI product up to phase I are reportedly around €10 million (mainly because the expertise was already present, they used their own antibody and a lot of the work was done in-house). [109]

- A3B1, monoclonal antibody generated >30 years ago at the Immunology Department of the clinic
- Demonstrating robust and reproducible lentivirus production in a GMP facility Creatio, which is located at the Faculty of Medicine and Health Sciences at the University of Barcelona (In 2017, Creatio began producing the first lentiviruses under GMP conditions for the Hospital Clínic in Barcelona) (see Box 7)
- Clean room at the immunology department with closed semi-automatic bioreactor CliniMACS Prodigy® equipment (bought at the moment the clinical studies started)

Box 7 – Public CDMO in Spain (Creatio)

Creatio is a contract manufacturing organisation that is part of the University of Barcelona, specifically within the Faculty of Medicine and Health Sciences. This affiliation allows Creatio to leverage academic resources and collaborate closely with various research institutions and hospitals to advance cell and gene therapies. Creatio also has contracts with private players. The annual report of 2023 showed 34% of the budget coming from private and 66% public projects.[110]

Creatio played a crucial role in the development of CAR-T (Chimeric Antigen Receptor T-Cell) by the public Hospital of Barcelona as it provided the lentiviruses (in its GMP compliant manufacturing facilities) and part of the translational expertise.

The main funders of this public-civil cooperation included the crowdfunding ‘‘ARI Project,’’ but also several public grants of the Instituto de Salud Carlos III, Spanish Ministry of Health, Fondo Europeo de Desarrollo Regional (FEDER), Generalitat de Catalunya, and ‘‘La Caixa’’ Foundation.

In October **2020**, ARI-0001 was licensed to Immuneel Therapeutics, Bengaluru, India, in an effort to bring affordable CAR-T therapy to India.[111]

Figure 2 shows the major deliverables of the ARI-0001 development.

Figure 2 – Timeline of ARI-001 development (from Juan et al 2021)[66]

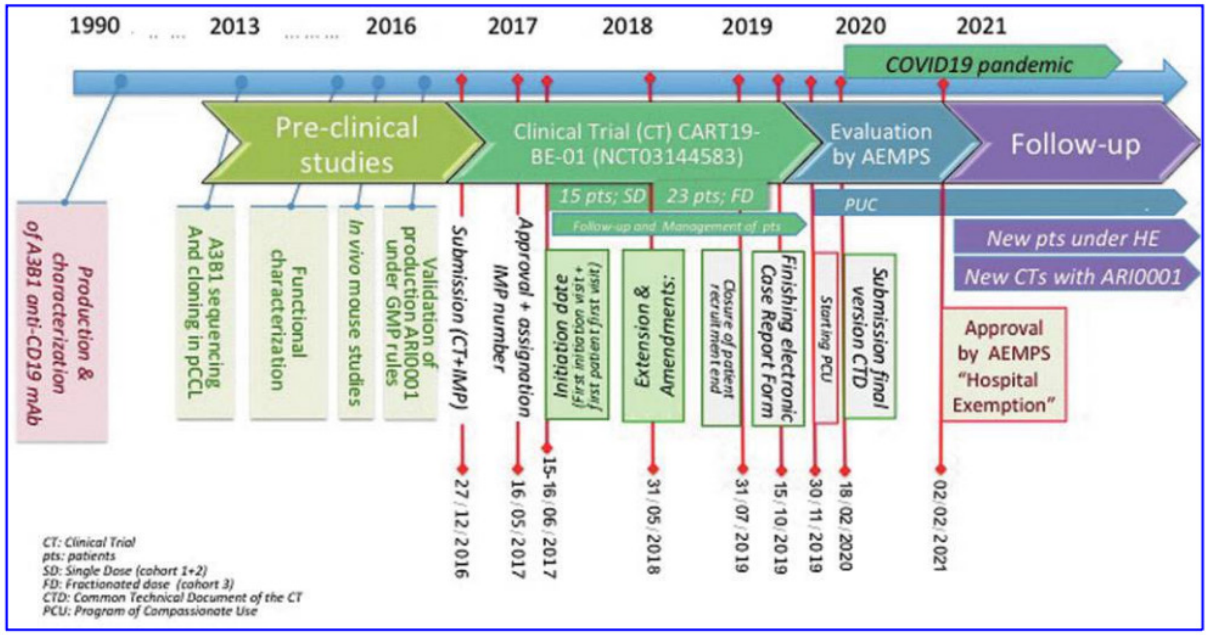
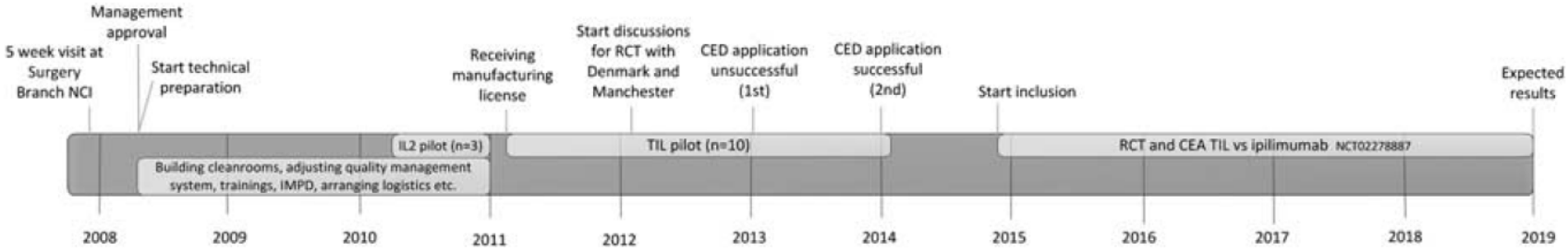


Figure 1. Chronology of events developed until final approval of ARI-001 under HE by AEMPS. Milestones are pointed out by *ended-with-dots lines* and a specific date. AEMPS, Spanish Agency of Medicines and Medical Devices; CT, clinical trial; CTD, common technical document; FD, fractionated dose (cohort 3); HE, hospital exemption; pts, patients; SD, single dose (cohort 1+2). Color images are available online.

Figure 3 – Timeline of TIL therapy implementation (from Lindenberg et al 2018) [99]



ARI-0001 is currently being further investigated in a single arm Phase 2 study in adult patients with R/R CD19+ ALL (**CART19-BE-02,** NCT04778579) entitled "*Phase 2 Study of the Infusion of Differentiated Autologous T-cells From Peripheral Blood, Expanded and Transduced With a Lentivirus to Express a Chimeric Antigen Receptor With Anti-CD19 Specificity (A3B1) Conjugated With the Co-stimulatory Regions 4-1BB and CD3z (ARI-0001 Cells) in Patients With CD19+ Acute Lymphoid Leukemia Resistant or Refractory to Therapy*." The administration of the CAR-T is spread over 4 days. This trial investigates the tolerability and long-term remission after a higher dose of 3 million CAR T cells/kg administered over 4 days (instead of 1 million cells/kg). The trial recruited 50 patients in 12 Spanish centres and was planned to be complete by mid-2022. The cost of this trial is €1.2M and €1.44M in cell production only.[112]

ARI-0001 was granted PRIME designation by EMA on 16 **December 2021** for patients older than 25 years of age with R/R ALL.[113] and the Hospital Clinic de Barcelona project continues to pursue a **centralised authorisation from the EMA** for its CAR-T ARI-0001 for ALL. In this context, a Paediatric Investigation Plan (PIP) was submitted in July **2022** and a revised version submitted in January 2023. An agreement on the PIP was reached in May 2023. The requested trial **CART19-BE-03Ped** will be conducted in pediatric ALL. The initial trial cost was estimated at €1.4M plus €1.35M for cell production. The EMA pediatric committee (PDCO) requested 70 pediatric patients to be studied, including 30% from EU countries, different from Spain. There is an interest from IT, NL, FR.

Scientific Advice sessions at the EMA started in July 2022. A matched-indirect comparison of the phase 2 results has been planned, using an external database (PETHEMA). The goal of the application is to obtain a conditional marketing authorisation (CMA) based on the demonstration of a "major therapeutic advantage" over fully approved products (Blincyto®, Besponsa®). A third EU-based trial will be needed in case of CMA: **CART19-EU-04 (CARTALLEU)**. This will require a budget of €9.8M (trial in ES, FR, NL, BE, AT), and is granted via a pooling of cancer charity organisations. The study is expected to start in summer **2024**.[114] First, a network of certified academic and production unit is set up in Spain, Belgium, France and the Netherlands to manufacture the advanced therapy. Then, 60 adult patients will be recruited in 2025. It is vital to ensure that each country manufactures the cells in an identical way to how it is done in Spain. The CAR-T vector production however remains centralised in Barcelona and will be provided to each centre .

Box 8 – Creation of a public-private company (Terafront Farmatech)

Terafront Farmatech is a public-private partnership in Spain, established to develop and bring to market advanced therapies derived from leading Spanish research groups. They plan to have two therapies authorised and commercialised by 2027.[qqq]

Ownership Structure: Terafront Farmatech is 49% publicly owned and 51% privately owned. The public contribution is managed by the Ministry of Science, Innovation, and Universities through Innvierte (public structure implementing the science, technology and innovation policy for the Spanish State), while the private sector includes Insud Pharma and Rovi.

Financial Contributions: The public sector has invested €36.7 million, and the private sector has contributed €38.2 million, making the total initial capital approximately €74.9 million. Future investments could reach up to €220 million, depending on project needs.

Governance: The board of directors includes representatives from both the public and private sectors. The presidency is held by Insud Pharma, with Rovi and Innvierte also playing significant roles.

Facilities: Terafront Farmatech will establish its own manufacturing facilities rather than using existing ones from its founding companies.

This collaboration is part of Spain's Strategic Project for Economic Recovery and Transformation (PERTE) for cutting-edge health. The PERTE projects are designed to align with the broader goals of the EU recovery plan, which aims to make Europe greener, more digital, and more resilient.

As detailed in the Supplement (section 6.2), the participation of the public authorities in the form of a stake will not amount to the conferral of an advantage if the public authority has acted as a private investor. When a transaction is conducted under identical terms and conditions, with both public bodies and private operators sharing the same level of risk and rewards in comparable situations (a "pari passu" transaction), it can generally be inferred that the transaction aligns with market conditions. No state aid is conferred in this situation.

Note that ARI-0001 is also being tested in refractory diffuse large cell B-cell lymphoma in The Netherlands with UMC Groningen as the sponsor (NCT05641428). The ARI-0001 CAR-Ts are produced in the GMP approved facility in Groningen. On October 20, 2024, 105 patients had been recruited at 7 sites. A total of 300 patients are to be randomised 1:1 in this non-inferiority trial versus standard care Yescarta® CAR-T therapy. Zorginstituut Nederland finances the trial for about 30M euros.[116] (see Box 9)

[qqq] Sources: articles of association of Terafront Farmatech and statements in the press [115]. Farmespana Industrial. New data on Terafront Farmatech, the Commercial Company for Advanced Therapies in Spain [Web page].2024. Available from: https://www.farmaindustrial.com/noticias/nuevos-datos-sobre-terafront-farmatech-la-sociedad-mercantil-de-terapias-avanzadas-en-HUY2F https://cincodias.elpais.com/companias/2024-04-10/la-nueva-farmaceutica-publico-privada-inicia-sus-operaciones-con-el-nombre-terafront-farmatech.html ; https://www.cnmc.es/sites/default/files/5492625.pdf.

Box 9 – 30 million euros public funding for a comparative trial with CAR T-s in the Netherlands

In the context of 'Promising Care Subsidy Scheme'[rrr] project the National Health Care Institute (ZIN) is subsidising a comparative study (care and research costs) to determine whether point-of-care produced CAR T-cells should be included in the basic health insurance package (and compare them to Yescarta® which is reimbursed in the Netherlands). The funding amounts to 30 million and is implemented on behalf of the Minister of Health, Welfare and Sport. This funding aims to fund research into the **(cost-)effectiveness** of CD19 CAR T cells produced point of care in patients with relapsed or refractory diffuse large cell B-cell lymphoma (DLBCL).

Only health care providers are eligible for such programme.

The criteria to be selected under this programme include the following:

- The only reason that the care is not yet reimbursed from the basic package is the lack of research results that show that the care is at least as effective as the usual treatment in the Netherlands. Care that is not (yet) reimbursed from the basic package due to a legal restriction (for example cosmetic surgery) is not eligible for subsidy.
- The care is demonstrably safe and the efficacy has been demonstrated in the patient population concerned. This is substantiated by results from clinical research.
- The risks to the patient are acceptable in relation to the expected health gain.
- The Advisory Committee on Promising Care (Advezo) considers the subject to be minimally relevant.
- The Advezo finds the quality of the research proposal at least sufficient. This means, among other things, that the Advezo expects that the Healthcare Institute can use the future results of the research to assess whether the care in question complies with the state of science and practice.
- There is a market failure.

The research results should enable the Healthcare Institute to assess whether the care treatment complies with the state of science and practice. The cost-effectiveness should also be assessable on the basis of these research results.

Under the programme, ZIN has combined care and research activities, which fall under two different state aid regimes. The care activities are governed by the regime for Services of general economic interest (essential services of great importance to society that are not sufficiently provided by the market), while the research activities are covered by the General Block Exemption Regulation (state aid exempted from notification or approval). Both funding schemes are further discussed under the state aid section (see section 8.2.3).

Both activities are inseparable and are funded together under the same programme The contract and all details are published on the funding public authority website. [117] [118]

[rrr] https://www.zorginstituutnederland.nl/financiering/subsidieregelingen/subsidieregeling-veelbelovende-zorg/criteria-en-procedure/criteria-subsidieregeling-veelbelovende-zorg

7.4 Strimvelis gene therapy for ADA-SCID - Fondazione Telethon ETS (Italy)

The Fondazione Telethon ETS is an Italian non-profit organisation founded in 1990. It is a funder of research in rare genetic diseases. An amount of over 250 M euros has been funded so far, money raised i.e. in collaboration with the Italian national broadcaster RAI. The first gene therapies approved for a rare condition (Strimvelis® and Libmeldy®) were developed through a partnership between private organisations and the work of Fondazione Telethon ETS.

Strimvelis® was based on research funded by Fondazione Telethon ETS at its San Raffaele Telethon Institute for Gene Therapy.[119] The treatment consists of autologous CD34+ cells transduced with a retroviral vector encoding for the human ADA cDNA sequence. Strimvelis 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. Strimvelis was designated an orphan medicine in 2005 and licensed to GlaxoSmithKline (GSK) in 2010. The GSK holding obtained EMA marketing authorisation in 2016. This first *ex vivo* autologous gene therapy approval by the EMA was based on a study involving 12 patients from 6 months to around 6 years old with ADA-SCID. In 2018, the marketing authorisation was transferred to Orchard Therapeutics (Netherlands) B.V.

However, in 2022 Orchard Therapeutics decided to divest from the commercialisation of Strimvelis because it was not economically viable.[120] Fondazione Telethon ETS intervened to avoid the discontinuation of the product and in July 2023 the transfer of the Marketing authorisation was granted to Fondazione Telethon ETS becoming the first charity holder of a Marketing authorisation.[119] Thanks to a clause in the first licence agreement between Fondazione Telethon ETS and GSK there was no need to re-buy IP rights and know-how and they went back to the initial holder (Fondazione Telethon ETS). In order to become MAH, Fondazione Telethon ETS established a dedicated scientific service and hired staff to manage pharmacovigilance.[120] This big financial commitment is possible because it is a non-profit organisation that 'just' needs to balance the costs. Revenues also come from reimbursements of the product and related care by the National Health Services for Italian and European Union patients, private funds and insurance for patients outside the European union.[120]

The gene therapy product will still be manufactured by the same pharmaceutical facility located on the San Raffaele campus of the Telethon Institute for Gene therapy, which was also previously manufacturing them on behalf of Orchard. The treatment will be administered exclusively at the San Raffaele Hospital as the product is not cryopreserved and it has a limited shelf-life

A similar transfer of the marketing authorisation to a hospital (Great Ormond Street Hospital (GOSH) is ongoing for this product in the UK supported by Life Arc Charity and Great Ormond Street Hospital (GOSH) own charity. Given the withdrawal of the above-mentioned companies, IP and additional data were recuperated by the hospital. An academic lentiviral vector will be used for this development.[121]

7.5 Lessons learned from the case studies

The three above mentioned cases are well advanced cases of academic ATMP development.

7.5.1 Strimvelis

Strimvelis® was not 'commercially viable' for industry (a market failure) and a non-for-profit organisation decided to take over the production and distribution and to hold the MA (and bear the related costs: liability costs, staff to maintain the MA and manage pharmacovigilance etc.). Fondazione Telethon's decision demonstrates the feasibility and potential for non-profit organisations to step in and ensure the continuation of critical therapies.[120]

The case also highlights the challenges of sustaining treatments for rare diseases, which often have high production costs and limited patient populations. One could even be inclined to state that medicinal products targeting a very rare disease are likely not 'commercially viable'. However, determining whether an ATMP is not 'commercially viable' will depend on several factors including the medical need and the efficacy seen in the clinical

trials. This can thus be described as a (fast) moving target[24, 70]. Therefore, the case rather underscores the necessity for the Academia and the funding body, to possess the necessary expertise to assess this moving target and adapt their strategy. This includes in particular intellectual property, regulatory and financial expertise and requires a continuous and open dialogue between the clinical setting where the product was developed, the funders, the regulatory authorities and public and private stakeholders in the field.[81]

Finally, having the reimbursements in place for the products was also a key success factor.

7.5.2 ARI-001 and TILs

The other two academic developments show it is feasible to advance towards a market authorisation for ATMPs despite the fact that there are also commercial products in the same ATMP category (CAR-Ts, TILs) although not identical to commercial products. It might be needed to use another legal vehicle to apply for a MA (a public-private company in the Barcelona case and a non-for-profit company for the TILs), not because non-for-profit organisations cannot be MAH but for liability reasons (possibly also to ensure a structural funding and avoid state aids problems). Although marketing authorisation has yet to be obtained, some common features can be observed.

Regarding the **scientific context**, it should be noted that in the two above mentioned cases, the basic concepts of the therapies were public knowledge and that, based on those concepts, high-quality pre-clinical and clinical evidence was generated by non-for-profit institutes in non-commercial clinical trials (conducted over a long period, e.g. 8 years for the phase IIb/III trial using TILs).

Regarding **the academic expertise,** the academic teams have developed a unique and extremely high expertise in the field (and worked in a centre that was recognised for those therapies within teams that were trained by the leading scientists in the field).

In both cases academic manufacturing expertise and facilities were developed and investment were made by the Academics accompanied by public funders and charities to fund those GMP accredited facilities.

Public funders and charities were also the parties funding the clinical trials and the preparations of the marketing application of the ARI-0001 and the TILs.

Regarding **the regulatory road**, in the Spanish case, early interactions with regulators help in navigating the intricate regulatory landscape (preparing comprehensive documentation such as the Investigational Medicinal Product Dossier (IMPD) and later a MA dossier, as well as keeping up with regulatory changes). The Barcelona case has been selected under the EMA pilot for non-commercial developers (see Box 13). Importantly, the **hospital exemption framework** has been used to make the ATMP accessible to patients locally, but is used as a temporary option, as it is intended for, to bridge to the moment an MA is possible. In both cases HE (and reimbursement) was obtained based on the positive results of a clinical trial.

It should also be underlined that in Spain the development was supported by **clear positions of the regulatory authorities** regarding the regulatory (and reimbursement) roads and by **a transparent and public positioning of the health care and economic authorities** regarding the public support to the related therapies.[117 108, 118]

The development and regulatory road have been (and remain) extremely complex. The **commitment** of the chief investigator and public funders are key to help the project advance.

8 CHAPTER 5 - STRATEGIC AND LEGAL OPTIONS FOR THE ACADEMIC DEVELOPMENT OF ATMPS

QUINZ

Key points

- In each of the authorisation pathways (hospital exemption, clinical trials, and marketing authorisation), Academia are confronted with important hurdles and restrictions that limit the development of their ATMP and their access for the patient.
- However, the role of Academia in ATMP development is evolving, leading to increased attention to the potential of academically developed ATMPs to improve access for patients and potentially decrease the prices of ATMPs.
- Support on different fronts is needed to enable this role for Academia, including funding by public authorities at EU and national level, but also non-financial support mechanisms, which enable sharing of expertise and knowledge between government, Academia, and industry, and the development of manufacturing networks. Indeed, novel manufacturing approaches are explored, including decentralised and bedside manufacturing, which could have the potential to improve accessibility and availability of ATMPs.
- In the provision of support by public authorities, state aid principles need to be taken into account:
  - supporting research and infrastructure building is generally allowable
  - providing support to Academia to progress an ATMP through hospital exemption would, under certain conditions also be allowable.
  - supporting economic activities, including commercialisation efforts of Academia in relation to ATMPs is complex and require a careful and balanced evaluation (e.g. assessment of a possible market failure, specific condition to organise SGEIs or a funding under the GBER, etc.)
- A combination with charitable funds (not State aid) or funds directly allocated by the European authorities (also State aid if allocated without State intervention) is also an interesting possibility.
- In the implementation of publicly (and charity) funded drug development, increased attention is going to the social responsibility of drug developers, especially if the product is partially developed through support by public authorities. It is argued that drug developers, particularly within Academia, should ensure that their products are accessible, available and affordable for the patient. Different implementations could be envisioned, including compulsory licensing provisions and march-in rights, open-science models etc. with the understanding that socially responsible licensing models might decrease the interest of commercial actors in licensing such technologies. However, in order to put such clauses in place and implement them, important expertise is needed at an early stage of the development process.
- In the most advanced academic business model, one could theoretically envision that Academia holds MA. However, despite emerging cases, this role is still extremely theoretical. Hurdles for Academic MAs are not limited to expertise and resources, but are also legal in nature:
  - limitations under state aid considerations,
  - unclarity on the legally permissible, activities of hospitals,
  - incompatibilities between certain functions of a hospital and aspects of MA holders,

- and misalignments between compliance frameworks and the role of Academia as MA holder

Additionally, Academia is not well equipped to comply with legal obligations flowing down from MAs, such as pharmacovigilance requirements and product liability risks.

8.1 Introduction

Academia currently has a central role in the initial phase of ATMPs development including small first phases clinical trials.[70] However, the majority of Phase IIb/III, III and IV trials are still sponsored by commercial actors.[122]

It is often argued that an increased role of Academia in ATMP development (further progressing ATMPs internally) could lead to reduced costs for the health insurance: for example, it is estimated that selected CAR-T therapies which are manufactured in-house (under hospital exemption) at hospitals show final costs significantly lower (35.000 – 60.000 EUR) (or 89 000 EUR as for Barcelona) than commercially developed CAR-T therapies.[73] However, it should be underlined that the available data on the costs of academic production are limited and that those data cannot be easily compared to the prices set by the industry for which there is a general lack of transparency.

Moreover, increased activity of Academia in areas and diseases for which there is insufficient interest of industry provides opportunities for improved access to ATMPs for patients. [20]

However, developing ATMPs requires significant financial investments, specialised personnel, regulatory expertise, and manufacturing capabilities which Academia generally do not sufficiently possess to progress ATMPs beyond early stage development.

An increased role for Academia in ATMP development consequently require additional resources and support. Public authorities play a key role in providing and coordinating such support and efforts, both as key funders in this field, as well as generators of knowledge and drivers of policy. In this context, a game changing trial might be the publicly-funded 1:1 randomised non-inferiority phase 2 clinical trial currently recruiting 300 patients in The Netherlands (HOVON-161 trial, https://hovon.nl/en/trials/ho161-1 and https://clinicaltrials.gov/study/NCT05641428).[123] It compares a CAR-T (ARI-0001) against a commercial counterpart (axi-cel, Yescarta) in patients with relapsed or refractory diffuse large cell B-cell lymphoma (DLBCL). Zorginstituut Nederland and ZonMw (public payer organisations in The Netherlands) finance the trial for 29 653 093 euros.[116] (see Box 9)

Of course, Academia may choose to stay focused on their core missions of patient care and scientific research. In this context, Academia can drive the early stages of ATMP development and then partner with industry players—such as pharmaceutical companies, biotech firms, or commercial spin-offs—that are equipped to handle the later stages of development and commercialisation. This strategy is already the dominant path. The academic approach explored in this report could complement the classical path.

In fact, Academia's unique strengths in ATMP development, including expertise in fundamental research, preclinical studies, and early-phase clinical trials, with increased focus on future authorisation possibilities could potentially persuade industry to overcome its reluctance to invest in certain ATMPs. By leveraging Academia's contributions, the investment risks could be reduced, thereby making the prospect of investing in such ATMPs more appealing to industry

Legal and policy considerations should underpin any support provided to Academia towards such increased role. As such, the public authorities should establish an overarching policy framework to ensure that support measures adhere to applicable laws, in particular state aid regulations and lead to socially desirable outcomes (including for example through social responsibility commitments attached to support by public authorities.

It will be crucial for any such policy framework to strike a good balance between public interest and industry interests, ensuring that an increased role of Academia does not restrict the commercialisation pathway from remaining appealing to both Academia and industry. Academia should also be rewarded in case of such a successful effort with a high value for society.

In this chapter, we will delve into the strategic issues crucial for supporting ATMP development by Academia.

We begin by outlining the key principles for public funders aiming to enhance the role of Academia in ATMP development. This includes designing compliant public funding schemes and developing an adequate IP strategy.

Next, we will discuss how to foster research and translational expertise, as well as manufacturing capacities which were the most frequently expressed needs in this area identified in the report.

In the Supplement, we also conducted a theoretical exercise to explore the feasibility of Academia (in particular a hospital) holding a marketing authorisation (see Section 4 in Supplement). Our analysis suggests that this scenario is highly unlikely for ATMPs (although several public entities hold MA for more traditional -nationally authorised- medicinal products) due to numerous legal hurdles.

8.2 Public funding: necessity and approaches

The successful contribution of Academia to the development of ATMPs hinges on the availability of sufficient financial resources. Funds obtained by Academia are mostly project-based and limited in time, not covering a full pharmaceutical development. Academic actors are therefore not inclined to attract long-term personnel or set-up long term clinical trials for ATMPs. Early-stage research on ATMPs, conducted to date, is mainly funded by a combination of public and charity money.[36]

The lack of structural funding has been identified as a key hurdle for Academic ATMP development.

8.2.1 Types of public funding for ATMP projects

In general, funding of scientific research can be driven by a public authority (on a regional, national, or European level), by charitable organisations, by for-profit organisations, or through collaborations and partnerships of any of the foregoing. Indeed, pharmaceutical companies, as for-profit organisations, frequently fund research conducted by hospitals, also outside of clinical trials performed by the hospital on a fee-for-service basis. There is, however, little chance that pharmaceutical companies will fund medicinal product development without obtaining additional rights to the product. Subsequently, by relying on funding by a pharmaceutical company for Academic ATMP development, a potential risk arises of fostering a “contract research” dynamic between hospitals and the pharmaceutical company in question. If the company secures IP rights on the research outcomes, there is a concern that the undertaking may want to shelve the further commercialisation or afterwards increase prices for the respective ATMPs, potentially hindering the drugs’ accessibility and affordability. This would run counter to the purpose of the current study, which aims to explore academic development pathways to promote the accessibility and affordability of ATMPs. Moreover, relying entirely on charitable funds is not ideal either, as it is not a guaranteed source of incomes, and the available funding may be limited.

As a result, it seems appropriate to rely, at least for a part of ATMP developments by Academia, to funding provided by a public authority.

In many instances, however, funding by public authorities is currently given to initiatives in which public and private actors are collaborating, fostering partnerships between both types of actors.

Examples of financial public support

Public funding can take a multitude of forms. A public authority may, for example, provide direct support in the form of grants or subsidies. Depending on the pathway pursued, public authorities may provide direct support for the R&D, manufacturing and/or commercialisation activities. Many examples of public funding schemes exist.

On a European level, the most prominent funding scheme for research and innovation is the framework of **Horizon Europe.** With a budget of 95.5 billion EUR, it is one of the largest public funding schemes that currently exist. While Horizon Europe is not solely focused on research in the pharmaceutical and healthcare sectors, ‘Health’ is one of the key clusters under Pillar II of the programme. Moreover, cancer is designated as one of the 5 cores ‘Missions’ of the programme. Funding under the Horizon Europe framework can broadly take 3 forms:

- **A direct research grant**, based on calls for proposals, in which the beneficiaries (public and private) receive reimbursement for eligible costs.
- **Co-funded project** (specifically for health, generally under the Innovative Health Initiative Joint Undertaking), in which public and SME beneficiaries receive reimbursement of eligible costs, and (large) private partners provide in-kind contributions to the partnership.
- **A direct investment** by the EU in innovative companies under the European Innovation Council. The European Innovation Council is a programme that provides research grants for supporting new technologies (EIC Pathfinding), maturing a novel technology and developing a business case to bring it to market (EIC Transition) and supporting start-ups and small and medium-sized enterprises to develop and scale up to new markets or disrupt existing ones (EIC Accelerator). The EIC Fund is an investment fund under private law with the European Commission as a shareholder that was created to fund companies selected under the EIC Accelerator. This last option is available for SME's and start-ups and not (directly) for Academia.

Other European initiatives include the **InvestEU programme** (based on regulation 2021/523),[124] which through its 26.2 billion EUR InvestEU Fund provides a European guarantee for private investments in among others research, product development and innovation activities, the transfer of technologies and research results to the market. Notably, the Belgian case Novadip (see section 6.4.2.4) is backed by the European Investment Bank under the InvestEU Fund. In addition, Novadip received 9.4 million (5.7 for the product NVD-003 in particular) of non-dilutive capital by the Walloon Region (in 2020) and 16 million in non-dilutive capital in 2022.

In Belgium, regional initiatives such as Biowin[sss], Medvia, (and the regional economy authorities) Innoviris[ttt], Vlaio[uuu] support research and innovation projects in the field of health, boosting the economic landscape in the region. Their key focus is to stimulate regional economic redeployment in their respective regions. Primarily the public-private partnership is fostered, and there is a requirement to have private investors.[125]

Examples of public-private partnerships fostered by regional government include:

- VLAIO finances ICON-projects where at least three independent Flemish companies need to gear up with a research partner. This led for example to the creation of the Persomed consortium, including academics from the Vrije Universiteit Brussel (VUB) and three industry partners. They planned to conduct a clinical study using dendritic cells loaded with mRNA coding for neoantigens in patients with colorectal cancer. However, the consortium was not able to secure financing for the study.
- The Walloon Government (via BioWin) funds ATMP projects (ATMP-Partenariat d'Innovation Technologique). An example is the PDC*neo project which is a partnership between UCLouvain, ULB and PDC*Line Pharma to initiate a phase I clinical trial with allogeneic dendritic cells in patients with colorectal cancer.

sss BioWin is a not-for-profit organisation and manages the Health competitiveness cluster of Wallonia supporting research and innovation in the fields of biopharma, medtech and digital health.

ttt Innoviris is the public organisation from Brussels Capital Region supporting innovation and research

uuu VLAIO "Vlaams Agentschap Innoveren en Ondernemen" is the public organisation supporting and financing Innovation and Entrepreneurship

In other EU countries, a notable publicly funded initiative is the Oncode Accelerator, a 320 million project, funded by the Dutch government, as part of the Nationaal Groeifonds, that aims to build and improve the infrastructure in the Dutch healthcare system for preclinical development of cancer treatments.[vvv] Through public-private cooperation, the research infrastructure in the Netherlands will be strengthened and validated, including in relation to ATMP capabilities. Another initiative of note includes RegMed XB, a Dutch-Belgian platform that includes a non-for-profit Belgian company and a Dutch foundation fostering public-private (Academia & industry) collaboration on regenerative medicines (see also 8.4 and Box 11).

In Italy, the National Center for Gene Therapy and Drugs based on RNA Technology secured funding (320 million euro) under Investment 1.4 of the National Recovery and Resilience Plan (PNRR) (NextGenerationEU). This program unites 46 organisations, including universities, research institutes, and private companies. It supports the creation of two infrastructures to the benefit of all the National Center members and the broader Italian scientific community. The Gene Therapy Center will take advantage of pre-existing facilities located at Bambino Gesù Children's Hospital in Rome (OPBG), San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) and the Tettamanti Foundation. The RNA Production Platform will be implemented in a dedicated space at the University of Naples Federico II.[126]

In any case, in the provision of any public financial support to ATMP development efforts, consideration should be given to a number of issues.

- Care should be taken to ensure such support is focused to achieve its intended goals, which not only includes fostering ATMP development by Academia, but also includes a desire to promote accessibility and affordability of ATMPs.
- Any public support should be mindful of and in compliance with state aid requirements.

8.2.2 *Funding conditions to ensure accessibility and affordability and social responsibility*

The COVID-19 pandemic has sparked the long existing debate about public investment in pharmaceutical R&D and resulting profits for drug developers. An often-heard criticism is that commercial drug developers benefit from the derisking of research and development efforts but that such derisking is not adequately reflected in the market price or other access terms of the product. In relation to vaccines, a 2023 IPOL study[18] proposes that a new policy framework is needed to avoid that future vaccine science supported by the taxpayer will be fully privatised without any guarantees concerning intellectual property rights (IPR), equitable distribution, and affordable prices for resulting products. Scientific literature also advocates for more transparency and accountability, including licensing terms and pre-negotiations on use and pricing in the interest of public health.[127, 128]

In addition, Academic technology transfer offices (TTOs) could exercise an important leverage by incorporating legally binding access provisions into licensing agreements. While changes to licensing practices are theoretically immediately actionable, Academia face an inherent tension between their public benefit mission and financial incentives to maximise licensing income to supplement institutional operating costs. As the success of TTOs is in part measured by the number of agreements signed and royalties received, these offices may be concerned that potential licensees will reject access provisions and opt to work with other universities who provide more favorable terms. Meaningful change will require university trustees to empower TTOs to both implement licensing access plans and enforce them and will need major academic institutions to work together such that access obligations in patent licenses become the norm. [128]

[vvv] See https://www.oncodeaccelerator.nl/. The ruling confirming the grant under the Nationaal Groeifonds can be consulted at https://www.rvo.nl/sites/default/files/2022-12/Maatwerkbeschikking%20221209%20NGFOP2201%20Besluit%20tot%20verlening%20subsidie.pdf.

In this regard, the Netherlands Federation of University Medical Centres (NFUMC) has established a list of 10 principles that should be considered in order to ensure that scientific developments of Academia that are outlicensed to commercial partners still benefit the public interest, such as ensuring that academic institutions can continue using the outlicensed technology for research and teaching purposes, selecting appropriate commercial partners that have effective means to bring the technology to the public, etc.[129] Similar principles have been established by the Vlaamse Interuniversitaire Raad.[130] However, the NFUMC principles specifically also include a consideration for general accessibility and affordability of the resulting product on the market. It is elaborated that "*When arranging a licence, it can therefore be agreed that the partner will endeavour to make a reasonable commercial effort to ensure that the final price of the product or service will not hinder its availability in a particular market […]*".

These so-called 'socially responsible licensing clauses' indeed are a valuable tool for governmental and charitable organisations to ensure that funding they provide does not merely support and reduce risks for companies and their investors, but also ensure accountability of the recipient of the funding in relation to the products that are developed (partially) with such funding.

A notable example of such a socially responsible licensing clause can be found in the Horizon Europe scheme's '3A' provision in the Innovative Health Initiative Joint Undertaking[www]. According to such provision, the products and services developed by participants in these EU-funded projects and (partly) based on the results of clinical studies undertaken as part of such project, are affordable, available and accessible to the public at fair and reasonable conditions. If made applicable, the provision is included in the specific conditions in the call for proposals for the relevant project, and further made binding in the respective grant agreement with the participants under the project. Considering that the projects under Innovative Health Initiative are situated in the pre-competitive space and early research, the actual impact of these 3A provisions is relatively minor, and participants are able to limit the applicability of 3A to their final products and services.

Other examples of socially responsible licensing clauses can also be found in charitable organisations' funding conditions, such as the humanitarian license that the Bill & Melinda Gates Foundation imposes in its research grants that ensures that scientific developments funded through its grants will be made available and accessible at an affordable price to people most in need within developing countries.[131] More specifically, the Foundation is granted a non-exclusive license to make available such developments in these countries. The funding contracts of NIHR[132] (and KCE Trials)[xxx] also contain a non-shelving clause.

While these socially responsible licensing clauses create upfront expectations in pricing, in reality their impact may be limited. An important issue remains to establish which price would be considered reasonable and affordable. If no agreement on appropriate pricing, or at least agreement on a procedure to determine appropriate pricing, can be reached, the product will not be accessible. Enforceability of such affordability commitment could be strengthened by the inclusion of compulsory licensing provisions together with the socially responsible licensing clause, ensuring that in the event of inappropriate pricing, an alternative manufacturer obtains the right to manufacture the product at the envisioned appropriate price. However, such far-reaching compulsory licensing arrangements should be carefully considered before their implementation.[133] A notable example is the 'reasonable pricing' clause that the NIH did include in its research agreements in the 1980s, but which was abolished due to the backlash from pharmaceutical companies. [134]

[www] See in particular Article 125 of the COUNCIL REGULATION (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, EU) No 561/2014 and (EU) No 642/2014, https://eur-lex.europa.eu/eli/reg/2021/2085/oj, Conditions applicable to indirect actions

[xxx] Research agreement template (Word) version 6.3, 14 May 2024 - https://kce.fgov.be/en/kce-trials/calls/closed-calls/kce-trials-2024-investigator-led-call

On a European level, the desire for societal accountability of drug developers has also been (indirectly) recognised in the EC Pharma Proposal, which introduces measures for greater transparency of public funding of medicines development. In particular, Article 57 of the Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC under the EC Pharma Proposal introduces a requirement for marketing authorisation holders (and applicants) to publicly declare any "direct financial support received from any public authority or publicly funded body" in relation to "any activities for the research and development of the medical product". This includes both products covered by a national or centralised MA, irrespective of which legal entity has received the support. It should be noted that only direct public financial support such as direct grants or contracts are targeted, since indirect support is more difficult to quantify.[yyy] According the explanatory memorandum, greater transparency around public funding for medicinal products development is expected to help maintain or improve access to affordable medicinal products.[zzz]

An overarching policy framework should be developed by public authorities, ideally in international alignment, underscoring the social responsibility of drug developers, including the establishment of licensing restrictions for products that have been developed with Academia involvement and support by public authorities.

8.2.3 State aid

8.2.3.1 State aid considerations in public support of Academic ATMP development.

Market failures in pharmaceutical and Advanced Therapy Medicinal Product (ATMP) sectors

Market failures are a common feature of today's pharmaceutical industry[17]. Following standard welfare economics, market failures occur when the market has failed to allocate its resources optimally or efficiently. They may cause a net loss from a societal point of view. In other words, if a market does not achieve its most efficient and equitable outcome it may subsequently produce market failures.

In the pharmaceutical sector, market failures result from a combination of factors, including the market structure, legal barriers, regulatory authorisations, and information asymmetry.[17] Crucially, the presence of market failures holds significant implications for patients as they lead to a misalignment between the pharmaceutical industry's R&D priorities and public health needs. Moreover, market failures may cause out-of-reach drug prices and drug shortages.[17]

Notable examples of the existence of market failures within the pharmaceutical sector can be observed in the domain of ATMPs. Despite positive outcomes for certain patient groups of ATMPs, certain patients are left without adequate treatment in the pipeline of the traditional industry players. In addition, affordability of newly commercialised ATMPs is becoming an increasing issue.

A lack of assured returns on investment, among others due to the very specific, but therefore often limited patient population that can sometimes benefit from ATMPs, and the complexities of ATMPs, bring forth elevated

yyy Recital 131 of the Directive.

zzz See p. 17 of the explanatory memorandum on the Directive, https://eur-lex.europa.eu/resource.html?uri=cellar:bfcb9e00-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF

development costs. Additionally, scientific uncertainties and manufacturing barriers may contribute to the lack of industry development efforts in certain disease areas. As a consequence, the pharmaceutical market appears, in certain area, inefficient and does not generate optimal results concerning the development of and patient access to ATMPs.

Market failures indicate areas where support by public authorities might help address these issues, with the goal to solving such inefficiencies, including by exploring alternatives to industry-driven marketing pathways, and supporting Academia in such exploration, or strengthening the capabilities of Academia in their relationship with industry.

Support measures by public authorities to address market failures could be implemented on different levels. In its 2021 ERPS Report, the European Parliament advocated for the establishment of a pan-European Research & Development infrastructure and delivery organisation to ensure the availability, under all circumstances, of safe, effective, innovative, and affordable medicines in areas of the pharmaceutical market impacted by market failures. Nevertheless, the exploration of possible initiatives at the national level also stands as a viable approach to mitigate market failures in the pharmaceutical sector.[17] In this regard, diverse set-ups or scenarios can be envisioned at the national level to facilitate the development and distribution of ATMPs to patients. [17]

Supporting measures targeted at Academia in support of ATMP authorisation pathways can be envisioned throughout the different phases and pathways of ATMP authorisation, including facilitating efficiency improvement and building of additional capacities in Academia. Moreover, for Academia to progress ATMP beyond early R&D, maybe even up to commercialisation (however see also section 6.3), additional resources, expertise, and capabilities are needed (see section 8.2.1.). One could imagine efficiencies in early R&D that could lead to reduced prices for resulting ATMPs, increased capabilities and expertise in Academia that can lead to more ready to use ‘data in later development, improving the negotiation position towards potential licensees, or feeding into potential additional treatments under hospital exemption. Support by public authorities will be indispensable to enable such enlarged role. However, support by public authorities is subject to strict conditions, including state aid regulations, which seek to ensure that competition is not distorted in the European Union through such public funding.

8.2.3.2 Basic description of state aid rules

A. Introduction to state aid principles

To prevent financial support measures by public authorities from distorting competition and affecting trade between Member States, Article 107 (1) of the Treaty on the Functioning of the European Union (“**the Treaty**” or “**TFEU**”) lays down the rule that state aid is – a priori – prohibited. Article 107 (1) TFEU defines state aid as any aid granted by a Member State or through state resources in any form whatsoever which (threatens to) distort(s) competition by favouring certain undertakings or the production of certain goods. Nevertheless, not all state aid is prohibited. Article 107 (2)– (3) TFEU specifies certain types and categories of state aid which the European Commission (the “**Commission**”) considers to be compatible with the internal market.

Following Article 108 (3) TFEU, any future support measures qualifying as state aid must be notified to the European Commission before implementation. The Commission then analyses the compatibility and decides on their admissibility. The notification obligation is, however, subject to exceptions; certain exempted aid measures and certain small amounts of support (“De Minimis aid”) for particular activities are not subject to a notification obligation.

The notification procedure is a bilateral procedure between the Commission and Member States. An aid measure implemented without prior notification is automatically deemed "illegal" or "unlawful." The Commission can still investigate such aid to assess after its implementation. The Commission may decide that the measure is either not aid, compatible with the internal market, or incompatible with the internal market. If deemed incompatible, the aid must be recovered from the beneficiary unless recovery would violate a general principle of EU law.

If the financial risk lies with the state aid beneficiary, Member States bear a significant responsibility to determine whether a proposed support measure qualifies as state aid and, if so, whether it needs to be notified to the European

Commission. This assessment is carried out before the support is granted. Typically, the government and the recipient entity agree on the intended use of the support in advance. It is crucial that the support is used solely for the agreed-upon activities. The determination of whether a particular aid measure constitutes state aid and whether it requires notification hinges on these agreed details. If the aid is used for purposes other than those initially agreed upon, the entity risks invalidating the initial state aid analysis.

B. Relevance of state aid principles

The aforementioned state aid principles are relevant to support by public authorities for academic ATMP development, especially considering the appropriateness of relying on public funding – for at least a portion of the development. Where a public authority only grants financial support measures to certain entities, the recipients are ought to obtain an "advantage" following EU state aid rules, which is not provided to other players in the pharmaceutical market. After all, the entity in question receives an economic benefit which it would not have received under "normal market conditions". (Definition of an advantage in para. 66, Commission Notice on the notion of State aid) Following from this preferential treatment of the state aid recipients, a distortion of competition may occur which affects trade between Member States. Therefore, reliance on public funding for the realization of academic ATMP development can trigger the application of state aid rules.

Importantly, the fact that an academic ATMP development is prompted by an existing market failure will be considered in the state aid analysis. In this regard, the European Commission acknowledges that public intervention may be necessary to incentivise the development of certain economic activities. In certain circumstances, public funding may therefore qualify as funding for the development of a service of general economic interest ("**SGEI**") Moreover, as further discussed below (cf. infra), specifically in the context of research, development and innovation ("**R&D&I**"), the Commission acknowledges that market failures may arise. Following state aid rules, market failures may exist, for instance, because market players do not consider the wider positive effects of certain ATMP developments for the European economy, or if they qualify reaching a positive economic result as overly risky. In the absence of state aid, companies involved would consequently engage in R&D&I activities at a level that is insufficient for society's benefit (i.e. no affordable or accessible ATMP exists for the relevant diseases). Likewise, the Commission acknowledges that certain R&D&I projects may suffer from insufficient access to finance in the absence of state aid. (para. 3, Commission's Research Development and Innovation Framework Communication or "**R&D&I Framework**")

C. Steps of analysis

Since state aid is, in principle, prohibited, the circumstances in which public support measures to academic ATMP development qualify as a state aid measure should first be analysed. The analysis subsequently discusses the situations in which state aid may be considered compatible with the internal market following a notification to the European Commission in certain cases. The text further formulates interim conclusions with guidelines for public authorities that want to provide support, or entities that want to participate in the development and distribution of ATMPs and receive support for doing so. The final conclusion summarizes these guidelines comprehensively.

8.2.3.3 Existence of state aid

A. Core analysis (see Supplement section 6)

A state aid analysis must first consider whether a particular support by public authorities qualifies as state aid at all. We refer to Chapter 6 in the Supplement for an in-depth analysis regarding when support by public authorities is considered state aid in ATMP development. Below is a brief summary of the analysis for the reader's understanding.

For a measure to qualify as state aid, several conditions should be met. The conditions include the following (i) the recipient should qualify as an "undertaking" which engages in an economic activity, (ii) the support measure must confer a selective advantage on the beneficiary, (iii) the measure must have the potential to distort competition, and (iv) the support measure must origin from the state, using state resources.

This section highlights three important topics that will influence the question of whether these conditions are met.

First, central to the analysis is the question of when entities, including academic institutions, qualify as undertakings. In this regard, the analysis explores the distinction between **economic and non-economic activities** by means of the R&D&I Framework.

The R&D&I Framework distinguishes between economic and non-economic activities performed by "research organisations" and "research infrastructures", of which academic hospitals are an example. Economic activities include, for example, contract research performed for another entity, the commercial exploitation of research results, and collaborative research with commercial entities. Non-economic activities encompass independent research aimed at acquiring new knowledge, educational activities, and the wide dissemination of research results on a non-exclusive basis. Knowledge transfer activities, such as licensing intellectual property or creating spin-offs, are also considered non-economic if all profits are reinvested in the primary activities of the research organisation.

Where a research organisation or infrastructure performs both economic and non-economic activities, a specific rule applies. If a research organization or infrastructure funded by public funding is primarily used for non-economic activities, its funding may be exempt from state aid rules if the economic activities are ancillary. This means the economic activities must be directly related to and limited in scope compared to the non-economic activities. They must use the same input and not exceed 20% of the entity's overall annual capacity.

The distinction between economic and non-economic is crucial for compliance with state aid rules. Public funding for non-economic activities is not considered state aid, whereas funding for economic activities qualifies as state aid and is subjected to a compatibility analysis.

Second, a support measure is not deemed to be state aid if public funding is provided for the **development of a service of general economic interest**. Member States have significant discretion in appointing certain services as SGEIs. For ATMP development, the SGEI qualification is justifiable due to existing market failures and societal benefits. Specifically, the existence of a market failure is a prerequisite for qualifying an activity as SGEI.

Where the SGEI funding scheme meets the Altmark requirements (as further explained in the SGEI Communication (OJ 2012 C8/4) or the support amount does not exceed €750,000 over a three-year period (SGEI de minimis Regulation of 2023 C(2023) 9701), the funding does not qualify as state aid.

Third, a support measure is generally deemed not to distort competition if the **measures' financial value is below certain financial thresholds**. Subject to exceptions for certain sectors – aid awarded to a single undertaking by a Member State may not exceed €300,000 over three years to benefit from the exemption. (Article 3, (2) General De Minimis Regulation 2023) Such aid will thus not qualify as state aid.

B. Conclusion on the existence of state aid

Building on the above, the following guidance is applicable to public authorities intending to offer aid, or entities aiming to receive funding, for the development and dissemination of ATMPs.

- From this section, it becomes clear that support by public authorities to academic ATMP development might be considered state aid under Article 107 (1) TFEU, unless public funding to ATMP development qualifies SGEI funding and fulfills the Altmark-conditions to avoid being classified as state aid. Ouside of the SGEI regime, entities, like hospitals, research centres or manufacturing facilities potentially qualify as "undertakings" under EU State Aid law depending on the set-up of the project and the responsibilities of each actor. Moreover, support for ATMP development can take a variety of forms, ranging from "positive measures" to a "relief of economic burdens". Public authorities intending to provide ATMP-related support must therefore always analyse if the aid in question qualifies as state aid and carefully choose and consider the set-up of the project.
- It is worth emphasising that public support via the European level is still a viable option for funding from a state aid perspective. However, EU funding granted by public authorities of the Member States may still be subject to state aid rules. Resources coming from the European Union

will qualify as state aid if national authorities have discretion on their use. Exploring opportunities to obtain funding, from e.g. the European Investment Fund, remains an interesting possibility to avoid an extensive state aid analysis.

8.2.3.4 Compatibility of state aid to Academia in the different pathways

A. Introduction

After establishing that a support measure by a public authority meets the criteria to qualify as state aid, the next step is to analyse the measure's compatibility with the internal market. In this regard, Member States must, in principle, notify a state aid measure to the European Commission following Article 108 (3) TFEU, before putting the measure into effect. The Commission subsequently decides on the legality and compatibility of the measure with the internal market. A notification and approval by the European Commission provides the Member State and the receiving entities with the certainty that the notified aid may be disbursed under the agreed conditions, time, and amounts. Therefore, as long as the aid is used for the approved purposes and meets the agreed disbursement conditions, its compatibility and legality cannot be reversed.

Where aid is granted without prior authorisation by the European Commission, the aid qualifies as unlawful. Upon receiving information regarding alleged unlawful aid, the Commission is obligated to promptly investigate. This investigation typically begins with a preliminary inquiry, followed by a more thorough examination if there are concerns about the compatibility of the aid measure. The Commission has the authority to request information from Member States, halt further aid disbursements, or impose interim recovery obligations if necessary. If a final decision deems the aid incompatible with EU rules, the Member State must recover the aid already provided, along with accrued interest.

The recovery of illegal state aid involves restoring the competitive situation that existed before the aid in order to eliminate the financial advantage gained by the beneficiary. This process is mandatory and must be executed by the Member State who provided the initial support. The Member State is responsible for identifying the beneficiaries and quantifying the aid to be recovered. The European Commission assists in this process by providing methodologies and tools.

Recovery must respect EU law principles, such as legal certainty and the protection of legitimate expectations, although these are interpreted restrictively. In cases of insolvency, the aid must be recovered through liquidation or other measures ensuring the cessation of activities. If a Member State fails to comply, the Commission can initiate infringement proceedings, potentially leading to penalties. Additionally, new aid can be made conditional on the repayment of previous unlawful aid to prevent cumulative distortions of competition.

For more information, we refer to the Commission Notice on the recovery of unlawful and incompatible State aid (2019/C 247/01).

B. Services of general economic interest

To begin, the SGEI Decision (No. 2012/21/UE) ("**Decision**") is applicable solely to aid for SGEI projects. An appeal is possible only if the development of ATMP qualifies as an SGEI and the aid provided qualifies as state aid.

This Decision exempts certain forms of SGEI funding, such as aid amounts below EUR 15 million or aid granted to hospitals and social housing, from the compatibility test and the duty of notification to the Commission.

Specifically relevant for ATMP development, is the fact that the decision **exempts compensations for the provision of SGEIs by hospitals including the pursuit of ancillary activities directly related to the hospital's main activities, notably in the field of research**. (Article 2, (b) Decision) The exemption is not subject to financial limits. Unlike other aid covered by the Decision, aid for research by hospitals may exceed EUR 15 million and will still be covered by the exemption. However, the exemption only applies when the period during which the hospital is entrusted with the operation of the SGEI does not exceed 10 years (Article 2, 2 SGEI Decision). This rule applies unless a longer period is justified due to the need for a significant investment to develop the SGEI (such as the development of social housing) (para. 12 SGEI Decision).

To rely on the exemption, the hospital involved must be explicitly entrusted with the management of the SGEI. This can be done through one or more decisions by the relevant authorities. Article 4 of the Decision outlines the information that must be included in the SGEI entrustment decision. Additionally, it must be ensured that the involved company does not receive more support than is strictly necessary (i.e., avoid overcompensation). For a specific example of public funding for an SGEI-project in the field of ATMPs, we refer a case study in the Netherlands (Box 9).

C. Exemption of notification obligation following the General Block Exemption Regulation

Not all state aid measures are, however, subject to the notification obligation. Hence, certain aid enjoys an exclusion from the obligation following the "General Block Exemption Regulation" ("**GBER**"). All state aid measures fulfilling the substantive and procedural conditions stated in the Regulation are considered compatible with the internal market and exempted from the obligation. Consequently, there is no in-depth analysis of the compatibility of the relevant aid measure. Instead of notifying the European Commission, Member States only need to inform the Commission of the aids by way of standard information sheets (Article 9 GBER).

The GBER only exempts aid to certain projects from the notification obligation (Article 1 GBER). A category that could, for example, be relevant to academic ATMP development is "aid for research, development and innovation" (Article 1 (d) GBER). To fall under this category, an academic ATMP development must qualify as one of the R&D&I categories described under para. 83 – 98 (a) GBER. This category also includes aid for research infrastructures and for testing and experimentation infrastructures In line with the R&D&I Framework, the GBER covers, for example R&D&I projects intended for fundamental research, industrial research, experimental development (and more). To be exempted from the notification obligation, aid for R&D&I projects may not exceed certain amounts, which are expressed as thresholds (Article 4 (i) – (m) GBER). For example, the aid limits are EUR 55 million per project for fundamental research, EUR 35 million per project for industrial research, EUR 25 million per project for experimental development, EUR 35 million per research infrastructure, and EUR 25 million per testing and experimentation infrastructure.

Additionally, only specific costs, such as personnel costs, are eligible to enjoy the exemption (for R&D projects see, for example, Article 25, (3) GBER). The GBER also establishes specific rules regarding aid intensities (for R&D projects see, for example, Article 25, (4) GBER).

D. Compatibility exercise following a notification to the European Commission

General description

State aid measures – which are not covered by one of the above-mentioned categories – need to be notified to the European Commission, who will assess the measures' compatibility. The Commission will authorise the aid measure if it contributes to the achievement of one or more of the objectives of common interest (which do not explicitly mention health care) – identified in Article 107 (2), 107(3), 106(2) or 74 TFEU – and fulfils certain conditions. Generally speaking, the Commission must always balance the positive effect of the aid measure – reaching an objective of common interest – against its potentially negative side effects – possible distortions of trade and competition –.

Article 107(3), point (b) TFEU, for example, allows public aid that promotes the execution of an important project of common European interest to be considered compatible with the internal market. Considering this Article, the 2021 IPCEI communication was issued by the European Commission that provides guidance on the assessment of public financing for important projects of common European interest under Union State aid rules. The IPCEI rules enable Member States to jointly fill the gap to overcome important market failures by providing public funding for certain projects.

In May 2024, the European Commission has approved the first Important Project of Common European Interest in the health sector, named "IPCEI Med4Cure", involving six Member States: Belgium, France, Hungary, Italy, Slovakia, and Spain. The initiative aims to address market failures in the health care sector by supporting research, innovation, and the industrial

deployment of healthcare products and pharmaceutical production processes, contributing to the European Health Union's goals. The project will receive up to EUR 1 billion in public funding, expected to unlock an additional EUR 5.9 billion in private investments, and involves 13 companies undertaking 14 innovative projects. These projects focus on advancing drug discovery, particularly for unmet medical needs like rare diseases, and developing sustainable pharmaceutical production processes. [135]

There are different instruments that provide guidance on the compatibility exercise, depending on the set-up.

Compatibility analysis following the SGEI Framework

To start, the SGEI Framework (2012/C 8/03) specifies several conditions under which SGEI aid can be considered compatible based on Article 106 (2) TFEU. The Framework is generally used to assess larger SGEI compensation amounts that were not exempt from the notification obligation by the previously mentioned SGEI Decision.

First, the responsibility for the operation of SGEI must be formally entrusted to the undertaking concerned through one or more acts. These acts must specify the content and duration of the public service obligations, the undertaking and territory concerned, the nature of any exclusive or special rights assigned, the compensation mechanism, and the arrangements for avoiding and recovering any overcompensation.

Second, aid will only be considered compatible with the internal market if the responsible authority complies with applicable Union rules in the area of public procurement when entrusting the provision of the service. This includes requirements of transparency, equal treatment, and non-discrimination.

Furthermore, the amount of compensation must not exceed what is necessary to cover the net cost of discharging the public service obligations, including a reasonable profit. The Framework provides methodological tools to analyse this condition.

Member States must also ensure that the compensation granted meets the requirements set out in the Framework and that undertakings do not receive compensation in excess of the necessary amount. Regular checks must be carried out at the end of the period of entrustment and at intervals of not more than three years, or at least every two years for aid granted by means other than a public procurement procedure with publication.

Lastly, Member States are required to report to the Commission every two years on their compliance with the principles set out in the Framework. These reports must provide an overview of the application of the principles to different sectors, the total amount of aid granted, any difficulties or complaints, and any other relevant information.

Compatibility analysis following the R&D&I Framework

Where ATMP development would not qualify as a SGEI, there are other instruments to analyse the compatibility of notified aid.

In this regard, the R&D&I Framework provides guidance on how to assess the compatibility of (individual) aid schemes related to research, development and innovation on the basis of Article 107 (3) (c) of the Treaty. The Framework outlines eligible R&D&I measures who can benefit from the clarifications. Relevant to academic ATMP development, the Framework applies to aid given for R&D projects, which consists of industrial research, experimental development and fundamental research. (para 13 and 16, R&D&I Framework Communication)

For a R&D&I support measure to be considered compatible, certain conditions must be met. Firstly, the R&D&I aid must facilitate the development of an economic activity, which involves identifying the supported activity, assessing its incentive effect, and ensuring compliance with EU law. Secondly, the aid should address market failures, providing improvement that the market cannot achieve independently, with consideration given to the necessity and proportionality of the state intervention. Additionally, transparency and compliance are crucial, requiring that aid minimizes negative effects on competition and trade, adheres to transparency standards, and balances negative impacts with positive contributions to wider EU policies. (para. 36 and following, R&D&I Framework)

Compatibility analysis following Article 107 (3) (c) TFEU

Outside of the R&D&I Framework, Article 107 (3) (c) TFEU can also serve as an independent argument supporting the compatibility of an aid measure. The paragraph is commonly utilized by the European Commission and provides it with the authority to approve a diverse range of aids[aaaa]. An argumentation based on Article 107 (3) (c) TFEU is thus not limited to aid for R&D&I projects. Aid measures might be regarded as compatible if they facilitate the growth of specific economic activities or areas. It is worth noting, however, that in existing legal precedents, Article 107 (3) (c) TFEU is primarily cited to support "sectorial state aid". Sectorial aid is aid directed towards the development of a specific sector like, for instance, energy. (see, for example, T-101/18, Austria v. Commission) Given its broad language and discretionary application, the Article's relevance as a justification for supporting academic ATMP development can, however, not be ruled out.

Although each case necessitates individual evaluation, the Commission has outlined a set of "common assessment principles". These principles specify the particular cumulative conditions that the Commission must consider when assessing the compatibility of a measure (para. 18 Commission Communication on State aid modernisation COM (2012) 209). Furthermore, the Court's case law has provided clarity on each subparagraph of Article 107 (3) of the TFEU, including paragraph c, offering guidance applicable to academic ATMP developments (Decision SA.38454 — 2015/C, Hungary v. Commission, para. 274)[bbbb]

To start, the support measure must facilitate the development of economic activities or economic areas and must be an appropriate policy instrument to address this objective. In this regard, aid for the development and distribution of ATMPs may contribute to the advancement of a specific economic activity, particularly the development of life-sustaining medicines, i.e., ATMPs. As explained in the introduction to this state aid section, the use of public funding to support academic ATMP development is appropriate for the purpose and is in some instances arguably preferred compared to funding by pharmaceutical companies, considering the need for equitable pricing.

Next, the Commission examines the need for state intervention to bring about a material improvement that the market cannot deliver for itself. In the context of this condition, the Commission considers the existence of a market failure. See, for example, decision SA.38454 — 2015/C, Austria v. Commission, para. 296-323. A market failure exists when the market, if left to their own devices, is unlikely to produce efficient outcomes. State aid measures may improve the level of efficiency of the economy if the benefits of such public intervention outweigh the costs (para. 60-61, R&D&I Framework). The main market failures which may be relevant in the context of State aid are externalities, imperfect information, in particular asymmetric information, coordination failures, and market power. Externalities occur when actions by one party affect others without being considered in the decision-making process, leading to inefficiencies. Information asymmetries occur when one party in a transaction has more or better information than the other. Coordination problems in markets can lead to inefficiencies when challenges such as high contracting costs, uncertainty over outcomes, and divergent interests hinder effective agreements among parties avoiding them from engaging in research cooperation agreements. Moreover, market power, can lead to inefficient outcomes with higher prices and reduced economic efficiency. State aid measures can potentially mitigate this by encouraging market entry that wouldn't otherwise occur.

As explained in the introduction to this state aid section, market failures are a distinctive element of the pharmaceutical sector due to the sector's specific characteristics. The pharmaceutical sector is characterized by an oligopolistic core with few companies in different submarkets. This structure is due to high fixed costs of investment, patent protection, market authorisation systems, and information asymmetry between drug companies and consumers, all of which create barriers to competition. This leads to the misalignment between R&D priorities and public health needs, out-of-reach drug prices, and drug

[aaaa] Bellamy & Child, European Union Law of Competition, Oxford University Press, 2018, 1490.

[bbbb] Bellamy & Child, European Union Law of Competition, Oxford University Press, 2018, 1486.

shortages. While the Commission will perform a case-by-case analysis, the presence of a market failure in the ATMP field seems indisputable and will likely be considered by the European .

Furthermore, to be compatible, a measure must have an incentive effect, changing the behavior of the undertakings involved. It should encourage them to engage in additional activities that they wouldn't undertake without the aid, or in a more limited or different manner. For academic ATMP development, it is clear that support by public authorities provides a strong incentive for Academia to develop ATMPs.

Lastly, the measure should be proportionate to the needs on the basis of which it is implemented and should not result in an undue distortion of competition and trade between Member States.

E. Examples

Research centre receives support by public authorities for commercial research on ATMPs

An academic research centre, primarily responsible for performing clinical trials for ATMP development, receives funding by public authorities. At a more mature stage of clinical development, the centre out licenses the results of the research to an entity responsible for commercialisation of the ATMPs. This example assumes a situation where ATMP development does not qualify as an SGEI.

The activities of the research centre qualify as economic research in case the unit sells or commercialises the results of its R&D activities with a profit motive, rather than merely transferring knowledge in which no profit is pursued and all income is returned to the research activities. For more information we refer to title 6.2.1.2. in the Supplement on the Guidance in R&D&I Framework on the notion of “undertaking”.

Where the centre qualifies as an undertaking, support by public authorities to this project qualifies as state aid and must potentially be notified to the European Commission. However, it should first be checked if the support measure is not exempted from the notification obligation following the specifications for R&D&I support in the GBER. If not exempted by the GBER, the aid should be notified to the European Commission. The European Commission will further analyse the compatibility of the support measure.

Example: for-profit CMO receives support by public authorities for manufacturing of ATMPs

A for-profit CMO is responsible for manufacturing ATMPs for commercial purposes. A public authority is investigating providing funding to such CMO for performing its activities in relation to academically developed ATMPs under a marketing authorisation pathway. This example assumes a situation where ATMP development does not qualify as an SGEI.

In this case, the manufacturing unit performs economic activities and qualifies as an undertaking (cf. supra). As the support measure does not fund R&D&I, (manufacturing does not qualify as an R&D activity) the GBER and the R&D&I Framework do not apply. The aid has to be notified to the European Commission. Parties involved may argue in favour of the aid measure based on, for example, Article 107 (3) (c) TFEU.

F. Conclusion on the compatibility of state aid for academic ATMP developments

Building on the above, the following guidance is applicable to public authorities intending to offer aid, or entities aiming to receive funding, for the development and commercialisation of ATMPs.

- When it is established that aid for academic ATMP development qualifies as state aid, Public authorities must assess the compatibility of its planned aid measures with the internal market. In this regard, Member States must, in principle, notify a state aid measure to the European Commission following Article 108 (3) TFEU, before putting the measure into effect. However, certain aids are exempt from this oblgiation. Depending on the specific set-up, different instruments should be considered.
- Where support for ATMP development qualifies as SGEI support, the SGEI Decision and Framework should specifically considered. Smaller amounts of aid will be exempt from the notification obligation by the SGEI

Decision. Larger amounts that need to be notified may be analysed by the European Commission based on the SGEI Framework.

- Outside of the SGEI Framework, the GBER, R&D&I Framework and other relevant Treaty provisions should be considered. Both the GBER and the R&D&I Framework require that, to benefit from their clarifications, support measures qualify within the categories of aid for an “R&D&I” or for an “R&D” project. Whether academic ATMP developments can benefit from these two legislative instruments for the compatibility exercise will depend heavily on which set-up is used and what part of the ATMP development is funded by public authorities. In any event, as a “last resort” argument, Article 107 (3) (c) TFEU can be invoked to justify state aid for academic ATMP developments more generally.
- Generally speaking, authorities are advised to highlight the existence of a market failure in their argumentation, as the European Commission pays explicit attention to this.

8.2.3.5 General guidelines following from state aid section

In summary, the following guidelines can be derived from the state aid section for ATMP development.

It is crucial for public authorities to establish clear contractual terms with Academia regarding the permissible use of the aid. These agreements serve as a basis for determining the provided aid measure qualifies as state aid and if notification to the European Commission is necessary. For instance, if the public authority provides support exclusively for hospitals' R&D activities, for which no notification to the European Commission is required, it is advisable to bind hospitals not to engage in subsequent commercialisation activities. Indeed, the commercialisation element would necessitate a notification and a compatibility analysis. In summary, contractual clauses thus prevent the aid from being used for purposes other than the public authority intended. This also limits risk that the aid granted as a result would be considered "unlawful" if it was not properly notified; leading to the potential reclamation of the aid along with accrued interest.

As set forth above under section 8.1 of this report, to overcome potential state aid challenges, it is recommended that state entities provide support by public authorities to academic ATMP development with the aim of having such developed ATMPs eventually outlicensed to industry partners at a more mature stage of clinical development (when safety and efficacy are more clearly demonstrated and potential commercialisation may appear more “attractive”), or to be used under hospital exemption only. An additional advantage for funding entities of working towards an out-licensing scenario could be that in doing so funding entities will have more leverage to pass-through socially responsible licensing clauses in the out-license agreement (e.g. by rendering R&D funding contingent upon the inclusion of such terms in a potential future out-license deal).

Alternatively, public authorities should consider to qualify ATMP development as a “service of general economic” interest. As explained in this section, funding for SGEIs is subject to a more flexible state aid regime. On the condition that certain requirements are fulfilled, public funding of SGEIs will either (i) not qualify as state aid, (ii) enjoy an exemption from the notification obligation to the European Commission, or (iii) may be cleared after notification.

8.2.4 Other competition law concerns

In the context of academic ATMP development, it is essential to also consider the overarching principles of competition law. In this regard, both the Belgian Competition Authority and rulings from the Court of Justice of the European Union affirm that (University) hospitals and other academic entities such as universities might fall within the scope of European and national competition rules as they qualify as undertakings. When providing services for remuneration, whether directly from patients or via insurance, hospitals are regarded as engaging in economic activities and thus classified as

undertakings.[cccc] However, as previously mentioned, where hospitals perform academic research, they might not qualify as an undertaking as such.

Therefore, depending on whether the entities involved in the project qualify as an undertaking, implementing an academic ATMP development project might necessitate adherence to the fundamental principles of competition law incorporated in Articles 101 and 102 TFEU.

Article 101 (1) TFEU (and its Belgian equivalent, Article IV.1, §1 of the Code of Economic Law ("**CEL**") prohibits "anti-competitive agreements" between undertakings, both in horizontal set-ups (between competitors) and in vertical set-ups (between companies operating at distinct levels of the supply or production chain). Hence, it is essential to ensure that any collaboration among different undertakings in academic ATMP developments avoids resulting in a prohibited anti-competitive agreement. In horizontal relationships, it is crucial, for example, to avoid any illicit sharing of commercially sensitive information. Information is to be considered as commercially sensitive if it has the potential to influence an undertaking's commercial strategy. (para. 384, Horizontal Guidelines or "**HGL**"). This prohibition does not apply when academic players, such as a hospital, conduct academic research and subsequently disseminate knowledge and results to the public or the pharmaceutical industry, for example, via publications or conferences. After all, in such case, the hospital or academic entity involved does not qualify as an undertaking as such. Furthermore, following the prohibition in Article 101 (1) TFEU, participating undertakings who commercialise the ATMPs are also prohibited from engaging in price fixing agreements regarding the ATMPs. (para. 222, HGL)

Moreover, Article 102 TFEU (and its Belgian equivalent, Article IV.2 CEL) prohibits abusive conduct by companies that have a dominant position on a particular market. The medical and pharmaceutical sectors have long been on the radar of the European Commission and national competition authorities. (See for example, Decision No.1204/09.12.2021 of the Bulgarian Competition Protection Commission on medical institutions in Bulgaria and the Report from the European Commission COM(2024) 36 final providing an update on competition enforcement in the pharmaceutical sector between 2018-2022) An abuse can take a multitude of forms; from predatory pricing in which a dominant company foregoes short-term profits by pricing below cost in order to drive out or discourage their competitors; to excessive pricing where a dominant firm charges a price that is excessive relative to an appropriate competitive benchmark in a way that deems it unfair.[dddd]

Recent examples of an abuse of dominance case are the following.

First, the European Commission has recently fined Teva EUR 462.6 million for abusing its dominant position to delay competition to its multiple sclerosis medicine, Copaxone. The decision, dated 31 October 2024, concluded that Teva misused patent procedures and conducted a systematic disparagement campaign against a competing product. Teva extended the patent protection of Copaxone by filing multiple divisional patent applications, creating a web of secondary patents, and strategically withdrawing them to avoid invalidity rulings, thereby prolonging legal uncertainty and delaying market entry of cheaper alternatives. Additionally, Teva spread misleading information about a rival medicine's safety and efficacy, despite its approval by health authorities, to hinder its market uptake. The Commission's investigation revealed that Teva's conduct spanned between 4 and 9 years across several Member States, including Belgium, Czechia, Germany, Italy, the Netherlands, Poland, and Spain.

Moreover, in the past; several European competition authorities have fined the enterprise Leadiant for excessive pricing of their orphan drug, CDCA-Leadiant. The Dutch Authority for Consumers and Markets imposed a fine of

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[cccc] Position Paper Belgian Competition Authority of 22nd of July 2020; Decision Belgian Competition Authority ABC-2023-C/C-50, Centre Hospitalier Universitaire et Psychiatrique de Mons Borinage SCRL / ABSL Pole Hospitalier Jolimont; judgement ECJ of 23 April 1991, C-41/90, Höfner et Elser, § 21; of 12 July 2001, B.S.M. Smits, wife of Geraets v. Stichting Ziekenfonds VGZ and H.T.M. Peerbooms v. Stichting CZ Groep Zorgverzekeringen, C-157/99, ECLI:EU:C:2001:404, §§ 53-58.

[dddd] Chapter 12: Special Sectors, Section: Pharmaceuticals (chapter updated January 2023)', in Van Bael & Bellis (ed), Competition Law of the European Union (Sixth Edition), p. 1527 – 1561.

nearly EUR 20 million on Leadiant for abusing its dominant market position by charging excessively high prices. (Decision ACM, case ACM/20/041239) Similarly, the Spanish National Commission for Markets and Competition fined Leadiant EUR 10.25 million for applying excessive prices for the only drug available in Spain for treating a rare disease. (Decision CNMC, case S/0028/20: LEADIANT) These fines highlight the ongoing efforts by EU competition authorities to regulate drug prices and ensure that essential medicines remain accessible and affordable.

8.3 Intellectual property strategy

8.3.1 Introduction

A critical question during (the early stages of) drug development is indeed the way in which new drug discoveries should be protected. Obtaining some form of exclusivity over an invention is often seen as the only way to ensure a proper return on investment for intensive research and development efforts and one of the most important incentives for drug development. Protecting a developed therapy via intellectual property mechanisms can help in eliminating competitors, creating consistent revenue streams and facilitating and ensuring qualitative collaborations.

On the other hand, a lack of collaboration and sharing of results until they reach patent or publication stage can result in different lab groups making the same costly mistakes.[136] Therefore, some authors advocate for moving to an open science model, where all protocols, data, and materials are available for all to see, and technologies are not patented, encouraging collaboration and industry partnerships to foster rapid development of novel technologies and prevent recurring failures due to the lack of availability of negative or unsuccessful data.[137] As an important downside, such a non-patenting approach could, on the other hand, negatively affect the impact the potential interest of industrial partners to take the technology forward.

State aid considerations may also impact the freedom of Academia to protect, and more importantly license the outcomes of their scientific research to other parties. In addition, socially responsible licensing clauses attached to their funding should be considered in the shaping of the IP strategy for their drug development program. When public funders aim to support academic development of ATMPs, it is crucial for them to have expertise in intellectual property (IP). This ensures they can protect innovations and maximise the impact of their investments. implementation, effective collaborations or safeguarding innovations if needed[eeee].

In any case, intellectual property management is a theme that needs to be addressed at an early stage of the development process, since it impacts the potential future trajectory of the ATMP. A drug development plan should be established at the pre-clinical stage, including an IP management strategy for further product development.

8.3.1 Patentability of cell-and gene based technologies

The ATMP-field is quickly evolving and along with it, patent practise is currently developing and adapting. Despite exceptions to patentability, multiple aspects of cell and gene therapies are eligible for patent protection.[138] A Belgian report showed the number of patents for ATMPs tripled over the last decade and that Belgium takes position 15 in the international ranking of patent filings.[139]

Cell and gene therapy development has shown particular challenges in this area, as the patentability of such therapies is not straight-forward. Adding to the complexity is the fact that exceptions or immunities encountered when trying to patent developments in the field of cell and gene therapy differ across jurisdictions, whereas it is in the inventor's interest to develop an

[eeee] See the National Institute for Health and Research on the importance and implementation of IP in publicly funded research[132.] National Institute for Health and Care Research. Intellectual Property and Commercialisation Guidance. 2021 Available from: https://www.nihr.ac.uk/about-us/who-we-are/policies-and-guidelines/intellectual-property-and-commercialisation-guidance.

internationally uniform intellectual property strategy. But even if innovators succeed in protecting their novel ATMPs through traditional intellectual property mechanisms, certain (national) immunities may prevent them from effectively benefit from such patent protection due to enforcement difficulties.

The difficulties in protecting gene and cell therapies through traditional intellectual property mechanisms may be one of the reasons why the early development of ATMP's is currently predominantly taking place at academic and public level and less at industry level. While this gap may also pose a threat to (academic and public) players investing in research and development of complex ATMPs, the lack of (robust) protection also means an opportunity for the ecosystem to bring products to the market or patient without needing to put in (all) research and development efforts themselves.

8.3.1.1 The European framework

The principal patentability of (human) biological material and gene sequences

In Europe, the Biotech Directive[ffff] specifies the scope of patentability of biotechnological inventions and clarifies that inventions consisting of or containing biological material, or a process by which biological material is produced, processed or used, is protectable by patents to the extent the general patent eligibility criteria are met, i.e. novelty, inventive step and industrial applicability. More specifically, Article 5 of the Biotech Directive deals with biological material originating from the human body and provides that the simple discovery of the sequence or partial sequence of a gene cannot constitute a patentable invention[gggg]. However, if such sequence is isolated from the human body or otherwise produced by means of a technical process this in turn may be patentable even if the structure is identical to that of a natural element[hhhh].

The principal patentability of gene sequences was further confirmed in the EPO's Boards of Appeal caselaw:

- In the *Relaxin* case, the appeal board confirmed that claims to DNA encoding a human protein obtained by technical processes are patent-eligible and do not fall within categories of alleges inventions that are excluded from protection as mere discoveries[iiii];
- In the *BRCA1 sequences* cases this reasoning was confirmed in relation to a claim to DNA which encoded the BRCA1 gene , corresponding to a claim from the same patent at issue in the US Myriad case (see further below at 8.3.1.2)[jjjj].

Notwithstanding their principal patentability, several hurdles for the patenting of gene sequences used in cell and gene therapy exist under EU law. Particularly relevant to the field of cell therapy are (i) inventions whose commercial exploitation would be contrary to public policy or morality and (ii) the prohibition of patenting methods for treatment.

Protecting the public order and morality

Article 6, paragraph 1 of the Biotech Directive prohibits the patenting of inventions of which the commercial exploitation would be contrary to *ordre public or morality*. Paragraph 2 of that same article clarifies that this exclusion *inter alia* serves to protect human life and unconditionally prohibits interventions in the human germ line, cloning and uses of human embryos for industrial or commercial purposes. These exclusions have potential implications on the patentability of certain cell and gene therapies, especially

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[ffff] Directive of the European Parliament and of the Council nr. 98/44/EC, 6 July 1998 on the legal protection of biotechnical inventions, *Pb. L*. 30 July 1998, ep. 213, p. 13 (the "Biotech Directive" or the "European Biotech Directive").

[gggg] Article 5, paragraph 1 of the Biotech Directive.

[hhhh] Article 5, paragraph 2 of the Biotech Directive.

[iiii] EPO, T 272/95 (*Relaxin/HOWARD FLOREY INSTITUTE*).

[jjjj] EPO, T 1213/05 (*Breast and ovarian cancer/UNIVERSITY OF UTAH*).

these using human embryonic stem cells or germline gene-editing technologies.

In recent years, European case law has shed further light on the scope of the limitation contained in Article 6(2)(c) of the Biotech Directive:

- In 2011[kkkk], the Court of Justice of the European Union ("**CJEU**") broadly interpreted the prohibition in Article 6(2)(c) and clarified that a process which involves removal of a stem cell from a human embryo at the blastocyt stage, entailing the destruction of an embryo cannot be patented. Although the CJEU, in its decision prohibited the patenting of uses of human embryos for industrial or commercial purposes, it acknowledged the possibility of patenting embryonic stem cell products to the extent the development thereof did not involve the destruction of an embryo.[140] The definition of human embryos applied by the CJEU in this ruling included non-fertilised ova after somatic cell nuclear transfer (SCNT) and parthenotes, created through artificial activation of an oocyte. This decision had significant implications for hESC research, particularly regarding patents using publicly available stem cell lines[141];
- In 2014[llll], the Court issued a ruling on the patentability of therapies relying on hESC by opening the possibility for patents on parthenogenetically stimulated human ova as long as they haven't been genetically modified to acquire the ability to develop into humans. The CJEU ruled that Article 6(2)(c) of the Biotech Directive must be interpreted to exclude unfertilised human ova stimulated by parthenogenesis from the definition of 'human embryo' if they lack the inherent capacity to develop into a human being. This decision empowers national courts to determine, based on current scientific knowledge, whether parthenotes are capable of human development.[141]

Prohibition of the patenting of methods for the treatment of the human body

Another hurdle to patentability in the EU is that the European Patent Convention prohibits the patenting of medical treatment methods[mmmm]. The exclusion is prompted by social-ethical and public health considerations. In Europe, the consensus is that the healthcare sector should not be prevented from providing suitable medical treatment to patients. The exception does not apply to products, in particular substances or compositions for use in a method of treatment.[142] For a method to be considered captured by the exclusion in article 53, c) of the EPC, it needs to be:

- deemed to be performed by or under the supervision of a medical practitioner (although this is not an essential requirement);
- applied to the human body (the treatment of body tissues or fluids only falls under the exception if they return to the same body) ;
- carried out by means of a surgical procedure or therapy (in the broadest sense of the word);[143]

This means that while gene therapies themselves may be patentable, methods involving their direct application to the human body are not. This distinction between products and methods potentially influences the commercial direction of gene therapies, favouring their application in medical products.[142] As a result, it becomes pivotal for pharmaceutical companies to attempt to describe and present their cell and gene therapies as products rather than treatment methods.[144] The question arises to what extent presenting a cell and gene therapy as a product rather than a method is in line with the reality of these therapies.

Whereas, gene therapy involves the introduction, removal or modification of a person's genetic code, cell therapy involves the administration of living cells

[kkkk] CJEU, *Greenpace v. Brüstle*

[llll] CJEU, C-364/14, ISCC.

[mmmm] Article 53, c) EPC.

to a patient. As a result, such therapies at least involve one step that is performed *in vivo*. [143]

The EPO guidelines[145] have clearly distinguished between methods that only involve the removal of body tissue or fluid and methods – which are not excluded from patentability – and those that also involve reintroduction into the same patient. Cell and gene therapies will generally belong to the latter category. Patent applications for cell therapies have attempted to circumvent this hurdle by focusing on the *ex vivo* or *in vitro* steps of the method in their patent publication, but whether such strategy will hold in the future is questioned in literature [143].

EU immunity of patent infringement in case of magistral preparations in EU legislation

Even if the above hurdles to patentability are overcome by innovators, the question of enforcement remains. Particularly in the case of autologous cell therapies, the individualized nature of these products makes it difficult to formulate product claims that sufficiently cover (and hinder) competing products[nnnn]. A further relevant question specifically in the area of ATMP's, is whether ATMP's , prepared in the hospital for an individual patient might fall under the immunity for pharmacy preparations. Indeed, the majority of EU Member States law[oooo] provide for some form of immunity to patent infringement for pharmacy preparations under certain conditions. In Belgium, Article XI.34, §1, e) of the Belgian Code of Economic Law provides that the patent holder may not oppose the preparation of medicines in pharmacies, provided that the medicine is intended for individual use and is issued on medical prescription. This exception also covers acts concerning medicines thus prepared. A pharmacist can, therefore, prepare and sell medicines protected by a patent, provided that they are prescribed in individual cases. In the Netherlands so-called "compounding" pharmacies have recently resurged, challenging the pharmaceutical industry to improve accessibility and affordability of medicinal products.[146] The question arises whether ATMPs prepared in hospital (pharmacies) can benefit from this immunity, and if not whether it is aspirable that the exception for officinal preparation in national patent legislation is extended to cover the scope of the therapies benefiting from the hospital exemption.[133]

8.3.1.2 The US framework

Although the US position on the patentability of medical treatment methods has not always been straightforward in the past decades, the current consensus is that medical treatments are patentable in the United States, as opposed to Europe.[143] However, in the United States other hurdles to the patenting of cell and gene therapies exist, since natural products and principles are not patentable[147], and fall within the "natural phenomenon" judicial exception to patentability.[pppp] In the famous Myriad case[qqqq], the US Supreme Court concluded that DNA segment and the information that they encode are not patent-eligible simply because they have been isolated from the surrounding genetic material. In order, for gene sequences to be patentable, the product must be modified in such a way that it has a property that is clearly different from its natural counterpart (the so called "inventive concept" in US patent law). This vision deviates from the position adopted by the EU policy makers in the Biotech Directive. However, the prohibition is not insurmountable and with careful patent drafting, innovators might be able to amend a *prima facie* ineligible natural product claim such that it becomes eligible.[148]

Furthermore, also in the US, the question of enforceability of cell and gene therapies is not a straightforward one. Section 278, c) of the U.S. Patent Act in principle creates a limited immunity from patent infringement for physicians and related health care entities that engage in patented medical activity. Given the numerous exclusions to this immunity the US approach does not inhibit the enforcement of patents covering drugs against commercial

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nnnn San Martin & Mulryne, 2019

oooo See e.g. the Galenic exception in article 68 of the Italian Industrial Property Code or article 53(3) of the Netherlands Patent Act.

pppp See 35 U.S.C.S.§ 101.

qqqq Ass'n v. Myriad, 2013. I

interests, but only shields clinics, hospitals and physicians from liability for performing patented treatment procedures[rrrr]. This immunity may be of particular interest for hospitals wishing to bring externally developed ATMPs to patients in the US.

Another interesting mechanism which Academia may want to rely on to use externally developed intellectual property for ATMP commercialisation is currently under review in the US. At the end of 2023, the US NIST finalised a draft revision of the existing March-In rights under the US Bayh-Dole Act of 1980. The Act allows recipients of federal research funding to retain patents on inventions resulting from their research, while at the same time including protections such as the March-In right, which authorises federal agencies to require licensees to grant licences to other responsible applicants if the inventor does not commercialise the technology or if action is needed to protect public health or safety. Although the law went into effect in 1980, no federal agency has exercised this right until recently.

In 2023, the National Institutes of Health (NIH) rejected a petition about the high price of the prostate cancer drug Xtandi. In response, the Department of Health and Human Services and the Department of Commerce announced that they would review the government's March-In rights. The draft guidance outlines a three-step process for agencies to determine whether to exercise march-in rights, including assessing whether the invention was funded federally, if statutory criteria apply, and if exercising march-in rights aligns with Bayh-Dole's policy objectives, such as the practical application of the invention and/or health and safety needs of the population. The draft Framework explicitly acknowledges that an agency is permitted to take into account when assessing whether march-in is warranted whether the price at which the product is currently offered is reasonable and whether only a narrow set of customers may access a product due to its high price in its determination of whether march-in is warranted or is exploitative or unjustified in light of the health or safety need. A public consultation of the draft is currently ongoing. The impact of this measure is relatively limited, considering that while there are inventions in scope developing drugs usually involve many patents and that many of them are not subject to march-in-rights. [149]. In addition, politically exercising such march-in rights is not an easy step, hence they have largely remained dormant. [134]

Interestingly, in the US, the government itself (and its agents) is generally allowed to use patented technologies without permission from the patent holder, provided that under Section 28 USC § 1498, patent holders have the right bring a lawsuit against the US for reasonable and entire compensation. It is sometimes argued that this could allow the government to generate generic versions of existing medicines for public health reasons, including unaffordability. In practice, however, patent rights are not the only protections attached to a medicinal product, many other protections, such as regulatory data protection and market exclusivity, restrict actually employing such pathway.[134]

8.3.1.3 Conclusion

Given the inherent uncertainties and difficulties associated with patenting cell and gene therapies, innovators may want to consider other means of protecting their discoveries, such as strictly keeping any knowhow developed in relation to a cell and gene therapy confidential. Adopting the right IP protection strategy (patenting and disclosure vs. confidentiality protection) will prove complex for cell therapy products given the differing views in the EU and US patent systems on the issue of patentability of cell and gene therapies. Nevertheless, a harmonised strategy is crucial. It will prove impossible to patent an invention in the US while trying to protect its confidentiality as a trade secret in the EU or *vice versa*.

Even where certain cell and gene therapies are patentable, there are further hurdles to enforcement:

[rrrr] *Ibid*, 731.

- A rise in contentious proceedings regarding cell and gene therapy patents is expected, as patient organisations and the public opinion wonder aloud whether it is ethical for such important technologies, which (i) often have a basis in nature and (ii) are the result of successive independent research endeavours, often funded by public money, to end up in the hands of private companies that then make a profit every time the technologies are used for new medical and urgent needs.[150] [151]
- Particularly in the case of autologous cell therapies, the individualised nature of these products makes it difficult to formulate product claims that sufficiently cover (and hinder) competing products.
- the existing US and EU legal immunities for hospitals and physicians might hinder patent holders from effectively enforcing their patents against cell and gene therapies developed, manufactured and administered in a hospital setting. The question is whether these immunities extend to situations in which cell and gene therapies are developed and manufactured at large scale in hospital settings.

8.3.2 IP strategies under the academic pathway

In contrast to the landscape of marketing authorisations for ATMPs, the ATMP patent landscape is dominated by Academia. [139] It is noted that this is not surprising in view of the technology and the way it develops, taking into account that pharmaceutical companies tend to be risk-adverse and pick up on promising technologies once the potential is clear and production and logistics are proven to feasible. Academia deliver proof-of-concept and show feasibility; once established, an out licensing to industry is often exercised.

As stated above, Academia have several options to approach IP rights related to ATMPs.

- Not filing for IP protection might negatively impact future valorisation or interest of pharmaceutical companies in furthering an ATMP, which could hamper patient access to ATMPs.
- Rigid IP protection brings forth overhead and potentially limits research; technologies covered by multiple patents owned by various institutions are often opaque in their use (patent holders would infringe other patents through their use caused by so-called 'patent thickets'). This makes them unattractive for potential pharmaceutical companies and makes translational research difficult.[152]
- Keeping inventions confidential is not aligned with the general purpose of Academia to share and disseminate knowledge.
- Innovative patent approaches such as patent pooling might alleviate some of these concerns. (see Box 10).

Box 10 – Patent pools

- Patents pools in drug development are collaborative arrangements where multiple patent holders agree to pool together their patents related to pharmaceutical products, technologies, or processes and license them through a centralised entity.[153] These pools aim to streamline the licensing process, reduce litigation risks, and accelerate drug development by providing broader access to essential patents. Patent pooling allows pharmaceutical companies and researchers to obtain licenses for multiple patents through a single agreement, simplifying the process of accessing the necessary intellectual property for drug development, and by consolidating patents and providing a clear licensing framework, patent pools can reduce the potential for patent infringement disputes.[154]
- Patent pools have been used in the area of public health, for example under the Medicine Patent Pool, a patent pool established under the auspices of Unitaid in 2010. The MPP focuses on increasing access to HIV, hepatitis C, tuberculosis, and other essential medicines in low- and middle-income countries. The MPP negotiates with patent holders to license their patents to generic manufacturers, ensuring affordable access to their drugs in these countries.
- For example, in the field of ATMPs, patent pools for CRISPR-Cas9 are subject of a long debate. Considering that patents covering this technology are owned by multiple patent holders (Broad Institute, UC

Berkely, Vienna University, etc.), a patent pool of relevant patents would allow for streamlined access to the technology and avoid litigation.

Academic patent pooling approaches could help Academia in streamlining their IP approaches and negotiations with potential partners, including by pre-defining licensing for academic ATMPs and commercial ATMPs, as well as including socially responsible licensing clauses.

From a funder perspective, as mentioned above, this could include mandating that revenues generated from out-licensing activities be reinvested into research and development (refer to Section 8.2.3 above and Section 6 in the Supplement for a comprehensive analysis of state aid regulations and strategies to prevent potential conflicts with these regulations). Additionally, this policy framework could be leveraged to incorporate other conditions aimed at retaining control over the societal cost of the final product through so-called socially responsible licensing clauses. These clauses aim to ensure that the benefits of publicly funded research are accessible to the broader community and contribute to the public good (see also section 8.2.2 of this report). Such clauses may include provisions that (i) aim to increase the availability, accessibility and affordability of the therapy; (ii) encourage or mandate companies to collaborate with Academia to further develop and improve the licensed technologies, leveraging additional expertise and resources to maximise societal impact (iii) reserve sub-indications for treatment under hospital control; and (iv) require open access to research findings and data, to facilitate broader dissemination of knowledge and foster further research and innovation on ATMPs. Clearly, striking a well-balanced approach is essential to ensure that the commercialisation pathway remains appealing to both Academia and industry. Academia should also be rewarded in case of such a successful effort with a high value for society.

8.4 Translational expertise

In addition to providing funding, authorities may extend support indirectly, by facilitating the development of expertise and sharing thereof within and between Academia, with the goal to improve translation into clinical practice of ATMP research performed at Academia. Increasing Academia's translational capabilities, even if Academia would not progress ATMP towards commercialisation themselves, potentially increases potential interest from industrial partners that could benefit from translational efforts made by Academia and reduces hurdles to bring the therapy to patients. It could also increase leverage of Academia to require social responsibility commitments from such partners.

Under Section 8.2.2 of this report, it is argued that an aligned policy on a European (and national) level that identifies gaps in funding and areas to invest in academic centres to build ATMP capability would help guide governmental actors in their decision making regarding grants and investments into projects. As part of such policy, it should also be considered to establish pharmaceutical development units/ translational offices, pooling expertise from Academia and public authorities, addressing the identified gaps, helping Academia in shaping their research activities, providing regulatory IP and business development advice to improve translational potential of the results into clinical pathways, including marketing authorisation. This also includes a mapping of expertise in different institutions, and incentivizing training of researchers and sharing of knowledge through collaborative platforms.

A notable example of an previous EU-funded initiative aiming to increase the exchange of information and consultation, was the 2-year AGORA program under FP7 (ATMP GMP Open Access Research Alliance from 2013-2015) designed to create a source of information to support biomedical and clinical research through a platform, also providing support for ATMPs academic

programmers to comply with legislation, while promoting the development of early-stage therapies to commercial trials.[ssss] [155]

On a national level, public-private partnerships such as RegMed XB provide opportunities for Academia to share expertise on specific projects in regenerative medicine and receive specific advice and government-funded consultation towards a specific target product profile to enhance translation into clinical practice.

Box 11 – RegMed XB (Netherlands and Flanders)

- RegMed XB (REGenerative MEDicine crossing Borders) is a Dutch-Flanders collaboration between research institutes, governments, provinces, health funds, and industry in the Netherlands and Flanders that started in 2017, with the goal to ultimately find curative treatments for several diseases, with the commitment to invest 250 million in the following decade. For example, in 2021, the Dutch Nationaal Groeifonds allocated a grant of 23 million euros to Stichting RegMed XB (later increased to 56,3 million euros)[tttt] to build a physical infrastructure (a network of different pilot factories for regenerative therapies). This network includes 5 facilities in different regions and covers the entire chain of development and production of stem cells, mini-organs, tissues and smart (bio) materials. The second part of the grant up to a maximum of 33 million is intended for further development and upscaling). [uuuu]
- Pursuant to this work, the Netherlands Centre for the Clinical Advancement of Stem Cell and Gene Therapies (NecstGen BV) was established in Leiden, as CDMO owned by Leiden University Medical Centre (LUMC). NecstGen controls a state-of-the-art facility for development and GMP manufacturing and additionally offers cleanroom rental to allow organisations to maintain control of production while de-risking the capital investment required.
- NecstGen aims to increase the development and GMP production capacity available for cell and gene therapies. The facility is open to partners based worldwide, focusing on academic clients, hospital based clinicians or start-up companies, but also to industrial partners.[156]
- Based on a limited number of examples the pilot factory platform confirmed that such national pilot factory network can offer cheaper prices than the ones offered by the private sector. (eg. projections were made for ChondroCelect production by NecstGen resulting in less expensive manufacturing than commercial providers).
- The aim of these pilot factories is to support universities, research institutes, start-ups and industry with developing, testing, upscaling and producing their new regenerative medicine therapies. The services are however limited to production for explorative studies (not to place the products on the market). On the other hand, every pilot line is expected to become self-supporting in the coming years, i.e. attract customers who can help pay for their operations.
- In 2017, the Government of Flanders already approved a € 2 million grant to RegMEd XB. Aditionally, in 2024, 15 million were granted by the Departement Economy, Science and Innovation fo the Flemish government to RegmedXB vzw, the Flemish part of the RegMedXB

[ssss] See for a list of achievements: https://www.atmp-group.org/pdf/AGORA-summary-of-achievement.pdf

[tttt] The ruling confirming the grant under the Nationaal Groeifonds can be consulted at https://www.rvo.nl/sites/default/files/2021/12/Maatwerkbeschikking%2020211221%20NGFRM2101%20besluit%20tot%20verlenging%20subsidie_0.pdf and https://www.rvo.nl/sites/default/files/2022-12/Maatwerkbeschikking%20221223%20NGFRM2101%20Pilotfabriek%20voor%20regeneratieve%20geneeskunde.pdf

[uuuu] https://www.rvo.nl/sites/default/files/2022-12/Maatwerkbeschikking%20221223%20NGFRM2101%20Pilotfabriek%20voor%20regeneratieve%20geneeskunde.pdf

collaboration, by Flanders to develop new regenerative therapies targeting chronic diseases, including osteoarthritis and eye diseases. The funding is spread over 5 years.

- Regmed XB vzw requires a target product profile to be established for each project ('Moonshot') funded thereunder (such target product profile is validated by publicly funded experts), allowing the collaborations to work towards clearly defined goals and deliverables, with the aim to facilitate translation of the results into clinical practice.

Initiatives of note that seek to foster intra-institution collaboration include GATE Health. GATE Health is a collaborative platform of excellence in Cell and Tissue Engineering created under the umbrella of U(Z)Gent, partnering with VIB and imec. The mission of GATE is to promote collaboration and innovation in regenerative medicine by sharing knowledge, technologies and infrastructure in order to bring better therapies faster to the patient.[vvvv]

The EU has created a specific framework in which multinational research infrastructure collaborations are set up, referred to as European Research Infrastructure Consortia (or ERICs). [157] An ERIC is a specific legal form that facilitates the establishment and operation of research infrastructures with European interest, i.e. it is a joint venture that includes multiple Member States, in which research infrastructures are created and/or operated. The framework is laid out in Regulation (EC) No 723/2009 concerning the Community legal framework for a European Research Infrastructures Consortium (ERIC).[wwww] An ERIC should operate on a primarily non-economic basis. [xxxx] ERICs benefit from some advantages, such as a separate legal entity, and some qualities of an international organisation such as tax exemptions and exemptions from public procurement rules. More importantly, they are institutionalized cross-border collaborations on research infrastructure in the EU. In addition to the ERIC "ECRIN" of relevance for international academic trials, particularly relevant for translational research, is the ERIC "EATRIS" (see Box 12), set up in 2008 with as goals to:

(i) provide easier access to state-of-the-art research and development facilities and translational knowhow for all scientists and researchers.

(ii) overcoming fragmentation along the translational research pathway;

(iii) fostering knowledge exchange and standardisation;
(iv) providing training programmes for the next generation of translational researchers; and
(v) facilitating and encouraging cooperation between Academia and industry.[yyyy]

There are other examples, including national government supported translational offices, such as LifeArc in the UK[zzzz], and a public translational office within the National Institute of Health (USA NCATS)[aaaaa].

[vvvv] https://www.gatehealth.be/about

[wwww] For more information ,see also https://research-and-innovation.ec.europa.eu/document/download/8352b6d2-d179-4ab2-afc0-b4848ebd1859_en?filename=eric_faqs.pdf and https://eur-lex.europa.eu/EN/legal-content/summary/european-research-infrastructure-consortium-eric.html

[xxxx] See Article 3 (2) of the ERIC Regulation

[yyyy] https://cordis.europa.eu/project/id/212435/reporting

[zzzz] See also About us - LifeArc

[aaaaa] See also NCATS Overview | National Center for Advancing Translational Sciences (nih.gov)

Box 12 – Eatris

- EATRIS (European Advanced Translational Research Infrastructure) is a non-profit consortium of facilities and experts, recognised as a permanent European infrastructure. It is partially funded by Member State contributions and is self-sustaining through service fees and competitive grants, primarily from the European Commission. Service fees vary based on the type of service and the stakeholder group accessing it.
- All services (including the translational feasibility assessment) are available to anyone (Academia, public funders, charities, industry SME's etc.) from any country. The fees can vary depending on the type of service and the stakeholder group accessing it.
- Additionally, European countries can join EATRIS. In return, their national community can be part of the infrastructure, collaborate in projects, provide EATRIS services, and benefit from the community's best practices, training, and standardisation.

Sharing of knowledge and expertise in the development process is also stimulated at the level of the regulators:

Examples of expertise sharing in the regulatory process can be found in the EMA Academic Pilot (see details in Box 13), which seeks to support Academia at an early stage in the development of ATMPs to increase chances of the investigational approach to be translated into clinical practice and potentially ultimately be marketed.

Box 13 – EMA Academic Pilot

- A pilot project involving the provision of increased dedicated guidance *and direction*, as well as fee reductions and waivers, to *up to five selected* academic and non-profit *ATMP developers* is currently ongoing at EU level.[bbbbb] Applying to be included in the pilot *is* possible until five candidates have been selected (by Q4 2024 at the latest). To be eligible to participate, the following selection criteria must be met:
  - the product is an ATMP;
  - the ATMP is expected to address an unmet medical need (product should offer a major therapeutic advantage over existing treatments, or benefit patients with no or few treatment options.);
  - the applicant is from the academic sector (i.e. public/non-profit hospitals or research organisations, higher education institutions, public-private partnerships/consortia, and international research organisations);
  - the applicant is established in the EU;
  - the product is at a relatively mature stage of development: convincing non-clinical (animal) data or, ideally, FiH clinical data on mechanism of action can be provided;
  - the quality development of the product, including the manufacturing process, is sufficiently mature for the early clinical trial stage*;*
  - the developer has the freedom to operate and full access to data related to development and manufacture of product (i.e. the IP is not controlled by a commercial company);

bbbbb https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

- the developer shows willingness to collaborate with EMA and follow recommendations; and
- the developer has sufficient resources available.

- The pilot focuses on all the needs of non-profit academic developers. The guidance provided is hence not limited to scientific advice but includes enhanced regulatory support throughout the entire development and market access process, starting from best practice principles for manufacturing to planning clinical development that meets regulatory standards. Beginning of 2024, three participants have already been selected: (i) ARI-0001, a chimeric antigen receptor (CAR) product based on patients' own T-cells, that is developed by the Hospital Clínic Barcelona; (ii) regTacRes, a medicine based on modified T-cells, intended for use as add-on therapy after transplantation, under development by Berlin Centre for Advanced Therapies – Charité; and (iii) Telethon 003 (Etuvetidigene autotemcel), which is being developed by Fondazione Telethon and intended for the treatment of Wiskott-Aldrich Syndrome, a rare, life-threatening immunodeficiency.[ccccc]
- The aim of the pilot is to assess the level of regulatory support needed to enhance the number of ATMPs reaching patients in the EEA and identify potential gaps in the existing EU regulatory tools and guidance. For this purpose, no new regulatory tool is introduced as part of the pilot but the participants benefit from all available flexibilities and support measures in the existing regulatory framework, including financial incentives (i.e. the same as under PRIME and for SMEs). Initial results of the pilot are expected to be available in 2025.

8.5 Manufacturing facilities and expertise

Key points

- ATMP manufacturing requires expertise (as each ATMP has its unique features) and requires GMP, which is pharmaceutical quality system and requires not only specific cleanroom environment, but also encompasses concepts such as traceability, documentation, adequate quality control testing, thus including highly experienced dedicated staff
- Not only the initial investment is substantial but also maintaining a GMP facility for ATMPs is costly (cleanroom environment, infrastructure and staff)
- This results in a volatile ATMP manufacturing field where unbridled growth may compete with existing facilities leading to waste of limited resources.
- While all marketed ATMPs have a centralised manufacturing, there is an interest in more decentralised manufacturing, with Point of care (POC) as the ultimate example. The interpretation of POC at the moment might be misleading as it is not always the case (yet) the manufacturing is done at the same hospital of administration. Oftentimes it is somewhat more centralised in a facility close to the patient. Developing regulatory frameworks and enhancing manufacturing standards will be critical in realising the potential of decentralised manufacturing and POC.
- Manufacturing expertise in Academia can be enhanced by more collaboration (e.g. in a network), transparency, training and knowledge sharing.

[ccccc] Progress update on pilot for academic and non-profit developers of advanced therapy medicines https://www.ema.europa.eu/en/news/progress-update-pilot-academic-non-profit-developers-advanced-therapy-medicines

8.5.1 ATMP manufacturing is complex

8.5.1.1 Each ATMP is unique

As ATMPs encompass a broad range of products (tissue, cell and gene therapy), each ATMP product is unique, as well as its production process and its quality control procedures. The complexity level of production varies as some require the use of cells which need to be kept alive during the process, while others not (e.g. in vivo gene delivery of mRNA via viral vectors or liposomes), some include substantial manipulation of cells, such as genetic modification, others include more detailed cell cultivation steps, and some combine the use of cells and gene modification (e.g. CAR-T). Moreover, there are different ways of gene modification, either via a viral vector or via a nonviral delivery method such as electroporation or lipid nanoparticles.

In addition, working with biological material (human cells, viral vectors), results in a high degree of variability in both the starting and raw materials and the finished products, therefore imposing challenges with characterisation and standardisation. Autologous treatments where living cells from the patient are used, combined with genetic modification are considered most complex for manufacturing. Often one batch equals one product for one patient.[158]

The rapid pace of innovation and the **diversity of ATMPs** highlight the need for **dedicated expertise and highly skilled operators.** Technology is advancing fast and important details of manufacturing processes and quality control test methods, are not standard publicly shared.[14, 159]

8.5.1.2 The big leap between manufacturing for research/preclinical use and for clinical use: GMP

There is legislation governing each stage of the ATMP development process. Depending on the specific ATMP characteristics different legislations apply: are cells and tissues used, then the SOHO legislation (European Union Tissue and Cells Directive) applies; is there use of genetic modified organisms (e.g. integrating versus non integrating viral vectors), then the GMO legislation applies.[88, 155] During the preclinical stage, adherence to Good Laboratory Practice (GLP) is required. As the process moves to the clinical stage, compliance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) becomes essential. To assist developers, several guidance documents have been published (Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products,[160] or being updated or drafted (Draft guideline for investigational advanced therapy medicinal products in clinical trials[161]). However, regulators need to balance between clarity in the guidance, while also leaving room for flexibility.

Especially the move to the clinical stage is challenging because from the moment a candidate ATMP product will be administered to humans, the ATMP manufacturing must comply with **GMP**, a quality management system to ensure that products are consistently **processed and controlled** according to quality standards. This system guarantees **traceability at all times**, covering every aspect of manufacturing and distribution from the starting materials, premises, and equipment to staff training and personal hygiene. In order to comply with GMP there is not just need for qualified infrastructure and the requirements to work aseptic to prevent microbial contamination[ddddd], there is also a need for qualified staff and documentation rigour. The European commission foresaw a specific guideline “Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal

ddddd Because most ATMPs cannot be terminally sterilised, the manufacturing steps should be conducted aseptically. Specific cleanroom requirements are mentioned in the ATMP GMP guideline, depending on whether the production is in a closed system or an open system. The classification of clean rooms is done according to ISO 14644-1 norms and uses the Grade system, with Grade A as the “cleanest”. As a default rule, all manipulation production steps should be done in a closed system (e.g. an isolator, biosafety cabinet which guarantees Grade A cleanliness), and a background clean area of minimum Grade D. If the product is exposed to the environment, a cleanroom Grade A with a background clean area of Grade B is required.

Products" issued in 2017.[162] This guideline also applies to manufacturers of ATMPs in early phase of study (phase I clinical studies), i.e. investigational medicinal products, and for ATMPs under hospital exemption (Article 3(7) of Directive 2001/83/EC). The **GMP requirements for investigational medicinal products can exceptionally be adapted based on the risk** and knowledge of the product (e.g. air quality in very early phase/proof of concept trials, calibration, maintenance activities, inspection, level of formality and detail for the documentation can be adapted to the stage of development). Nevertheless, GMP and manufacturing standardisation for clinical trials is necessary to ensure patient safety and product quality, and to guarantee that clinical trial results are reliable (e.g. not influenced by manufacturing issues). There must be **consistency between batches** of the same investigational medicinal product. In the EU, also for clinical trials, the ATMP must be **released by a qualified person** which is a dedicated person who needs to verify and certify that each batch produced is according to prevailing regulations.[162]

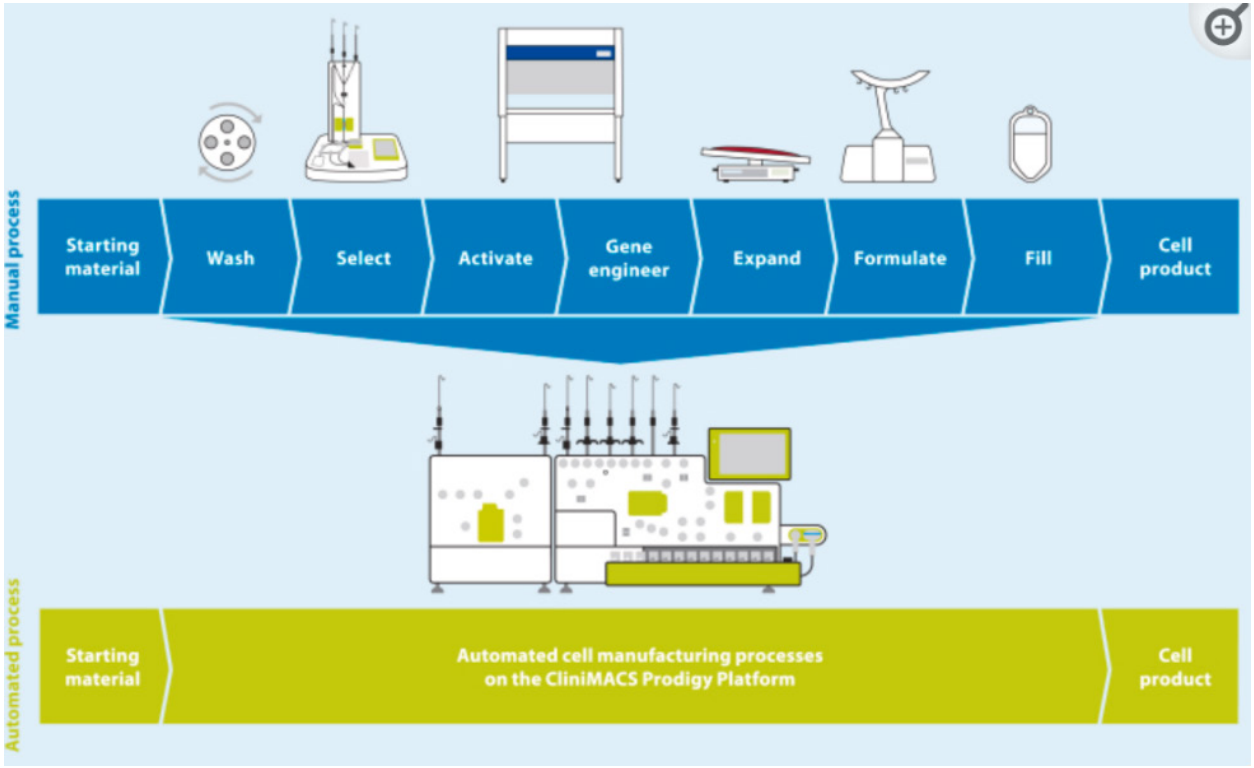
The components used in the manufacturing process (cell culture reagents, growth factors, cytokines, antibodies, viral vectors) also impact the overall quality, safety, and efficacy of the final products. The manufacturer must ascertain the quality of all components, and for certain components the principles of GMP apply (e.g. viral vectors, starting materials).[163]

8.5.2 Automatisation in the manufacturing and decentralisation of production

In recent years, the manufacturing process has been improved by advancements in **automated closed-system manufacturing platforms** and the use of single-use disposable consumables. These innovations help eliminate many open-process steps impacting cleanroom environmental requirements, reduce the risk of human error, increase product quality, reproducibility, operator safety and allow parallel manufacture of multiple products in the same room.[158, 164] Commercial players have developed and continue to innovate closed and automated manufacturing devices that meet GMP requirements. Examples of these platforms include *CliniMACs prodigy® platform, T-Charge™ platform, Cocoon® platform*, etc.[165] The main challenge with the use of automated platforms and their related software programs is the poor cross-compatibility between devices due to innovation gaps and increased dependency on a specific supplier for that particular automation platform, limiting flexibility.[14]

Several projects and clinical trials are working with automated closed manufacturing platforms. For example, at the CDMO Anicells they introduced various closed, and automated platforms within its GMP-certified cleanrooms as part of a research fund (EFRO-project ended in December 2023). At the VUB there is an ongoing project to produce personalized dendritic cell vaccination via a closed automation system with the RoteaTM technology as a modular system.

Figure 4 – Manual versus automated manufacturing process for T cell therapies



Source: Copyright © 2023 Miltenyi Biotec B.V. & Co. KG. [166]

Most marketed ATMP products have a centralised production location, also when autologous cells are used as starting material (e.g. CART-T). The logistical barriers for the centralised procedure include the cryopreservation and the transport under robust cold chain conditions. Not seldom this concerns intercontinental shipments. Centralised manufacturing leads to a longer time to administration as vein-to-vein time, potentially exceeding a month. Consequently, some patients may require additional therapy to bridge this period.[167]

In some cases, manufacturing of the ATMP needs to take place in sites close to the patient and needs to be **decentralised to multiple sites** (e.g. ATMPs with short shelf-life, when no freezing is possible). When the manufacturing is done "on site", at/near the facility that treats the patient it is often referred to as "*point-of-care manufacturing*". The emergence of automated, closed manufacturing platforms facilitates to produce therapy **on several locations, close to the patient,** to overcome the logistical barriers and decrease vein-to-vein time. For example, the firm Galapagos has three clinical trials running with point-of-care manufactured CAR-Ts with a median vein-to-vein time of 7 days, and recruits in Belgian hospital sites (EUPLAGIA-1, ATALANTA-1, PAPILIO-1). However, the production of the CAR-T is not (yet) at the point of care, meaning in the treating hospital, but more often at a certified GMP facility close by. Although there is **no dedicated legislation on decentralised manufacturing, there is some guidance** in section 11 of the "Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products".[162]. It emphasizes the need for batch certification and release at the sites, and the need for a central reference site responsible for the oversight of the decentralised sites. Therefore, qualified and trained staff should be at the sites (the Qualified Person can be the same for all the sites). It must be guaranteed that the **ATMPs produced at the different sites are comparable**[109], and a suitable comparability program is required (as explained in a 2019 EMA FAQ document[168]).[33] The comparability of the product manufactured at different sites should be comprehensively substantiated. The first step should be to perform a comparability assessment of the manufacturing process and equivalence of the analytical methods on both sites by evaluation of process parameters and in-process control, to validate the process transfer. Secondly, the comparability of the product itself through release and suitable characterisation testing should be demonstrated. These requirements bring along challenges for decentralised manufacturing: coordination, standardized training and certification, ownership of quality control and release, IT infrastructure assuring data accuracy.

The interest for decentralised ATMP manufacturing and point-of-care production represents a transformative trend in healthcare. Developing regulatory frameworks and enhancing manufacturing standards will be critical in realizing the potential of decentralised manufacturing in delivering high-quality, patient-specific therapies. Some clarifications, e.g. on certifying the different sites is underway. The situation in the UK is clarified in Box 14 – UK POC manufacturing. [169-171] Whether centralised production or point-of-care is the best manufacturing strategy for ATMPs depends on the anticipated demand, where centralised manufacturing is a preferred option for lower demand levels.[170, 172]

Box 14 – UK POC manufacturing

In 2021, the UK introduced a public consultation to establish a specific regulatory framework for point of care manufacturing of innovative medicines.[169]

With the new framework, the Medicines and Healthcare Products Regulatory Agency seeks to support the safe development of medicines which need to be manufactured and supplied in close proximity to patients or new supply chains that enhance patient access.

The envisaged framework introduces the concept of Control Site, the institution responsible for establishing and overseeing the POC

[109] Comparability is the conclusion of the comparability exercise demonstrating that no adverse impact on the quality, efficacy and/or safety profile of a product has occurred when a manufacturing process change/transfer is introduced for the drug substance/product. A comparability exercise should not only cover evaluation of equivalency of manufactured products but should include also comparison of processes themselves,

manufacturing process, with responsibilities that will include staff training, quality control, provision of manufacturing equipment, adverse event reporting, auditing of manufacturing sites, and others. The Control Site will take the product from the development phase to the market, which will comprise securing a clinical trial authorisation, conducting the clinical trial, and obtaining a marketing authorisation. The Control Site will be required to maintain a POC Master File, which will name all of the individual POC manufacturing sites, to be authorised. The Control Site will oversee all aspects of the POC manufacturing system, including the individual manufacturing locations and their activities, and be named on clinical trial and marketing authorisation applications.[173]

8.5.3 ATMP manufacturing is costly

Manufacturing costs are an essential contributor to high market price of ATMPs, due to among others small scale, ATMPs unique and complex production characteristics and specific supply chain.[7, 174] There are the GMP requirements that call for having and maintaining controlled cleanrooms including qualified staff. The introduction of closed-automated platforms allows for simultaneous manufacturing of multiple and different therapies in the same room, which can lower the staff cost.[175] However the capital investment in such platforms, which have their own specific and costly consumables is significant.[166] Depending on the specific production path of an ATMP it might be necessary to have GMP-grade starting materials. Often the gene-editing technologies (plasmids, viral vectors) are patented / licensed and drive production cost.[172] The quality control of the ATMP requires customized analytical methods, which sometimes need to be outsourced.[24]

A 2020 paper analysing 8 different ATMPs in 4 small-scale facilities showed that the production cost varied between €23 033 and €190 799 euros per batch, with batch yield varying between 1 and 88 doses.[174] The TIL case study reported manufacturing costs of around € 67 547 (min € 45 031 and max € 101 320) depending on the number of patients that should be receiving TIL therapy. The costs of goods for CAR-T range between $ 60 000 and $ 90 000 per dose,[128] though the CAR-T pioneer Carl June suggested in 2012 the cost for production is about $ 20 000 per patient, and is expected to decline when manufactured at scale.[7]

8.5.4 Manufacturing routes for Academia

Generally, the expertise of manufacturing, quality control testing, release of pharmaceutical products for human use, as well as the resources for the late stage development and scale-up resides mostly with the industry. That said, over the past two decades, within the field of ATMPs, there has been a revolution in the traditional set-up, with Academia significantly contributing to both the development and the manufacturing of ATMPs (see also case studies).[176] Throughout the world, several Academia have built their own patient treatment programs and with it have built their **own in-house manufacturing capacity**.[177]

If Academia manufacture ATMPs, they need, just like the industry, to ensure compliance with applicable tissue regulations and GMP, and have to guarantee that outsourced activities (*e.g.,* cryopreservation, storage, testing), where relevant, are adequately monitored under applicable laws. Moreover, they will have to ensure they have the appropriate licenses and permits.

8.5.4.1 Knowledge - Training - Transparency

The ATMP production methods often change from the small scale preclinical-research phase to clinical stage to commercialisation, and necessitate extensive comparability assessments with validated analytical assay.[128] To make the translation from research bench to clinical use and avoid lengthy production process optimization and unnecessary repetition of experiments, it is important to have a "**GMP state of mind" from early-on.**

Specific initiatives to smooth the transition have been set up: The **pre-GMP facility** at Karolinska Institute aims to act as an intermediate step between early ATMP production in research settings and GMP manufacturing, a "*manufacturing fitness room*" before the transfer to GMP suites.[178] In Utrecht, a similar initiative of a **GMP simulation unit** was started to facilitate the translation from research-grade to clinical-grade manufacturing in accordance with Good Manufacturing Practices and to facilitate the transfer

of a fully developed GMP-grade production process between different GMP facilities.[14]

In addition, education, training and support of the academics involved in these processes is required.[24, 70] Within this context, conventional training programs offered by universities, research institutions or governmental bodies typically fall short in terms of their alignment with the training requisites and practical insights currently essential for academic institutions, biotechnology enterprises, major pharmaceutical companies and regulatory authorities—entities that will invariably require this expertise in the years to come."[123] A recent initiative from University Ghent (not focused solely on ATMPs) also aims to optimise production technology with flexible 'plug & play' GMP like test facility (Centre of Excellence in Sustainable Pharmaceutical Engineering & Manufacturing) and provides a new master program in pharmaceutical engineering. ViTalent also provides training for GMP for ATMPs in mock cleanrooms.

As mentioned above, manufacturing processes are typically not made public, making it difficult for academics to learn from existing practice. Nonetheless, there are initiatives to enhance transparency and are mainly targeted to academic researchers (EU- AGORA project 2013-2015[110]).[155, 163, 179] For example, in the USA, the California Institute for Regenerative Medicine has established open-source manufacturing protocols.[180] T**he Dutch** DARE-NL initiative brings together Dutch and Belgian academic experts with the aim of **exchanging information** between **academic centers** and harmonising specific procedures needed to produce ATMPs in accordance with GMP guidelines.[179]

8.5.4.2 Development of not-for profit CMO network

Establishing and maintaining a GMP facility comes with certain challenges to ensure adherence to the relevant applicable laws and regulations . Moreover, the cleanroom requirements and the high skilled staff are resource intensive. It requires substantial start-up investments to build the facility and buy the necessary equipment, but also substantial financial capacity and dedicated staff to keep it running.[24, 128] The dynamic field with spinoffs, bankruptcy and takeovers shows that it is not easy to maintain such a facility. Therefore, several GMP facilities diversify their portfolio so they can attract several projects with ATMPs.

The rise in academic involvement in manufacturing activities is thus yet to shift, or just even disperse, the concentration on expertise in respect of manufacturing and the various regulatory requirements in relation thereto from the industry players to Academia. Some recommend centralised ATMP facilities to address the limited availability of resources including expertise.[24]

A viable alternative might be the establishment of regional networks of organisations leveraging their accumulated expertise in ATMP manufacturing, early-phase clinical trials, specialised knowledge in treating severe and rare diseases and late-stage clinical trials. ATMP networks can either be built with only academic facilities or, collaboration between Academia and contract manufacturing organisations (CMOs) can be fostered, developing a not-for profit CMO network (see Box 7 and Box 11).

That said, there are clear indications that a dedicated GMP facility within a hospital setting has many operational advantages allowing patients to access innovative and personalised treatments.[158]

110 AGORA project, coordinated by the UK and designed to create a source of information to support biomedical and clinical research through a platform. This platform facilitates the consultation among researchers working in the field, as well as support for ATMPs academic programmers to comply with legislation, while promoting the development of early-stage therapies to commercial trials

As of today, there are already a couple of Academia in Belgium that have obtained the necessary manufacturing authorisations for the manufacturing of ATMPs. These manufacturing authorisations are however limited to investigational ATMPs only and which means that there is thus yet an Academia to be licensed to manufacture ATMPs for commercial purposes (see section 5.2 of this report).

GMP readiness for academically developed ATMPs hence would benefit from further capacity building in Academia, supported by public authorities, and organised as a platform or network. In addition, even though the specificity of ATMPs has been recognised in ATMP GMP Guidelines, novel approaches to decentralised manufacturing should be recognised and fostered by specific GMP guidelines capturing these modalities, which may limit the burden on Academia in setting up their GMP facilities.

9 CHAPTER 6 - DISCUSSION AND CONCLUSIONS

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9.1 Discussions with experts and stakeholders

In addition to conducting a literature review and examining the legal framework, we conducted semi-structured interviews with experts from Belgium and various EU States and organised three stakeholder meetings to validate our findings against real-world experiences in Belgium. These meetings included Belgian participants from Academia, funders, and a broader group of stakeholders[111], including patients and industry representatives (see section 3 of the report for the methodology).

Regarding academic development as a complementary pathway for ATMPs in Belgium, the case studies and finding were discussed and the following conclusions emerged:

- **Classification issues are impacting clinical practice and making ATMP development more complex**

The report identified the classification of ATMP products, particularly *versus* SoHO products, as a grey area. Several Belgian stakeholders confirmed the concrete impact of this issue on their daily practice. The grey zone to classify a product as an ATMP creates significant source of uncertainty and might force the clinicians to organising care and specific interventions differently to avoid the burden of being classified as an ATMP. According to some clinicians, the introduction of the ATMP legislation significantly reduced the number of ATMPs that were available to Belgian patients and limited the initiation and progress of new academic projects in Belgium. Some experts

[111] Participants to this this broader meeting were Belgian clinicians, Technology Transfer Offices (TTOs), Clinical Trial Units (CTUs), academic institutions, industry representatives, patient representatives, public and charity funders, and regulatory and reimbursement authorities.

questioned the appropriateness of the criteria used to classify a product as an ATMP, particularly the "substantial manipulation" criterion and suggested placing greater emphasis on product risk assessment.

As discussed in Chapter 1 of the report, this issue exists in many European countries. In the European Union, the newly adopted SoHO Regulation, which foresees some advice from the SoHO advisory board and a possible decision of the European Commission in case consensus is lacking, was emphasised as a possible improvement. Additionally, the definition of ATMP in future pharmaceutical legislation may also be revised to address classification issues.

- **Hospital exemption should be revised at EU and Belgian level**

Regarding HE, the literature highlights the need to clarify certain areas of HE **at EU level** to avoid safety risks for the patient and improve access in the different EU countries.[64, 74, 82]

There is indeed a wide variation across countries regarding the implementation and interpretation of the criteria and conditions for the authorisation of a HE. For instance, some Member States allow the co-existence of a commercial alternative or clinical trials with a product under HE, whereas others do not. Quality and data requirements differ between Member States (more stringent in Spain and Belgium).[81] This leads to an unequal playing field; Academia willing to use the HE are facing more or less strict (and costly) requirements depending on the Member State. For patients, this may lead to unequal access to potentially innovative therapies, as Member States with more 'liberal' regimes are likely to have more products under the HE. Moreover, cross-border exchange of ATMPs under HE is currently prohibited.

On this particular point, several academic players but also experts involved in very specific rare genetic diseases welcomed the proposal of the European Parliament in the context of the EU pharmaceutical legislation to allow cross-border exchange in exceptional cases of medical need when no other solution exists. To that end, consistency in the interpretation of conditions for HE across countries seems to be primordial. Therefore, some form of harmonisation is needed so the HE route is a valuable and realistic route in each Member State. It should however be noted that the current proposals to harmonise these conditions vary significantly depending on the proposer. The industry tends to favour harmonisation to restrict the use of HE to very strictly defined unmet medical needs with no other commercial alternatives available.

Regarding some aspects, harmonising regulations can be complex and time-consuming, requiring coordination and cooperation among Member States. The healthcare system and regulatory environments in different EU countries vary significantly, making it challenging to create a one-size- fits-all approach. Therefore, a first step in the direction of more harmonisation could be for the European Commission to publish a 'best practice guide' and to regularly monitor how HE is enforced at national level (e.g. on the uniformity of interpretation of GMP) and to publish an 'EU mapping of national regulatory frameworks' to list all requirements country by country, publicly informing about differences between countries and strengthening EU harmonisation. Measures should be adopted to improve transparency of the use of the Hospital Exemption, including the establishment of a register of exempted products, as currently proposed by the European Commission under the proposal for a new EU pharmaceutical legislation (see Box 1).

In Belgium, the implementation of HE was perceived by academic stakeholders as overly restrictive compared to other European countries (e.g. the documentation required for HE is very extensive, the perception that data obtained via HE cannot be used for publication). In addition, HE is only allowed for a limited number of patients (non-routine criterion), making it impractical and expensive for Academia in a small country to invest in full GMP compliance for a small patient base. Moreover, HE cannot be applied if a MA was delivered for 'the same product', which seems to be interpreted broadly by Academia. These perceptions may partly explain why Academia never attempted to apply for a hospital exemption (the only example of HE in Belgium was introduced by a spin-off). Although a guidance document for the interpretation of the legislation has been published, several misperceptions continue to exist. During a stakeholder meeting, clarifications were made by the FAMHP. The publication and communication of an updated guidance document seems necessary to correct the current misunderstandings.

In addition, as regulators need to balance between allowing flexibility in their guidelines while also providing clarity, it would be good option to promote a low-threshold, free-of-charge communication channel between the FAMHP and the applicants for an HE to discuss in advance the application of the eligibility criteria and the overall feasibility of an HE for the ATMP in question. The Inspectorate for Health Care and Youth in the Netherlands sees this as a systematic step before the application for a HE is formally submitted and can serve as a good practice example for Belgium.

Some stakeholders and experts underlined that for certain innovative treatments, in particular autologous products that are highly personalised and not prepared on a large scale, and for treatments targeting very small populations, there is a need to design a route to the patient that does not envision market authorisation by the EMA, and does not focus on commercialisation.[25] Opinions seem to diverge slightly on the question of whether the hospital exemption framework could be revisited for that purpose. Given the national nature of HE, some stakeholders would prefer a more centralised model guided by the EMA.

There was however a consensus that HE or any other adapted framework should not be used to circumvent clinical trials and should be regulated and followed up via high quality registries.

- **Cautious interest in reaching more advanced stages of ATMP development**

For most Belgian academic institutions and charities, holding a Marketing Authorisation is not their primary focus and is deemed challenging due to the significant funding required, regulatory hurdles, and the need for ongoing funding to maintain the MA and meet post-authorisation obligations and liabilities. The two advanced case studies on academic development also suggest that a separate entity is (or is planned to be) utilised for the last steps preceding the MA (see section 7 of the report).

Currently, academics tend to focus on preclinical and first-in-human studies and then license out to spinoff companies or industry partners, partly due to the lack of funding of larger clinical trials and partly because they prefer to concentrate on scientific research and valorisation thereof via publication, licences or patents (not a product). This does not preclude the exploration of public-private partnerships or options for a more advanced role of Academia presented in the case studies as viable alternatives, but securing adequate and continued funding remains the foremost condition (see next point).

Expertise and knowledge sharing on the clinical aspects is currently happening organically but without a structured dedicated national platform. In addition, funding such ATMPs projects also require a large dissemination and sharing of IP and State Aids expertise and the promotion of a culture to advance such academic pathways. The latter aspects are approached more cautiously in Belgium than in the countries where the case studies emerged or in countries with another health care system such as the United Kingdom. On several occasions, the research team sought input from stakeholders on their concrete translational expertise to span clinical research to clinical practice. The team attempted to assess the extent of IP and State Aid expertise within Academia and public funders, as well as the willingness or readiness to utilise socially responsible licensing clauses or other mechanisms increasing the public control over the implementation of publicly funded studies for ATMPs. While some of this expertise exists within the Technology Transfer Offices (TTOs) of universities and within regional authorities, it is not widely shared and often offered only to SME's and enterprises to support regional economic development. Unlike some neighbouring countries (see for instance the State aid transparency of ZonMw and ZIN programmes in the Netherlands here[112] and their service for State aids analysis here),

- **More public and charity funding is needed**

Academia often relies on philanthropic, institutional, and grant funding to develop new ATMP products. In Belgium, academic stakeholders reported that grants are too small to cover the advanced clinical development of ATMPs. Typically, the regional research (via the Flemish Department of

112 All programme calls disclose the complete analysis and contract signed with the beneficiaries of State Aids are published on their website)

Economy, Science and Innovation or FNRS) grants for such projects are around 1 or 2 million euros, covering only preclinical, fundamental studies. Regional innovation grants managed by innovation clusters or support mechanisms from regional economic authorities are higher but directed to the private sector (or public-private partnerships with important private investments). Charity funding is also around one million euros per project. There is currently no federal research or health care budget for clinical trials with ATMPs. Existing figures show these amounts are largely insufficient. , with around 10 million euros needed to reach phase 1 and obtain HE with CAR Ts in Barcelona, and a minimum of 25 to 50 million euros required for a full development to obtain a MA. In the Netherlands, a budget of around 8 million for a phase III study on TILs was considered 'cheap'.

Currently, the best funding option for academia is to focus on activities of ATMPs with a potential commercial interest, set up a company, partner with the industry, and apply for subsidies from regional authorities.

The main areas where more or more structural public – charity funding is needed include:

- Non-clinical studies and animal models (where applicable)
- Manufacturing
- Late stage clinical trials (and translation to the patient)

Experimental research and pre-clinical phase

In the pre-clinical/experimental phase, there are several existing project-based funding sources available, including charities and public authorities at both the European and regional levels. Typically, the budgets required for this phase are smaller than those needed for later stages of development. However, to advance a product to clinical development, the non-clinical phase must meet regulatory requirements. Given the complexity of ATMPs, conventional strategies for robust non-clinical assessment of proof-of-concept, mechanisms of action, and toxicology are not always transferable to ATMPs.[181] A dialogue with regulatory experts may be key to select and perform appropriate non-clinical studies.

The Barcelona case highlighted that approximately 10 million euros are needed to reach a phase 1 clinical study. Funding for preclinical/experimental research is often included in the innovation cluster of government budgets, with a clear focus on innovation and no national consensus on healthcare needs or priorities.

While public funders often focus on job creation and innovation, it is essential to collaborate with healthcare authorities and consider regulatory requirements for later-stage clinical translation. By joining forces and mapping out joint projects, including funding from both innovation and healthcare budgets, there may be an increased potential to deliver high-quality candidates for further clinical development.

Manufacturing facilities are a specific point of attention

From the moment a clinical trial needs to be set up, more financial resources are needed for conducting the trial, and manufacturing the ATMP under GMP. The expertise and facility to manufacture under GMP has been cited as an expensive hurdle.

In the examples studied (e.g. case studies), the GMP certified facilities were financed via academic hospitals own investments (TILs), often accompanied with a public funding (NecstGen funding received from Nationaal Groeifonds, Provincie Zuid-Holland and Universiteit Leiden). The Barcelona CAR-T project received funding from the Spanish ministry of health and the Catalunya government).

At the moment, two Belgain academic hospitals already have manufacturing licenses including GMP facilities for manufacturing cell and gene ATMPs, and more will follow. Experts explained that running and maintaining a cleanroom is resource intensive. Consequently, the academic facilities also have CDMO activities for public and private partners/projects to keep the cleanrooms running. To avoid an overabundance of facilities—each requiring substantial start-up investments, highly skilled staff, and a portfolio of projects/contracts to keep the facility going —the government should incentivise collaboration and the sharing of expertise (on quality control tests, on GMP in general). A direct lump sum for a scala of Academic facilities might not be the preferred route. Funding the projects (foreseeing a reimbursement route for hospital exemption, funding confirmatory clinical

trials) that keep the facility going while generating evidence might be an option (although that is a more product specific option). The early phase clinical trials are often financed via charities and crowdfunding.

Organisation of the manufacturing field was also discussed. If we take the example of manufacturing facilities, we see that the Belgian public authorities already invested in different structures. For instance, Anicells was originally an academic CMO within UA-UZA and is now a separate private CDMO funded by provincial authorities (POM) and by VLAIO (regional economic authorities - EFRO) and for a small part by a private investment fund (Hermes). The platform RegMed XB was funded by another budget directly by the Flemish government (Ministry of Economy). In Wallonia, manufacturing facilities are also partly funded by the Walloon Government under the Walloon Recovery Plan. This funding scheme is implemented by BioWin, the health cluster of Wallonia, and the Research and Technology Development Department of the Public service of Wallonia for the Economy, Employment and Research. The project involves 26 partners and has a budget of €81 million ($88.9M). Around 60% of this comes from public funds, with 40% being privately funded. Important to note is that this funding is primarily aimed to stimulate the economy and the employment. The two academic facilities currently accredited for ATMPs are only accredited for research and at the moment, most industry owned facilities are also only accredited for research.

Academic stakeholders would like to see a collaborative platform to help the field organise itself organically based on the strengths of each facility (e.g.,

UGent with mRNA, UZA with dendritic cells, UZLeuven with AAV vector research, etc.). This could be done via a non-for-profit platform involving all stakeholders (industry and academia) supported by the government (model ATMP Sweden) or it can also be focused on Academia (model GATE).

A current hot topic is the “point-of-care CAR-T manufacturing” though it has many challenges to guarantee that every ATMP manufactured at every site is comparable: the quality control and release steps including the responsibility for these processes, coordination, and IT infrastructure. As a result, there is currently a hybrid approach, with ATMPs being manufactured at facilities located near multiple hospitals (decentralised) but not at the treating facility *per se*.

Support for platform trials for rare diseases, informative for regulators and payers

The discussion highlighted the critical need for structural and consolidated funding throughout the entire ATMP development pathway, particularly for supporting translational efforts and late-stage clinical trials. While a single arm trial might be sufficient for regulators to judge benefit-risk and to conditionally approve ATMPs, such trial design in most cases does not allow HTA bodies and payers to evaluate the added therapeutic benefit. For rare indications, platform trials mandated by the EMA, sponsored by independent parties, and funded by Member States could quickly generate pre-market randomised evidence for regulators and payers on all innovations, including those developed by Academia. Another benefit of this approach is the use of uniform endpoints for different new treatments, which currently poses a challenge in comparing efficacy across ATMPs, for instance, in diffuse large B-cell lymphoma (DLBCL). This platform trial model would likely necessitate discussions with the EMA, FDA, and other regulatory bodies, as clinical development for rare indications increasingly involves international collaboration. The current discussion of funding the infrastructure for platform trials is currently limited to pandemic preparedness (at HERA) and is not yet fully extended to platform trials in rare diseases in Europe, making use of disease registries.

Strengths of the Belgian ATMP field include:

- In addition to research on ATMPs (or biotech in general), there is important clinical expertise within Academia (including ongoing academically sponsored studies - mainly on dendritic and mesenchymal cells - and significant participation in commercial clinical trials.
- Academic and industry expertise in the production of ATMPs (or their components such as viral vectors or RNA) especially in cell & gene therapy
- Very active innovation clusters implementing economic and innovation regional policies (BioWin & Medvia/VLAIO) and fostering public-private partnership in the ATMP field.
- Growing interest for ATMP projects from regional funders in charge of fundamental research like FWO (Flemish Region) and FNRS (French

speaking Community) or Biotechnology institutes (VIB - Vlaamse Instituut voor Biotechnologie in Flanders and WELBIO Walloon Excellence in Life Science and Biotechnology in the French speaking Community)

- An industry that invests in manufacturing facilities and clinical trials

Barriers to Academic Development in Belgium are however present:

- Scattered public funding possibilities (and criteria) due to fragmented research and healthcare competencies, complicating the organisation of an aligned, efficient, and long-term public funding flow for ATMPs project, serving health care policies at national and EU level.
- Scattered expertise amongst the different public funders on regulatory, HTA, IP or other translational aspects.
- Public funding is not sufficient to cover:
  - Early phase and non-clinical trials
  - Large-scale phase 2 or 3 academic clinical studies with
  - Translational services
  - Manufacturing solutions (and improvement thereof)
- Underuse and need for more clarity and guidance on the national interpretation of hospital exemption
- Unclarity on the reimbursement possibilities (e.g. for products under hospital exemption)
- Absence of a common approach of Academia and public funders to implement socially responsible licenses anti-shelving clauses (and incentive to use them)

9.2 Conclusions on the legal and strategic options for academic development of ATMPs in Belgium

ATMPs have proven to be a risky and volatile field, with promising therapies often disappearing during development and market failures even after product launch. Additionally, most ATMPs are extremely expensive, often beyond the reach of payers (or not able to demonstrate added therapeutic benefit for HTA). As a result, ATMPs developed by academia get "lost in translation" despite promising initial outcomes, due to insufficient expected financial returns or unsuitability for market strategies.

To address this issue, the idea of exploring publicly supported models allowing Academia to reach more advanced stages of ATMP development and translation to the patient, has been circulating for some years. Supporting a more complete academic development pathway can have several purposes:

- It can help de-risking ATMPs development and help Academia build efficient partnerships in a later stage (including with industry)
- It can support the Hospital Exemption pathway
- It can support health care policies designed to ensure access to affordable ATMPs

These ideas gained attention during the pandemic in relation to vaccines [19] and are also being considered for ATMPs, following cases of academic development in Spain and the Netherlands [20, 70]

This reports shows that successfully leading an academic pathway depends on various internal and external factors. Internally, these include a.o. the capacities of the academic field, its clinical and regulatory expertise, and its network. Externally, they encompass for instance market characteristics, including the interest of the industry and available public support and funding. However, as these criteria evolve in time, the eligibility of products for academic pathways is a moving target. (ref Coppens) .

Therefore, to manage these factors, Academia needs:

- Significant funding channels to support pre-clinical and advanced clinical development as well as translational expertise, from pre-clinical

to clinical stage and from late-stage trials to patient access (ranging from 20 to 50 million euros)

- High (and easily accessible) expertise in areas such as regulatory affairs, intellectual property, and state aid (both within the Academia and the public funders)
- Structured collaborations between all the stakeholders, especially around clinical aspects, and manufacturing expertise to prevent underuse of costly facilities and dilution of expertise
- Clear regulatory pathways and product rules (and centralised, easily accessible portals for advice in this regard)

Of course, to meet the health-related needs of the patient and society, all these pre-conditions require substantial but also efficient and consistent public funding policies (often combined with charity money). Substantial funding from authorities requires an in-depth analysis of priorities and feasibility, State aid, and additional guarantees that the fruits of publicly-funded research are and remain available and affordable to society (through clauses in contracts.

As highlighted in the report and acknowledged by the European Commission in the impact assessment report and the executive summary accompanying the revision of the general pharmaceutical legislation, several funding channels exist and can be used to support the development of ATMPs. These include:

- Public Funding: This encompasses grants and financial support from public institutions to facilitate research and development of ATMPs.
- State Aid: Specific provisions for state aid to ensure that public funding does not distort competition and complies with EU rules.
- Charitable Funding: Contributions from non-profit organizations and charities to support academic and clinical research in ATMPs.
- Collaborative Funding: Structured collaborations between public and private entities to pool resources and expertise for the development of ATMPs.

APPENDICES

APPENDIX 1. ATMP LANDSCAPE

Appendix 1.1. Overview of ATMPs on the European market since 2009 till September 2024

ATMP product	Indication	details	Regulatory status + reason
Tissue engineered therapy			
Chondrocelect®	cartilage disease in knee	**ex vivo** expanded autologous cartilage cells expressing specific marker proteins	Withdrawn at the request of the marketing-authorisation holder
Holoclar®	moderate to severe limbal stem-cell deficiency caused by burns, including chemical burns, to the eyes	**ex vivo** expanded autologous human corneal epithelial cells containing stem cells	Conditional MA + orphan medicine
Matrix-induced autologous chondrocyte implantation (MACI	cartilage disease in knee	**ex vivo** expanded autologous cartilage cells	MA expired holder's decision not to pursue the renewal of the marketing authorisation
Spherox®	cartilage disease in knee	**Ex vivo** spheroids of human autologous matrix-associated chondrocytes	MA
Gene therapy			
Glybera®	lipoprotein lipase deficiency and severe or multiple attacks of pancreatitis	**In vivo** gene therapy: viral vector (AAV) delivers an intact copy of the human lipoprotein lipase (LPL) gene to muscle cells	MA expired following the marketing-authorisation holder's decision not to apply for a renewal
Imlygic®	Unresectable melanoma	**In vivo** gene therapy: oncolytic herpes simplex virus has been modified so it can infect and multiply inside melanoma cells	MA
Strimvelis®	Rare inherited immune disorder ADA-SCID for whom bone marrow transplant is not possible	**Ex vivo** Autologous CD34+ stem cells in which the functioning human ADA cDNA sequence is incorporated via a retroviral vector	Orphan medicine + under additional monitoring
Yescarta®	Refractory B-cell lymphoma	**Ex vivo** Autologous T cells modified via viral vector (retrovirus) to express 'chimere antigenreceptor (CAR-T) that can attach to CD19 protein	Orphan medicine + under additional monitoring
Kymriah®	Refractory B-cell lymphoma	**Ex vivo** Autologous T cells modified via viral vector (lentivirus) to express 'chimere antigenreceptor (CAR-T) that can attach to CD19 protein	Orphan medicine + under additional monitoring
Luxturna®	inherited retinal dystrophy	**In vivo** gene therapy: viral vector (AAV) that contains normal copies of the RPE65 gene	Orphan medicine + under additional monitoring

Zynteglo®	Inherited beta thalassaemia	**Ex vivo** autologous CD34+ stem cells in which the functioning beta-globin gene via viral vector (lentivirus)	withdrawn at the request of the marketing-authorisation holder
Zolgensma®	Inherited spinal muscular atrophy defect in a SMN1 gene	**In vivo** gene therapy: viral vector (AAV) that contains normal copies of functional SMN1 gene	Conditional MA + Orphan medicine + additional monitoring
Libmeldy®	children with metachromatic leukodystrophy with the ARSA gene	**Ex vivo** Autologous CD34+ stem cells in which the functioning ARSA gene is incorporated via a viral vector (lentivirus)	Orphan medicine + additional monitoring
Tecartus®	B cell lymphoma (acute lymphoblastic leukaemia or mantle cell lymphoma)	**Ex vivo** Autologous T cells modified via viral vector (retrovirus) to express 'chimere antigenreceptor (CAR-T) that can attach to CD19 protein	Conditional MA (Dec 2020) + Orphan medicine + additional monitoring
Skysona®	Early cerebral adrenoleukodystrophy with mutation in the ABCD1 gene and when a Hematopoetic stem cell transplantation is not possible	**Ex vivo** autologous CD34+ stem cells in which the functioning ALDP gene is inserted via lentivirus	withdrawn at the request of the marketing-authorisation holder
Abecma®	Relapsed or refractory multiple myeloma	**Ex vivo** Autologous T cells modified with viral vector (lentivirus) to express 'chimere antigeenreceptor (CAR-T) that can attach to B cell maturation antigen	Conditional MA (Aug 2021) + orphan medicine + additional monitoring
Breyanzi®	Relapsed or refractory B-cell lymphoma	**Ex vivo** Autologous CD4+ and CD8+ T cells genetically modified via viral vector (lentivirus) to express chimeric antigen receptor (CAR-T) that can attach to CD19 protein	MA + additional monitoring
Carvykti®	Relapsed or refractory multiple myeloma	**Ex vivo** Autologous T cells modified via viral vector (lentivirus) to express 'chimere antigeenreceptor (CAR-T) that can attach to B cell maturation antigen	Conditional MA (May 2022) + orphan medicine + additional monitoring
Upstaza®	Genetically confirmed severe aromatic L-amino acid decarboxylase (AADC) deficiency	**In vivo** gene therapy, viral vector (AAV) that contains normal copies of functional AADC gene	MA under exceptional circumstances + orphan medicine + additional monitoring
Roctavian®	severe haemophilia A	**In vivo** gene therapy, viral vector (AAV5) to contain the gene for factor VIII	Conditional MA (Aug 2022) + orphan medicine + additional monitoring
Hemgenix®	Severe haemophilia B	**In vivo** gene therapy, viral vector (AAV5) to contain the gene for factor IX	Conditional MA (feb 2023) + orphan medicine + additional monitoring
Casgevy®	beta thalassaemia and sickle cell disease	**Ex vivo** Autologous stem cells, edited (by CRISPR/Cas9 technology) to produce more hemoglobine	Conditional MA (feb 2024) + Orphan medicine +additional monitoring

Beqvez® (previously Durveqtix)	severe or moderately severe haemophilia B	**In vivo** gene therapy, viral vector (AAV rh74) to contain the gene for factor IX	Conditional MA (July 2024) + PRIME status + additional monitoring
Somatic Cell therapy			
Provenge®	asymptomatic or minimally symptomatic metastatic (nonvisceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated	Ex vivo autologous peripheral-blood antigen presenting cells (dendritic cells) including a minimum of 50 million autologous CD54+ cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor	withdrawn at the request of the marketing authorisation holder.
Zalmoxis®	adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies	Ex vivo allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	withdrawn at the request of the marketing authorisation holder
Alofisel®	complex anal fistulas in adults with Crohn's disease when a conventional or biological medicine has not worked well enough	Ex vivo Allogeneic **mesenchymal stem cells** from the fat tissue, selected and cultivated in the laboratory to increase their number	Orphan medicine + additional monitoring
Ebvallo®	Relapsed or refractory blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease	Ex vivo Allogeneic T cells, are first mixed with B cells from the same donor which have been infected with the Epstein-Barr virus, so that the T cells learn to recognise infected B cells as 'foreign'. The T cells are then grown in the laboratory to increase their numbers	MA under exceptional circumstances + orphan medicine + additional monitoring

Source: Info retrieved mainly from EMA

Appendix 1.2. Clinical trials activity with ATMPs in Belgium

ATMP trial applications to the FAMHP in timeframe from 2021 till end 2023

Study identification	Sponsor	ATMP	Indication	Study details
Non commercial sponsor				
ADDICT-pedGLIO Eudract 2020-004125-23 **NCT04911621**	Antwerp University Hospital (UZA)	Somatic cell therapy: Autologous Wilms' tumor 1 (WT1) mRNA-electroporated **dendritic cells**	Brain (stem) tumors (High-grade Glioma or Diffuse Intrinsic Pontine Glioma)	Single centre **phase I/II study** in 10 pediatric patients – arm A with newly diagnosed and arm B with pre-treated patients (recruit UZA)
PERSOMED *Eudract 2021-003303-17*		*Autologous monocytic derived **dendritic cells** electroporated with two types of mRNA (Tetramix via plasmid DNA and Neoantigen via a synthetic DNA)*	*Metastatic microsatellite stable colorectal cancer*	*Did not start Persomed consortium did not secure investment* *Phase I*
CARTITUDE-6 Eudract 2021-003284-10 NCT05257083	European Myeloma Network (EMN), The Netherlands	Gene therapy (CART-T): Carvykti®	Newly Diagnosed Multiple Myeloma who are Transplant Eligible	Phase III randomised trial (recruit:UZA, UZGent, UZLeuven)
Immuno-MESODEC Eudract 2021-003229-31 NCT05765084	Antwerp University Hospital (UZA)	Somatic cell therapy: Autologous WT1 mRNA loaded **dendritic cells**	Pulmonary membrane cancer - Malignant pleural mesothelioma	Phase I/II multicenter single arm **t**rial in 15 adult patients in addition to first line therapy (recruit: Maria Middelares, VITAZ St Niklaas, UZA)
MS-tolDC_Phase2-RESTORE Eudract - 2022-003465-38	Antwerp University Hospital (UZA) & Hospital Universitari Germans Trias I Pujol	Somatic cell therapy: Autologous myelin peptide-loaded tolerogenic **dendritic cells**	Multiple sclerosis	**Phase II** study in 72 patients is to determine whether intradermal (in Belgium) or intranodal (in Spain) injection of tolDC is effective and safe
Eudract 2022-003833-21 **NCT03901235**	CHU of Liège	Somatic cell therapy: Allogenic bone-marrow derived **mesenchymal stromal cells**	Crohn's Disease	Single centre, single arm, **phase I/II** in 50 adult patients (recruit CHU Liège)

Study identification	Sponsor	ATMP	Indication	Study details
IL15-TransDC Eudract : 2020-004124-42 NCT05964361	Antwerp University Hospital (UZA)	Somatic cell therapy: Autologous **dendritic cells** electroporated with mRNA encoding WT1, IL15 and IL15 receptor alpha subunit	refractory or advanced solid tumors of the esophagus, liver, pancreas and ovaries	Single centre, First-in-human – **phase I i**n 10 patients (recruit UZA)
Commercial sponsor				
EBVision **2020-000177-25 (new umber: 2024-516623-14-00)** **NCT04554914**	Atara Biotherapeutics, USA	Somatic cell therapy: Ebvallo®	Epstein-Barr Virus-associated Diseases post-stem cell transplant	Phase II Open-label, Single-arm, Multicentric, in 190 adults (recruit: AZ ST Jan Brugge, AZDelta, Hopital des Enfants Reine Fabiola)
ZUMA-4 2015-005010-30 NCT02625480	Kite pharma (Gilead)	Gene therapy (CAR-T): Tecartus®	Pediatric and Adolescent with Relapsed/Refractory B precursor Acute Lymphoblastic Leukemia	Phase I/II Multi-Center Study in 31 children (recruiting in UZGent)
ELARA **2023-508127-13-00 (before: 2017-004385-94)** **NCT03568461**	Novartis, Switzerland	Gene therapy (CAR-T): Kymriah®	refractory or relapsed follicular lymphoma	Phase II, single arm, multicenter open label in 98 (recruitment ended in 2020)
PAVO **2023-508128-37-00 (before:2014-001673-14)** **NCT02445222**	Novartis, Switzerland	Gene therapy (CAR-T):e.g. Kymriah®	Exposed to Lentiviral-Based CAR T-CellTherapy	Phase III follow-up (recruiting UZGent)
2022-501346-30-00	Celgene Corp (Bristol Myers Squibb°	Gene therapy (CAR-T): Abecma®	Multiple Myeloma	Phase III randomised open label (recruiting: UZbrussel, Insitut Jules bordet, cliniques universitaires St Luc)
CARTIDUDE-5 2021-001242-35 NCT04923893	Janssen-Cilag	Gene therapy (CAR-T): Carvykti®	newly diagnosed Multiple Myeloma (no option for stem cell transplant)	phase III randomised, open label multicentric trial in 650 adults (recruit ended UZGent, AZ St Jan Brugge, UZA)
2023-505530-10-00 (before: 2020-005521-84) **NCT05201781**	Janssen - Cilag	Gene therapy (CAR-T): Carvykti®	all those received Carvykti	Phase IV (follow-up study)

Study identification	Sponsor	ATMP	Indication	Study details
SMART 2020-005995-37 NCT04851873	Novartis, Switzerland	Gene therapy: Zolgensma®	Spinal Muscular Atrophy	Phase III, open-label, single arm, multi-center study in 24 children
2021-006781-21 **NCT05335876**	Novartis, Switzerland	Gene therapy: Zolgensma®	Spinal Muscular Atrophy	Phase IV (follow-up study)
STRENGTH 2021-006709-31 NCT05386680	Novartis, Switzerland	Gene therapy: Zolgensma®	Spinal Muscular Atrophy	Phase IIIb, Open-label, Multi-center
EMBARK 2019-003374-91 NCT05096221	Sarepta Therapeutics, USA	Gene therapy: Elevidys®	Duchenne Muscular Dystrophy	Phase III Multinational, Randomised, Double-Blind, Placebo-Controlled (recruit UZGent)
ENVOL 2022-000691-19 NCT06128564	F. Hoffmann-La Roche, Switzerland	Gene therapy: Elevidys®	Children (<4y) with Duchenne Muscular Dystrophy	Phase II, multicentre, open label single arm in 21 children (recruit Centre Hospitalier Regional de la Citadelle)
ENVISION 2020-002372-13 NCT05881408	Sarepta Therapeutics	Gene therapy: Elevidys®	Duchenne Muscular Dystrophy	Phase III, Multinational, Randomised, Double-Blind, Placebo-Controlled in 148 adults (recruiting UZGent)
2023-505043-39-00 **NCT05967351**	Sarepta Therapeutics	Gene therapy: Elevidys®	All those receiving Elevidys®	Phase III, Multinational, Long-Term Follow-Up (UZGent)
2023-503765-37-00	CSL Behring	Gene therapy: Hemgenix®	Hemophilia B	Phase II/III follow-up study (recruitment not started (UZLeuven, Cliniques Universitaires St Luc)
2022-503140-41-00 **NCT05727904**	Iovance Biotherapeutics	Somatic cell therapy: autologous TILs - *Amtagvi® (registered by FDA, introduced at EMA)*	untreated, unresectable or metastatic melanoma	Phase 3, multicenter, randomised, open-label,recruiting (UZBrussel, CHU Liège, Cliniques universitaires St Luc)

Study identification	Sponsor	ATMP	Indication	Study details
DALY 2-EU 2023-506270-13-00 (before: 2020-003908-14) NCT04844866	Miltenyi Biomedicine GmbH	Gene therapy (CAR-T): Zamtocabtagene Autoleucel cd20-cd19 CART	relapsed/refractory diffuse large B-cell lymphoma	Phase II randomised, multi-centre, open-label recruiting (UZLeuven, CHU Dinant-Godinne-Namur, Institut Jules Bordet)
2023-507820-22-00 **NCT06220201**	Celgene Corp (Bristol Myers Squibb)	Gene therapy (CAR-T): CD19 CART	Multiple sclerosis	Phase I Study (recruiting UZGent)
2023-503823-24-01	Celgene Corp (Bristol Myers Squibb)	Gene therapy (CAR-T): CD19 CART	Systemic Lupus Erythematosus	Phase 1 study (recruitment 1 BE site: UZLeuven)
EXPAND **2023-503830-27-00** **NCT05714345**	Allogene Therapeutics Inc	Gene therapy (CAR-T): allogenic CAR-T	Relapsed/Refractory Large B-Cell Lymphoma	Phase II, randomised, open label, (recruiting UZleuven, UZbrussel, ZNA, Cliniques universitaires St Luc)
KEYNOTE-B79 **2020-005132-30** **NCT04991948**	Celyad Oncology	Gene therapy CAR-T: allogeneic CAR T	Unresectable metastatic colorectal cancer	Phase 1b trial, open label (recruit: UZA, UZLeuven, UZGent)
PAPILIO-1 **2022-500782-27-00**	Galapagos/cellpoint	Gene therapy (CAR-T): Point of Care manufactured	Multipel Myeloma	Phase 1/2, open-label, multi-center (recruiting : UZA and CHU Liège, UZ Leuven; Cliniques Universitaires Saint-Luc)
ATALANTA-1 **2022-502661-23-00** **(before: 2021-003272-13)**	Galapagos/cellpoint	Gene therapy (CAR-T): Point of Care manufactured	relapsed/refractory B-cell non-Hodgkin lymphoma	Phase I/II (recruitment stopped (Uzleuven, CHU Liège, Cliniques universitaires StLuc, UZA)
EUPLAGIA-1 **2022-501686-47-00**	Galapagos/cellpoint	Gene therapy (CAR-T): Point of Care manufactured	lymphocytic leukemia	Phase I/II (recruitment CHU Liège)
LIBERATE **2021-001379-18** **NCT05234190**	Quell Therapeutics Limited, UK	Gene therapy: autologous CARTreg targeting HLA-A2	mismatch Liver Transplant Patients	Phase I/II study, FIH, single-arm, open-label, multi-centre, in 33 adults (recruiting Cliniques Universitaires Saint-Luc, Erasme, UZLeuven)
STEADFAST Long Term **2022-002440-40** **NCT05987527**	Sangamo Therapeutics, France	Gene therapy: autologous CARTreg targeting HLA-A2	Kidney transplant rejection, end stage renal disease	Follow-up study of the 21 patients in the FIH (recruitment UZLeuven)

Study identification	Sponsor	ATMP	Indication	Study details
2023-508524-35-00 (before: 2019-003908-13) NCT04625205	BioNtech US	Gene therapy: autologous T cells targeted against neoantigens	advanced or metastatic melanoma	Phase 1 study (recruitment UZBrussel)
PROCLAIM 2019-003159-12 NCT04408625	Prevail Therapeutics (Eli lilly)	Gene therapy: AAV 9 vector expressing codon-optimized human GRN gene	Fronto-Temporal Dementia with Progranulin Mutation	Phase 1/2 Study in 15 adults (recruitment UZLeuven of 2 patients)
ASPIRE-FTD 2022-002568-62 NCT06064890	AviadoBio Ltd, UK	Gene therapy: Recombinant AAV-9 vector expressing the human progranulin protein	frontotemporal dementia (FTD) with progranulin (GRN) mutations	Phase 1/2 Open-Label, Ascending Dose, Multicenter (not yet in BE)
2020-002255-37 NCT04794101	Janssen-Cilag International	Gene therapy: adeno-associated virus vector with a serotype 5 capsid human rhodopsin kinase promoter	X-linked Retinitis Pigmentosa	Phase III Follow-up Study (recruit Uzgent)
2020-002873-88 NCT04671433	Janssen-Cilag International	Gene therapy: adeno-associated virus vector with a serotype 5 capsid human rhodopsin kinase promoter	X-linked Retinitis Pigmentosa	Phase III Randomized, Controlled Study (recruit UZGent)
2022-500746-16-00 NCT05811351	Janssen - Cilag International	Gene therapy: recombinant AAV serotype 2 that expresses a soluble form of CD59	Age-related Macular Degeneration (AMD)	Phase IIb, Randomized, Double-masked, Multicenter, Dose-ranging, Sham-controlled (recruit: UZGent, Uzleuven, CHULiège, ZOL)
2022-503112-17-00	Sarepta Therapeutics Inc	Gene therapy: AAV with full-length human SGCB transgene	Limb-girdle muscular dystrophy	Phase 3 Multinational, Open-label (recruiting UZGent, UZLeuven)
2021-002823-40 NCT04041310	Nouscom S.r.l., Italy	Gene therapy: in vivo viral vector vaccine targeting 209 neoantigens (NOUS-209)	Microsatellite Unstable Solid Tumors	Phase I/II, multicenter, open-label, recruiting (Cliniques Universitaires Saint-Luc, CH de l'Ardenne, CHU Liège)
2022-001282-12 NCT05693558	Novadip Biosciences	Tissue engineered: Autologous osteogenic Cells	Congenital pseudarthrosis of the tibia in pediatric	Phase I (BE recruitment 1 site: Cliniques Universitaires Saint-Luc)

Study identification	Sponsor	ATMP	Indication	Study details
2021-003273-66 **NCT04612413**	Enlivex Therapeutics R&D, Israel	Somatic cell therapy: Allogeneic peripheral blood mononuclear cells induced to apoptotic state Allocetra	Organ Failure in Adult Sepsis Patients	Phase II, Multi-Center, Randomized, Placebo-Controlled in 160 patients (recruit: St Pierre Bruxelle, St Luc Bruxelles, CHU de Charleroi, ZOL)
2022-501423-25-00 **NCT05938387**	Curevac AG	Gene therapy: mRNA encoding a single fusion protein comprising 8 epitopes from tumor associated antigens	Glioblastoma or astrocytoma	Phase 1/2 FIH in 16 patients (recruiting in UZBrussel, CHULiège)
2022-502404-73-00	Genentech Inc	Gene therapy: mRNA encoding neoantigens	Pancreatic Ductal Adenocarcinoma	Phase II, Open-Label, Multicenter, Randomized Study(recruiting: UZLueven, UZA, UZGent, AZMariamiddelares, Erasme)
INTerpath-001 **2023-503652-27-00** **NCT05933577**	Merck Sharp & Dohme LLC	Gene therapy: mRNA individualised with neoantigens	Stage II-IV Melanoma	Phase III, Randomized, Double-blind, Placebo- and Active-Comparator-Controlled (recruiting in UZLeuven, UZBrussel, UZGent, ZOL, Institut Bordet, AZGroeningen)
INTerpath-002 **2023-504923-20-00**	Merck Sharp & Dohme LLC	Gene therapy: mRNA coding for 34 neoantigens	Non-small Cell Lung Cancer	Phase III, Randomized, Double-blind, Placebo- and Active-Comparator (recruiting: UZA, Vitaz, OLV Aalst, CHY Dinant-Godinne-UCL Namur)
2021-001081-38 NCT05526066	Arcturus Therapeutics, USA	Gene therapy: mRNA encoding modified Ornithine transcarbamylase in a lipid nanoparticle	Ornithine Transcarbamylase Deficiency	Phase II randomised double blind, placebo controlled recruiting (recruit Cliniques universitaires Saint Luc)
TIGER 2021-004277-31	eTheRNA immunotherapies NV (Horizon 2020 grant)	Gene therapy: mRNA encoding human papilloma virus (HPV)16 E6	Recurrent or metastatic HPV16-positive tumors	Phase I/IIa open label, First-in-human multicentric (in BE 1 site: Saint-Luc university clinic)

Study identification	Sponsor	ATMP	Indication	Study details
AHEAD-MERIT 2020-001400-41 NCT04534205	BioNTech - Germany	Gene therapy: mRNA coding for HPV-16 encapsulated in liposomes	Head and Neck Squamous Cell Carcinoma (HNSCC) which is positive for human papilloma virus 16 (HPV16+) and expresses PD-L	Phase II randomised, open-label
2022-000763-45	AlloVir, USA	Somatic cell therapy: Viralym-M (allogeneic multivirus specific T cells		Phase IV (follow-up study)
2020-000722-26 **NCT04390113**	AlloVir, USA	Somatic cell therapy: Viralym-M (allogeneic multivirus specific T cells	Virus-Associated Hemorrhagic Cystitis After Allogeneic Hematopoietic Cell Transplantation	Terminated (Sponsor decision dec 23- no effect) Phase III Multicenter, Double-Blind, Placebo-Controlled Trial
2021-005105-27 **NCT05305040**	AlloVir, USA	Somatic cell therapy: Viralym-M (allogeneic multivirus specific T cells	Post-Allogeneic Hematopoietic Cell Transplant	Terminated (Sponsor decision dec 23- no effect) Phase II/III, Multicenter, Randomised, Double-Blind, Placebo-Controlled
REGEN-016 **2022-000289-16** **NCT05286853**	ProKidney, USA	Tissue engineered: Renal Autologous Cell Therapy (REACT) - rilparencel	Type 2 Diabetes and chronic kidney disease	Terminated (Sponsor decision sept '24 to focus more on phase III study in US) phase III randomised controlled
IMAG1NE 2021-004158-49 NCT05430555	T-Knife GmbH	Autologous T cells transduced with retroviral vector coding for a chimere MAGE-A1 TCRs (TK-8001)	HLA-A*02:01 genotype and advanced-stage/metastatic, MAGE-A1 + solid tumors	Terminated (Sponsor decision-feb '24) Phase I/II, First-in-human, open-label
2022-500251-22-00 **(before: 2017-003989-27)** **NCT03343756**	Cellaïon	Somatic cell therapy: HepaStem	Acute on Chronic Liver Failure	Terminated by sponsor (May '24 bankruptcy) Follow-up study
DHELIVER **2022-500252-28-00** **(before: 2019-003051-11)** **NCT04229901**	Cellaïon	Somatic cell therapy: HepaStem	Acute on Chronic Liver Failure	Terminated by sponsor (May '24 bankruptcy) Phase IIb Randomised, placebo-controlled, double blind, multi-centre

Study identification	Sponsor	ATMP	Indication	Study details
FORTIFY 2023-503457-35-00 NCT05165433	Akamis Bio Limited, UK	Gene therapy: AAV with tumourselective antiCD40	Metastatic or advanced epithelial tumours	Terminated recruitment in EU (sponsor decision dec 23) phase 1a/1b, multicentre, open-label (recruitment in 1 BE site: Cliniques universitaires St Luc)
NEBULA **2023-503525-19-00** **NCT05043714**	Akamis Bio Limited	Gene therapy: AAV expressing tumour selective and transgene	Metastatic or advanced epithelial tumours	Terminated recruitment in EU (sponsor decision dec 23) phase 1a/1b, multicentre, open-label (recruitment in 1 BE site: Cliniques universitaires St Luc)
2023-504422-19-00	Galapagos	Gene therapy: CAR-T	Systemic lupus erythematosus	Terminated (sponsor decision feb '24) Phase 1b study
2023-504786-23-00 **NCT05668741**	Vertex Pharmaceuticals	Gene therapy: mRNA with CFTR gene in lipid nanoparticle	Cystic Fibrosis and a CFTR Genotype	Temporary halt (July '24) phase I/II
Trial numbers listed by FAMHP but already withdrawn				
2017-002460-41				Withdrawn - Phase II
2022-002643-21				Withdrawn - Phase I
2022-004109-64				Withdrawn - Phase I
2023-503823-24-00	Celgene		Systemic Lupus Erythematosus	Withdrawn -Phase I
2023-506180-34-00				Withdrawn -Phase II
2023-506273-36-00	Bristol Myers Squibb	Gene therapy (CAR-T): Breyanzi®	Chronic lymphocytic leukemia (CLL), or small cell lymphoma (Small Lymphocytic Lymphoma (SLL)	Withdrawn - Phase III

*Source: *FAMHP referred to the public data of the clinical trial applications on ATMPs between 2021 and 2023 inclusive. The info on the type of ATMP, the status, etc. was based on own search in clinicaltrials.gov and relevant websites*

Appendix 1.3. Clinical trial pathway of authorised ATMPs, implication of Academia

Authorised ATMP	Early phase clinical trial	Pivotal registration trial	Commercial manufacturer
Tisagenlecluecel **Kymriah®**	University of Pennsylvania and Children's hospital of Philadelphia	Novartis	Novartis
Axicabtagene ciloleucel **Yescarta®**	National Cancer Institute (USA national institute of health)	Kite pharma	Gilead
Lisocabtagene maraleucel **Breyanzi®**	Seattle Children's hospital and Fred Hutchinson Cancer centre	Juno therapeutics	Bristol Myers Squibb
brexucabtagene autoleucel **Tecartus®**	National Cancer Institute (USA national institute of health)	Kite Pharma	Gilead
idecabtagene vicleucel **Abecma®**	Bluebird bio	Celgene Corporation	Bristol Myers Squibb
Ciltacabtagene autoleucel **Carvykti®**	Legend Biotech	Janssen Biotech	Janssen Biotech
Exagamglogene autotemcel **Casgevy®**		CRISPR Therapeutics and Vertex Pharmaceuticals	Vertex Pharmaceuticals
Atidarsagene autotemcel **Libmeldy®**	San Raffaele Telethon Institute for Gene Therapy	GlaxosmithKline	Orchard therapeutics
Voretigene neparvovec **Luxturna®**	Children's Hospital of Philadelphia	Spark Therapeutics (spinoff of university)	Spark Therapeutics (subsidiary of Roche)
Etranacogene dezaparvovec **Hemgenix®**	UniQure	CSL Behring GmbH	CSL Behring GmbH
Strimvelis®	San Raffaele Telethon Institute for Gene Therapy	GlaxosmithKline	GlaxosmithKline - Orchard Therapeutics - Telethon
Holoclar®	University of Modena and Reggio Emilia	Holostem (university spinoff)	Holostem

Onasemnogene abeparvovec **Zolgensma®**	AveXis (spinoff of nationwide children's hospital) based on preclinical research in INSERM France and University of Sheffield UK	AveXis	Novartis
Roctavian®	University College London and St Jude Children's Research Hospital	Biomarin	Biomarin
Spherox®	CO.DON AG		
Betibeglogene autotemcel **Zynteglo® (market authorisation withdrawn in EU due to commercial reasons)**	Bluebird bio	Bluebird bio	Bluebird bio
Elivaldogene autotemcel **Skysona® (market authorisation withdrawn in EU due to commercial reasons)**	Hospital Saint-Vincent de Paul, Paris	Bluebird bio	Bluebird bio

Appendix 1.4. Design features of pivotal clinical trials for the approved advanced therapy medicinal products in the EU

Trade name	Pivotal study	Non-randomised	Non-controlled	Historical control	Intermediate endpoints	Population/no. patients (enrolled)	Of
Gene therapy medicinal products							
Kymriah (ALL)	Phase II	X	X	x	X	Children/92	
Kymriah (DLBCL)	Phase II	X	X	X	X	Adults/147	
Yescarta	Phase I/II	X	X	X	X	Adults/111	
Tecartus	Phase II	X	X			Adults/105	
Imlygic	Phase III				X	Adults/437	
Glybera	3 Phase II/III	X	X		X	Adults/45	
Strimvelis	Phase I/II	X	X	X		Children/12	
Luxturna	Phase III				X	Children and adults/31	
Zynteglo	Phase I/II and Phase III	X	X		X	Children and adults/41	

Zolgensma	Phase III	X	X	X		Children/22
Libmeldy	Phase I/II	X	X		X	Children/22
Skysona	Phase II/III	X		X		Children/32[a]
Abecma	Phase II	X	X	x	X	Adults/140
Somatic cell therapy medicinal products						
Provenge	Phase III					Adults/512
Zalmoxis	Phase I/II and Phase III	X (Phase I/II)		X (Phase I/II)	X	Adults/71
Alofisel	Phase III					Adults/212
Tissue-engineered medicinal products						
Chondrocelect	Phase III			X		Adults/138
MACI	Phase III			X		Adults/144
Spherox	Phase II and Phase III		X (Phase II)	X		Adults/177
Holoclar	Observational retrospective	X	X			Adults/104[a]

ALL, refractory B cell acute lymphoblastic leukemia; DLBCL, diffuse large B cell lymphoma.
[a]Number of patients in the intervention arm.

Source: Iglesias-Lopez C, Agustí A, Vallano A, Obach M. Current landscape of clinical development and approval of advanced therapies. Mol Ther Methods Clin Dev. 2021 Nov 11;23:606-618. doi: 10.1016/j.omtm.2021.11.003. PMID: 34901306; PMCID: PMC8626628.

APPENDIX 2. STATE AIDS DECISION-THREE

Step 1: Establish if the aid measure qualifies as state aid based on four cumulative conditions

1. Aid recipient qualifies as undertaking, i.e., entity engages in an economic activity.

- Consider the Research & Development & Innovation Framework – research organisation (or infrastructures) are not considered an undertaking if the entity's primary goal is to independently conduct fundamental research, industrial research* or experimental development** or to (widely disseminate the results of such activities by way of teaching, publication or knowledge transfer***. (para. 18-22)
  - * including pre-clinical tests, both in vitro and animal testing
  - ** including phase I, II and III clinical trials
  - *** all profits from those activities must be reinvested in the primary activities of the research organisation or infrastructure
- Consider if the funding is provided to a Service of General Economic Interest and if the "Altmark" criteria are fulfilled in order to argue that state aid rules are excluded.

2. Aid confers a selective advantage on the recipient, i.e., recipient receives economic benefit which it would not have received under "normal market conditions"; this benefit puts the company in a more advantageous position vis-à-vis non-receiving undertakings.

- Advantages may be conferred directly (to the receiving entity) or indirectly* (to an entity at a subsequent levels of activity)
  - * following Research & Development & Innovation Framework no indirect state aid is passed on from a research organisation to a subsequent undertaking if (i) research organisation receives an "adequate compensation" for its services in the context of a contract research or (ii) if, in collaboration projects between undertakings and research organisations or infrastructures, the participating undertakings did not receive support via "favourable collaboration conditions".

3. Aid threatens to distort competition/ affect trade between member states.

4. Aid measure must have state origin, i.e., it should be imputable to the state and provided by (in)directly using state resources.

If one of the state aid criteria is <u>not</u> satisfied, the support measure is not considered state aid and is not subjected to compatibility analysis.

If <u>all</u> four conditions are met, the support measure qualifies as state aid and is subjected to a compatibility analysis.

Step 2: Some state aid measures are deemed compatible with the internal market and thus do not need to be notified to the European Commission. However, other state aid measures must be submitted to the European Commission for a compatibility assessment.

Mandatory notification to the European Commission

Non-exempted aid should be notified to European Commission before implementation

No notification to the European Commission

• European Commission performs compatibility test balancing the positive effect of the aid measure – reaching an objective of common interest – against its potentially negative side effects – possible distortions of trade and competition –. • The compatibility of SGEI aid may be analysed according to the SGEI Framework. • The compatibility of non-exempted aid for research, development and innovation may be analysed on the basis of the Research & Development & Innovation Framework. (para.36 et seq.) • Aid for other parts of the project may be analysed following Article 107 (3) (c)TFEU, stating certain aid measures might be compatible with the single market if they facilitate the growth of specific economic activities.	• Check if the aid concerns SGEI aid and is exempt from the notification obligations by the SGEI Decision. • Check if aid is exempted from notification obligation by General Block Exemption Regulation. • Check if aid is exempted from notification obligation following the Framework for Services of General Economic Interest.
Non-exempted state aid implemented without prior notification is "illegal". Commission may investigate and check compatibility on its behalf. If incompatible, aid must be recovered unless recovery violates EU law principles.	

APPENDIX 3. COMPASSIONATE USE AND SPECIAL NEEDS FOR ATMPS

In addition to Marketing Authorisation (MA), Hospital Exemption (HE), and Clinical Trials (CT), some Member States use national exemptions to permit access to ATMPs under specific conditions. This section provides general information on these national exemptions.

Appendix 3.1.1. Special needs or named patient use (NPU)

Article 5 (1) of Directive 2001/83/EC provides that "*a Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility*".

This exception covers the supply of an unauthorised medicines (or authorised medicines from a different country) for individual patients in response to requests by doctors on behalf of specific, or "named", patients and is limited to the requested named patient or patients only. Unlike Compassionate Use Programmes, NPUs are entirely initiated by doctors, addressing their request directly to the company to treat an individual patient under the doctor's direct responsibility. This programme covers any access to a non-authorised medicine at any time of its development provided it is not made available under a cohort approach.

In addition, NPU can also refer to a medicine for a specific patient or patients that is not (yet) authorised and available to them in their own country. Such medicine should or must (depending on legislation) be authorised in at least one country, from which it can be imported into the patient's country under an NPU. These may be medicines that are:

- Authorised but not yet available to be prescribed in the patient's country
- Authorised and available in one country but not authorised and available in the patient's country
- Discontinued in the patient's country but not in another country
- In shortage in the patient's country but not in another country

'Named Patient use' can only be used when there is no other alternative ('special needs'). In accordance with the case law of the CJEU, national exceptions under article 5 must be justified on the specific ***clinical*** needs of the patient and cannot be driven by economic motives only.[113]

This exemption is implemented at national level with some variations within the Member States.

Under Belgian law, article 6quater, §1, 4° of the Medicines Act and Article 105 of the Royal Decree of 14 December 2006 allow Belgian pharmacists to import and deliver medicines not authorised in Belgium (but authorised in the country of origin) on the basis of such individual prescription. In principle, in line with the CJEU case law, these special needs exception should only apply to industrial products that fall under the scope of the Directive (and thus not to preparations.[114]

Although some countries (UK before Brexit) have chosen to apply this "special needs" framework (which in principle covers products falling within the scope of Directive 2001/83/EC, i.e. "industrial" and "on the market") also

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113 CJEU, C-619/18, Judgment of 24.06.2019, European Commission v Republic of Poland.

114 See advice of the Belgian Council of State confirming this http://www.raadvst-consetat.be/dbx/avis/56080.pdf#search=%22besoins%20sp%C3%A9ciaux%22

to ATMPs[115], this interpretation is not obvious. Indeed, the lex specialis status of the ATMP framework allows this position to be questioned.

Appendix 3.1.2. Compassionate use (CU)

Compassionate use in Europe is a treatment option that allows the use of an unauthorised medicine (falling into the scope of the Directive 2001/83) under strict conditions. It applies to products in development and can be made available to patients who have a disease with no satisfactory authorised therapies and cannot enter clinical trials.

CU is available only for medicines that are under development -which are the subject of an application for marketing authorisation or for which clinical trials are ongoing- outside the scope of a clinical trial in individual patients who suffer from a chronic illness or a seriously debilitating or life-threatening disease and do not have the possibility to participate in a pending trial (if any). Compassionate use programmes are established by Article 83 of *Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency* but coordinated and implemented by Member States. The Belgian compassionate use program is governed by Article 6quater, §1, 2° of the Medicines Act and Articles 106 and 107 of the Royal Decree of 14 December 2006. It should be distinguished from the Belgian medical need program, which concerns the off-label use of *authorised* medicines.

In Belgium such cohort approaches are embedded in the law on medicinal products of the 25th of March 1964 that accepts 2 situations where medicinal products that are not authorised in Belgium or only authorised in different indications can be provided to a patient:

- **Compassionate Use Program (CUP)** for the use of an unlicensed product for a **group of patients** with a life threatening disease, a chronic disease or a seriously debilitating disease which cannot be satisfactorily treated with a product that is licensed, commercially available in Belgium **and reimbursed for this indication**. The medicinal product concerned must either be the subject of an application for a marketing authorisation by the centralised procedure (Cfr. article 6 of Regulation 726/2004) or must be undergoing clinical trials for the related indication. It is unclear whether this can be used for products developped by Academia (for instance if they are the sposnor of a CT and ask for a CU for the non eligible patients). AT the moment CU have only been granted for comemrcial products (
- **Medical Need Program (MNP)** for the use of licenced products for a group of patients with a life threatening disease, a chronic disease or a seriously debilitating disease which cannot be satisfactorily treated with a product that is licensed, commercially available in Belgium **and reimbursed for this indication**.

Clinical trials should be running with the medicinal product for the CUP indication or a Marketing Authorisation Application (MAA) should have been submitted to the EMA (Cfr. article 6 of Regulation 726/2004) for the medicinal product for the CUP indication. As such academics are not excluded from this pathway, provided they meet the above mentioned conditions.

115 https://assets.publishing.service.gov.uk/media/5a7dcbbde5274a5eaea66623/Guidance_on_the_UK_s_arrangements_under_the_hospital_exemption_scheme.pdf
see also
https://assets.publishing.service.gov.uk/media/645e19f5ad8a03000c38b3bc/The_supply_of_unlicensed_medicinal_products__special_GN14.pdf

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