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ASSOCIATION GÉNÉRALE DE L'INDUSTRIE DU MÉDICAMENT
ALGEMENE VERENIGING VAN DE GENEESMIDDELENINDUSTRIE

Advanced Therapeutic Medicinal Products (ATMPs) in Belgium: a roadmap for the future

Recommendations of pharma.be following multistakeholder consultation

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1. Executive Summary

Definition, value and challenges of ATMPs

Advanced Therapy Medicinal Products (ATMPs) are a group of medicines that include gene therapy, cell therapy and tissue-based therapy. They are also often referred to as 'cell and gene therapies' or 'advanced therapies'. ATMPs are **a fast growing field** of innovative therapies: EMA expects the submission or approval of 10 to 20 ATMPs per year during the next 5 years. In 2021, there were 2.600 trials (phase I to III) for ATMPs ongoing in the world, of which 50% in the field of oncology.
ATMPs differ from traditional medicines in the way they are **produced**, **administered** to patients and in the type of **benefits** they can provide.

1. ATMPs are highly sophisticated treatments that require **complex and specialized, biotechnological manufacturing processes**. Moreover, some ATMPs are considered **Genetically Modified Organisms** (GMO), subject to specific additional regulatory requirements. The follow-up of the patient is done in **specialized hospital centers**, with the appropriate know-how/expertise to ensure compliance with the highly regulated biologic material collection, manufacturing, transport, storage and administration procedures.

2. ATMPs have the particularity to target the underlying cause of disease, often a gene or a protein, instead of its symptoms. Cell and gene therapies have a **disease-modifying or even curing potential**, with evident and significant benefits for patients and society. The diseases targeted by ATMPs are often rare, severe diseases with a high unmet medical need. Changing the course or even curing these diseases will have a major impact on the patient's life as well as on the caregivers and society as a whole. Not only will the overall health and quality of life of patients improve, there will also be broader, direct or indirect benefits incurred by these novel therapies: productivity (work capacity) will be improved, costs associated with the follow up and standard treatment of the disease will be reduced, caregiver's burden will be reduced, etc...

3. ATMPs are designed to have therapeutic effects lasting for years but are **often administered only once or a few times** in a short period. This administration mode differs dramatically from more conventional therapies which are often given chronically or during longer periods of time. While benefits of conventional therapies can also span a lifetime, the particularity of administering a therapy once, upfront and potentially leading to life-long benefits is a major change in the treatment paradigm.

Besides the great benefits ATMPs could provide, they also bring along specific challenges that need to be anticipated and tackled. In 2021, pharma.be organized a broad stakeholder consultation to explore the opportunities and challenges for ATMPs in Belgium. All interviewed stakeholders agreed on the importance of safeguarding **rapid and broad access to ATMPs** for Belgian patients and mentioned the following most important **challenges**:

- Complex treatments, requiring highly skilled teams, adaptation of infrastructure and additional investments in the hospital
- Authorities need to develop specific expertise for ATMPs

- Need for strong, future-proof regulatory framework
- Speed and breadth of access
- Uncertainty around clinical benefits (hence budget)
- Affordability, long-term sustainability
- Unadapted HTA framework

pharma.be presents a series of recommendations and practical solutions to address the challenges of ATMPs in Belgium. These recommendations mainly address the **regulatory and access challenges** of ATMPs and are presented as a basis for dialogue and reform.

A modern regulatory framework

In order to keep Belgium on the map as a "health and biotech valley" for the development of novel therapies, there is a need for an innovative Federal Agency of Medicines and Health Products (FAMHP) that has a focus on ATMPs and medicines with a GMO component to consolidate the current environment in Belgium for the (clinical) development and manufacturing of cell- and gene-therapies:

- By building strong expertise and domain of excellence for the early phase development of ATMPs
- By setting up a progressive and open policy for the research and development of ATMPs ensuring for instance streamlined procedures for clinical trials with GMOs, and for the production of ATMPs with an optimized "future-proof" regulatory framework for their manufacturing
- By setting up a unique contact point at the FAMHP for all questions related to human biological material

Sense of urgency for ATMPs with a GMO component

When an ATMP presents a GMO component, its use in a trial necessitates an **additional environmental safety assessment (biosafety assessment)** next to the evaluation of the trial itself. The national requirements and timelines for this biosafety assessment are highly variable across the EU member states. This complexity can lead to a delay in patient access to these innovative treatments. Some European countries have already installed a more streamlined and simplified GMO framework, and tend to align the process with the review of the trial under the new Clinical Trial Regulation entered into force in January 2022, while in Belgium, the existing framework remains long and complex due to federal and regional competencies.

Today, the attractivity of conducting clinical trials for ATMPs with a GMO component in Belgium is at risk. To maintain its position as one of the preferred locations in the EU for conducting clinical trials, Belgium has to urgently adapt its clinical trial and biosafety assessment framework at federal and regional levels.

Fast, broad and sustainable access to ATMPs

Several reforms and solutions are proposed to enable fast, broad and sustainable access to ATMPs in Belgium. It must be stressed that some of the proposals formulated in this paper can also be applied to other types of medicines but are nonetheless highly necessary to ensure access for Belgian patients to ATMPs.

1. pharma.be proposes to improve **two procedures to enable faster access to groundbreaking medicines, including ATMPs**, and thus shorten timelines for patient access to innovative medicines in Belgium. The 'Improved Unmet Medical Need procedure' and the 'Faster Reimbursement procedure' would allow patients to have access to medicines at most **17 and 10 months earlier**, respectively.

   An improved and better funded Unmet Medical Need procedure starting already before marketing authorization is essential to allow for early access not only because of their high production cost but, more importantly, because ATMPs are often a single shot or very short treatment with a curing potential. Consequently, patients treated with ATMPs before marketing authorization/launch will often no longer be treated afterwards which is a major difference with more chronic breakthrough treatments initiated before marketing authorization that need to continue after marketing authorization.

2. Because of their inherent characteristics, ATMPs may carry a **higher level of uncertainty around the therapeutic effect** compared to traditional medicines. To ensure broad and rapid access for patients, pharma.be supports the use of **outcome-based agreements** between payers and pharmaceutical companies, in which data on the real-life performance of the medicine can be collected and, if relevant, linked to payment ('pay for performance'). In this context, further efforts are needed to ensure an optimal preparation and roll-out of these agreements: **payers and companies should engage in an earlier exchange of ideas on outcome data collection, the infrastructure for data collection must be optimized and a longer maximum duration of agreements should be considered to allow sufficient time for solid data collection**.

3. A particular challenge of ATMPs is their **high upfront investment cost**. While the value extends over several years in the future, the cost of the treatment needs to be tackled upfront, often in a one-time or short payment and there is often an important prevalent pool of patients that will be treated at initial reimbursement, generating a peak in patients/budget expenses. **Spread payments**, also called annuities, are an alternative, novel funding mechanism that can be used to **alleviate the affordability challenge** of certain ATMPs at initial reimbursement. Spread payments lead to the **spreading of expenditure over time instead of spreading patients over time**, at **no additional cost to the authorities.** If applied to several ATMPs, the use of spread payments continues to lead to more favourable budgetary situations. Within the existing legal European and Belgian framework, spread payments can be considered especially, but not exclusively, if they are tied to specific outcomes achieved by the medicine in real-life in the context of clinical and budgetary uncertainty. The usefulness of spread payments depends on the characteristics of the ATMP and the nature of the disease and is therefore not appropriate in all cases.

4. The current **Health Technology Assessment (HTA)** procedure in Belgium requires adaptations to consider ATMPs' characteristics. Early collaboration between industry, the European Medicines Agency (EMA) and

Health Technology Assessment (HTA) agencies is needed to **harmonise evidence requirements and facilitate greater acceptance of ATMP evidence upon regulatory approval**. Pharma.be supports the re-use of European clinical evaluations in the Belgian reimbursement procedure. Also, **budget impact analyses** should allow to capture a holistic view of both ATMP costs and savings over the patient's lifetime. Therefore, both the nature of the costs as well as the time horizon used for budget impact analyses should be re-evaluated for ATMPs. The **methodology for cost-effectiveness analyses should also be re-assessed** in order to ensure the full value of ATMPs is reflected.

5. Due to the specialized care that ATMPs require, some of them will be administered in a small number of specialised treatment centres around Europe, not always located in Belgium. **With the introduction of ATMPs to the European market, cross-border health care will therefore gain further importance**. Pharma.be supports the use of specialised treatment centres, both within Belgium and in the case of more rare conditions also outside Belgium, through cross-border care (CBC). Only in this way can sufficient qualitative care for the patient be guaranteed. Three approaches in the current regulatory framework are proposed in this paper. to make cross-border care successful.

2. Details on the methodology and involved stakeholders

Between April and September 2021, pharma.be organized 14 dialogue sessions with a large group of Belgian stakeholders on the opportunities and challenges for ATMPs in Belgium. The stakeholders that participated in these dialogue sessions were:

- Academics, researchers (UGent, KU Leuven, Vlerick Business School, UZ Gent, VUB, Universiteit Antwerpen, CHU Liège)
- Cabinet of the State Secretary of Budget
- Cabinet of the Minister of Health and Social affairs
- Federal Agency for Health and Medicinal Products (FAMHP-FAGG-AFMPS)
- Clinical Trial College (Federal Public Service Public Health)
- Hospitals (hospital managers, hospital association, clinical trials units, clinical biology, hospital pharmacy) (RUZB-CHAB, Cliniques Universitaires Saint-Luc, UZ Brussel, UZ Gent, UZ Leuven)
- Inovigate
- National Institute Health and Disability Insurance (NIHDI-RIZIV-INAMI)
- Patient organisations (RadiOrg, BOKS, AHVH) and Antikankerfonds
- Physicians (CHU Liège, UZ Brussel, UZ Leuven, UZ Gent)
- Sciensano
- Sick funds (Christelijke Mutualiteit, Socialistische Mutualiteit, Onafhankelijke Ziekenfondsen)
- Trade associations (bio.be, Flanders bio, Biowin)

Each stakeholder was invited to a session where representatives of the same or similar stakeholders were present. A standard list of questions was used as a basis for the dialogue session (see annex 1). The questions consisted of broad, general questions on ATMPs as well as detailed questions on manufacturing, clinical trials, treatment centres, cross-border care regulatory approval and market access. The topics discussed during each dialogue session were adapted to the type of stakeholder, depending on their domain of interest and expertise. Stakeholders received a summary of their dialogue session; summaries were not shared across stakeholders. The feedback from each dialogue session formed the basis for the identification of remaining hurdles for ATMPs in Belgium and the elaboration of pharma.be's recommendations.

3. Definition, value and challenges of ATMPs

3.1. Definition of ATMP and current development of ATMPs

Advanced Therapy Medicinal Products (ATMPs) are a category of medicines for human use that consist of gene therapies, cell therapies and tissue-based therapies. They are used to treat a variety of diseases, including severe genetic disorders, cancer or long-term diseases (Regulation (EC) No 1394/2007 and Directive 2001/83/EC) (EMA n.d.):

- **gene therapy medicines** are designed to restore the function of a patient's defective gene by introduction of a healthy copy of the gene, with the potential to permanently correct the abnormality and cure the patient.
- **cell-based therapies** involve transplanting substantially manipulated (sometimes genetically modified) cells or cellular material into a patient, after being collected from the patient him/herself or from a donor.
- **tissue-engineered medicines** contain cells or tissues that have been modified ex-vivo so they can be used to repair, regenerate or replace human tissue;

Various terms are used interchangeably to refer to ATMPs: advanced therapies, regenerative therapies, cell and gene therapies, etc...

ATMPs with a genetically modified organism (GMO) component

As per the European Directive 2001/18/EC, a Genetically Modified Organism (GMO) is an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by matting and/or natural recombination[1]. This means that certain medicinal products, including some ATMPs, are considered as GMO and therefore are subject to additional regulatory requirements. There are a variety of those investigational medicinal products (IMPs): human somatic cells modified ex vivo (for example CAR-Ts); vaccines; recombinant virus-based vectors (for example recombinant Adeno-Associated Virus (AAV) vectors), including those containing genome editing nucleic acid sequences (which may also be delivered non-virally) and bacterial vectors..

ATMPs are a fast growing field of innovative therapies

In the European Union ATMPs benefit from a dedicated, centralized regulatory assessment and authorization procedure (EU Regulation (EC) 1394/2007). The Committee for Advanced Therapies (CAT) has been created specifically within the European Medicines Agency (EMA) for the evaluation of ATMPs. It provides a draft opinion to the Committee for Medicinal Products for Human Use (CHMP), which in turn formulates a final opinion on the quality, safety and efficacy of a given therapy. The European Commission makes its formal decision on the marketing authorization on the basis of the CHMP opinion (EMA n.d.).

Today there are 14 ATMPs with a valid marketing authorization in the European Union (status end of December

[1] For more information about the definition of a GMO, please refer to https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF

2021). Of these, 5 are available and reimbursed in Belgium (EMA n.d.) (INAMI n.d.).

Product	**Indication**	Year of EU marketing authorization	Reimbursed in Belgium
Holoclar®	Severe limbal stem cell deficiency in the eye	2015	Yes
Imlygic®	Melanoma	2015	No
Strimvelis®	Adenosine Deaminase Severe Combined Immunodeficiency	2016	No
Spherox®	Cartilage defects in the knee joint	2017	No
Alofisel®	Perianal fistulas in Crohn´s disease	2018	No
Yescarta®	Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma	2018	Yes
Kymriah®	Diffuse Large B-Cell Lymphoma Acute Lymphoblastic Leukaemia	2018	Yes
Luxturna®	Inherited retinal dystrophy	2018	Yes
Zynteglo®	Transfusion-dependent β-thalassaemia	2019	No
Zolgensma®	Spinal muscular atrophy	2020	Yes
Tecartus®	Mantle cell lymphoma	2020	No
Libmeldy®	Metachromatic leukodystrophy	2020	No
Skysona®	Early cerebral adrenoleukodystrophy	2021	No
Abecma®	Multiple myeloma	2021	No

An important growth in the number of ATMPs to reach the market is expected in the near future: EMA expects the submission or approval of 10 to 20 ATMPs per year during the next 5 years (ARM, Alliance for Regenerative Medicine Responds to EU Pharmaceutical Roadmap 2020). The vast majority of the ATMPs in development (over 95%) are cell and gene therapies. In 2021, there were 2.600 trials (phase I to III) for ATMPs ongoing in the world, of which 50% focused on oncology indications and 60% concerned rare diseases. (ARM, Regenerative Medicine in 2021: A Year of Firsts & Records, H1 2021) (ARM, Rare Disease & Regenerative Medicine 2019).

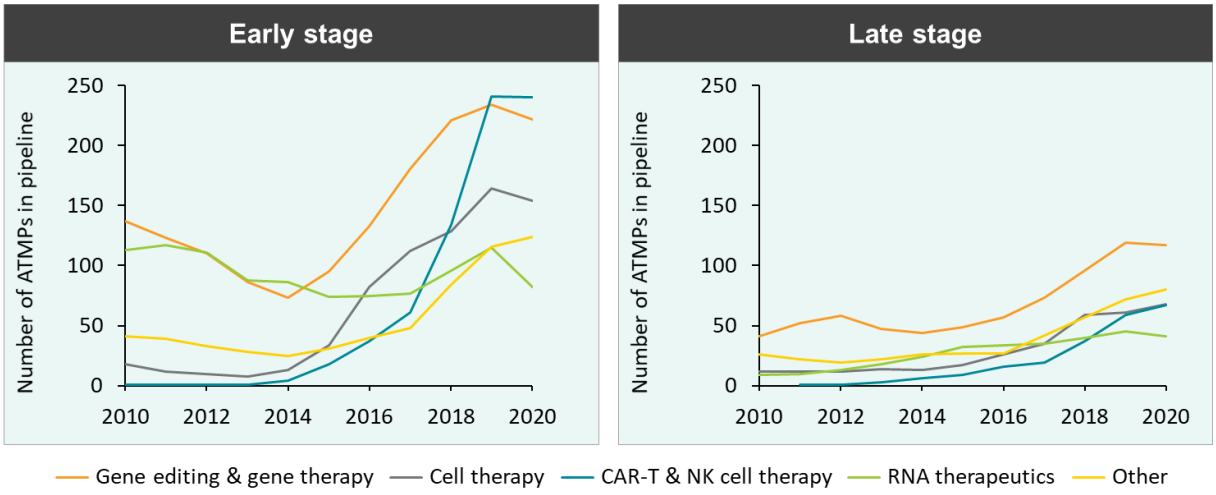
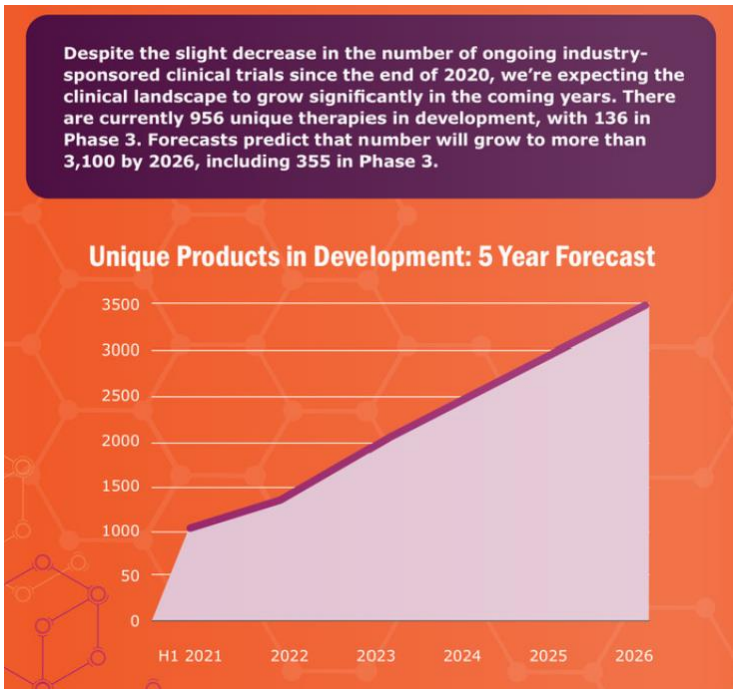


Figure: ATMP early- and late-stage pipeline by mechanism (EFPIA, 2022)



(ARM, Regenerative Medicine in 2021: A Year of Firsts & Records, H1 2021)

3.2. While ATMPs can generate tremendous value to patients and society, their unique characteristics also pose a challenge to the current healthcare system.

ATMPs differ from traditional medicines in the way they are produced, administered to patients and in the type of **benefits** they can provide.

1. ATMPs consist of genes, cells or tissues that are either directly administered to a patient or produced by collecting tissue or cells from a patient or a donor and then altering them 'ex vivo' to produce a therapy that is administered to the patient. ATMPs are therefore highly sophisticated treatments that require **complex and specialized, biotechnological manufacturing processes** and can often not be manufactured and stored in advance, as is the case for more conventional medicines (ARM, Getting Ready: Recommendations for Timely Access to ATMPs in Europe 2019). Moreover, some ATMPs are considered as a genetically modified organism or GMO. The follow-up of the patient is usually done in **specialized hospital centers**, with the appropriate know-how/expertise to ensure compliance with the highly regulated biologic material collection, manufacturing, transport, storage and administration procedures.
2. ATMPs have the particularity to target the underlying cause of disease, often a gene or a protein, instead of its symptoms. Cell and gene therapies have a **disease-modifying or even curing potential**, with evident and significant benefits for patients and society. The diseases targeted by ATMPs are often rare, severe diseases with a high unmet medical need. Changing the course or even curing these diseases will have a major impact on the patient's life as well as on the caregivers and society as a whole. Not only will the overall health and quality of life of patients improve, there will also be broader, direct or indirect benefits incurred by these novel therapies: productivity (work capacity) will be improved, costs associated with the follow up and standard treatment of the disease will be reduced, caregiver's burden will be reduced, etc...
3. ATMPs are designed to have therapeutic effects lasting for years but are **often administered only once or a few times** in a short period. This administration mode differs dramatically from more conventional therapies which are often given chronically or during longer periods of time. While benefits of conventional therapies can also span a lifetime, the particularity of administering a therapy once, upfront and potentially leading to life-long benefits is a major change in the treatment paradigm.

Besides the great benefits ATMPs could provide, they also bring along specific challenges that need to be anticipated and tackled. During our dialogue sessions with the Belgian stakeholders, the following challenges were cited most frequently:

- Complex treatments, requiring highly skilled teams, adaptation of infrastructure and additional investments in the hospital
- Authorities need to develop specific expertise for ATMPs
- Need for strong, future-proof regulatory framework
- Speed and breadth of access
- Uncertainty around clinical benefits (hence budget)
- Affordability, long-term sustainability
- Unadapted HTA framework

Among the **regulatory challenges**, keeping the attractivity of conducting clinical trials with ATMPs in Belgium is of utmost importance. When an ATMP presents a GMO component, its use in a trial will necessitate an additional environmental safety assessment (biosafety assessment) next to the evaluation of the trial itself. Due to the lack of harmonized biosafety requirements across European Member States, the initiation of CTs with GMO-IMPs remains a time-consuming and resource-intensive process, leading to significant delays to patient access to these innovative and promising advanced therapy technologies.

All interviewed stakeholders agreed on the importance of safeguarding rapid and broad access to ATMPs for Belgian patients but also acknowledged ATMPs could put healthcare systems under pressure, as payers face **specific funding challenges** that cannot always be tackled by traditional HTA process criteria and traditional funding mechanisms.

In the context of the recently published **Pharmaceutical Strategy for Europe**, the European Commission recognises ATMPs as a generational milestone and acknowledges the need for new pricing and reimbursement frameworks that help address the shift from payment over time for chronic treatments to upfront costs for these often one-time therapies (European Commission, 2020).

As indicated above, there is an exponential growth in the number of ATMPs under development. The upfront cost associated with these therapies alongside the growing number in development has led to concerns regarding their affordability. The delivery of affordable treatments to ensure health system financial and fiscal sustainability is also one of the key initiatives of the EU Pharmaceutical Strategy (European Commission, 2020).

Because these treatments are administered once or over a short time period, the payment for ATMPs is condensed into a single figure and drives concerns regarding the individual price of ATMPs. During price negotiations ATMPs are benchmarked to a current Standard of Care that could include other innovative medicines, poor-performing treatment options or best supportive care. When comparisons are made between the price of ATMPs vs. non-ATMPs, it is important that the overall cost of chronic treatment is considered. Pricing plays a vital role in ensuring the economic viability of drug development and in turn, continued sustainable innovation, particularly for treatments such as ATMPs that target small populations. As ATMPs are highly innovative drugs leading to improvement in health outcomes, it is important that prices are based on value and focused on achieving access for patients (EFPIA, 2022).

The sustainability of aggregate drug expenditure, of which ATMPs are one element, is an important topic. To make informed decisions regarding the affordable reimbursement of ATMPs, assessments must be able to accommodate for their unique characteristics. However, at present, these systems are not always appropriately configured to reflect the nature of single administration curative therapies. Longer time horizons and a broader scope need to be adopted to be able to determine the true long-term affordability of ATMP reimbursement. Also, budgets allocated for pharmaceutical expenditure can be disconnected from the wider healthcare budget, further hindering holistic reimbursement decision-making for ATMPs (EFPIA, 2022).

4. A modern regulatory framework

In Belgium there is a unique ecosystem for biopharmaceutical research and development and clinical research by having a network of 7 academic hospitals, 12 universities with internationally recognized life science departments, and over 50 pharmaceutical (and biotech) companies active in research and development and clinical development as well as several biopharmaceutical companies producing ATMPs in Belgium. Belgium thus concentrates world-renowned research centres for cell and gene therapies. Moreover, Belgium has a leading position in Europe in terms of number of clinical trials per inhabitants, with a specific expertise in early development. Such a position offers a rapid access to innovative treatments in development to patients in the country.

Currently, Belgium coordinates 5.1 to 7.2 % of all applications for ATMP-related clinical trials in the EU. Moreover, in recent years, across Europe and in Belgium, we have witnessed an increase in the number of clinical trials with cell and gene-therapies and vaccines that consist of GMO (e.g. CAR-Ts, vaccines against COVID-19,..). In 2019, 3% (=14 trials) of the total authorised clinical trials in Belgium involved an investigational medicinal product consisting of or containing a GMO (GMO-IMP) (Deloitte, 2019).

In order to keep Belgium on the map as a "health and biotech valley" for the development of novel therapies, there is a need for an innovative Federal Agency of Medicines and Health Products (FAMHP) that has a focus on ATMPs and medicines with a GMO component to consolidate the current environment in Belgium for the (clinical) development and manufacturing of cell- and gene-therapies.

4.1. Creation of ATMP Spearhead at FAMHP

The FAMHP should keep pace with those novel medicinal products and novel scientific research to consolidate the current environment in Belgium for development and manufacturing of cell and gene-therapies:

- By building strong expertise and domain of excellence for the early phase development of ATMPs
- By setting up a progressive and open policy (i) for the research and development of ATMPs for instance ensuring streamlined procedures for clinical trials with GMOs (see next section), and (ii) for the production of ATMPs with an optimized "future-proof" regulatory framework for their manufacturing (the latter via the concertation platform ATMPs hosted by the FAMHP)
- By setting up a unique contact point at the FAMHP for all questions related to human biological material

This would imply that the FAMHP develops strong expertise in the early development of ATMPs:

- Via scientific advice (at national and at EU level) and its innovation office as well as the European Innovation Office network
- Via participation in the EMA Innovation Task Force (IATF) and Committee for Advanced Therapies (CAT)
- Via an increase of the number/level of (Co-)rapporteurship at European level (for PRIME, Marketing Authorizations)
- By extending collaboration with external investigators/academics who can bring practical insights

from the field about ATMPs trials

In addition, the FAMHP should ensure a clear communication about this expertise and its vision about developments of ATMPs

From a policy or legislative point of view, the law on the use of human body material for the manufacturing of ATMPs and its applicable royal decree need to be reviewed. This would allow an optimisation in line with the practice in the field, e.g., the momentum of the serology testing, the qualification of the responsible person within a tissue establishment, the procedure to amend an accreditation of a tissue establishment, as pointed out within an ad hoc working group of the ATMP platform at the FAHMP.

4.2. Clinical trials with GMOs

Belgium holds a leading position in Europe in terms of number of clinical trials per inhabitants and has developed specific expertise in early phase clinical trials and vaccines trials. Between 1996 and 2021, a total of 278 trials with a medicinal product containing a GMO have been notified in Belgium[2].

As already mentioned in the introduction, certain (investigational) medicinal products are considered as GMO and therefore are subject to additional regulatory requirements. This means that the conduct of clinical trials with investigational medicines with a GMO component is governed in Europe by different legislations that need to be combined to assess the participation of the subjects in the clinical trial itself, but also several aspects related to the impact on the environment and the public health (non-patients) of the involved GMO component (the biosafety assessment).

Hence, the European Clinical Trials Regulation 536/2014 (replacing the European Clinical Trials Directive 2001/20/EC) that has entered into application on the 31st of January 2022 with a 3-year transition period has to be considered together with the current European GMO directives 2001/18/EC and 2009/41/EC for the conduct of this type of trials, as the Clinical Trials Regulation is not addressing the environmental risk associated with clinical trials with GMOs. Although GMO legal framework was enacted primarily to regulate the introduction of GMO plants and food products within Europe, this legislation is also applicable for the introduction of medicinal products containing or consisting of GMO. National Biosafety requirements and timelines are highly variable across the member states, and hence can generate significant delays in starting a clinical trial. This makes the GMO framework an important determinant for the country and clinical sites selection process to conduct a trial with ATMPs or vaccines as some EU Member States have already a more streamlined and simplified GMO framework then other EU Member States.

This issue has been recognized by the European Commission, in its communication about the Pharmaceutical Strategy for Europe (European Commission, 2020), which mentions that the regulatory requirements for GMO products in the EU "*should be fit for purpose*", but are "*currently hindered by the fragmentation of national requirements*". The Commission has also granted a temporary derogation from some provisions of the GMO

[2] https://www.biosafety.be/content/clinical-trials-gmos-some-figures

requirements for potential COVID-19 treatments and vaccines due to the urgency of the pandemic situation. Such an exemption was made on the basis of a clear recognition of such complexities and resulting delays to clinical development.

Moreover, a good coordination between the GMO regulatory processes and the clinical trial authorisation via the new European Clinical Trial Regulation (CTR) is critical to maintain clinical trials testing medicines with a GMO component possible.
However, in Belgium the existing GMO framework has not been adapted yet. This becomes especially imminent when the Clinical Trials Regulation 536/2014 (CTR) will enter into application (currently foreseen on 31 January 2022). The CTR will fundamentally change the process of the submission, assessment and life cycle of clinical trials and will harmonize the regulatory timelines for CTAs across Europe. This means that Belgium will not only lose its competitive advantage of short regulatory timelines for CTAs but start up timelines in Belgium will be negatively impacted by the timelines of the current GMO regulatory framework for IMP's in Belgium . Moreover, in Europe, several Member States have already adapted their GMO regulatory framework (for example The Netherlands) or are in the process of doing so (for example Austria, France, Germany) (Lambot, 2021).

Therefore, the current regulatory framework for clinical trials with GMOs should urgently be streamlined, simplified and aligned with the process under the CTR as soon as possible in Belgium, which implies that Belgium must urgently and proactively **adapt its framework at the federal level:**

- With a maximum and predictable timeframe for the deliberate release procedure, for evaluating the environmental risk assessment of the clinical trial testing a medicine with a GMO component, and keep it equal to the upcoming Clinical Trials Regulation timelines in order to be able to start rapidly a clinical trial after its approval via the Clinical Trial Regulation process and hence, to remain competitive as compared to the other member states where the trial is conducted. For instance, in Germany the upcoming version of the German Drug Law (AMG) that will apply after the implementation of the Clinical Trials Regulation, stipulates that the clinical trial authorization will also include a GMO release authorization in the future (Lambot, 2021).
- This timeframe could be achieved
    - by bridging conclusions from Environmental Risk Assessments of Investigational Medicinal Products that employ the same technology;
    - with a shortened timeframe between issuance of the final biosafety advice and the final decision from the FAMHP for clinical trials with a GMO.
- To ensure continuous expertise/learning at the level of the involved competent authorities. A suggestion is to further build on the collaboration between Sciensano and the FAMHP for learning sessions and include the collaboration with external experts, external investigators who can bring practical insights from the field
- To harmonize the Belgian contained use requirements for GMOs across regions

5. Preparing for access of ATMPs in Belgium: how to ensure faster access and which solutions can address the funding challenges of ATMPs?

5.1. Faster access

The journey of new medicines from the laboratory to patients is very long. After years of clinical research and development, new medicines must receive marketing authorisation followed by reimbursement discussions before patients have access to them. Recent experiences have illustrated that such **a long delay in access to groundbreaking medicines is considered unacceptable**, especially for people with serious or life-threatening conditions who have no other treatment options.

How long can it take to have access to a new medicine?

Before Belgian patients can have access to a new medicine, marketing authorisation approval is needed from the European Medicines Agency (EMA) and reimbursement decision from the Belgian Minister of Social Affairs.

A European Marketing Authorisation is granted by the European Commission (EC) following a final positive scientific opinion by the EMA's Committee for Medicinal Products for Human Use (CHMP). The administrative process between CHMP and EC officially takes 67 days. In total, **EMA has a maximum of 210 days to decide on the European marketing authorisation**. In Belgium, reimbursement applications for medicines that are categorized as Class 1, Orphan Drug or modification of reimbursement conditions, may be submitted directly following a positive CHMP opinion. By starting the reimbursement process earlier, patient access can be accelerated with more than 60 days.

The reimbursement procedure itself should take no more than 180 days, as required by the European Transparency Directive. However, this deadline does not take into account any interruptions to allow the company to answer questions. An additional reason to interrupt is when the company and the payer start negotiating a managed entry agreement (MEA). This negotiation procedure may not last longer than 120 days. This implies that for innovative medicines, it may take **in theory 360 days from the submission of the reimbursement request** at the Committee for Reimbursement of Medicines **to the effective availability** of the reimbursed medicine for Belgian patients.

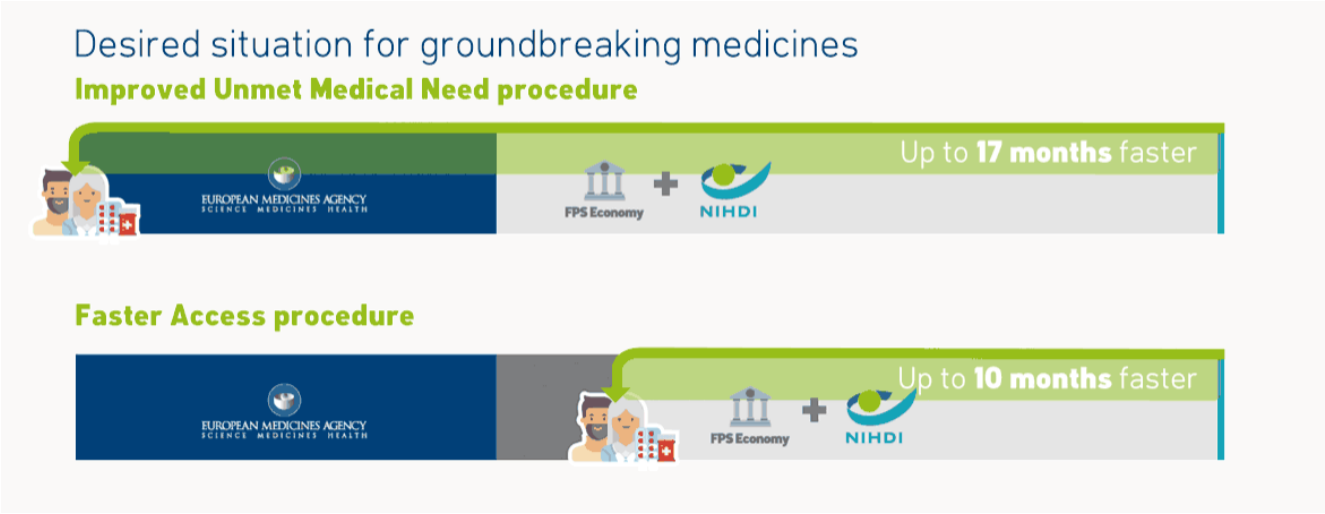
These long timelines urged our association to improve two procedures that allow companies to apply for a faster access to groundbreaking medicines and thus shorten timelines for patient access to innovative medicines in Belgium.
It must be emphasized that both procedures are applicable to all groundbreaking medicinal products, now and in the future. Although they fit perfectly with ATMPS, they are not exclusive for ATMPs.

Two procedures which could accelerate access at least ten months

pharma.be proposes **two different faster access procedures starting respectively before and after the positive CHMP opinion**. The main elements of both procedures are explained in the table below.

	Improved Unmet Medical Need procedure (UMN)	**Faster Reimbursement procedure**
Start of procedure	Before or during EMA evaluation (before CHMP opinion)	As of positive CHMP opinion
Eligibility criteria / Scope For which groundbreaking medicines would the procedure apply?	Medicine treats a condition that is serious or life-threatening and for which no therapeutic alternative is available, and that is mentioned on Unmet Medical Need list of NIHDI	Accelerated Assessment label or Orphan designation or CUP/MNP ongoing or Indication on Unmet Medical Need list of NIHDI or medicines given early access via UMN procedure
Institution that performs the **scientific evaluation**	**FAMHP**: risk/benefit assessment of compassionate use and medical need programmes (CUP/MNP)	**EMA**: CHMP report/EPAR **CRM**: Evaluation of **eligibility for faster access by Day45**; then the CRM continues the HTA evaluation
Duration of procedure	**55 days** FAMHP & NIHDI combined (plus additional days for agreement negotiations)	**45 days** CRM
Acceleration of patient access when compared to usual CRM procedure that would start at CHMP opinion	**At most 515 days/17 months faster access** (210 EMA + 360 days reimbursement procedure – 55 days UMN procedure)	**At most 315 days/10 months faster access** (360 days reimbursement procedure - 45 days)
Early **funding**	**Compensation** (≠ price)**: choice between lump sum and agreement**	Value-based funding based on published list price & retro-active **refund**

For ATMPS, funding is essential to allow for faster access not only because of their high production cost but, more importantly, because ATMPs are often a single shot or very short treatment with a curing potential. Consequently, patients treated with ATMPs before marketing authorization/launch will often no longer be treated afterwards which is a major difference with more chronic breakthrough treatments initiated before marketing authorization that need to continue after marketing authorization.



1. Improved Unmet Medical Need procedure

In 2014, a so-called Unmet Medical Need (UMN) procedure was installed in Belgium which allows for early access to innovative medicines answering an unmet medical need. For certain innovative medicines, a compensation can be granted even before they are registered (i.e., before CHMP opinion). This is possible when they are used in the treatment of a serious or fatal disease for which no therapeutic alternative exists.[3]
Because the procedure was not very successful, the Minister of Social Affairs De Block proposed end 2018 changes to improve its use by pharmaceutical companies. Our proposal builds on this and consists in general of the following improvements:

- 1 integrated procedure at FAMHP and NIDHI: Company applies for compassionate use or medical need program on the one hand, and for the compensation on the other hand, at the same moment
- Acceleration of the integrated procedure (55 instead of 130 days)
- Compensation: company has the choice between a lump sum (currently set at €25.000/cohort and €2.500/patient/year) and an agreement because the lump sum will not be sufficient for single treatment ATMPs. In case of important clinical uncertainties, an agreement could also include arrangements to invest in additional Real-World data collection.
- Administrative simplification: No treatment of individual patient requests
- Specification in the law that the compensation and thus CUP/MNP is limited to patients who are insured by a Belgian health insurance fund (via the exclusion criteria) to prevent that compassionate use or medical need programmes in Belgium attract patients from other countries

Applying the improved Unmet Medical Need procedure, would allow patients to have access to medicines at most 515 days earlier! This is the equivalent of maximum 17 months. The longer before the CHMP decision the company applies for the Unmet Medical Need procedure, the more time is gained.

[3] https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/Paginas/unmet-medical-need.aspx

2. Faster Reimbursement/Access procedure

But even if a company waits for the positive CHMP opinion before submitting its reimbursement application at the Committee for Reimbursement of Medicines (CRM), the proposal would be that they can still accelerate access for patients by applying for the Faster Reimbursement procedure.
In the proposal, only specific medicines with a "groundbreaking" character or "answering an unmet medical need" will be eligible for this procedure, i.e., those that were granted an Accelerated Assessment label or Orphan designation by EMA, or that got the approval from the FAMHP to start a compassionate use of medical need programme (CUP/MNP) because they answer an unmet medical need, or of which the indication was added to the Unmet Medical Need list of the NIHDI. And, of course, also the medicines for which early access was provided via the improved Unmet Medical Need procedure. In the future, the International Horizon Scanning Initiative (IHSI) will allow to identify upcoming ground breaking therapies including ATMP much earlier.
The CRM will take 45 days to decide if the medicine is truly eligible for faster access based on the **scientific evaluation performed by the European Medicines Agency**. As soon as the eligibility is confirmed, the medicine is considered temporarily reimbursed and is available for Belgian patients.
Whilst the patients can benefit from this access, the CRM procedure continues the HTA evaluation. If, at the end of the procedure, there is a difference between the original price set by the company and the final price negotiated during the CRM procedure, the company will retro-actively refund the difference and give back part of the payments it received during the temporary reimbursement period (principle of value-based refund).

Applying the Faster Reimbursement procedure would allow patients to have access to medicines within 45 days after the positive CHMP opinion which would be at most 315 days earlier, the equivalent of maximum 10 months!

5.2. Outcome-based agreements: addressing uncertainties

ATMPs are designed to have therapeutic effects lasting for years, potentially over a lifetime, but are often administered only once or a few times in a short period. The complete value and duration of the benefit can most often not be fully captured in a clinical trial.
Also, because ATMPs predominantly target rare diseases, with small patient populations and no to limited treatment options, they usually receive regulatory approval based on single-arm, small-scale studies (ARM, Getting Ready: Recommendations for Timely Access to ATMPs in Europe 2019).
Moreover, the very nature of ATMPs and the lack of long-term experience with these innovative treatments leads to unpredictability around the level, time of onset and duration of therapeutic effect for a given individual.

Therefore, ATMPs may struggle to deliver the robust evidence traditionally demanded by payers at launch. To safeguard rapid and broad patient access to these novel therapies, payers and companies should agree early on the right solution to manage the **uncertainty around the short- and long-term, real-life effectiveness** of these therapies.

The early **collection of real-world data** is an important tool in building evidence on effectiveness and value of ATMPs. Seeking independent advice from experts might help payers and companies in selecting the appropriate

outcomes that reflect care patterns and patient experience, that are not always covered in clinical trials (EFPIA 2020).

Finance and/or outcome based **managed entry agreements (MEA)** between payers and pharmaceutical companies can facilitate access to ATMPs depending of the most relevant clinical or budgetary uncertainties. **Outcome-based agreements** imply that pre-agreed additional clinical evidence (Randomized controlled trials (RCT) and/or real-world outcome data) is collected after initial reimbursement. Depending on the type of outcome-based agreement, the additional clinical evidence can support health technology reassessment decisions on further reimbursement of the medicine and/or the level of payment for the medicine by the payers (Gerkens, 2017).

Within the outcome-based MEAs a distinction can be made between 2 subtypes: MEAs with additional evidence collection with or without pay for performance (P4P) modalities. Outcome-based agreements with a P4P component define upfront the payment/coverage modalities linked to the performance of the medicine.

The use of outcome-based agreements is possible within the current legal framework in Belgium. However, the implementation of such agreements is often deemed too complex because of suboptimal data infrastructure and/or because the dialogue between payers and companies on these types of agreements often occur in the late stages of the reimbursement procedure.

In a recent publication co-signed by Jo De Cock, discussing the collection of real-world evidence for highly innovative medicines, notably in the context of outcome-based agreements, the authors similarly conclude that "All stakeholders need to be involved, to agree what real-world data is needed for what purpose, how it can be collected, when, by whom and how". The pharmaceutical industry should "actively engage with other stakeholders to develop and implement plans for RWD collection, analysis, and reporting over the lifecycle of a highly innovative technology to generate robust real-world evidence that helps resolve Payer/HTA decision uncertainties" (Facey 2020).
It is recommended to develop a **local governance model** to facilitate the **early collaboration** of all concerned stakeholders which is essential to enable the implementation of RWE projects. pharma.be is willing to work with the Belgian authorities to develop this governance model, in the context of the recent decision to invest in a Belgian Health Data Authority.

Next to this, the announced **International Horizon Scanning Initiative** will allow to identify upcoming ATMP launches requiring early dialogue between regulatory authorities, HTA agencies, payers and industry. Also, early **collaboration between industry, the European Medicines Agency (EMA) and Health Technology Assessment (HTA) agencies** is needed to harmonise evidence requirements and facilitate greater acceptance of ATMP evidence including indirect treatment comparisons, surrogate endpoints, and real-world evidence (RWE).

Development of innovative outcome-based agreements should be grounded in a co-creative process that could begin at the point of early discussions to identify uncertainties and appropriate models as well as infrastructural

requirements. To facilitate real world data collection and the implementation of OBAs, pharma.be wants to put forward 3 recommendations:

To foster earlier discussions around outcome-based agreements, pharma.be recommends the creation of a multidisciplinary outcome-based reimbursement platform that can be consulted by NIDHI (CRM/CTG or Working Group art.111/112) as well as by companies, as early as the start of the regulatory approval procedure by EMA, to receive advice on the applicability and feasibility of outcome data collection, on the definition of specific outcome parameters and on the concrete set-up of data collection in the context of OBAs**.** A detailed description of this proposal can be found in pharma.be's White Paper on managed-entry agreements.

In this context, the collection of data on the real-world 'performance' of ATMPs is crucial. Outcome-based agreements can only be successful if the infrastructure for collecting such real-world evidence (RWE) is in place. **Therefore pharma.be encourages authorities to further invest in the building of a RWE 'ecosystem' in which public databases are connected, accessible to all relevant stakeholders through a single point of contact ('one-stop-shop') and able to provide qualitative data**. Pharma.be applauds the recent decision of the Belgian authorities to invest in the creation of a **Health Data Authority** during the next 5 years (https://www.riziv.fgov.be/SiteCollectionDocuments/budget_2022_algemene_raad.pdf) and looks forward to collaborate with the authorities to share past experiences, to ensure data are accessible and serve the purpose of all involved stakeholders.

The duration of managed-entry agreements in Belgium is limited to maximum 3 years, which is often too short to collect sufficient outcome data in the context of clinical uncertainties. **pharma.be therefore recommends changing the maximal duration of MEAs to 5 years.** A detailed description of this proposal can also be found in pharma.be's White Paper on managed-entry agreements.

5.3. Spread payments: addressing the budget impact of the peak in investment cost

A particular challenge of most ATMPs is the budget impact of the **upfront investment cost leading to savings afterwards**. Spread payments lead to the **spreading of expenditure over time instead of spreading patients over time**, at **no additional cost to the government**. This leads to a number of benefits for the patients, such as a faster significantly increased quality of life, stopping the disease or stopping health deterioration due to the disease, being able to stop the chronic medication consumption; and also offers benefits for the government: an overall lower cost, because patients stop taking their chronic medication sooner, in addition to a decrease in other ancillary care related to the patient's disease.

What are spread payments?

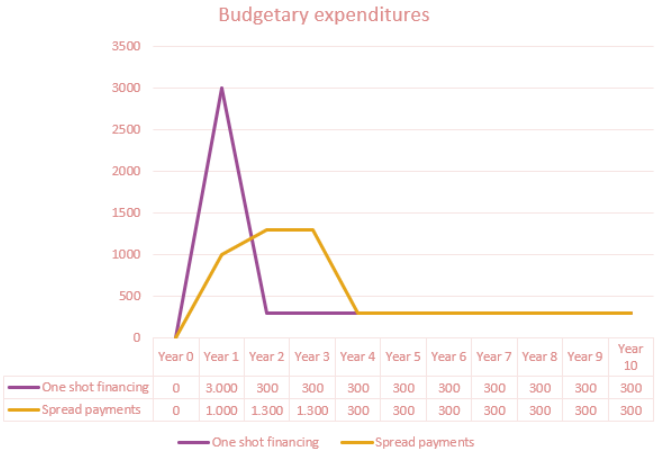
Compared to traditional treatments, ATMPs are administered once or during a short timeframe and procure benefits for many years, potentially spanning a lifetime. Also, because of the disease-modifying or curing potential of ATMPs and the frequent lack of satisfactory therapeutic options in the targeted diseases, a

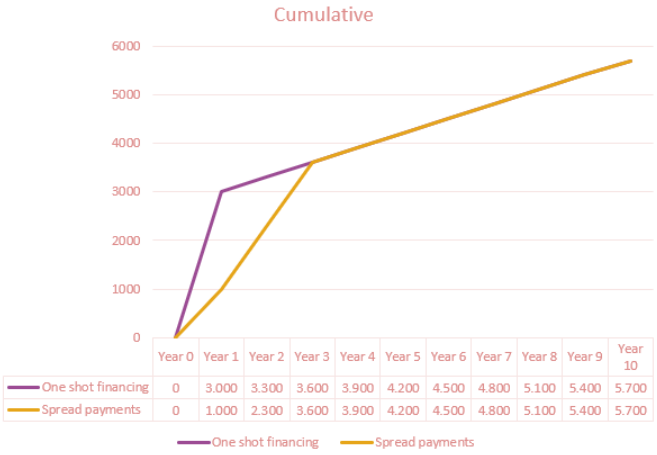
relatively high number of already diagnosed patients can be expected for some diseases to be treated in the first year(s) after launch ('waiting room' concept due to a high prevalence but low incidence) while the years thereafter, only the incident (newly diagnosed) patients are eligible. This initial peak in the number of patients and therefore in the investment cost of the treatment often entails an **affordability challenge** for our healthcare system (EFPIA 2020) (ARM, Getting Ready: Recommendations for Timely Access to ATMPs in Europe 2019) (Maes 2019).

The limitations of current reimbursement mechanisms without the use of spread payments were illustrated with the introduction of the new hepatitis C medicines in Belgium in 2015. These new innovative medicines cured hepatitis C for the first time, greatly improving the quality of life of the patient who previously underwent lifelong treatments. In order to manage the upfront investment cost and peak in budgetary pressure at initial reimbursement, patient access was initially limited to a subgroup of priority patients and expanded progressively over several years (Gerkens 2016). Due to this spread of patients, **patients in the waiting room suffered from the degenerative aspect of hepatitis C**. If the spread payments over several years approach proposed in this paper had been implemented at the time of reimbursement of the new hepatitis C medicines, all patient groups could have benefited from the innovative therapy and increased quality of life from the moment of introduction, while the spread payments would have created the same budgetary effect as the progressive expansion of the patient population: the **payments would have been spread instead of the access to the patients with the same yearly and total budgetary impact**.

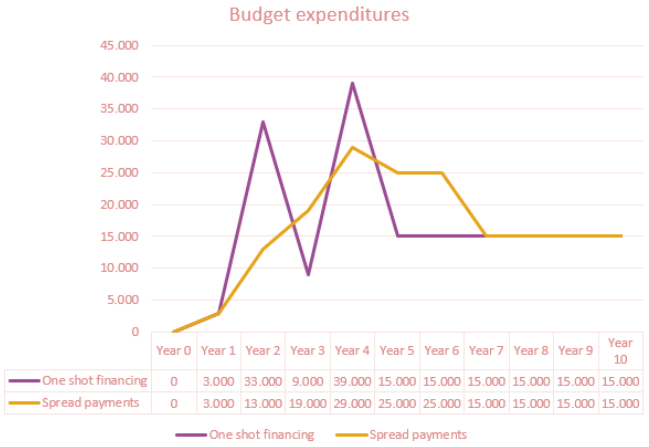
This funding model allows payers to make payments to the manufacturers over a pre-determined fixed period, for each patient receiving treatment, instead of a one-time payment upfront or the spreading of patients. Structuring payments this way allows a spread over several years of the high upfront investment costs associated with one-off therapies together with a peak of patients at initial reimbursement, during which the benefits (and cost savings) of ATMPs will be realized on the level of both patients and payers (EFPIA 2020) (ARM, Getting Ready: Recommendations for Timely Access to ATMPs in Europe 2019) (Maes 2019).

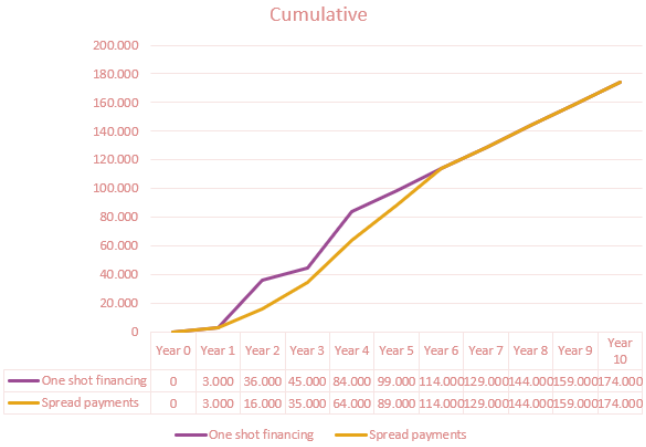
The following graph shows the effect of spread payments for <u>one</u> therapy with a cost of 300 and an initial waiting room of 10 patients and 1 additional patient per year: spreading over 3 years resulting in a cost of 100 a year. The use of spread payments for new patients can be halted after 2 years as the 'waiting room' of patients has been reduced: all new patients from year 3 on are classic one-off payments as the use of spread payments is not useful anymore: the budgetary impact of the peak of patients is no longer there. On the left side, we can see the budgetary expenses for each year. On the right side we can see the cumulative amount of expenses, showing that **spread payments don't lead to higher expenses**: they only smoothen the budgetary effect of the initial peak of patients.





If applied to <u>several</u> ATMPs in different years (same variables as previous graph), **the use of spread payments continues to lead to more favourable budgetary situations**. In the example below, several new medicines are launched each year, with in years 2 and 4 the introduction of ATMPs with a waiting room effect. **The positive effect of spread payments is enhanced when several medicines are involved**:



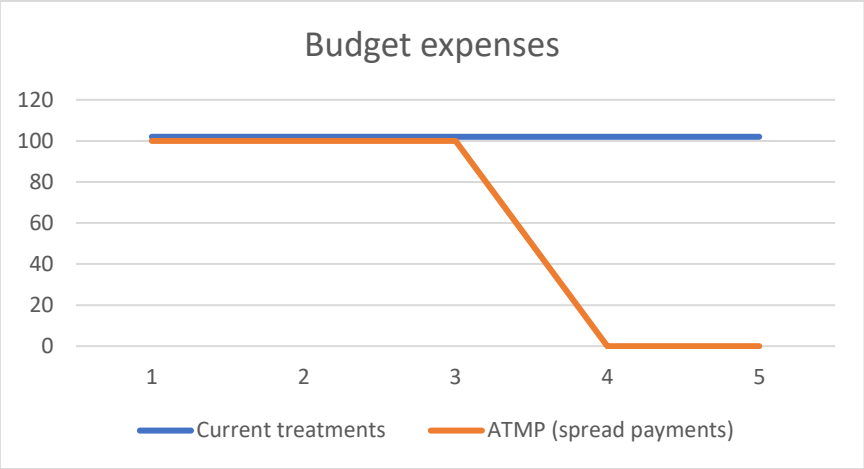


Spread payments do not lead to higher expenses but to a better affordability and faster access.
As the graphs show, the use of spread payments leads to the smoothening of the budgetary impact of the patient waiting room without increasing expenditure.

The example of the haemophilia case in France

In France, the use of spread payments in ATMPs has been approved and is being implemented in regulations since the end of 2021. Here, the case-study was used for an ATMP for haemophilia without a pay for performance component. The level of the annual spread payments was set at the price of the existing haemophilia medicines that require chronic use. As a result, the annual budgetary impact was at the same level as the previous situation without ATMP, but after the end of the period of spread payments, the budgetary impact and expenditure was significantly lower as there was no longer any expenditure on either the ATMP or the chronic use medicines for those patients: this expenditure disappeared. As a result, the use of spread

payments during that period did not lead to increased expenditures compared to a situation without ATMP but led to significant savings for the healthcare budget after the end of the spread payment period.



Due to the limited duration of spread payments, this does not lead to higher expenditure in the short term, but to large savings in the medium and long term.

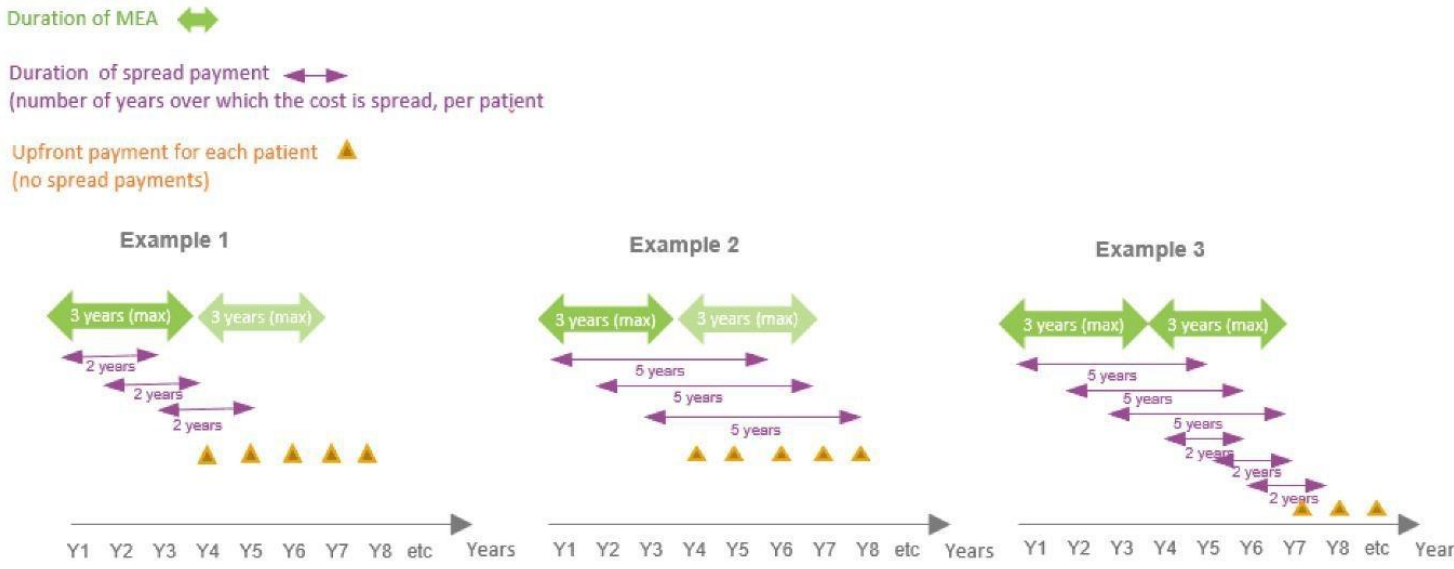
When can spread payments offer a solution to payers and companies?

Below is a set of general recommendations to help to decide whether a spread payment solution is useful or appropriate. The list is inspired by the guiding principles presented by EFPIA (EFPIA 2020) and by a recent policy report based on Belgian multi-stakeholder consultations (including policy makers, sick funds, academia, manufacturers and patient organizations) (Maes 2019).

General recommendations to determine when spread payments may be appropriate:

- Spread payments should only be considered **in case there is a peak of budget expenses** at initial reimbursement **due to a pool of patients waiting to be treated for diseases with high prevalence and low incidence**, allowing to smooth the peak in budget expense and hence a better management of the budget in a context of growth norm.
- Spread payments **should address an affordability issue**: their main purpose should not become to incentivize outcome data collection.
- Spread payments should be a **temporary solution, to be used for a defined period after the initial reimbursement of a novel therapy**. The need for spreading payments as well as the duration of the payment itself should be re-discussed periodically by payers and manufacturers. Also, the duration of managed-entry agreements in which spread payments are convened should be carefully chosen, balancing between the time needed to smooth the peak in budget expense and a timely re-evaluation of the need for spread payments. As illustrated in the figure below, **the duration of a managed-entry agreement and the period over which payments are spread, can be different**.
- The use of **spread payments should be the exception rather than the rule**: it should only be used when it's useful or appropriate.

- The use of spread payments aims to facilitate funding and should not interfere with the therapeutic value assessment and price and reimbursement process. **For those ATMPs for which the CRM/CTG recommends reimbursement, spread payments can bridge the gap between willingness to pay for the whole patient population and possibility to pay**.



How would the decision process with regard to spread payments be?

Today, discussions between payers and companies on spread payments mainly occur within the WG art.111/112 and the final decision lies with the Ministers of Social Affairs and Budget. The decision to implement spread payments for a given therapy should remain the result of a dialogue between payers and manufacturers. However, we believe that the **identification of eligible candidates for spread payments should start earlier**. Horizon scanning exercises could be helpful.

If there's a mutual agreement that spread payments are justified, the duration of the application of the principle of spread payment as well as the structure and duration of the over-time payments/patient, should be tailored to the specific product, reflecting its value to patients and society (EFPIA 2020).

The budgetary processing of use of spread payments for ATMPs in Belgium

The reimbursement of ATMPs must comply with Belgian budget and accounting regulations. The Belgian federal budgets and accounts are drawn up in accordance with ESA 2010. ESA 2010 is a European framework with which all European member states must comply when budgets and accounts are submitted to the European Commission and Eurostat in the context of the European semester, among other international

agreements (ESA n.d.). The Belgian budget regulations relevant to the pharmaceutical budget have been determined accordingly (Belgian Social Security n.d.).

In the ESA 2010 framework, any given NIHDI expense is imputed when 4 criteria are met:

1. The amount is exactly known and determined
2. The identity of all parties involved is known
3. The obligation to pay exists (law, contract,…) regardless of the date of payment
4. The possession of an accountability document

This implies, among other things, when booking expenses:

- The full amount is booked in its entirety at the moment when the right to payment is created: this is the moment when the therapy is administered (or a proxy: e.g., moment of delivery to the patient in the retail pharmacy); the date of the actual payment, a cash transaction, is irrelevant.
- Once the amount is known, the full amount is imputed in its entirety: the use of depreciations, provisions, etc. is not used, unless in specific cases.

Spread payments are in line with ESA2010 legislation in the following 2 cases:

1) The use of spread payments is compatible with ESA2010 when the future payments are accounted as a debt
2) Spread payments in an outcome-based agreement with a pay for performance component (P4P): future payments don't have to be booked as a debt if the uncertainty about the future payments is high enough

The pay for performance agreement is a tool that already exists but is used very little up to this moment. This tool has several advantages:

- The payer pays for results: the payment is linked to the achievement of predefined milestones at given timepoints after the initial administration of the therapy
- The risk is thereby shared with the company
- Due to the system of conditional milestone payments due to the use of a pay for performance agreement, the initial high investment cost is spread over several years if the therapy is successful: this flattens out the budgetary impact of a new therapy over several years, leading to a more predictable and manageable drug budget.

Considering the uncertainty of reaching certain milestones described in the agreement, the exact amount is only known and determined at the moment the milestones are reached, resulting in an obligation to pay and imputation in the accounts following the ESA 2010 framework.

The processing of ATMP's following this procedure within the pharmaceutical budget and thus ESA 2010 proceeds as follows:

- On the moment of the administration of the treatment: first initial payment to the company as described in the agreement and imputation of this first payment in the accounts of NIHDI following the budgetary legislation, and thus in the ESA 2010 framework.
- On reaching a milestone at a given timepoint, as described in the agreement: payment of the amount linked to reaching that specific milestone to the company and imputation of this milestone amount in the accounts of NIHDI following the budgetary legislation, and thus in the ESA 2010 framework.
- The use of conditional milestone payments is considered as a contingent liability to the payer under the ESA 2010 framework due to the uncertainty of the creation of an obligation of the payment as they are included in the agreement (ESA 2010, 5.08).
- Examples of such milestones could be the absence of relapse after a certain period (e.g. annually after the administration of the therapy), the discontinuation of the old therapy in the months after the administration of the new therapy or any other key performance indicator (KPI), including disease specific KPI's.
- If a milestone is not met, no obligation to pay will be created and no payment will be made to the company nor is any expense registered in the NIHDI accounts.

In order to allow the implementation of spread payments in Belgium over a period longer than 2 years, a change in the NIDHI law of 14 July 1994 is needed. Today, article 174 3° of the NIHDI law of 14 July 1994 stipulates that hospitals should bill medicines to sick funds within two years after delivery of the medicine (date of prestation). In order to allow pay-for-performance agreements and resulting spread payments in Belgium that can span over a period longer than 2 years, a solution should be found to expand the notion of 'date of prestation' to the moment of the due payment date in case of spread payments and the moment of the milestone in the case of an outcome-based P4P agreement: this means that the limited period of 2 years should start at that date instead of the real date of prestation (only applicable for the first payment).

Since hospitals are not consolidated with sector S13 within the ESA2010 framework, the imputation of spread payments in the accounts is done at the moment of imputation in the NIHDI accounts, on the basis of hospital data that are transferred to the NIHDI via the health insurance funds. The hospitals' invoicing system will have to be adapted to spread payments. However, this is not a major problem as hospitals already use spread payments in different guises such as depreciation of buildings or heavy medical equipment.

A good billing system for spread payments should have the following characteristics:

- It must not lead to a heavier administrative burden on hospitals
- No pre-financing by the hospitals: i.e. no system whereby they pay the company for the full amount and only request funding from the health insurance funds in instalments
- The system should support outcome-based agreements with a P4P component

Based on these criteria, the following billing process could be used, independently of the use of an outcome-based agreement with a P4P component: when invoicing an ATMP using spread payments, the hospital imports as many invoicing codes as there are spread payments, similar to the depreciation of a building: each code corresponds to a (spread) payment and a payment date, most of which are in the future. Each time a payment becomes due, the hospital pays the company, and a reimbursement request is submitted to the health insurance

funds. Because each payment has a different code, the instalments can be followed up, as can the P4P component, by both the health insurance funds and the NIHDI.
The annual follow-up of the P4P component is done by the NIHDI, or a government institution authorised by the NIHDI, such as Sciensano. The financial settlement of this P4P component can be done in the same way as is currently being used in outcome-based agreements.

5.4. Changes in the HTA process: capturing long term benefits and broad value of ATMPs

Adaptations to Belgian HTA processes are recommended for ATMPs specifically, aiming at recognition and consideration of ATMP-specific limitations. The adaptations should aim at solutions that allow both timely patient access and parallel generation of further evidence in the target population being granted access. **RWE collection will be key** (see also point 5.2)**, next to a holistic outcome assessment of innovative or surrogate endpoints.**

The evidence package of ATMPs at time of EMA approval or access approval may not address all questions posed in traditional health technology assessments. For full validation of their value, ATMPs targeting a long-term or curative benefit in small populations with rare and severe disorders require far longer evaluation than typical trial durations. Also, the use of well-established or hard endpoints to determine long-term effect is not always feasible due to the chronic, severe, or poorly understood nature of the indications ATMPs often target.

The EMA grants marketing authorisation on a basis of positive benefit-risk ratio of a drug. The EMA has a flexible approach recognising both the therapeutic potential and need for ATMPs, utilising expedited processes such as conditional marketing authorisation[4] and/or accelerated assessment through PRIME[5] designation.

In current HTA processes, the EMA's evaluation of benefit-risk and level of unmet medical need is considered, but the HTA bodies are assessing comparative efficacy, budget impact, and/or the cost-effectiveness of a therapy, with less flexibility regarding lack of treatment options and limitations of evidence collection. **Early collaboration between industry, the European Medicines Agency (EMA) and Health Technology Assessment (HTA) agencies** is therefore needed to harmonise evidence requirements and facilitate greater acceptance of ATMP evidence including indirect treatment comparisons, surrogate endpoints, and real-world evidence (RWE). **Pharma.be also supports the re-use of European clinical evaluations in the Belgian reimbursement procedure** (such as the joint clinical assessment reports foreseen in the future EU HTA Regulation).

[4] Conditional marketing authorisation is a pragmatic tool used by the European Medicines Agency (EMA) for the fast-track approval of a medicine that fulfils an unmet medical need.
[5] PRIME is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. Through PRIME, the EMA offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicine applications.

ATMPs are directed at the underlying cause of a condition and offer durable, potentially curative, or near-curative benefits. The recurring treatment costs of chronically managed patients can be greatly reduced and even eliminated with a one-time administration or short course of these novel therapies.

These treatments could potentially end the patient's burden of illness and have a major impact on the patient's quality of life, resulting in cost offsets (eliminating or reducing the need for long-term treatment, hospitalizations, and other care) and productivity gains that could span a lifetime. As a consequence, payers need new models for assessing their value and all relevant aspects to assess economic value should be considered (ARM, A Transformative Therapy Value Model for Rare Blood Diseases 2020) (Seboio 2020).

HTA should be performed from the broader societal perspective, in order to take into account the potential important benefits these type of innovations may have on the society as a whole.

Budget impact analyses should allow to capture a holistic view of both ATMP costs and savings over the patient's lifetime. Therefore, both the nature of the costs as well as the time horizon used for budget impact analyses should be re-evaluated for ATMPs.

- The current regulatory framework requires budget impact analyses to include both costs for the drug budget but also those for the healthcare budget (RD 01.02.2018). To assess the full economic value of ATMPs, the broader societal perspective should also be added to the budget impact analysis, hence including savings **going beyond the healthcare budget**.

- Today, neither the RD of 01.02.2018 nor the KCE guidelines on budget impact analyses impose a restriction in the **time horizon for budget impact analyses**. The KCE guidelines state that 'an assessment of the budget impact of a given intervention should be performed over a time period that is sufficient to reach a steady state impact on the general annual health care budget. Many factors, such as the diffusion rate, type of treatment and disease survival, long-term events, evolution of target population, etc. may thus have an impact on the appropriate time horizon for the BIA.' (Cleemput 2012). In practice, however, a time horizon of 3 years is used in the CRM evaluations, as indicated in NIHDI's guidelines for reimbursement dossiers (www.inami.fgov.be). We therefore suggest an adaptation of these guidelines as well as the evaluation by the CRM of budget impact analyses with time horizons longer than 3 years for ATMPs.

It is recommended to reconfigure budget silos to ensure funding allocated to pharmaceuticals incorporates the savings made in the wider health and social care system resulting from ATMP benefits. In case the savings of ATMPs in other RIZIV/INAMI budgets are much larger than the pharmaceutical budget expense, **payers should consider gain sharing** between the budget benefiting from the advanced treatment intervention and the budget providing access to the enabling treatment (i.e., the pharmaceutical specialties budget) next to more **dynamic budget allocations** (Maes 2019).

We would welcome an **adaptation of the existing cost-effectiveness frameworks** for reimbursement applications and decisions for ATMPs. In that context, we would welcome that health economics and outcomes

research experts would be consulted, in order to ensure the full value of ATMPs can be reflected in possible cost-effectiveness analyses. Examples of potential changes are the use of a societal perspective, in which all relevant costs and outcomes are valued independently on whom these costs and consequences fall, and adapted discounting rates for costs and outcomes (EFPIA 2022).

5.5. Cross border care

In a 2017 study, the KCE concluded that specialised and complex care is best centralised in centres of expertise to improve quality and survival rates because the care on offer in Belgium is often too fragmented (Van de Voorde, 2017). This was the case for pancreatic, oesophageal and lung cancer, but also for other complex care. This study shows that a minimum critical mass is required to provide quality care. This also applies to ATMPs and the field of (ultra) rare diseases where Belgium lacks a critical mass to provide quality care and cross-border care can provide a solution. In addition, centralization offers the opportunity to share investments over a larger population, as is the case with proton therapy centres, making care less costly.
For patients with rare diseases, travelling abroad may be the only option to access treatments – these can be complex and need to be administered in specialist centres. Research by the European Commission shows that the integration of cross-border care ensures all patients in Europe can have access to appropriate care and leads to a lower budgetary pressure on the healthcare budgets of European countries in the field of cost-intensive/highly specialized medical equipment (European Commission, 2016).
Cross-border care within the framework of specialised centres of expertise has a number of advantages for the national authorities:

- A better distribution of investments in expensive infrastructure
- Avoiding investments in under-utilised capacity
- A better distribution of investments in building highly specialized knowledge in the case of rare diseases: this avoids costs
- Improved access to appropriate and quality care for patients: better treatment for patients at a lower cost
- Aggregated improved knowledge and clinical expertise in complex, rare interventions that these ATMP medicines might require
- Avoiding financial barriers for patients to benefit from specialist care and thus avoiding a two-tier healthcare system
- Avoiding patient waiting lists if supply is limited domestically.

With the introduction of ATMPs to the European market, cross-border health care will gain further importance: ATMPs are highly innovative technologies, administered often in a few specialised treatment centres around Europe (sometimes also in Belgium, sometimes not) with patients in small number all around Europe (e.g., in Belgium also in very few numbers).
Due to the specialised care that many ATMPs require, the **use of specialised treatment centres is necessary**: both within Belgium, and in the case of more rare conditions also if those centres are located outside Belgium, through cross-border care (CBC). Only in this way can sufficient qualitative care for the patient be guaranteed.
The following approaches are proposed to make the use of specialised treatment centres via cross-border care successful:

1) The traditional route for patients in cross-border care via Regulation 883/2004 with its implementing provisions in Regulation 987/2004: form S2 is used. This means that the medicines in question have successfully completed a CTG/CRM procedure. The problem that may then arise is that the medicine is not available on the Belgian market, but this problem is being solved via a change in the law (Wet houdende diverse dringende bepalingen inzake gezondheid / Loi portant des dispositions diverses urgentes en matière de santé, art. 96), although in some cases the same problem could arise as well for the technical acts of preparing and administering the drug. Given the positive decision of the CTG/CRM, it seems advisable and acceptable that patient approval should be quicker than is currently the case (maximum 45 days): given that the administration of ATMPs is often time critical, an automatic or rapid approval with the same deadlines as for domestic care is appropriate, with the least possible administrative burden for the patient: a maximum period of 1 week should be possible. We suggest that special attention be paid to the possible cost and accommodation for a travelling relative, for example in the case of a paediatric indication.
2) Through an agreement with one or more foreign specialised treatment centres as is the case for proton therapy[6].
3) Special solidarity fund (BSF/FSS)[7]: this option appears to be useful only in the event that the number of patients per year is so low that it makes little sense to initiate a CTG/CRM procedure: e.g., a maximum of 1 patient per year. This pathway should remain the exception to the rule and should only be used in the case of rare or ultra-rare diseases. A recent example is the case of the lifesaving ATMP Strimvelis, where one Belgian patient once in 10 years is excepted and the only specialized treatment centre is located in Milan, Italy, where less than 5 European patients a year are treated. This extremely low number of patients makes it difficult to use a proper reimbursement procedure in all individual European member states.

The European Commission has set up the European Reference Networks (ERNs) in order to better exchange information on complex and rare diseases and improve the quality of care. Belgian patients currently have the right to a second opinion for care. Given the specialist nature of many conditions, it seems a positive step for patients to **extend the Belgian right to a second opinion to the ERNs**: this would allow a Belgian patient to exercise his right to a second opinion via an ERN.

[6] https://www.riziv.fgov.be/nl/professionals/verzorgingsinstellingen/ziekenhuizen/zorg/Paginas/hadrontherapie.aspx
[7] https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/bijzonder-solidariteitsfonds/Paginas/default.aspx

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Annex 1 List of questions used to guide stakeholder dialogue sessions

(non exhaustive)

General questions

1 What is your experience with ATMPs until now? Are ATMPs a priority for you?
2 According to you, which societal benefits could ATMPs bring to patients and the healthcare system?
3 What are the 3 most important changes needed to overcome current hurdles for ATMPs according to you? What is the level of urgency of these changes?
4 Compared to other EU countries, how would you qualify Belgium's position on ATMPs in your field of expertise: pioneer, rapid follower or lagging behind?

Questions on specific topics

Shift in treatment paradigm

1 From your perspective, what are the important events in the gene & cell therapy patient journey and treatment process? What do you consider to be the challenges and implications for patients and their families that should be considered?
2 According to you, how will ATMPs impact doctors/healthcare professional's daily work? Do you think these changes, if any, pose a challenge and should be anticipated for? How?

Clinical trials

1 Which formats between health authorities, patients, scientists and industry representatives can ensure that innovation aspects are sufficiently considered for clinical studies of ATMPs in rare diseases?
2 According to you, how can patient organizations play a role in the development of ATMPs for rare diseases?
   - Who should take the initiative?
   - Who organizes and leads the discussions?
   - How to ensure we reach representative patients?
3 What steps can be taken to harmonize the Genetically Modified Organism (GMO) requirements and process across EU member states and therefore accelerate study startup and maintain EU competitiveness for the development of ATMPs? Could the experience of regulatory flexibility given by the EU Commission for clinical trials in COVID-19 treatment/prevention, which foresees an exemption of the GMO requirements, be considered?
4 Acceptability of common application form for GMO ATMPs along with the CTA submission in context of coming into force Clinical Trial Regulation?
5 More Clinical trials in ATMPs are performed outside EU than in EU. What would be your suggestion on how to attract/make EU more attractive for ATMP clinical studies?

Regulatory

1 What are opportunities for international collaboration, as e.g. within ICH as EU in its forth pillar of the Pharma Strategy strives to strengthen international capacity building in harmonizing standards or/ and as e.g. strengthening the EMA-US FDA agenda on ATMP and build respective capacities within the transatlantic agenda which would perfectly fit the EU´s proposal on EU-US agenda on innovation and standards?

2 ATMP are usually subjected to accelerated assessments which in most instances are not held by the Agency. Would you see an opportunity for review of ATMP data on rolling basis and in view of concept of dynamic regulatory assessment? This is a new concept developed by EFPIA in order to improve approval of drug applications which would also apply for ATMPs and should include learnings from COVID.19 drug approvals. How can learnings from COVID 19 be implemented in ATMP development and assessment?

3 How to measure disease modifying or curative effect ? What role can patient-reported outcomes play in measuring the impact of ATMPs and what unique aspects should be considered? Utilizing of real-world evidence in ATMP decision making process remains a challenge. Real world evidence can provide additional safety and efficacy consideration for ATMPs, adding therapeutic value and supporting positive reimbursement decision especially if conducting randomized control clinical trials deems unethical or impractical. How would you value the RWE in context of regulatory approval?

Manufacturing

1 As the manufacturing process of Advanced Therapy Medicinal Products (ATMPs) such as cell and gene therapy is complex, we would like to receive your opinion on possible collaborations on some steps. Availability/accessibility of national Bank of Human Biological Material?

2 Release of ATMPs e.g. AAV based therapies in EU usually require re-testing if they manufactured outside EU. Is there a possibility of an exemption and if not, which test you would consider as necessary for release?

Specialized treatment centers

1 According to you, which criteria should a hospital fulfill to be recognized as an expertise center for cell and gene therapy? Should these criteria be specific to ATMP therapy types, therapeutic areas of specific diseases?
2 Do you think an evolution is necessary to evolve to the uniform and standardized JACI accreditation? Is there a role for our country to drive the debate on a European level?
3 Do you see capacity issues on the long term by limiting treatment centers and how do we anticipate to this challenge?
4 What do you think could incentivize Belgian hospitals to become a center of excellence?
5 Can a hospital that is not a cell and gene therapy expertise center remain involved in the treatment of a patient that has received an ATMP? How could this be organized? What is needed for this?
6 How can we ensure an optimal referral system and how can we make sure that hospitals which do not provide ATMPs stay in touch with the (patients') outcomes after referral?
7 In the case of very rare & genetic diseases, should cross border care in the EU be considered? Under which conditions should Belgian patients be able to have access to ATMP treatment if there is no expertise center in Belgium? How can this be organized in practice?

Access

1 Outcome based agreements: what are the advantages of such agreements for ATMPs according to you and what are the challenges and potential solutions related to these?
   How should the outcomes be collected and reported?
   Who should organize and finance the data collection?
   Who needs to decide which data to collect?
   Who should be the Third Trusted Party?
   Should the data collection be Belgian or European?
   Why can the data from GMDs not be extracted?
2 What is your view on the use of spread payments for ATMPs? Should these be restricted to certain types of ATMPs?
3 According to you, should the current price and reimbursement legislation be adapted to create access to ATMPs while ensuring the sustainability of the HC system?
4 As the science of ATMPs continues to evolve and the number of products in development is increasing, how can health authorities and HTA bodies develop/maintain sufficient resources and expertise?
5 Cross-border healthcare: Would you welcome and recognise more joint clinical assessments under EUnetHTA or in the context of regional collaborative initiatives in assessing the viability of CBHC (S2) as a patient access route for BE patients going abroad?
6 Is there a need for a new/specific legal framework for early access to ATMPs in Belgium? What is your view on the ATU scheme in France, considered as best practice example?