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INTRODUCTION

The Idea Generation Process: Lack of Literature and Specific Industry Specific Needs

Around January 2021, an interesting request by a Swiss-based pharmaceutical company[1] was submitted to Professor Gigante and Professor Cerri. The company, a developer of Advanced Therapy Medicinal Products (ATMPs), asked to create a specific report, to be later presented to Italian regulators, on potential payment schemes that could sustain an overall increase in the usage of these innovative care treatments.

When we started to go through some literature on the field, finding relevant information has been extremely painful since almost nothing had been written on such specific – but extremely useful – topic. Lately, also going though some literature from Professor Jonsson[2], one of the few economists making some specific research about ATMPs[3], we were convinced about the economic problem and importance of ATMPs. When he confirmed us the potential ground-breaking and innovative role ATMPs could have, coupled with the general lack of literature and the resulting interesting impact that this research could achieve, especially on specific industry needs, we realised how this idea could be the right one for the final thesis.

Another point we want to make about the process of idea generation, before going in-depth with our analysis, is that the more we studied the topic, also from medical and ethical perspectives, the more we started to feel a moral obligation to develop

[1] Undisclosed for obvious reason

[2] Professor Emeritus at the Stockholm School of Economics, partner school of my double degree program

[3] Jonsson B., Hampson G., Michaels J., Towse A., von der Schulenburg J. M. G., Wong O. April 2019. "Advanced Therapy Medicinal Products and Health Technology Assessment Principles and Practices for Value-Based and Sustainable Healthcare".

this model that could help the widespread adoption, starting from the Italian territory, of these new cures for rare and terminal diseases.

In the first section of the thesis, we go through the literature review. Initially, with a focus on the definition of ATMPs, their current availability on the market, the main pros and cons for their adoption, and the current regulatory framework in the European landscape. Then, we move on with the analysis of the Italian eco-system, both from the National Health System structure and the approach followed with ATMPs – always maintaining an economic and regulatory point of view. Lately, we analyse the different potential payment schemes proposed and used for ATMPs – the main obstacle to their usage – and we propose a new payment model for these cures. Specifically, we propose a new payment scheme based on the idea of accounting for ATMPs as intangible assets, with the possibility of amortizing them through different years.

In Section II, we conduct an empirical analysis based on the Italian case. Firstly, by running a regression with the aim of proving how an increase in the population and in the average life expectancy, would lead to a major potential usage of ATMPs. Secondly, and most importantly, by creating a complex financial model with many different inputs, describing the economic situation of ATMPs usage in Italy in different scenarios – also showing the current economic non-sustainability of these drugs. Lastly, we demonstrate how with our proposed payment scheme, ATMPs would become definitely sustainable for the Italian National Health System, in the long run. In the last section, we draw some specific conclusions coupled with a general advice for the Italian legislator.

We would like to close the introduction part with a quotation from Professor Urbani[4], which we kept in mind throughout the research, and which we would like you to keep

[4] Urbani A. December 2019. Il Servizio Sanitario Nazionale guarda al futuro – Verso nuovi e più evoluti schemi di governance. P. 141.

in mind while reading this elaborate: "*Public health systems must be able to adapt effectively to a changing environment and find and apply innovative ways to deal with difficult situations such as skill or resource shortages in certain areas, unanticipated increases in demand with limited resources. In other words, they must increase and maintain their resilience*".

SECTION I: LITERATURE REVIEW

1. Advanced Therapy Medicinal Products – Definition and Main Challenges

a. What are ATMPs?

In the last decade, medical research has (also) been focused in developing new personalised medicinal strategies for extremely specific stages of major severe diseases. Advanced Therapy Medicinal Products (ATMPs) are one of the main results of these studies: this specific bucket is characterised by its high complexity, given they all contain either living cells or viral vectors. ATMPs is a comprehensive term for four main drug classes[5]:

- Somatic cell therapies, involving the placement of a human gene into a living person's somatic cell;
- Gene therapeutics, based on the replacement inactivation or introduction of genes in different parts of the human body;
- Tissue engineered products, using lab-created cells or tissues to regenerate, repair or replace human tissues not properly working;
- Combined ATMPs, which are a combination of these technologies within a medical product.

Given their intrinsic characteristics, ATMPs are different from traditional drugs and are characterised by[6]:

- Being one-shot, in fact, they are administered in a single treatment, unlike traditional drugs and protocols used for other diseases (which involve repeated and regular treatments), with an obvious time mismatch between current

[5] Eder C., Wild C. April 2009. "Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption".

[6] Sovani R., Marè M., Cicchetti A., La Licata P. July 2020. "La valutazione economica delle terapie avanzate: le caratteristiche, le ragioni e la proposta di un nuovo approccio economico e contabile".

costs, concentrated in the short term, and future benefits, spread over a longer time horizon;

- Having high investment costs, but also significant clinical, therapeutic, social and economic benefits for healthcare systems and patients' health;
- Offering new prospects of recovery to patients suffering from diseases that, until now, had no therapeutic solution;
- Intervening directly in the causes of the disease (and not only in the symptoms);
- Being biologic medicines composed of the patients' own cells, which are taken from the hospital and then engineered at the company's production sites;
- Being administered only in qualified and specialised centres and originate from extremely innovative and complex platforms;
- Generating additional benefits in terms of recovering productivity over long periods of life.

Similar definitions, with different shades, are given by literature (above), the European Medical Agency, and the specific regulatory framework.

EMA referred to ATMPs as "(…) *medicines for human use that are based on genes, tissues or cells. They offer ground-breaking new opportunities for the treatment of disease and injury*"[7]. With this definition, the European Medical Agency, strongly underlines the innovative nature of these therapies and its potential strong impact in curing rare and severe diseases.

The European Agency also classifies ATMPs with the already listed four categories, with specific definition for each category[8]:

- Somatic cell therapies, "(*…) contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be*

[7] EMA

[8] EMA

used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases";

- Gene therapeutics, "(*…) contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases*";
- Tissue engineered products, *"(…) contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue*";
- Combined ATMPs.

From a juridical standpoint, a comprehensive wide regulatory framework on ATMPs has been established within the European Union on 30th December 2008: the European Commission Regulation 1394/2007 (amending the Directive 83 of 2001).
With this regulation, the legislator defines specific parameters to identify each new ATMP into one of the specific buckets included in the general umbrella term.
This regulation defines ATMPs as any of the following medicinal products for human use:

- A gene therapy medicinal product, which *"(…) means 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; 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 shall not include vaccines against infectious diseases."*[9]

[9] European Commission Directive 83/2001, Annex I, Part IV

- A somatic cell therapy medicinal product, which "*(…) means a product that: contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue."*[10]
- A tissue engineered product, which "(…) *means a product that: contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue."*[11]

ATMPs are a relatively new (first advanced therapy approved in the European Union in October 2009[12]) and a continuously evolving phenomenon. In general, we are talking of a currently relatively small phenomenon, in which 16 ATMPs[13] (in addition, 5 licenses were withdrawn over time), of which only 14 are currently in use[14], have been approved in the European Union since November 2009. It must be noticed that, all ATMPs currently in use have been authorised after March 2015.

On the other hand, an increasing number of ATMPs are in an advanced trial phase, and an important pipeline of newly developed ATMPs is expected within the next 10 years (c. 628, active, individual, US-based clinical trials programs for durable gene and cellular therapies[15]).

[10] European Commission Directive 83/2001, Annex I, Part IV

[11] European Commission Regulation 1394/2007, Chapter 1, Article 2(b)

[12] OTS. July 2021. "Le terapie avanzate in Italia e in Europa".

[13] OTS. July 2021. "Le terapie avanzate in Italia e in Europa".

[14] Eder C., Wild C. April 2009. "Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption". Canonico P. L., Jommi C., Lanati E., Lucchetti C., Luccini F., Morani M., Raimondi M. October 2021. "Quarto report Italiano sulle advanced therapy medicinal products".

[15] Quinn C., Young C., Thomas J., Trusheim M. June 2019. "Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System".

ATMPs that received the EMA approval (not withdrawn) for being used in the member States are:

- Holoclar: the first stem-cell based ATMP approved by the European Union in March 2015, developed and patented by Chiesi Farmaceutici. This cure has been researched to cure severe stem cell eyes-deficiencies;
- Imlygic: the first gene therapy to cure oncologic patients that obtained the EMA approval in September 2015. The drug, patented by Amgen, is used for patients with severe melanoma;
- Strimvelis*:* gene therapy approved in May 2016, to cure severe combined deficiency due to adenosine deaminase deficiency (ADA-SCID) patients. The drug has been created by GSK;
- Spherox*:* a tissue engineered product developed by CoDon and approved in May 2017. The ATMP is used to cure severe cartilage defects in the knee joint;
- Alofisel*:* somatic cell therapy patented by Takeda Pharma, which received the approval in March 2018. The therapy is used to cure Chron's disease patients with perianal fistulas, through the implantation of stem cells in the relevant tract;
- Kymriah: a gene therapy developed by Novartis, approved by the EMA in early August 2018. The cure is intended for young patients with specific blood disease (ineligible for stem cell transplantation): refractory B-cell acute lymphoblastic leukaemia and large B-cell lymphoma;
- Yescarta: a gene therapy patented by Kite Pharma, approved in late August 2018. The drug is intended for patients with aggressive non-Hodgkin´s lymphomas (mainly B-cell lymphomas);
- Luxturna: a gene therapy developed by Novartis and approved in November 2018. This ATMP targets patients with hereditary retinal dystrophy, a cure with low or no cures other than this;

- Zynteglo: gene therapy developed by Bluebird Bio and approved by the EMA in May 2019. This ATMP targets patients olderthan 12 years old, suffering from beta thalassemia transfusion dependent without β_0/β_0 genotype;
- Zolgensma: gene therapy approved by the EMA in May 2020, patented by Novartis. This therapy cures Spinal Muscular Atrophy (SMA1), a very aggressive disease that normally leads patients to death in less than 10 years;
- Tecartus: gene therapy licensed by Kite Pharma and approved by the European Agency in May 2020. It cures patients with a rare and aggressive lymphoma: the relapsed or refractory mantle cell lymphoma (MCL);
- Lybmeldy: gene therapy approved in December 2020, developed by Orchad Therapeutics. The therapy aims at curing metachromatic leukodystrophy patients;
- Skysona: gene therapy approved in July 2021, licensed by BlueBird. The drug cures patients with adrenoleukodystrophy disease (i.e. patients with a the genetic mutation ABCD1);
- Abecma: gene therapy licensed by Celgene Europe, approved by the EMA in August 2021. It targets patients with multiple myeloma at specific (aggressive and late) stages.

It must be noticed that some of these ATMPs have not received (yet) the Italian approval for commercialisation:

- Skysona and Abecma, for timing purpose, since they were only recently approved by the EMA;
- Imlygic, since the request has never been submitted by its parent company.

As mentioned before, more ATMPs are expected to be available in the market in the upcoming years, even in the very near future. Specifically, there are at least 8

ATMPs[16] in the process of marketing authorisation by the EMA and / or with a planned marketing launch by 2023. This clearly does not mean that by 2023 only 8 more ATMPs will be available in the European market: as Casey Quinn, PhD, Colin Young, PhD, Jonathan Thomas, BSc, Mark Trusheim, MSc studied in "Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System", more advanced therapies are expected to be developed and made available in the US market, and consequently in the European market as well, in the foreseeable future. Specifically, only considering gene therapies, up to 60 new ATMPs are expected to be launched by 2030 (c. 5.3 times more compared to the actual available ATMPs in the market) with a targeted number of US-based cumulated patients of up to 350,000 by 2030. Considering this proportion with the Italian population[17], this would mean that at least[18] 64,000 Italians could be cured with ATMPs by 2030 (around 0.1% of the current population), leading to a strong impact not only on the standards of living of these patients, but also on major macro-economic indicators[19].

In general, the expected development of ATMPs is that of curing more and more also severe disease that are not that rare, such as different types of cancers or different minor hereditary disease of specific organs (e.g. keratoconus in eyes, others). Clearly, this would lead to an even broader impact both socially and economically, with the potential target population that could become much wider than currently projected.

Other than traditional pharmaceutical companies, such as Novartis or GSK, there are also biotechnology companies purely focusing on gene therapies (e.g. Orchad

[16] Eder C., Wild C. April 2009. "Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption".

[17] 60.36m divided by 328.2m – considering the population of the two states in 2019

[18] Only expected new gene therapies are considered, not all classes of ATMPs

[19] Demographic and GDP growth, increase in the life expectancy. This topic is further investigated in Section II

therapeutics, Atara Biotherapeutics) – which are raising funding of required capital through the public (IPOs), or via investors with specific know-how and expertise in the sector[20] – which are investing in the R&D of new ATMPs[21].

[20] McKinsey

[21] Understanding, in future research on the topic, how the European Union and member States could facilitate the R&D of new ATMPs with bonuses and updated regulations could be extremely interesting

b. Pros and Cons of ATMP Usage

The usage of ATMPs leads to different advantages and disadvantages: we will analyse them from the medical, ethical and economical point of view.

From the medical perspective, Advanced Therapies have major advantages, and it is hard to find impacting cons on their usage. In fact, many of the diseases that can currently be cured with ATMPs are health problems that cannot be treated, or that can be treated only partially, with traditional therapies. As a result, these drugs offer new solutions and improved standards of living for patients that otherwise would either die in a few years from the diagnosis (e.g. SMA1 patients[22]), or would be convicted to a lower-level lifestyle than the ones they could have if cured (e.g. hereditary retinal dystrophy[23] patients).

Lastly, a major advantage of ATMPs is that patients can be cured with a one-shot treatment; i.e. ATMPs can be injected (or administered in other ways) with a single session that could cure a very rare and / or strong disease.

All of this is possible because ATMPs have a completely different idea behind their realisation, which differentiates them from standard pharmaceuticals and biologics. ATMPs have curative potential by addressing underlying genetic or cellular mechanisms of disease, and by acting through multiple mechanisms on different cellular targets[24] (i.e. dramatic and long-lasting positive impact on health).

One disadvantage is that these therapies are currently available only for a very tiny group of rare diseases. As listed before[25], only a few ATMPs are currently available in the European market and, as a result, a very small group of diseases can be cured

[22] There is no existing cure other than ATMP for this fatal disease

[23] There is no existing cure other than ATMP for this disease

[24] Magrelli M. F., Merra A., Pellegrini G. June 2020. "Surgery Versus ATMPs: An Example From Ophthalmology".

[25] Section II, Chapter 1.a

with these therapies. Also, research is mainly focusing on finding ATMPs to cure rare disease that cannot be cured, or only partially cured, with traditional therapies and not on more common illnesses. On the other hand, this is a transitory phenomenon since research is at a first stage in this environment; indeed, there is a firm expectation that in the (near) future, even more research will be conducted, resulting in a greater number of diseases, that could be cured with ATMPs.
In conclusion, it must be noticed that ATMPs do not guarantee the complete working of the treatment completely. On average, they work only on c. 60% of targeted patients[26].

Secondly, from the ethical point of views there is a small debate, partially solved in the last years, leading to two different "factions", about the overall usage of stem cells, for medical reason, or the application of gene therapies.
Thankfully[27], only a small fraction of ATMPs uses stem cells and, since these cures treat patients that would probably die in a few years without the usage of ATMPs, even the most convicted faction cannot deny the evidence of medicine and the fundamental role of stem cells and of gene therapies as unique possibility to save human lives. Overall, ethically it is obviously largely accepted that curing patients is better than letting them die – obviously a very large advantage compared to the whole stem cell / gene therapies issue.
In addition, some literature poses the focus on the Health Technology Assessment (HTA) and financing decisions, particularly to the issue related to the accessibility to these cures[28]: *"(…) given the nature and disruptive consequences of ATMPs the assessment and adoption of these medicinal products raises important ethical*

[26] This is a fundamental step, that must be kept in mind, for the payment schemes analysis we will conduct later

[27] In our opinion

[28] Goncalves E. April 2020. "Advanced Therapy Medicinal Products: Value Judgement and Ethical Evaluation in Health Technology Assessment".

questions, both at a policy and at society level that should be properly addressed. HTA can be made more transparent and reliable, and simultaneously promote robust and accountable decision making, by turning explicit the value judgments implicit in HTA. Ultimately, there should be no core conflict between ethical requirements and HTA in a scenario where the goal is to promote equity and access of patients to truly innovative therapies such as ATMPs, while assuring the sustainability of healthcare systems". Specifically, one of the main underlined issues on ATMP usage is the difficulty to deliver them to all the targetable population due to their expensiveness.
The final goal of our research is in line with solving this issue: we aim at delivering a model that could be useful in increasing the number of treated patients – and, as such, the accessibility of all population – with ATMPs, by making them sustainable for the National Health System.

For our research, the most interesting point of view is the economic one, whereas the analysis must be conducted rationally on ATMPs impact on the National Health Systems' financial statements to value their sustainability.
The main economic concern is that, on average, ATMPs cost a lot. We are speaking of an average price ranging from €400,000 to €600,000[29] with peaks of medicines that cost more than €2,000,000; resulting in cures that cost much more compared to traditional therapies (e.g. a traditional chemotherapy R-CHOP treatment with 6 cycles costs around than €35,000[30]).
Moreover, while today only a few ATMPs exist, in the near future more and more ATMPs will be available[31] on the market and, the total population and the average life

[29] The Economist

[30] Hornberger J.C., Best J.H. April 2005. "Cost utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma".

[31] Section II, Chapter 1.a

expectancy would increase[32]: more and more patients would be potentially treatable, resulting in an even larger problem for National Health Systems.

This huge price requested for ATMPs leads to some sort of disorder: only a small fraction of the targetable population is treated with ATMPs. Indeed, current National Health Systems, to maintain the economic sustainability with actual payment schemes[33], can only support to cure a relatively small part of potential patients. For example, as indicated on the Fourth Italian Report on ATMPs[34], the National Health System is expected to support the treatment of up to 10% potential patients per annum for targeted potential diseases with more than 1,000 patients that could be treated in Italy.

There are different explanations and analyses that literature offers on the topic.

As The Economist explains in its columns "The Economist explains"[35], there are different reasons why gene therapies (the main fraction of ATMPs) are extremely expensive:

- The making process is extremely labour intensive since tailored to each patient (resulting in different R&D processes for each patient);
- The approval scheme is particularly long and expensive. After the initial R&D process, an extensive, long and expensive trial scheme – different trial phases, with many patients – is required by the EMA to achieve the authorization to be sold in the unique market;

[32] Correlation proved in Section II, Chapter 1

[33] Payment-by-result scheme, upfront payments of ATMPs (reimbursed if not properly working on patients)

[34] Canonico P. L., Jommi C., Lanati E., Lucchetti C., Luccini F., Morani M., Raimondi M. October 2021. "Quarto report Italiano sulle advanced therapy medicinal products".

[35] N.L. August 2016. "Why gene-therapy rugs are so expensive". The Economist

- The pharmaceutical / biotechnology companies producing ATMPs sustain that these cures more than offset their cost through the overall produced economic benefit distributed in different years[36].

Other academic research points out other main issues that heavily influence the pricing of ATMPs:

- General extremely high research and development costs, as well as other manufacturing costs[37];
- Stringent regulatory requirements, resulting in high costs for the trial and approval phase[38];
- Other reimbursement challenges combined with complex interventional procedures that must be applied[39].

Are these pricing disadvantages not surmountable (and not likely to change)? In terms of price reduction, many "positive" changes are expected when a larger number of ATMPs will be available on the market, for different reasons.

Firstly, important economies of scale are expected; when enlarging the usage of these ATMPs initial R&D costs are naturally amortized and the final price should decline[40]. Also, these economies of scale could also be possible by enlarging the number of different ATMPs and the curable disease. Indeed, some R&D costs could be amortized among the creation of two, or more, different medicines resulting in lower total cost and hopefully in a lower final price for public.

[36] A clear and complete model specifically focused on this issue can be found on Section II

[37] Abou-El-Enein M., Bauer G., Medcalf N., Volk H.D., Reinke P. August 2016. Cytotherapy 18, 1056–1061.

[38] Abou-El-Enein M., Bauer G., Reinke P., Renner M., Schneider C.K. December 2014. Trends Mol. Med. 20, 632–642.

[39] Abou-El-Enein M., Bauer G., Reinke P. December 2014. Nature Biotechnology. 32, 1192–1193.

[40] On the other hand, obviously, a larger usage of these ATMPs is required by the different National Health Systems to make economies of scale possible

Secondly, as already mentioned, the cost-opportunity of these medicines must be analysed both from the standard of living point of view – clear without a doubt – but also from the (less analysed) cost of alternative treatments. Indeed, many National Health Systems are not analysing the cost of non-treating patients with ATMPs both in terms of direct costs (other drugs such as palliatives) and of indirect costs, which are majorly underestimated[41] (transfusions, hospitality, demographic decrease, lower GDP, others).

Thirdly, there is a clear and common expectation in the possibility of reducing the labour-intensive part of the creation of these drugs into a more automated and cost-efficient process.

Lastly, it must be noticed how different drug patents do not last forever in the hands of pharmaceutical companies and this could favour a competition among different producers.

Overall, considering our ethical and medical analysis – underlying how ATMPs are clearly an opportunity to save more lives – finding a way to make ATMPs sustainable also economically speaking is somewhat a moral obligation for people with our academic background. The different governments and National Health Systems should try to solve this issue with different payments schemes, specific for these drugs: the aim of this thesis is to demonstrate, with an in-depth analysis of the Italian case, how a relatively easy solution is possible.

[41] Especially in the Italian National Health System, which is organised by silos and not horizontally. Topic further investigated in Section I, Chapter 1

c. The Regulatory Framework

Currently, European Commission Regulation 1394 of 2007 represents the regulatory framework for ATMP, amending in this respect Directive 83 of 2001, the Community code relating to medicinal products for human use, and European Commission Regulation 726 of 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMA). In addition, Directive 120 of 2009 (amending Directive 83 of 2001) updated the definitions and scientific and technical requirements for gene therapy and somatic cell therapy medicinal products. It also established detailed scientific and technical requirements for tissue engineered medicinal products, as well as for ATMPs containing medical devices. The development of ATMPs must comply with Directive 20 of 2001 relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Regulation 536 of 2014), which lays down specific rules for these types of medicinal products, precisely because of their complexity.

From the European Commission Regulation 1394 of 2007, the main things to underline are the following:

- The clear definition focused on the strong ground-breaking potential that these cures can have on saving human lives. This is an important point, indeed jurisprudential material states how this is signalling of how the European Commission is trying to push the member states in finding new regulation to sustain the rapid adoption of these drugs;
- The trial scheme to obtain the authorization for commercialisation is explained in full detail;
- An important, but also controversial, point is the authorization for specific private institutions to use directly on patients different, new, and not already approved, ATMPs. Indeed, on the one hand this clearly facilitates the research

and development of new drugs by reducing the trial costs of them. On the other hand, many criticize this point saying that the permit for this "fast-track" is too easy to be achieved and could be also risky from some point of view[42]. This critique is partially sustained by the fact that no specific European document listing all ATMPs being administered in this way is available to the public.

[42] Clearly treated patients sign a consent form before trying new therapies. However, many of these patients may be seen as "desperate", and these new, and not yet approved ATMPs, could represent their only chance to survive

2. The Italian National Health System, Current Situation and Eco-System

a. The Italian National Health System: a Brief Overview

The Italian National Health system was officially born in 1978.

Before this date, until 1943, the Italian health system was completely private, with around 95% of the population paying directly for cure – through a direct contribute from the salary (between 0.25% and 3%[43]) to the "Società di Mutuo Soccorso", an institute acting as insurance company to reimburse each sustained medical service to contributors.

After the second World War, in 1943, a new step towards the creation of a completely public Health System has been made. Workers' health coverage was entrusted to national compulsory and professional health insurance bodies, diversified according to contribution and welfare levels. Practically, the health system was based on specific mutualistic bodies, compulsory for all workers.

The last step has been made the 23rd December 1978, when the 'Sistema Sanitario Nazionale' was officially created and a free, public health system was available to all Italian citizens. The system was inspired by the British Health System (the first National Health System created globally), which has been created in 1946.

The Italian National Health System (Sistema Sanitario Nazionale – SSN – in Italian), is based on three fundamental principles[44] – that we must take into account when considering the potential impact of ATMPs usage:

- Universality, guaranteeing the extension of health services to the whole population;

[43] Urbani A. December 2019. Il Servizio Sanitario Nazionale guarda al futuro – Verso nuovi e più evoluti schemi di governance.

[44] Italian Law 833/1978

- Equality, all citizens must have access to health services without distinction of individual, social and economic conditions;
- Equity, all citizens must be guaranteed with equal access in relation to equal health needs.

In the more recent years, other important "principles" started to be felt as fundamental for the National Health System, especially from the governance point of view. One of them is clearly the economy of the system, indeed the National Health System shall maximise the efficiency of the resources publicly employed by guaranteeing the best possible services. Clearly, this lastly mentioned principle is extremely important to be considered in our analysis; indeed, when we consider the adoption of ATMPs we must always keep in mind the whole tenure of the NHS, the economic impact that these cures can have economically speaking, and the overall resulting cash flows and profit and loss profiles due to ATMPs usage.

A distinctive tract of the Italian NHS is the governance split between two different levels: national and regional.
On the one hand, at the National level, the State is responsible for:

- Defining the essential levels of care, to make known and shared the contents of the services to be rendered by each Regional Health Service and the co-participation rules for social and health services, as well as highlighting the services that are totally excluded from the Essential Levels of Care;
- Ensuring the necessary financial resources, under conditions of efficiency and appropriateness, for their provision in line with public finance constraints;
- Monitoring the effective delivery of health services in the national health system.

On the other hand, at the regional level, each region is responsible for:

- Organising the respective health services to ensure service delivery;

- The planning, organisation and management of the health system through local health authorities (i.e. Aziende Sanitarie Locali, ASL) and through hospital trusts (i.e. Aziende Ospedaliere), whose main task is to respond to the needs of individual territories.

Overall, it must be noticed the strong dualistic role: the operational role Regions have, coupled with the importance of the State in defining the essential health services. This dualistic tract sometimes is not extremely efficient and leads to some specific responsibilities that are somehow blurred (not always easy to understand whether specific tasks should be solved at a national or at a regional level).
Also, especially with the recent crisis of Covid-19, major differences in health services granted by different regions (with a few regional health systems suffering more the pandemic compared to other systems which proved their solidity) arose, leading to a strong debate on whether delegating all operational responsibilities to regions is always the best choice for the Italian National Health System[45].

Also due to this dualistic system, the system showed its limits – especially in terms of economic sustainability – in the 2000s. For this reason, in 2007, the government of that time run a financial due diligence of health systems' economics, which underlined the existence of more than €10 billions of debts (of which responsibility of non-virtuous regions for c. €4.1 billions)[46]. As such, the State divided the regions into virtuous and non-virtuous ones and created specific recovery plans for the latter group.
Overall, governments, especially from 2011 when the sovereign debt crisis exploded, run hard spending review programs aiming at an overall reduction of money waste within the National Health System. After shared efforts between the national and the

[45] Ius in Itinere

[46] Urbani A. December 2019. Il Servizio Sanitario Nazionale guarda al futuro – Verso nuovi e più evoluti schemi di governance.

regional levels, a re-organization of budgeting has been created with a new logic: a specific capping policy in major spending silos.
With this re-organization, the economic allocation of resources has been distributed by "silos" and not horizontally, specifically:

- Cap on salary costs (with more than 100,000 doctors, 260,000 nurses and other technician, administrators, others);
- Cap on drugs and medical devices;
- Cap on good and services;
- Cap on purchases from third private parties.

These re-organized governance and capital allocation lead, on the one hand, to strong results from the economic point of view, with a generalized reduction of relative spending for the National health System – from 7.25% of GDP in 2009, to 6.82% in 2017[47]. On the other hand, the major problem of a huge difference among treatments offered by regions, especially the Northern regions compared to the Southern regions, remained unchanged (or became even deeper with the overall reduction of relative allocation of resources to each regional operator).

The Italian National Health System faces major challenges for the future to continue its development:

- A change in governance could be needed. Indeed, although the "silos" ratio was needed to reduce money waste at a regional level, a horizontal-based reasoning – allocation logic based on specific budgeting for each major class of disease – is necessary both to continue to grant a high level of service and to promote the continue development of new cures. In particular, the silos logic leads to lose sight of the interdependencies between individual expenditure factors (i.e. if a new technology needs an important initial

[47] Urbani A. December 2019. Il Servizio Sanitario Nazionale guarda al futuro – Verso nuovi e più evoluti schemi di governance.

investment but it reduces the economic impact in terms of other needed drugs and hospitality, this could be missed with the current logic);

- A new modern logic implemented by the legislator based on the idea that innovation is an investment and not a cost, and that through innovation, if properly harnessed, we can stabilise the impact of chronicity on the country's system;
- More focus on the value-based healthcare idea[48] – intended as the healthcare delivery model in which providers, including hospitals and physicians, are paid based on patient health outcomes[49] – to reduce waste of money and to share the risk of non-favourable outcomes of cures with pharmaceutical companies.

Overall, on the one hand, the Italian National Health System represents a strong system also compared to other European member states (especially if compared to other Southern European countries), with potential future developments that can be deployed to even increase the standard of the system. On the other hand, the current governance by silos could represent a potential limit to future innovation, a better alignment of standards among different regions should be implemented, and the dualistic role between regions and the state should be improved not to leave any room for specific doubts on matters falling within the competence of both parties.

[48] Partially connected to the horizontal-based allocation of budget investigated above

[49] Massachusetts Medical Society. January 2017. "What is Value-Based Healthcare?".

b. Different Accounting Standard among Regions: Accounting Harmonisation and Auditing of Financial Statements

Before the harmonisation of accounting standards ruled out from law 42 of 2009; the accounting rules for Regional Health Systems were mainly based on Legislative Decree 502 of 1992, which made the Regions responsible for "issuing rules for the economic, financial and asset management of Local Health Units and hospitals, based on the principles of the Civil Code". Basically, other than specific required elements on uniformity at a state level[50], each Region could autonomously regulate the accounting system of its health agencies, as long as it ensured the transition from traditional financial accounting to economic and financial accounting.

As such, almost all regions issued specific regulations to clearly define their accounting standards, resulting in:

[50] Listed on Legislative Decree 502/92, for example when it states: (i) that the regional legislation must in any case provide for "b. the adoption of the multi-year economic forecast budget as well as the annual economic budget for the following financial year; c. the allocation of any surplus and the methods for covering any operating deficits; d. the keeping of analytical accounts by cost and responsibility centres that allow for comparative analyses of costs, yields and results; e. (i) the obligation of the local health units and hospital undertakings to publish, annually, the results of their analyses of costs, yields and results by cost and responsibility centres"; (ii) that "in order to give a uniform structure to the items of the multi-year and annual budgets and of the annual final accounts [...] a special scheme is prepared, by interministerial decree issued in agreement between the Ministers of the Treasury and of Health", a scheme initially approved by Ministerial Decree 20/10/94 and subsequently amended by Ministerial Decree 11/02/02. Moreover, the Treasury and Health Ministries initially sought to guide the introduction of general accounting in public health companies by issuing special 'guidelines for the financial statements of health companies' (1995), which were not binding, and by publishing a 'methodological path for the introduction of economic and financial accounting' (1996). More recently, a contribution to inter-regional homogeneity has come from the introduction and progressive refinement of the Financial Statements models, as well as from the drafting of the relative guidelines.

- An unsystematic nature of regional legislation and a consequent interregional heterogeneity;
- Important differences in financial statements across different regions, with relative difficulty in creating a consolidated financial statement across regions;
- High use of budgetary policies, leading to a deterioration in the reliability of expenditure and deficit figures.

Also due to this strong heterogeneity and freedom on accounting standards at a regional level, major negative performance indicators on the Italian National Health System has been discovered in 2007, as seen in chapter 2.a[51]. In particular, excessive recourse to hospitals, excessive territorial pharmaceutical expenditure, and low average essential levels of care, which were not guaranteed uniformly throughout the country, were noted. As a result, as already mentioned[52], an extraordinary due diligence on the financials of the National Health System was conducted. A very bad situation was pictured, the evidence that emerged triggered the red alert: the system's crisis and, above all, the risk that it would not be sustainable in the short term were evident.

As a consequence, in the upcoming years legislation on the accounting standards of the National Health System has been revised in different steps:

- Law 196 of 2009, law of 24th December of 2012, and law 243 of 2016 governing the criteria for drawing up the state budget (with specific reference to the National Health System);
- Decree 93 of 2016, 29 and 116 of 2018 which revised the notion of accounting commitment in order to bring the moment of legal competence (commitment) closer to that of cash (payment);

[51] Existence of c. €10 billions of debt

[52] Section II, Chapter 2.a

- Decree 118 of 2011, which has significantly innovated the financial and economic accounting rules of the Regions, Local Health Authorities, hospitals and the different regional health systems. The aim was to achieve greater control of public finance balances by the central government, with the provision of precise economic and financial rules for drawing up budgets and assessing expenditure and revenue. This step was compulsory to avoid situations of financial collapse of decentralised bodies, especially in the health sector, which has been characterised by huge deficits and considerable budget imbalances.

The main piece of legislation is definitely law 196 of 2009, which sets three main heterogenicity goals on:

- The accounting bases between regions and companies, with the regions still using only financial accounting and the companies having switched to economic and financial accounting at least ten years before;
- Regulations governing the accounting of public health companies in different regions;
- Company accounting practices even within the same Region.

The first two goals were partially achieved with the decree 118 of 2011, which specifically establishes:

- The application to public health companies of the provisions of the Civil Code (Articles 2423-2428), except for certain exceptions explicitly indicated as "valuation principles specific to the health sector";
- The application to public health companies of the provisions of the Civil Code (Articles 2423-2428), except for certain exceptions explicitly indicated as "valuation principles specific to the health sector";
- The definition of a financial statement scheme common to all public health agencies including the balance sheet, the income statement, the notes to the

accounts and the financial and cash flow statement and accompanied by the management report;

- The obligation for Regions that choose to manage directly a share of the financing of their health service to record in the economic and financial accounts the operations attributable to the "centralised management of healthcare in the region", instead of transferring this financing entirely to the companies;
- The adoption of the consolidated financial statements for each regional health system.

Lastly, another fundamental piece of legislation, whose reflection tends sometimes to be underestimated, is the Health Act between Regions and the State of 2010 – 2012[53]. In particular, with its signing, the Regions undertake to ensure that the quality of administrative and accounting procedures underlying the correct procedures, the correct accounting of business events, as well as the quality of the accounting data' and, to this end:

- They carry out an extraordinary assessment of the status of administrative-accounting procedures, resulting in the certification of the quality of the companies' accounting data and of the regional consolidation for 2008;
- If subject to the plans for recovery from health deficits (as a result of the due diligence), throughout the duration of the plans, they shall intensify the periodic audits of the administrative and accounting procedures, with a view to the annual certification of the financial statements and the consolidated regional health budget;
- They undertake to initiate procedures to pursue the certifiability of budgets.

[53] Italian Health Pact (Patto per la Salute) 2010 – 2012 – Art. 11. Also thanks to this act, the in-depth due diligence on the status of public health financials has been possible

Overall, the main trend of interests and the latest developments in terms of accounting regulation has been made to favour the harmonisation of accounting rules among different regions, a necessary condition for ensuring the reliability and comparability of financial statements – a crucial point also when considering how different drugs, and ATMPs, are considered in the financial statements of regions. This has overall been achieved, mainly thanks to the goals set by law 196 of 2009 and the related actuation decrees.

Lastly, for the purpose of our research, it must be noticed an important innovation introduced from decrees 29 and 116 of 2018. In particular, it sets a specific multiannual expenditure authorisation with aligned legal and economic competence, also in terms of financial coverage. As a matter of fact, starting from 2019, the commitment shall be made in the financial year, or years in which payments are expected to be made in accordance with the contractual or regulatory deadlines.
This is a strategic innovation and specification that, in our case, could be used to create a new payment scheme for specific drugs either in accordance with the supplier or by considering expenditure for specific drugs as investments to be amortized over a broad time horizon (e.g. 10 years).

c. How Different Regions Approach ATMPs

As seen before, each Region has a certain amount of freedom in organizing its internal structure of the regional health system and offering of treatments – other than essential levels of care[54] listed by the State at a central level. This led to a fundamental divergence on how Regions are approaching the ATMP issue.

The individual Regions, when interested in participating to ATMPs application, have selected the prescribing centres subject to the following mandatory minimum criteria defined by the Italian Drug Administration[55]:

- Certification of the National Transplant Centre, in accordance with EU directives;
- JACIE[56] accreditation for allogeneic transplantation, including clinical unit, collection unit and processing unit;
- Availability of an intensive care and resuscitation unit;
- Presence of a multidisciplinary team suitable for the clinical management of the patient and possible complications.

[54] So-called Livelli Essenziali di Assistenza, i.e. LEA

[55] AIFA, Agenzia Italiana del Farmaco. Decision undertaken during the CTS meeting of 3-5 April 2019 and transmitted to the "Health Commission" of the Conference of Regions with note protocol number STDG/P/42891 of 12/04/2019

[56] JACIE (Joint Accreditation Committee ISCT-Europe & EBMT) is the only official accreditation body in the field of haematopoietic stem cell transplantation (HSCT) and cellular therapy. It is represented by members of the European Group for Blood and Marrow Transplantation (EBMT) and the International Society for Cellular Therapy (ISCT), and promotes high quality patient care and medical and laboratory (collection, handling and transplantation) practice through a voluntary accreditation programme. The accreditation process involves the preparation of required documentation, inspections and continuous updating through audits and annual reports.

As a result, the ATMP prescribing centres selected in Italy to date[57] are 43, distributed among 15 regions[58] (out of 20). Furthermore, not all the selected centres have been qualified by the companies holding the marketing authorization, indeed, it is necessary for the Companies to qualify each specific centre, by checking the parameters established by the Companies themselves before this can proceed to administer the drug.

Overall, each region has a different approach towards ATMPs and how to offer them in their centres:

- 5 regions[59] decided not to enable any centre to distribute ATMPs;
- 8 regions[60] enabled only one centre and to fully concentrate the ATMPs offering in a single pole;
- 7 regions[61] enabled more than one centre, with different focus and specializations in each of them.

[57] October 2020

[58] Umbria, Emilia-Romagna, Liguria, Lazio, Puglia, Toscana, Sicilia, Veneto, Calabria, Abruzzo, Friuli-Venezia Giulia, Sardegna, Lombardia, Campania, Piemonte

[59] Basilicata, Marche, Molise, Trentino-Alto Adige, Valle d'Aosta

[60] Umbria, Emilia-Romagna, Liguria, Puglia, Veneto, Calabria, Abruzzo, Sardegna

[61] Lazio (3), Toscana (4), Sicilia (3), Friuli-Venezia Giulia (2), Lombardia (13), Campania (6), Piemonte (3). In brackets the number of enabled centres.

d. The Importance of the Italian National Health System Organisation and Accounting Standards in our Analysis

Overall, in our analysis, the specific valuation of the Italian National Health System, and its organization both from a governance, but in particular from an accounting point of view are fundamental. Indeed, the finally (partially) achieved accounting harmonisation is a starting point that enables us to conduct our analysis at a national level, and not at a regional level, and to give a clear overview of how the overall system currently works and how it may develop to sustain a major adoption of ATMPs throughout the Italian population. In addition, also thanks to decrees 29 and 116 of 2018[62], it is possible to think to different payment schemes for specific drugs. This has already been applied lately with ATMPs suppliers that are currently being paid by the National Health System through the payment-by-result scheme. With this policy, the Health System pays the specific suppliers only if the ATMP worked for each patient; this is a partial step forward, because in this way the sunk cost of patients that have been treated with an ATMP without the desirable results (c. 40%[63]) are deleted.

We would also like to make a last point regarding the approach that each Region follows towards ATMPs. In particular, in our opinion, the current difference among Regions is sustainable since the number of treated patients with ATMPs is relatively small; on the other hand, with the upcoming developments and approvals of new ATMPs, if we really want to make them more available, a clearer and broader picture of available centres should be outlined.

[62] Section 1, Chapter 2.b

[63] As explained in Section II, Chapter 1.b, each specific ATMP only cures a percentage (c. 60% on average) of targeted people

In addition, the approach of having different centres with specific specialization could make sense, since different Regions and territories have different incidences of diseases (e.g. β-talassemia in Sicily, Sardinia and in the Po delta).

3. Focus on the Swedish National Health System

After the analysis of the Italian National Health System, we will now focus on the Swedish National Health System, and mainly on the fundamental values at the basis of its functioning. Then, we will see how this Health System is actually comparable to the Italian National Health System, both for the system itself as well as for the status of ATMPs adoption.

a. The Swedish National Health System: a brief overview, with many parallelism with the Italian National Health Systems

Sweden (and the Nordics in general) has always been well known among other European States (especially Southern States), for how things in general "works well", the public health system with no exception. There is certainty a variety of facts behind the well working public machine of Sweden, one of them is the small population (c. 10m in 2022), one is the lower public debt created over the years, one is – for sure – the different sense of respect and expectations that Swedish citizens have towards Swedish public bodies.

Similar to the Italian National Health System, the Swedish National Health System is based on a straight forward and limited number of defining rules:

- Majorly publicly-run,
- Based on straightforward principles,
- Strong and clear division of responsibilities for different levels of governments (i.e. state vs regions).

Similar to the Italian National Health System, Sweden is a public service granted and it is driven by clearly outlined principles. The cornerstone of the Swedish Health

System is the Health and Medical Services Act of 1982, which outlined three founding principles in hierarchical order:

- Human Dignity, whereby everyone enjoys the same rights
- Need and solidarity, whereby priority in health care is given to those most in need
- Cost-effectiveness. whereby the choice between different alternatives must depend on the relationship between costs and benefits

Clear parallelism between founding principles of the Italian National Health System and of the Swedish National Health System can be driven. In particular, given the analysis we are conducting, very similar and relevant founding principles are the principle of economy of the Italian National Health System and the cost-effectiveness principle for the Swedish Health System – which are saying the same thing. These principles are taken very seriously by Swedish legislators. This is evidenced by a 1997 supplement, which, in order to allow for their practical application, spelled out the second principle in a hierarchy of four groups of conditions ordered by need: from the first, comprising life-threatening illnesses, chronic illnesses and (noteworthy) palliative care, to the fourth, with conditions such as cosmetic surgery.

Another strong parallelism between the Italian and Swedish National Health Systems is the clear division in responsibilities between the State and the regional level. Indeed, through the DAGMAR reform of 1985, the Swedish legislator shifted the financial responsibility for primary and secondary health care from the National Insurance to the Landstings, and the AEDEL reform of 1992 transferred that for care of the elderly and disabled (and later also for the mentally disabled) from the Landstings to the municipalities. The result is that the health care system reflects the three-tier organisation of the state, but the role of the Landstings exceeds that of the central and municipal levels.

The central level, with the Ministry of Welfare and Health, assisted by the National Committee for Health and Welfare (Socialstyrelsen), has planning tasks, which also include health promotion and prevention (the Folkhälsoinstituet, the National Institute of Public Health, takes care of this). Its successes are considerable: suffice it to mention the 'zero-vision' on road mortality, i.e. the goal of zeroing it (in 2007 it was 4.7/100,000 inhabitants/year, the lowest in Europe with the Netherlands); and the lowest proportion of smokers in Europe (male smokers almost halved in the 1990s).

At regional level, the 20 Landstings provide primary, secondary and tertiary care.
In particular, primary care (in multi-purpose outpatient clinics, at least one per municipality) and secondary care (in 40 district hospitals and 20 central county hospitals) are managed, in the majority of counties, by the Sanitary districts, authorities similar to the Italian hospital poles. Tertiary care, on the other hand, is organised in a peculiar way: the entire country is divided into 6 regions, each comprising several Landstings with a total of about one million citizens and served by a technology-intensive regional hospital. The local level, i.e. the municipalities, takes care of community services - social services, home care, care for the elderly, disabled and mentally handicapped.

The majority of providers are public employees: not only hospital doctors, but also general practitioners, pharmacists (since 1971) and dentists, marking a second important difference from non-Scandinavian Beveridge systems. The share of private providers varies considerably from area to area, peaking in urban areas.

Over the last fifteen years, the problem of waiting lists has received a lot of attention as one of the few reasons for the growth of the also small private health insurance market. In 2005, the '0-7-90-90' rule was introduced: each Landsting guarantees immediate contact with the health care system in an emergency, and a maximum wait of 7 days for a visit to a general practitioner, 90 days for a specialist diagnosis,

90 days for treatment; failure to comply with this timeframe entitles the citizen to turn to another Landsting or to private individuals at the expense of the Landsting to which he belongs.

In any case, that the Swedish healthcare system is very effective is shown by one indicator for all: avoidable mortality, the lowest in the OECD. The latest significant reforms have therefore focused on economic efficiency, especially in the field of pharmaceuticals:

- In 2002, an authority was established to decide which drugs are reimbursable
- Since 1997, all Landstings can contract separately with pharmaceutical companies
- Patients have an annual ceiling on their expenditure, above which state subsidies begin

The most topical issue is that of equity and access: considerable inequalities exist between rural and urban, and between different socio-economic groups. Yet, in the last years, the system has undergone profound changes, which will eventually tackle these critical issues.

b. ATMPs adoption in Sweden

The status of ATMPs in Sweden is extremely similar to the Italian ecosystem for two main reasons:

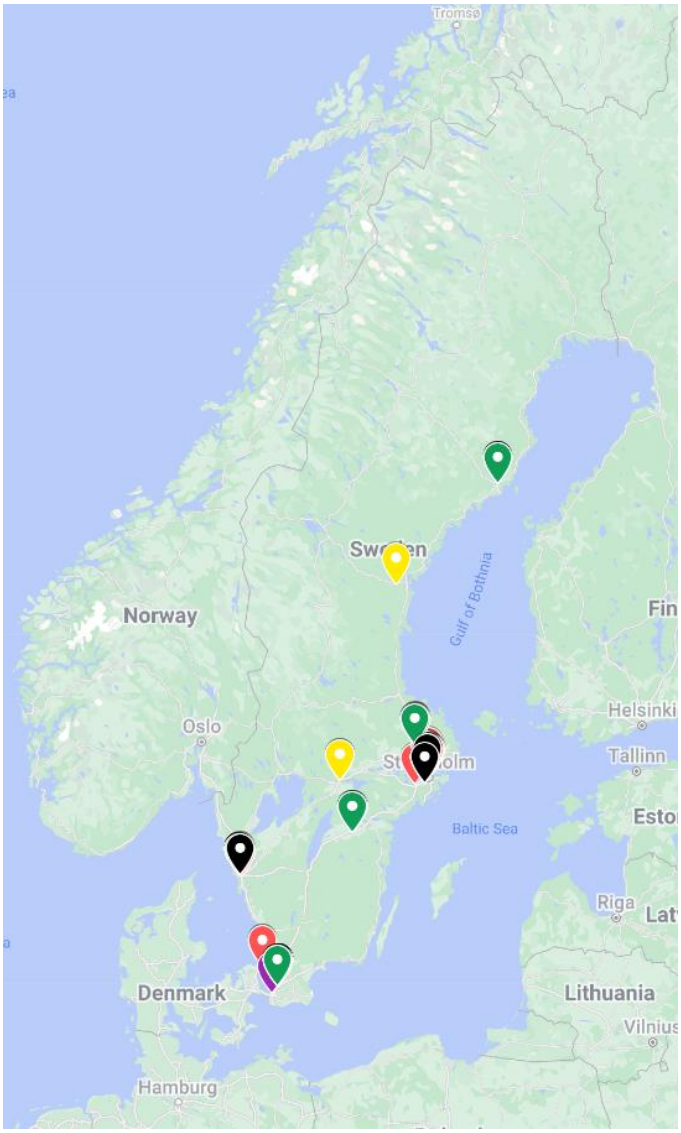
- As seen[64], the main piece of legislation is an European Directive which means that is guiding the adoption of these drugs in all European states (and they both are, although Sweden not part of the Euro zone)
- As analysed in the precedent paragraph, the two Health systems are extremely similar both in term of founding and guiding principles as well as on the key responsibilities of the Italian national health systems allocated between different layers of the public machine (State vs regional level).

Adoption of ATMPs in Sweden and Italy are extremely similar for these main reasons:

- The spectrum of currently adopted drugs is the same we analysed in the first paragraphs of this research
- Prices of specific drugs are negotiated at a European level and, as a result, are the same throughout the European Union (only minor differences due to different currencies, but negligible)
- The same payment scheme is applied throughout the European Union for each specific drug category
- Another similarity, of a smaller scale, is that both in Italy and Sweden – mainly due to the general architecture of the two health Systems and the specific requirements in the different locations – ATMPs adoption are different for specific regions

[64] Section I, Chapter 1.c

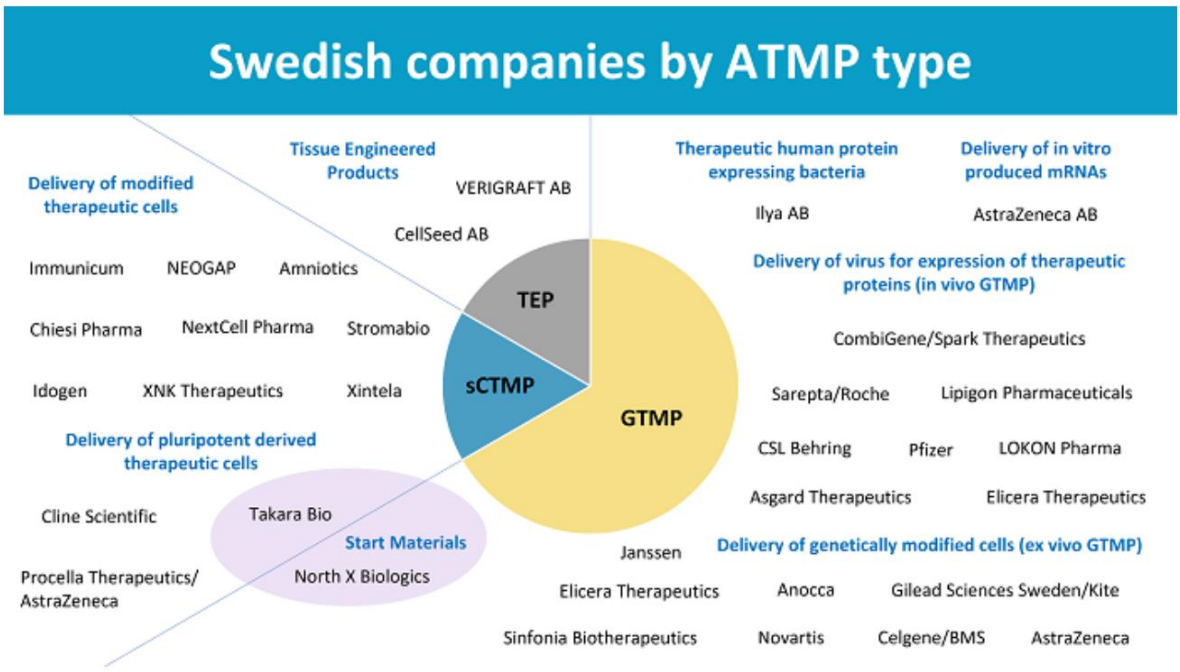
Exhibit 1. How different Swedish regions are involved with ATMPs



Another point worth mentioning – albeit out of the scope of this research – is about the overall ATMPs hub in Sweden is the strong presence of companies based in the region and focusing on studying, developing, applying ATMPs.

From the small chart below, is very easy to note how there are many companies, both international and from the Nordics, that are investing massively in research in the country – both in ATMPs and ATMPs related research.

Exhibit 2. Swedish companies by ATMP type



c. Overall parallelism between the Italian and National Health System in relation to ATMPs

Through these whole chapter we firstly went through the main characters and a brief story of the Swedish Health System.

We generally concluded that a large parallelism can be drawn for the series of the following reason:

- National Health Systems based on similar founding and guiding principles
- Different responsibilities at regional and national levels
- Different ATMP hubs with different focuses across different regions
- Adoption of the same ATMPs
- Same prices for ATMPs
- Same payment schemes for ATMPs

4. The Main Problem and Possible Solutions: The Economic Sustainability of ATMPs

a. The Economic Sustainability of ATMPs

As analysed before[65], although ethically and medically ATMPs are definitely convenient, the main problems and concerns with these cures are linked with their economic sustainability in the long run, when a potential greater usage and a wider adoption (broader range of diseases) than today will be experienced.

As a result, although being quite poor at the moment[66], the economic literature analysing these innovative cures mainly focus on analysing their apparent non-sustainability. For example, the main conclusion outlined by Jonsson B. et Al. in their paper[67], after an in-depth analysis reaching on how ATMPs are medically convenient, is that "*ATMPs face a challenge in demonstrating their value within current HTA frameworks. Consideration of current HTA principles and practices with regards to the specific characteristics of ATMPs and continued dialogue will be key to ensuring appropriate market access*".

Indeed, some ATMPs, and in particular gene therapies, have been launched with very high prices (and unit costs). These prices are justified by companies by the followings[68]:

- The intrinsic value of the therapies being launched, in particular the high level of unmet need and the prospects for recovery from the disease;

[65] Section II, Chapter 1.b

[66] This is also one of the reasons why we decided to analyse the problem and write this thesis

[67] Jonsson B., Hampson G., Michaels J., Towse A., von der Schulenburg J. M. G., Wong O. April 2019. "Advanced Therapy Medicinal Products and Health Technology Assessment Principles and Practices for Value-Based and Sustainable Healthcare".

[68] Partially seen in Section II, Chapter 1.a

- The high production costs, on which, however, evidence is still rather scarce and limited to specific studies;
- The low target population size and the consequent need to compensate low sales volumes with high prices, in order to cover fixed research and development costs, which are largely hidden, through high margins.

We must always remember that the problem is currently limited since the targeted population is quite small on the one hand, and the actual population cured with ATMPs is even smaller. However, in the future, ATMPs represent a clear opportunity (with a consequent economic problem that we must analyse), since more and more people would be able to be treated with this innovative care – as seen in Section I, Chapter 1.a, more than 64,000 will cumulative be treated with gene therapies in Italy by 2030 (i.e. ca. 0.1% of the all population); with a similar parallelism which can be drawn with the Swedish population

As a result, the importance of these innovative therapies will pose very delicate problems of choice and rationing in terms of access to treatment for patients, which could lead to fewer patients being treated than are eligible and therefore potentially treatable.

b. The Solution Must Be Outlined at Two Different Levels: Higher Sales of ATMPs and Accounting Treatment / Payment Schemes

As we previously concluded, we must feel morally obligated to find new payment schemes or other accounting / economic solutions to make ATMPs accessible and widespread to increase the number of lives saved, or radically changed, through these innovative cures.

By our analysis, there are two major layers that can impact in the economic sustainability of ATMPs:

- The increase in sales of ATMPs producers to maximise economies of scale mainly due to automatization of production, decrease in labour costs and amortisation of R&D costs;
- Considering innovative payment schemes, based on the dilution of payments by National Health Systems or on different accounting treatments for ATMPs.

Considering the former layer, we must consider that both as a consequence of a rapid and increasing adoption of ATMPs and as an impulse to increase the adoption of ATMPs. Indeed, by increasing sales of ATMPs' – larger economies of scale, minimised labour cost will, increased process automation – the final price of offered ATMPs should decrease. As we analysed before[69], and confirmed by different surveys and literature, this is possible when ATMPs usage will be widespread and increased. In fact, in this way a typical virtuous cycle will be established:

- Rapid adoption of ATMPs increase the production, impacting on economies of scale and on other important factors of final per-unit price;

[69] Section II, Chapter 1.b

- The decrease in price stimulates the demand and public health systems are able to increase the number of patients cured through ATMPs;
- More demand increases the production, returning to the first point, and so on and so forth;
- The virtuous cycle starts.

Focusing on the latter layer, traditionally drugs have been paid up-front[70] by the National Health System without any kind of conditionality on their actual working.
On the other hand, academic research highlighted different potential payment schemes, conditional market access agreements for innovative and / or high-cost drugs that allow new treatments to be made available to patients (despite the uncertainty of lacking information on therapeutic benefits or actual costs).
In particular, the main economic and financial techniques considered are:

- Payment-by-result (MEA);
- Netflix Model;
- Two-Part Pricing (2PP);
- Intellectual property-based payment;
- Fund-based payment;
- Annuity style payment.

MEAs, or Managed Entry Agreements, are defined[71] as "*Various types of formal accord between manufacturers and payers that stipulate terms of market access as a form of risk-sharing. Can be outcome based, as in pay-for-performance style agreements, where reimbursement is linked to clinical results, or financial-based, where, for example, payments are capped at a prespecified level*".

[70] Simplistic view, but useful for our analysis

[71] David R Carr R. D., Bradshaw E. S. February 2016. "Gene therapies: the challenge of superhigh cost treatments and how to pay for them".

The current state-of-the-art for the payment of ATMPs by the Italian and Swedish National Health Systems is the usage of a MEA, specifically the payment-by-result model. This is already a quite innovative payment scheme sponsored by the pharmaceutical companies to try to increase the sales of ATMPs, which definitely favours the public side. Under the payment-by-result model, the health system pays upfront for ATMPs but an immediate 100% payback for all patients who do not respond to therapy (pay-for-performance based) is provided by pharmaceutical / biotechnology companies. In this way, if we consider an average success of ATMPs of 60% of treated patients, the public is "only" paying for actual treated patients and not for all those patients for whom the treatment is not working.

Although being quite innovative – especially for the Italian landscape – this payment scheme alone is not sustainable by the National Health System in the long run, especially with a largely increasing number of patients[72], and this is one of the reasons why today the Italian and Swedish Public Health Systems are treating with ATMPs only a fraction of the potentially eligible patients.

The second potential payment model is the so-called "Netflix Model". With the name clearly inspired to the famous online video provider, the idea is to have a sort of subscription-based plan between the National Health System and the ATMPs provider. Basically, the model is based on the National Health System paying a flat yearly fee to pharmaceutical companies for all those years in which the drug is actually in use. For example, if treating a melanoma patient with a gene therapy, under this model the State should pay a specify flat amount to the provider of the treatment every year until a remission of the disease or the death of the patients for other non-related reasons[73]. This could be an attractive model for pharmaceutical companies, which could then have a certain revenue scheme for upcoming years, as well as for the National Health System because it is both a form of risk-sharing with the actual

[72] As analysed in Section II, chapter 3.b and 3.c

[73] Clearly, this is the most basic idea of the model which can be developed in a more defined framework, with a fixed fee for a fixed amount of years, or with other negotiated conditions

developer of the cure (paying only if the cure is actually working) and a way to dilute the payment over a broader time horizon.

The Netflix Model has not yet been proposed or studied for ATMPs, but there is some literature and proposals on this for other types of cures within the American Health System[74]. However, it seems to be pretty difficult to be in some way applied to public health systems; this is why it is not being largely considered by European literature.

Moving now to the Two-Part Pricing (2PP) model, this is a payment scheme that has been used in different industries but never to the pharmaceutical / medical industry. In particular, Herztman P. et Al.[75] proposed to try to use this new scheme for some new, expensive and specialised medicines. They define the method as "*(…) a frequently used payment method in other industries, which consists of an Entry Fee, giving the buyer the right to use the product, and a Usage Price charged every time the product is purchased. Introducing 2PP into biopharma could have cross-stakeholder benefits including broader patient access, and improvement in budget /revenue predictability. A concern however is the potential complexity of the negotiation between manufacturer and payer*".

In our view, for sure this approach could be considered and tested in some countries. However, we believe that given the Italian and Swedish landscape and structure of the National Health System (with power largely delegated to Regions, and even to single hospitals), the negotiation phase necessary between the manufacturer and the payer, as well as the overall complexity of the scheme (not that easy for a public and

[74] Trusheim M. R., Cassidy W. M., Bach B. P. November 2018. "Alternative State-Level Financing for Hepatitis C Treatment – The 'Netflix Model'".

[75] Hertzman P., Miller P., Tolley K. February 2018. "An assessment of innovative pricing schemes for the communication of value: is price discrimination and two-part pricing a way forward?".

largely known as heavy structure[76]) could limit its proper working within Italy and Sweden.

The intellectual property-based payment method is based on trying to reduce the prices of pharmaceuticals company. It is based on[77] "*Several variations, including prizes for patents, out-licensing of technology rights or prolonged patent rights, which may award innovation or take the burden from manufacturer to seek such high prices for treatments*". This payment scheme is interesting because of the completely different point of view, trying to act in a way to decrease public prices; on the other hand, it is quite difficult to be achieved, it could take a lot of time to be effective, inputs from private foundations may be needed.

The Fund-base payment is rather based on thirds parties mainly taking part to the funding and payment of ATMPs. The scheme is based on[78] "*Several variations, including national silo fund for specialist conditions, or social funds financed by private companies and / or insurers to take burden from national healthcare providers".* This scheme is interesting from an academic point of view, but all critics moved to the intellectual property-based payment method are valid. Moreover, imaging that third parties or insurers replace the public health system in the payment of high-cost treatment is, at the very least, utopic[79]*.*

Overall, we think the most accessible, functional, and interesting payment scheme given the Italian and Swedish National Health Systems, the ATMPs intrinsic

[76] Unfortunately, Italy is well-known for its massive red tape that is a clear limit to establishing these specific payment schemes and to conduct negotiation of such specific and diversified terms

[77] David R Carr R. D., Bradshaw E. S. February 2016. "Gene therapies: the challenge of superhigh cost treatments and how to pay for them".

[78] David R Carr R. D., Bradshaw E. S. February 2016. "Gene therapies: the challenge of superhigh cost treatments and how to pay for them".

[79] In private based health systems, the problem has been proven to be the opposite: insurers not covering for high-cost cures

characteristics[80], and its relatively easy to be applied scheme – compared to other academic proposals such as the two-part pricing – is a new payment scheme similar to the annuity payments method, which is the basis for the innovative payment scheme we are proposing in this thesis – analyses in the next paragraph of this chapter.

[80] One-shot treatment, life changing nature and high costs

c. Our Proposal: Fractioning the Costs Through an Innovative Payment Scheme

The main goal of the Annuity Payments method is to dilute the payment sustained for each ATMP in a broad range of years. In particular, the main idea of the model is[81]:

- Upfront payment of a fixed percentage of the total ATMP cost to the drug supplier;
- Payment of the remaining part of the ATMP in a number of diluted instalments throughout years only if the drug is working on the considered patient.

In this way the National Health System would, on the one hand, dilute the payment throughout a broad time horizon (similar to the "Netflix Model"), on the other hand, share the risk – in case the ATMP does not work – with the pharmaceutical / biotechnology producer.

Overall, to achieve the double objective of risk-sharing with suppliers and diluting the payment for the NHS, there are two ways:

- Make a specific agreement with the supplier to apply the Annuity Payments method;
- Make the total upfront payment to the pharmaceutical company with the currently used payment-by-result scheme. Then, capitalize the upfront expenses for ATMPs and amortize them throughout a specific number of years. Clearly, this idea is a sort of blend between the payment-by-result and annuity payments methods.

[81] Brennan T. A., Wilson J. M. September 2014. "The special case of gene therapy pricing".

If we consider the plain annuity payments method in the Italian and Swedish landscapes, although appearing as strongly attractive, it is also very difficult to be achieved. Indeed, an agreement between the Health System and pharmaceutical companies is necessary. This is very hard (and time consuming) to be achieved for the following reasons:

- Pharmaceutical companies must accept to be paid in different instalments, and this could improve an overall initial increase in the total price per unit;
- With the high differentiation among the different regional health systems (especially in the administration of the whole ATMP issue), different negotiations should be carried out between different regions with all different pharmaceutical companies. This would take a lot of time and the different Regional Health Systems would not have that strong bargaining power;
- Lastly, not relevant for the Swedish National Health System, an overall high level of red type intrinsic in the structure of the Italian State both either increase the necessary time as well as decrease the chances to reach an agreement, and generally obstruct the way to achieve a satisfactory accord.

For this reason, we are proposing a different approach, targeting the same goals – risk sharing and fractioning the payments – as the annuity payments scheme, that better fit the backbone and characteristics of the Italian and Swedish National Health Systems. In particular, with the thesis we are aiming at creating a model to demonstrate how ATMPs could become sustainable from the economic perspective by simply retaining the current payment-by-result scheme (to share the risk with producers), with a new accounting of the cost for ATMPs (capitalisation of the expenses for these drugs as fixed assets and consequent amortisation in a given time horizon, e.g. 10 years).

The fundamental theorical idea behind this intuition is that ATMPs are intangible assets with multi-year utility, specifically because, if working, they are actually

replacing future costs for the system to traditionally cure the targeted disease. In this way, ATMPs would not impact in the Profit and Loss statements only when the payment is made but, year-over-year with throughout their amortization period (over 5-10 years).

The main idea of the thesis is then to demonstrate how the application of this new payment method for ATMPs could be sustainable and convenient for the Italian and Swedish National Health Systems.

With the model we created we demonstrate how, if the National Health Systems applied the proposed payment scheme (i.e. fractioning the payment through the ATMPs' expenses capitalisation), it would be possible to cure all the current target ATMPs potential population – also, as a result, the potential increasing ATMPs target population that would exist in a few years from now.

Lastly, worth nothing that, in order for the proposed payment and accounting method to be applicable, probably a deeper amendment to these accounting standards should be made by legislators. From the jurisprudential perspective, although falling out of our field, we think this is just a necessary minor change – that can be easily made by the legislator and only for the specific ATMPs field, also considering a clear and complete definition for these innovative cures already exists[82].

[82] Although for the Italian National health System, thanks to the recent amendment of existing accounting standards – Legislative Decree 116 of 2018 and Legislative Decree 29 of 2018 – as of 2019, a greater accounting flexibility of costs is available for different Regional Health Systems (commitment must be made in the fiscal year or years in which payments are expected to be arranged according to the contractually or legislatively established deadlines)

SECTION II: THE MODEL APPLIED TO THE ITALIAN NATIONAL HEALTH SYSTEM

1. The Increasing Economic Impact: a Regression Analysis

As mentioned before in the research, the ATMP economic sustainability problem is an issue that seems currently "small" in terms of size. However, we decided to investigate this problem because, in a few years from now, it will become more and more serious. In particular, there are two main reasons:

- More ATMPs will be authorised;
- Targetable population will increase.

With reference to the first point, we already analysed the expected incremental number of new ATMPs to be approved in Section I, Chapter 1.
Clearly, the two points are correlated: as the number of ATMPs would increase, more diseases could be cured with ATMPs and a broader targetable population would exist. On the other hand, considering only the currently available, or soon to be available, ATMPs on the Italian market, the targetable population is expected to naturally increase. In particular, for many of the treatable diseases, the total population could be naturally related with macroeconomic variables, such as the total population, the average life expectation, or the amount of screening conducted to find specific diseases.

We decided to prove these matters empirically, through a regression trying to explain the specific number of cases, or incidence rate, of specific diseases based on macroeconomic variables. In particular, we conducted the analysis for three macro groups of diseases that could be cured by ATMPs[83]: non-Hodgkin Lymphoma, leukaemia, haemophilia A. We decided to analyse these macro-groups because, currently, they represent the largest share of potential spending – greater than 30% of total – of the Italian National Health System for ATMPs.

[83] Only a fraction of total population per each kind of disease is targetable through ATMP

For the non-Hodgkin Lymphoma and leukaemia, based on the Italian population, we analysed the relation between the incidence of each disease and the total Italian Population, the life expectancy, and the GDP per capita for all years between 1978 and 2014. We decided to include the GDP per capita in our analysis as an element related to the quantity and quality of screening that the state could conduct (as the average wealth increase, ceteris paribus, we expect the public sector to invest more in screening[84]).

We create the database for all data regarding population, life expectancy and GDP per capita using ISTAT as a source; while data on incidence comes from the European Cancer Information System database.

Exhibit 3. Summary Output regression non-Hodgkin Lymphoma

Regression Statistics	
Multiple R	0.88
R Square	0.77
Adjusted R Square	0.75
Observations	37.00

ANOVA

	df	SS	MS
Regression	3.00	485.07	195.02
Residual	33.00	144.85	2.57
Total	36.00	629.92	

	Coefficients	t Stat	P-value
Intercept	23.74	0.80	0.43
Total Population	0.58	2.39	0.02
Life Expectancy	1.78	2.23	0.03
GDP Per Capita	0.00	1.39	0.17

We saw a strong relation between the analysed variables, with a high R^2 in the north of 0.75. Moreover, both total population and the life expectancy are significant variables (both p-values are lower than 5%).

[84] Obviously, considering the total spending per capita in public health would have made more sense; unfortunately, that data is almost impossible to find due to the different accounting standards across different regions

Exhibit 4. Summary Output regression leukaemia

Regression Statistics	
Multiple R	0.72
R Square	0.52
Adjusted R Square	0.48
Standard Error	0.91
Observations	37.00

ANOVA

	df	SS	MS
Regression	3.00	30.22	10.07
Residual	33.00	27.42	0.83
Total	36.00	57.63	

	Coefficients	t Stat	P-value
Intercept	50.83	3.02	0.00
Total Population	0.45	2.43	0.02
Life Expectancy	0.62	2.25	0.03
GDP Per Capita	0.00	-0.62	0.54

Leukaemia regression is again significant with an R^2 greater than 50%. Again, both the total population and life expectancy variables show a very low p-value, as such we tested their significance in explaining the incidence of both leukaemia and non-Hodgkin Lymphoma.

Lastly, we conducted a similar analysis for haemophilia A. In this case, based on the Italian landscape, we consider the total number of cases in relation with the total population, life expectancy and GDP per capita between 2006 and 2019[85]. We create the dataset through data from the Istituto Superiore della Sanità (ISS), in particular from their yearly Istisan reports.

[85] Unfortunately, a dataset for the same period for which we conducted our analysis on non-Hodgkin Lymphoma and leukaemia is not available. As such, we considered this different time horizon

Exhibit 5. Summary Output regression haemophilia A

Regression Statistics	
Multiple R	0.93
R Square	0.87
Adjusted R Square	0.82
Observations	12.00

ANOVA

	df	SS	MS
Regression	3.00	2780844.43	960281.48
Residual	8.00	404817.23	30602.15
Total	11.00	3185661.67	

	Coefficients	t Stat	P-value
Intercept	-40.81	-4.60	0.00
Total Population	380.53	2.46	0.04
Life Expectancy	250.30	1.28	0.24
GDP Per Capita	31.28	1.44	0.19

Similarly to what we observed through regressions in exhibit 1 and 2, we see how the total number of cases of haemophilia A is largely explained by the three variables considered, with an R^2 greater than 0.85. In particular, the total population variable is highly significant with a p-value lower than 5% (rejection of null hypothesis). On the other hand, differently from the two other regressions, the life expectancy variable is not significant.

In addition, we want to notice how in all the three regressions, the GDP per capita variable is not significant, with p-values always quite high. As such, probably our assumption about this variable correctly representing the quality of quantity of screening was wrong, at least for the Italian case. Even though it would be interesting to investigate further this specific matter, it is quite far from the main objective of this thesis.

Overall, with these regressions, we wanted to empirically test and underline how the total number of targetable patients is dependent not only on the number of ATMPs on the market but also on other macroeconomic variables. In particular, we showed how, empirically, they are mainly dependent on the total number of the Italian population. As such, since we all hope that the Italian population will re-start to

increase in a few years from now, if this happens, we will experience an enlargement of the potential audience for ATMPs application. Once again, we showed how this research is truly important for the future, as we expect a rapid increase in the ATMPs potential adoption due to different factors; even tough, as of now, it may be seen only as a minor economic problem, due to the current size of the market.

2. Dataset

After we have proven, even empirically, why the ATMPs economic issue would become an even more relevant matter in the upcoming years, in order to understand the overall economic sustainability of ATMPs for the Italian National Health System, we decided to build a specific empirical model.

For the analysis we wanted to conduct, we calculate the total potential spending for ATMPs, and we compared this with the total spending for the Italian National Health System if the same patients were treated[86] with traditional therapies.

One of the most difficult problems in building the model has been the creation of a specific dataset, in a completely new field, and with only a few research and data available. Creating these datasets has been one of the most challenging steps to complete this work; indeed, we really had to go in-depth in the literature of the field to make estimates as reliable as possible. In addition, we had to collaborate with professionals active in the field of medicine to better and specifically understand traditional treatments for diseases that ATMPs could cure.

a. Dataset for ATMPs

On the one hand, specific data on ATMPs and their application had to be found:

- Potential target population that could currently be cured in Italy with available (and soon to be available) ATMPs between 2022 and 2026;
- Actual target population cured with ATMPs in Italy between 2022 and 2026;
- Current price of ATMPs for the Italian National Health System.

[86] It must be noticed that, for the specific rare diseases that ATMPs cure, almost no cure exists and, other than ATMPs, only therapies either palliative or purely targeting the symptoms are available

In Sweden a specific committee for ATMPs exists (ATMP Sweden[87]), and they produced specific research for the potentially targetable population in Sweden until 2030 – while we estimated the actually targeted population through an average percentage based on other European countries.

Thanks to these sources, as you can see in Exhibit 6, 7, 8, we came up with specific datasets, for:

- The total targetable population that could be cured with ATMPs between 2022 and 2026 in Italy;
- The total targeted population that would be cured with ATMPs between 2022 and 2026 by the Italian National Health System – estimated through a percentage of total target population for each specific disease;
- The total cost of each working[88] ATMP for the Italian National Health System.

[87] www. atmpsweden.se/

[88] Considering the payment-by-result scheme adopted

Exhibit 6. Potential and actual target population for each ATMP between 2022 and 2026 and, year of availability for each ATMP.

#	Disease	Total Current Potential Target Population	% Population To be Treated by the NHS	Actual Population To be Treated by the NHS	Available ATMP - Year
1	ADA - Scid	2	50%	1	2022
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	740	20%	148	2022
3	Retinal dystrophies (RPE65 mutation)	70	20%	14	2022
4	Type 1 Spinal Muscular Atrophy (SMA1)	27	60%	16	2022
5	Chondral lesions	5024	10%	502	2022
6	Metachromatic leukodystrophy (MLD)	81	20%	16	2022
7	Multiple myeloma	1800	10%	180	2022
8	AADC enzyme deficiency	60	20%	12	2022
9	Relapsing / refractory mantle cell lymphoma	80	20%	16	2022
10	Haemophilia A	1850	10%	185	2022
11	Cerebral adrenoleukodystrophy (CALD)	3	60%	2	2022
12	Glioblastoma	482	20%	96	2023
13	Wiskott-Aldrich syndrome (WAS)	13	60%	8	2023
14	β-thalassemia	1200	10%	120	2023
15	Choroideremia	1193	10%	119	2023
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	30	20%	6	2023
17	Indolent non-Hodgkin's lymphoma (iNHL)	728	20%	146	2023
18	Retinitis pigmentosa X-linked	255	20%	51	2024
19	Haemophilia B	314	20%	63	2024
20	Duchenne dystrophy	68	20%	14	2024
21	Chronic Lymphocytic Leukaemia (CLL)	454	20%	91	2025
22	Myxoid liposarcoma	210	20%	42	2025
23	Synovial sarcoma	350	20%	70	2025
24	Late-onset Pompe disease	166	20%	33	2026

Sources: Report Italiano sulle advanced therapy medicinal products – ATMP Forum. Le terapie avanzate in Italia e in Europa – Osservatorio Terapie Avanzate. AIFA. EMA. Gazzetta Ufficiale.

Exhibit 7. Forecasted spending for ATMPs for the Italian National Health System between 2022 with 100% success rate, figures in €/mln.

#	Disease	2022A	2023E	2024E	2025E	2026E
1	ADA - Scid	0.5	0.5	0.5	0.5	0.5
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	95.8	95.8	95.8	95.8	95.8
3	Retinal dystrophies (RPE65 mutation)	10.1	10.1	10.1	10.1	10.1
4	Type 1 Spinal Muscular Atrophy (SMA1)	6.2	6.2	6.2	6.2	6.2
5	Chondral lesions	5.5	11.1	11.1	11.1	11.1
6	Metachromatic leukodystrophy (MLD)	2.9	8.6	11.5	11.5	11.5
7	Multiple myeloma	29.1	58.2	58.2	58.2	58.2
8	AADC enzyme deficiency	3.9	7.8	7.8	7.8	7.8
9	Relapsing / refractory mantle cell lymphoma	5.1	10.1	10.1	10.1	10.1
10	Haemophilia A	36.2	108.1	143.9	143.9	143.9
11	Cerebral adrenoleukodystrophy (CALD)	0.6	0.6	0.6	0.6	0.6
12	Glioblastoma	0.0	31.1	62.4	62.4	62.4
13	Wiskott-Aldrich syndrome (WAS)	0.0	4.8	4.8	4.8	4.8
14	β-thalassemia	0.0	37.8	75.6	75.6	75.6
15	Choroideremia	0.0	42.8	86.0	86.0	86.0
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	0.0	2.2	4.3	4.3	4.3
17	Indolent non-Hodgkin's lymphoma (iNHL)	0.0	23.6	70.5	94.1	94.1
18	Retinitis pigmentosa X-linked	0.0	0.0	18.4	36.7	36.7
19	Haemophilia B	0.0	0.0	24.5	49.0	49.0
20	Duchenne dystrophy	0.0	0.0	2.2	6.3	8.5
21	Chronic Lymphocytic Leukaemia (CLL)	0.0	0.0	0.0	29.4	58.9
22	Myxoid liposarcoma	0.0	0.0	0.0	13.6	27.2
23	Synovial sarcoma	0.0	0.0	0.0	22.6	45.3
24	Late-onset Pompe disease	0.0	0.0	0.0	0.0	5.5
	Total	**195.9**	**459.5**	**704.6**	**840.9**	**914.3**

Sources: Report Italiano sulle advanced therapy medicinal products – ATMP Forum. Le terapie avanzate in Italia e in Europa – Osservatorio Terapie Avanzate. AIFA. EMA. Gazzetta Ufficiale. Others.

Exhibit 8. Current market price for each working ATMP for the Italian National Health System, figures in €/mln. ATMP associated to each cure and expected success rate.

#	Disease	Current Mkt Price	ATMP(s)	Success Rate
1	ADA - Scid	0.594	Strimvelis	75%
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	0.324	Yescarta / Kymriah	45%
3	Retinal dystrophies (RPE65 mutation)	0.360	Luxturna	80%
4	Type 1 Spinal Muscular Atrophy (SMA1)	1.945	Zolgensma	45%
5	Chondral lesions	0.011	Yescarta / Kymriah	45%
6	Metachromatic leukodystrophy (MLD)	0.360	Luxturna	80%
7	Multiple myeloma	0.324	Yescarta / Kymriah	45%
8	AADC enzyme deficiency	0.324	Yescarta / Kymriah	45%
9	Relapsing / refractory mantle cell lymphoma	0.317	Tecartus US	60%
10	Haemophilia A	1.945	Zolgensma	45%
11	Cerebral adrenoleukodystrophy (CALD)	1.575	Zynteglo	70%
12	Glioblastoma	0.324	Yescarta / Kymriah	40%
13	Wiskott-Aldrich syndrome (WAS)	0.594	Strimvelis	75%
14	β-thalassemia	1.575	Zynteglo	80%
15	Choroideremia	0.360	Luxturna	80%
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	0.360	Luxturna	80%
17	Indolent non-Hodgkin's lymphoma (iNHL)	0.324	Yescarta / Kymriah	40%
18	Retinitis pigmentosa X-linked	0.360	Luxturna	80%
19	Haemophilia B	1.945	Zolgensma	45%
20	Duchenne dystrophy	1.575	Zynteglo	80%
21	Chronic Lymphocytic Leukaemia (CLL)	0.324	Yescarta / Kymriah	45%
22	Myxoid liposarcoma	0.324	Yescarta / Kymriah	45%
23	Synovial sarcoma	0.324	Yescarta / Kymriah	45%
24	Late-onset Pompe disease	0.324	Yescarta / Kymriah	45%

Sources: Report Italiano sulle advanced therapy medicinal products – ATMP Forum. Le terapie avanzate in Italia e in Europa – Osservatorio Terapie Avanzate. AIFA. EMA. Gazzetta Ufficiale. Others.

b. Dataset for Traditional Therapies

The second set of data we need is specific for traditional therapies for diseases which instead could be cured through ATMPs. In particular, we need to define, for each associated disease:

- Direct costs to cure them for the Italian National Health System;
- Average age of diagnosis;
- Average life expectancy after the diagnosis;
- Quality of life for sick patients, and improvement if cured with ATMPs.

Two major, connected, difficulties in creating these datasets were found. Firstly, due to the silos' budgeting methodology used by the Italian National Health System, there are not pre-defined costs to cure each specific disease. Secondly, medicine is not our field and defining the specific cure used for each specific disease has not been easy. For this reason, we went through specific literature in the field of each disease, and we directly interacted with experts in the field.

In exhibit 7, the dataset with the total cost per year, and the total average years to treat each disease are shown. In particular, the cost and length associated to each disease were calculated, disease by disease, by understanding the traditional applied treatment, the average age of diagnosis, the average length of the treatment (all life, only for a few years if terminal disease or other specific lengths)[89]. To compute each of these topics, we studied specific medical literature, and we refer mainly to the Italian Gazzetta Ufficiale to find the price of each drug used. In Appendix, we outlined how we computed the cost associated for each analysed disease.

[89] Except for 6 diseases that accounted for less than 1% of expected spending in ATMPs in 2026: ADA-Scid, AADC enzyme deficiency, Cerebral adrenoleukodystrophy (CALD), Wiskott-Aldrich syndrome (WAS), Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation, Late-onset Pompe disease. For these diseases we considered the average cost and average length of cure as the average of these two datapoints for the other diseases

It must be noticed that we only considered direct costs associated to each disease (mainly drugs). We did this for two reasons:

- Also for ATMPs, we only considered the cost associated to each drug and not other relevant healthcare services that should be provided to each patient after the treatment. As such, as a proxy, we are not considering these indirect costs on traditional therapies either;
- It is almost impossible to estimate them correctly, due to the 'silos' budgeting policy applied by the National Government to the Italian National Health System, as analysed in the second section of our work.

Lastly, in exhibit 8, based on similar analysis conducted to create the dataset reported in exhibit 7, for each disease, we estimated the increase in the quality of life for each treated patient with ATMPs (from 0% to 100%), and the potential delta GDP per capita produced yearly after the cure (computed as the average GDP per capita in 2020 multiplied by the improvement in the quality of life associated to each disease). We want to underline how, to estimate the percentage of improvement in the quality of life, we considered different factors such as the mortality rate, the average age of diagnosis and others.

Exhibit 9. Average cost and length of cure for each disease, figures in €/mln

#	Disease	Cost	Years of cure
1	ADA - Scid	0.0293	24 Years
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	0.0935	4 Years
3	Retinal dystrophies (RPE65 mutation)	0.0010	73 Years
4	Type 1 Spinal Muscular Atrophy (SMA1)	0.0400	7 Years
5	Chondral lesions	0.0032	10 Years
6	Metachromatic leukodystrophy (MLD)	0.0300	10 Years
7	Multiple myeloma	0.0669	7 Years
8	AADC enzyme deficiency	0.0293	24 Years
9	Relapsing / refractory mantle cell lymphoma	0.0480	4 Years
10	Haemophilia A	0.0127	50 Years
11	Cerebral adrenoleukodystrophy (CALD)	0.0293	24 Years
12	Glioblastoma	0.0126	10 Years
13	Wiskott-Aldrich syndrome (WAS)	0.0293	24 Years
14	β-thalassemia	0.0198	39 Years
15	Choroideremia	0.0010	53 Years
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	0.0293	24 Years
17	Indolent non-Hodgkin's lymphoma (iNHL)	0.0345	4 Years
18	Retinitis pigmentosa X-linked	0.0010	50 Years
19	Haemophilia B	0.0338	50 Years
20	Duchenne dystrophy	0.0552	25 Years
21	Chronic Lymphocytic Leukaemia (CLL)	0.0030	35 Years
22	Myxoid liposarcoma	0.0347	4 Years
23	Synovial sarcoma	0.0357	4 Years
24	Late-onset Pompe disease	0.0293	24 Years

Sources: Gazzetta Ufficiale. AIFA. EMA. ISTAT. Goldman L., Schafer A – Goldman-Cecil Medicine. DeVita V. T., Rosenberg S. A., Lawrence T. S. – Cancer, Principles And Practice Of Oncology. Others.

Exhibit 10. Average quality of life improvement for each disease cured with ATMP, and consequent GDP per capita produced per year, figures in €/mln

#	Disease	Average quality of life improvement	GDP Produced per year
1	ADA - Scid	16%	0.004
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	10%	0.003
3	Retinal dystrophies (RPE65 mutation)	0%	0.000
4	Type 1 Spinal Muscular Atrophy (SMA1)	40%	0.011
5	Chondral lesions	0%	0.000
6	Metachromatic leukodystrophy (MLD)	20%	0.006
7	Multiple myeloma	20%	0.006
8	AADC enzyme deficiency	16%	0.004
9	Relapsing / refractory mantle cell lymphoma	20%	0.006
10	Haemophilia A	20%	0.006
11	Cerebral adrenoleukodystrophy (CALD)	16%	0.004
12	Glioblastoma	20%	0.006
13	Wiskott-Aldrich syndrome (WAS)	16%	0.004
14	β-thalassemia	20%	0.006
15	Choroideremia	0%	0.000
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	16%	0.004
17	Indolent non-Hodgkin's lymphoma (iNHL)	20%	0.006
18	Retinitis pigmentosa X-linked	0%	0.000
19	Haemophilia B	20%	0.006
20	Duchenne dystrophy	30%	0.008
21	Chronic Lymphocytic Leukaemia (CLL)	20%	0.006
22	Myxoid liposarcoma	10%	0.003
23	Synovial sarcoma	10%	0.003
24	Late-onset Pompe disease	16%	0.004

Sources: Gazzetta Ufficiale. AIFA. EMA. ISTAT. Goldman L., Schafer A – Goldman-Cecil Medicine. DeVita V. T., Rosenberg S. A., Lawrence T. S. – Cancer, Principles And Practice Of Oncology. Others.

c. Other Data

Other useful data we used in our model are:

- GDP per capita;
- Italian average life length;
- Discount Rate;
- Expected inflation.

As GDP per capita we used the 2020 figure: €27,780 (ISTAT). Moreover, when we calculated the GDP impact, we considered an average year growth rate for GDP per capita of 2%, i.e. the inflation targeted by the ECB in the medium-long term.

As Italian average Life expectancy, we considered 82 years (ISTAT, as of October 2021).

As Discount rate, we used the 10-years Italian Government Bond, yielding 0.968% (as of 26th October 2021, source Bloomberg). We decided to use this discount rate, since we are proposing a model for which the Italian National health System would depreciate ATMPs, accounted as intangibles, in 10 years (or less). As a result, for a perfect profile of asset liability management and to perfectly managed outflows due to ATMPs cost, the National Health System could finance its initial acquisitions with 10 years bond. In addition, even if the National Health System would not use debt to finance ATMPs acquisition, using this discount rate is fundamental to take into account the risky component of time. Moreover, to conduct our sensitivity analysis, we also considered the 30-years Italian Government Bond, yielding 1.834% (as of 26th October 2021, source Bloomberg).

3. Models' Layout and Results

a. Building the Model

When we decided to conduct this research, we wanted to understand clearly the economic sustainability of ATMPs for the Italian National Health System, with the currently applied payment-by-result payment scheme, compared to our new proposed payment scheme, based on the different accounting of ATMPs. As such, to empirically prove it, we built a predictive model with the aim of comparing the cost associated to curing specific diseases with ATMPs, with the same diseases cured with traditional therapies. Building this model has been extremely tough, mechanically we considered many inputs and different dataset were used (as analysed in Section II, chapter 1).

In our model, we considered different scenarios:

- As-Is Scenario. The current situation and the expected usage of ATMPs by the National Health System between 2022 and 2026 when the payment-by-result scheme is used;
- 10 Years Scenario targeting all potential population with payment-by-result. The economic result if ATMPs are used to all the potential available population between 2022 and 2031 and the payment-by-result scheme is used;
- 10 Years Scenario targeting all potential population with payment-by-result, and accounting of ATMPs as intangibles and consequent amortisation until Break-Even Point (BEP). The economic result if our proposed payment scheme is used: ATMPs are administered to all the potential available population between 2022 and 2031 and the payment-by-result scheme is used, coupled with the accounting of ATMPs as intangibles with the amortisation of these innovative drugs for a period enabling the reach of break-even;

- 10 Years Scenario targeting all potential population with payment-by-result, and accounting of ATMPs as intangibles and consequent amortisation for 10 years. The economic result if our proposed payment scheme is used: ATMPs are used to all the potential available population between 2022 and 2031 and the payment-by-result scheme is used, coupled with the accounting of ATMPs as intangibles with the amortisation of these innovative drugs for a period of 10 years.

For each scenario, we considered as negative flows[90] the cost associated to ATMPs, as positive flows the cost of treating the same number of patients through traditional therapies. We consider a long-time horizon, up to the year 2103, given the average expected life, and the expected life length to treat specific diseases with traditional therapies (e.g. retinal dystrophies, with an expected length of cure of 73 years[91]). We discounted the flows through the 10 years government bond rate (as explained in Section II, Chapter 1).

We decided to make the analysis with the assumption of the Italian national Health System to cure all the potential targetable population in 10 years, since it is a sustainable time horizon for the system to handle the pressure of delivering innovative therapies to all the available targetable audience.

Also, based on industry estimates[92], with a conservative approach, we estimated – in case of treating all available targetable patients – economies of scale up to 10% (reachable in 10 years, c. 1% per year).

[90] As explained in Section II, Chapter 1, considering these as flows make sense, since associated D&A that we propose with our payment scheme, could be financed through 10 years debt for the Italian National Health System

[91] Average age of diagnosis c. 10 years, average age of death for these patients c. 83 years

[92] Pharma Industry and Biotechnology Industry. Source: McKinsey

Lastly, it must be noticed how we are 'only' considering diseases that are treatable with ATMPs currently available in the market or that are soon-to-be-available, as defined in Section II, Chapter 1.

b. Expanding the Model – Accounting for the Macroeconomic Impact and Sensitivity Analysis

When going through some literature on the field, we noticed that the macroeconomic impact of ATMPs was one of the least investigated facets. For this reason, we decided to expand our predictive model to account, at least laterally, for the macro-economic impact of ATMPs.

As such, after the estimation of the improvement in the quality of life for each patient treated with an ATMP, we computed the related delta GDP per capita that could be produced by these patients in the expected years of life that they would sustain.

We considered the produced delta GDP as positive flows (offsetting ATMPs costs), in all the four scenarios already mentioned in the previous paragraph.

In addition, we decided to conduct, for each of the two main cases (with or without considering the GDP effect), a sensitivity analysis considering different:

- Discount rates, between 0.39% and 1.83% - 30 years government bond;
- Amortisation time horizons, between 4 and 10 years.

c. Results

Based on the mechanic of our models, in case the produced NPV, for each specific scenario, would be positive (the sum of present value of cost for traditional cures and the present value of delta GDP produced greater than the present value of costs for ATMPs), the usage of ATMP would be convenient even economically speaking.
It is again fundamental to notice that, as we explained in Section I of this work, this sector is expected to explode in size and become much larger in the upcoming years. As such, the results we will obtain should be considered as a starting point that could be exponentially larger when more and more therapies will be available, the targetable number of patients will be greater and greater, and the economies of scale would be larger and larger.

Exhibit 11. Results obtain in different scenarios without considering the GDP effect

Scenario 1 - As Is	
Payment Scheme	Payment-by-result
Population	Actual targeted
Years to treat population	5 Years
D&A of ATMPs	No
GDP effect	No
Net Present Value	**-147.3 €**

Scenario 2 - All Population in 10 Years	
Payment Scheme	Payment-by-result
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	No
GDP effect	No
Net Present Value	**-293.8 €**

Scenario 3 - All Population in 10 years, D&A until BEP	
Payment Scheme	Payment-by-result with D&A
Population	Actual targeted
Years to treat population	10 Years
D&A of ATMPs	**6 Years**
GDP effect	No
Net Present Value	**7.7 €**

Scenario 4 - All Population in 10 years, D&A in 10 years	
Payment Scheme	Payment-by-result with D&A
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	10 Years
GDP effect	No
Net Present Value	**96.7 €**

In the first part of our model, we consider the "basic" situation we described without including the GDP. Empirically, we are proving that, through the new proposed payment scheme, ATMPs would be sustainable even economically for the Italian National Health System. In the first scenario, we are considering the currently targeted population, and we see how this is economically inconvenient for the public health system. Moreover, if we include all the potential targetable population, we notice how this result is amplified, topping a negative NPV of €293.8 million.

On the other hand, if we consider ATMPs as intangible and we amortise them in a period of 10 years, we see how these innovative therapies become not only sustainable, but even profitable compared to traditional therapies currently used for the considered diseases. In particular, with our model we computed the break-even point of sustainability at a length of amortisation of c. 6 years.

Exhibit 12. Results obtain in different scenarios considering the GDP effect

Scenario 1 - As Is	
Payment Scheme	Payment-by-result
Population	Actual targeted
Years to treat population	5 Years
D&A of ATMPs	No
GDP effect	Yes
Net Present Value	**-54.9 €**

Scenario 2 - All Population in 10 Years	
Payment Scheme	Payment-by-result
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	No
GDP effect	Yes
Net Present Value	**-144.5 €**

Scenario 3 - All Population in 10 years, D&A until BEP	
Payment Scheme	Payment-by-result with D&A
Population	Actual targeted
Years to treat population	10 Years
D&A of ATMPs	**4 Years**
GDP effect	Yes
Net Present Value	**13.6 €**

Scenario 4 - All Population in 10 years, D&A in 10 years	
Payment Scheme	Payment-by-result with D&A
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	10 Years
GDP effect	Yes
Net Present Value	**357.4 €**

In the second part of our model we considered the impact of GDP in our analysis, as an input offsetting the spending for ATMPs, in order to account for the overall macroeconomic impact. With this new model, we are basically confirming what we noticed in Exhibit 9. Moreover, it must be noticed how ATMPs become extremely profitable with an amortisation period of 10 years, considering in fact, a break-even

point lower than 4 years (c. 3.5 years). We want to underline that we have been conservative in our estimation of the overall GDP impact, and that an even greater macro-economic effect could be possible thanks to the adoption of ATMPs; especially considering the number of available cures that will be available in a few years from now.

Exhibit 13. Sensitivity analysis without considering the GDP effect

Discount Rate \ D&A Time Horizon	4	5	6	7	8	9	10
1.83%	-220.28 €	-193.94 €	-132.95 €	-71.82 €	-32.12 €	-1.08 €	39.64 €
1.55%	-131.79 €	-105.38 €	-79.22 €	-38.97 €	1.33 €	28.19 €	68.99 €
1.26%	-64.10 €	-41.72 €	-19.52 €	2.50 €	24.81 €	41.48 €	56.18 €
0.97%	-23.56 €	-10.41 €	7.73 €	43.64 €	61.43 €	79.10 €	96.66 €
0.68%	37.69 €	50.75 €	83.74 €	106.68 €	139.56 €	162.38 €	185.14 €
0.39%	83.76 €	101.46 €	169.15 €	206.81 €	234.45 €	272.08 €	309.68 €

Exhibit 14. Sensitivity analysis considering the GDP effect

Discount Rate \ D&A Time Horizon	4	5	6	7	8	9	10
1.83%	-88.13 €	-59.97 €	-31.43 €	12.51 €	63.22 €	113.57 €	153.22 €
1.55%	-99.59 €	-53.10 €	1.34 €	57.30 €	103.98 €	187.40 €	216.55 €
1.26%	-29.98 €	12.92 €	75.68 €	108.25 €	179.63 €	212.83 €	283.57 €
0.97%	13.58 €	54.73 €	99.74 €	147.64 €	235.43 €	289.10 €	357.44 €
0.68%	59.13 €	92.19 €	125.18 €	190.12 €	251.00 €	313.82 €	386.58 €
0.39%	108.67 €	147.37 €	225.06 €	292.72 €	348.36 €	407.99 €	445.59 €

From these sensitivities analysis we can have a clear and broad overview of the outcomes of our model. In particular, even without considering the GDP effect, we still reach the breakeven point near 9 years, considering the 30 years government bond as discount rate. Also, considering the same highest band of discount rate and considering the GDP effect, we reach the break-even between 6 and 7 years of amortisation.

Overall, with these sensitivity analyses, we are confirming the soundness of our models and of our findings, which are solids even considering higher discount rates – especially considering the overall conservative approach we use towards the majority of inputs.

SECTION III: THE MODEL APPLIED TO THE SWEDISH NATIONAL HEALTH SYSTEM

1. Dataset

After the analysis conducted on the Italian National health Systems, we decided to apply and test the same research to the Swedish National Health System; which present, especially for ATMPs adoption, similar tracts to the Italian National Health System[93].

We created a series of datasets extremely similar to the ones created for the Italian case, in order to be able to apply a similar – but tailored – model, to test the functioning of the newly proposed payment scheme also to the Swedish Health System.

For the analysis we wanted to conduct, we calculate the total potential spending for ATMPs, and we compared this with the total spending for the Swedish National Health System if the same patients were treated[94] with traditional therapies.

Given the strong similarities of the two National Health Systems, and the prices of traditional therapies and of ATMPs that are almost the same across countries in the European Union, the used dataset of cost of treating patients with traditional therapies and the cost of ATMPs are the same within the two National health Systems.

a. Dataset for ATMPs

Similarly to the Italian case, on the one hand, specific data on ATMPs and their application had to be found:

- Potential target population that could currently be cured in Sweden with available (and soon to be available) ATMPs between 2022 and 2026;
- Actual target population cured with ATMPs in Sweden between 2022 and 2026;

[93] Section I, Chapter 3.a, 3.b, 3.c

[94] It must be noticed that, for the specific rare diseases that ATMPs cure, almost no cure exists and, other than ATMPs, only therapies either palliative or purely targeting the symptoms are available

- Current price of ATMPs for the Sweden National Health System.

In Sweden a specific committee for ATMPs exists (ATMP Sweden[95]), and they produced specific research for the potentially targetable population in Sweden until 2030 – while we estimated the actually targeted population through an average percentage based on other European countries.

Thanks to these sources, as you can see in Exhibit 15, 16, 17, we came up with specific datasets, for:

- The total targetable population that could be cured with ATMPs between 2022 and 2026 in Sweden;
- The total targeted population that would be cured with ATMPs between 2022 and 2026 by the Swedish National Health System – estimated through a percentage of total target population for each specific disease based on the Italian case and out comparable countries across the European Union;
- The total cost of each working[96] ATMP for the Swedish National Health System.

Last thing to be noticed, not for importance, is that all data are shown in euro for Sweden as well, instead of the local currency Swedish Krona. This choice was made to make the comparability between the two cases as clear as possible.

An exchange rate Euro / Swedish krona of 10.2884 was considered (excxhange rate as of 3rd January 2022, source Bloomberg).

[95] www. atmpsweden.se

[96] Same as the Italian case

Exhibit 15. Sweden – Potential and actual target population for each ATMP between 2022 and 2026 and, year of availability for each ATMP.

#	Disease	Total Current Potential Target Population	% Population To be Treated by the NHS	Actual Population To be Treated by the NHS	Available ATMP - Year
1	ADA - Scid	1	100%	1	2022
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	210	25%	53	2022
3	Retinal dystrophies (RPE65 mutation)	15	25%	4	2022
4	Type 1 Spinal Muscular Atrophy (SMA1)	27	50%	14	2022
5	Chondral lesions	892	20%	178	2022
6	Metachromatic leukodystrophy (MLD)	28	10%	3	2022
7	Multiple myeloma	340	15%	51	2022
8	AADC enzyme deficiency	8	15%	1	2022
9	Relapsing / refractory mantle cell lymphoma	10	15%	2	2022
10	Haemophilia A	320	15%	48	2022
11	Cerebral adrenoleukodystrophy (CALD)	1	60%	1	2022
12	Glioblastoma	64	20%	13	2023
13	Wiskott-Aldrich syndrome (WAS)	4	50%	2	2023
14	β-thalassemia	0	10%	0	2023
15	Choroideremia	194	15%	29	2023
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	12	25%	3	2023
17	Indolent non-Hodgkin's lymphoma (iNHL)	146	25%	37	2023
18	Retinitis pigmentosa X-linked	24	15%	4	2024
19	Haemophilia B	39	25%	10	2024
20	Duchenne dystrophy	9	25%	2	2024
21	Chronic Lymphocytic Leukaemia (CLL)	76	25%	19	2025
22	Myxoid liposarcoma	27	15%	4	2025
23	Synovial sarcoma	47	25%	12	2025
24	Late-onset Pompe disease	23	10%	2	2026

Sources: ATMP Sweden. EMA. Labiotech. ECA – ATMP Group.

Exhibit 16. Forecasted spending for ATMPs for the Swedish National Health System between 2022 with 100% success rate, figures in €/mln.

#	Disease	2022A	2023E	2024E	2025E	2026E
1	ADA - Scid	0.3	0.3	0.3	0.3	0.3
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	10.2	10.2	10.2	10.2	10.2
3	Retinal dystrophies (RPE65 mutation)	0.8	0.8	0.8	0.8	0.8
4	Type 1 Spinal Muscular Atrophy (SMA1)	18.4	18.4	18.4	18.4	18.4
5	Chondral lesions	2.0	2.0	2.0	2.0	2.0
6	Metachromatic leukodystrophy (MLD)	1.0	1.0	1.0	1.0	1.0
7	Multiple myeloma	16.5	16.5	16.5	16.5	16.5
8	AADC enzyme deficiency	0.4	0.4	0.4	0.4	0.4
9	Relapsing / refractory mantle cell lymphoma	0.5	0.5	0.5	0.5	0.5
10	Haemophilia A	93.4	93.4	93.4	93.4	93.4
11	Cerebral adrenoleukodystrophy (CALD)	0.7	0.7	0.7	0.7	0.7
12	Glioblastoma	0.0	4.1	4.1	4.1	4.1
13	Wiskott-Aldrich syndrome (WAS)	0.0	0.1	0.1	0.1	0.1
14	β-thalassemia	0.0	0.0	0.0	0.0	0.0
15	Choroideremia	0.0	10.5	10.5	10.5	10.5
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	0.0	0.9	0.9	1.7	3.5
17	Indolent non-Hodgkin's lymphoma (iNHL)	0.0	0.6	9.4	18.9	37.8
18	Retinitis pigmentosa X-linked	0.0	0.0	1.3	2.6	5.2
19	Haemophilia B	0.0	0.0	15.2	30.3	60.7
20	Duchenne dystrophy	0.0	0.0	2.8	5.7	11.3
21	Chronic Lymphocytic Leukaemia (CLL)	0.0	0.0	0.0	4.9	9.8
22	Myxoid liposarcoma	0.0	0.0	0.0	1.3	2.6
23	Synovial sarcoma	0.0	0.0	0.0	3.0	6.1
24	Late-onset Pompe disease	0.0	0.0	0.0	0.0	0.7
	Total	**144.1**	**160.3**	**188.4**	**227.3**	**296.5**

Sources: ATMP Sweden. EMA. Labiotech. ECA – ATMP Group.

Exhibit 17. Current market price for each working ATMP for the Swedish National Health System, figures in €/mln. ATMP associated to each cure and expected success rate.

#	Disease	Current Mkt Price	ATMP(s)	Success Rate
1	ADA - Scid	0.594	Strimvelis	75%
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	0.324	Yescarta / Kymriah	45%
3	Retinal dystrophies (RPE65 mutation)	0.360	Luxturna	80%
4	Type 1 Spinal Muscular Atrophy (SMA1)	1.945	Zolgensma	45%
5	Chondral lesions	0.011	Yescarta / Kymriah	45%
6	Metachromatic leukodystrophy (MLD)	0.360	Luxturna	80%
7	Multiple myeloma	0.324	Yescarta / Kymriah	45%
8	AADC enzyme deficiency	0.324	Yescarta / Kymriah	45%
9	Relapsing / refractory mantle cell lymphoma	0.317	Tecartus US	60%
10	Haemophilia A	1.945	Zolgensma	45%
11	Cerebral adrenoleukodystrophy (CALD)	1.575	Zynteglo	70%
12	Glioblastoma	0.324	Yescarta / Kymriah	40%
13	Wiskott-Aldrich syndrome (WAS)	0.594	Strimvelis	75%
14	β-thalassemia	1.575	Zynteglo	80%
15	Choroideremia	0.360	Luxturna	80%
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	0.360	Luxturna	80%
17	Indolent non-Hodgkin's lymphoma (iNHL)	0.324	Yescarta / Kymriah	40%
18	Retinitis pigmentosa X-linked	0.360	Luxturna	80%
19	Haemophilia B	1.945	Zolgensma	45%
20	Duchenne dystrophy	1.575	Zynteglo	80%
21	Chronic Lymphocytic Leukaemia (CLL)	0.324	Yescarta / Kymriah	45%
22	Myxoid liposarcoma	0.324	Yescarta / Kymriah	45%
23	Synovial sarcoma	0.324	Yescarta / Kymriah	45%
24	Late-onset Pompe disease	0.324	Yescarta / Kymriah	45%

Sources: EMA.

b. Dataset for Traditional Therapies

Considering the analysis we are conducting – parallel to the one we did in the previous chapter buy applied to a similar National Health System with a different capacity – the second set of data we need is specific for traditional therapies for diseases which instead could be cured through ATMPs. In particular, we need to define, for each associated disease:

- Direct costs to cure them for the Swedish National Health System;
- Average age of diagnosis;
- Average life expectancy after the diagnosis;
- Quality of life for sick patients, and improvement if cured with ATMPs.

As analysed before[97], the direct costs of therapies are almost the same throughout countries in the European Union. Moreover, obviously the age of diagnosys, the average life expectancy and the quality of life for sick patients are the same throughout countries.
As such, we will use the same dataset – now showed in exhibit 18 – used in the previous section also in this new model applied to the Swedish case.

Lastly, in exhibit 19, based on similar analysis conducted to create the dataset reported in exhibit 18, for each disease, we estimated the increase in the quality of life for each treated patient with ATMPs (from 0% to 100%), and the potential delta GDP per capita produced yearly after the cure (computed as the average Swedish GDP per capita in 2020 multiplied by the improvement in the quality of life associated to each disease). We want to underline how, to estimate the percentage of improvement in the quality of life, we considered different factors such as the mortality rate, the average age of diagnosis and others.

[97] Section II, chapter 3.b and 3.c

Exhibit 18. Average cost and length of cure for each disease, figures in €/mln

#	Disease	Cost	Years of cure
1	ADA - Scid	0.0293	24 Years
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	0.0935	4 Years
3	Retinal dystrophies (RPE65 mutation)	0.0010	73 Years
4	Type 1 Spinal Muscular Atrophy (SMA1)	0.0400	7 Years
5	Chondral lesions	0.0032	10 Years
6	Metachromatic leukodystrophy (MLD)	0.0300	10 Years
7	Multiple myeloma	0.0669	7 Years
8	AADC enzyme deficiency	0.0293	24 Years
9	Relapsing / refractory mantle cell lymphoma	0.0480	4 Years
10	Haemophilia A	0.0127	50 Years
11	Cerebral adrenoleukodystrophy (CALD)	0.0293	24 Years
12	Glioblastoma	0.0126	10 Years
13	Wiskott-Aldrich syndrome (WAS)	0.0293	24 Years
14	β-thalassemia	0.0198	39 Years
15	Choroideremia	0.0010	53 Years
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	0.0293	24 Years
17	Indolent non-Hodgkin's lymphoma (iNHL)	0.0345	4 Years
18	Retinitis pigmentosa X-linked	0.0010	50 Years
19	Haemophilia B	0.0338	50 Years
20	Duchenne dystrophy	0.0552	25 Years
21	Chronic Lymphocytic Leukaemia (CLL)	0.0030	35 Years
22	Myxoid liposarcoma	0.0347	4 Years
23	Synovial sarcoma	0.0357	4 Years
24	Late-onset Pompe disease	0.0293	24 Years

Sources: Gazzetta Ufficiale. AIFA. EMA. ISTAT. Goldman L., Schafer A – Goldman-Cecil Medicine. DeVita V. T., Rosenberg S. A., Lawrence T. S. – Cancer, Principles And Practice Of Oncology. Others.

Exhibit 19. Average quality of life improvement for each disease cured with ATMP, and consequent GDP per capita produced per year, figures in €/mln

#	Disease	Quality of life if works (0-100%)	GDP Produced per year
1	ADA - Scid	16%	0.007
2	Acute Lymphoblastic Leukemia (ALL) & Diffuse Large Cell Lymphoma B (DLBCL + PMBCL)	10%	0.004
3	Retinal dystrophies (RPE65 mutation)	0%	-
4	Type 1 Spinal Muscular Atrophy (SMA1)	40%	0.017
5	Chondral lesions	0%	-
6	Metachromatic leukodystrophy (MLD)	20%	0.009
7	Multiple myeloma	20%	0.009
8	AADC enzyme deficiency	16%	0.007
9	Relapsing / refractory mantle cell lymphoma	20%	0.009
10	Haemophilia A	20%	0.009
11	Cerebral adrenoleukodystrophy (CALD)	16%	0.007
12	Glioblastoma	20%	0.009
13	Wiskott-Aldrich syndrome (WAS)	16%	0.007
14	β-thalassemia	20%	0.009
15	Choroideremia	0%	-
16	Leber hereditary optic neuropathy (LHON) with MT-ND4 mutation	16%	0.007
17	Indolent non-Hodgkin's lymphoma (iNHL)	20%	0.009
18	Retinitis pigmentosa X-linked	0%	-
19	Haemophilia B	20%	0.009
20	Duchenne dystrophy	30%	0.013
21	Chronic Lymphocytic Leukaemia (CLL)	20%	0.009
22	Myxoid liposarcoma	10%	0.004
23	Synovial sarcoma	10%	0.004
24	Late-onset Pompe disease	16%	0.007

Sources: EMA. Eurostat. Goldman L., Schafer A – Goldman-Cecil Medicine. DeVita V. T., Rosenberg S. A., Lawrence T. S. – Cancer, Principles And Practice Of Oncology. Others.

c. Other Data

Other useful data we used in our model are:

- GDP per capita;
- Italian average life length;
- Discount Rate;
- Expected inflation.

As GDP per capita we used the real 2020 figure: €42,570 (Eurostat). Moreover, when we calculated the GDP impact, we considered an average year growth rate for GDP per capita of 2%, i.e. the inflation targeted by the ECB in the medium-long term.

As Italian average Life expectancy, we considered 82.4 years (Eurostat, as of December 2021).

As Discount rate, we used the 10-years Swedish Government Bond, yielding 0.302% (as of 3rd January 2022, source Bloomberg). We decided to use this discount rate, since we are proposing a model for which the Italian National health System would depreciate ATMPs, accounted as intangibles, in 10 years (or less). As a result, for a perfect profile of asset liability management and to perfectly managed outflows due to ATMPs cost, the National Health System could finance its initial acquisitions with 10 years bond. In addition, even if the National Health System would not use debt to finance ATMPs acquisition, using this discount rate is fundamental to take into account the risky component of time. Moreover, to conduct our sensitivity analysis, we considered a window between 0.000% and 1.500%.

2. Models' Layout and Results

a. Building the Model

When applying this analysis to the Swedish Health System, we replicated the model created for the Italian case and we fed this with the different inputs. Indeed, as mentioned before, the two health systems are extremely similar in their overall structure (considering the National level).

As a result, when conducting this analysis, we considered the same mechanic for the model and the considered same different scenarios, applied to the Swedish National Health System

- As-Is Scenario. The current situation and the expected usage of ATMPs by the National Health System between 2022 and 2026 when the payment-by-result scheme is used;
- 10 Years Scenario targeting all potential population with payment-by-result. The economic result if ATMPs are used to all the potential available population between 2022 and 2031 and the payment-by-result scheme is used;
- 10 Years Scenario targeting all potential population with payment-by-result, and accounting of ATMPs as intangibles and consequent amortisation until Break-Even Point (BEP). The economic result if our proposed payment scheme is used: ATMPs are administered to all the potential available population between 2022 and 2031 and the payment-by-result scheme is used, coupled with the accounting of ATMPs as intangibles with the amortisation of these innovative drugs for a period enabling the reach of break-even;
- 10 Years Scenario targeting all potential population with payment-by-result, and accounting of ATMPs as intangibles and consequent amortisation for 10 years. The economic result if our proposed payment scheme is used: ATMPs are used to all the potential available population between 2022 and 2031 and

the payment-by-result scheme is used, coupled with the accounting of ATMPs as intangibles with the amortisation of these innovative drugs for a period of 10 years.

b. Expanding the Model – Accounting for the Macroeconomic Impact and Sensitivity Analysis

In addition, as we did for the Italian case, we decided to take into account the macroeconomic impact ATMPs adoption could have.
As such, after the estimation of the improvement in the quality of life for each patient treated with an ATMP, we computed the related delta GDP per capita that could be produced by these patients in the expected years of life that they would sustain.
We considered the produced delta GDP as positive flows (offsetting ATMPs costs), in all the four scenarios already mentioned in the previous paragraph.

In addition, we decided to conduct, for each of the two main cases (with or without considering the GDP effect), a sensitivity analysis considering different:

- Discount rates, between 0.302% (10-years Swedish government bond rate, as of 3rd January 2022 , source Bloomberg) and 1.83%;
- Amortisation time horizons, between 4 and 10 years.

c. Results

Similar to the Italian case scenario, based on the mechanic of our models, in case the produced NPV, for each specific scenario, would be positive (the sum of present value of cost for traditional cures and the present value of delta GDP produced greater than the present value of costs for ATMPs), the usage of ATMP would be convenient even economically speaking.

It is again fundamental to notice that, as we explained in Section I of this work, this sector is expected to explode in size and become much larger in the upcoming years. As such, the results we will obtain should be considered as a starting point that could be exponentially larger when more and more therapies will be available, the targetable number of patients will be greater and greater, and the economies of scale would be larger and larger.

Exhibit 20. Results obtain in different scenarios without considering the GDP effect

Scenario 1 - As Is	
Payment Scheme	Payment-by-result
Population	Actual targeted
Years to treat population	5 Years
D&A of ATMPs	No
GDP effect	No
Net Present Value	**-36.2 €**

Scenario 2 - All Population in 10 Years	
Payment Scheme	Payment-by-result
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	No
GDP effect	No
Net Present Value	**-90.0 €**

Scenario 3 - All Population in 10 years, D&A until BEP	
Payment Scheme	Payment-by-result with D&A
Population	Actual targeted
Years to treat population	10 Years
D&A of ATMPs	**5 Years**
GDP effect	No
Net Present Value	**-3.9 €**

Scenario 4 - All Population in 10 years, D&A in 10 years	
Payment Scheme	Payment-by-result with D&A
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	10 Years
GDP effect	No
Net Present Value	**33.1 €**

In the first part of our model, we consider the "basic" situation we described without including the GDP. Empirically, we are proving that, through the new proposed payment scheme, ATMPs would be sustainable even economically for the Swedish National Health System as well. In the first scenario, we are considering the currently targeted population, and we see how this is economically inconvenient for the public health system. Moreover, if we include all the potential targetable population, we notice how this result is amplified, topping a negative NPV of €90.0 million.

On the other hand, if we consider ATMPs as intangible and we amortise them in a period of 10 years, we see how these innovative therapies become not only sustainable, but even profitable compared to traditional therapies currently used for the considered diseases. In particular, with our model we computed the break-even point of sustainability at a length of amortisation of c. 5 years.

Exhibit 21. Results obtain in different scenarios considering the GDP effect

Scenario 1 - As Is	
Payment Scheme	Payment-by-result
Population	Actual targeted
Years to treat population	5 Years
D&A of ATMPs	No
GDP effect	Yes
Net Present Value	**-12.2 €**

Scenario 2 - All Population in 10 Years	
Payment Scheme	Payment-by-result
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	No
GDP effect	Yes
Net Present Value	**-47.8 €**

Scenario 3 - All Population in 10 years, D&A until BEP	
Payment Scheme	Payment-by-result with D&A
Population	Actual targeted
Years to treat population	10 Years
D&A of ATMPs	**4 Years**
GDP effect	Yes
Net Present Value	**0.9 €**

Scenario 4 - All Population in 10 years, D&A in 10 years	
Payment Scheme	Payment-by-result with D&A
Population	All potential targetable
Years to treat population	10 Years
D&A of ATMPs	10 Years
GDP effect	Yes
Net Present Value	**113.8 €**

As we did in the Italian case, in the second part of our model, we considered the impact of GDP in our analysis, as an input offsetting the spending for ATMPs, in order to account for the overall macroeconomic impact. With this new model, we are basically confirming what we noticed in Exhibit 9. Moreover, it must be noticed how ATMPs become extremely profitable with an amortisation period of 10 years,

considering in fact, a break-even point of 4 years. We want to underline that we have been conservative in our estimation of the overall GDP impact, and that an even greater macro-economic effect could be possible thanks to the adoption of ATMPs; especially considering the number of available cures that will be available in a few years from now.

Exhibit 22. Sensitivity analysis without considering the GDP effect

Discount Rate \ D&A Time Horizon	4	5	6	7	8	9	10
1.83%	-58.09 €	-46.69 €	-34.78 €	-23.85 €	-7.18 €	4.15 €	9.14 €
1.52%	-48.30 €	-38.71 €	-27.09 €	-16.08 €	-1.15 €	6.70 €	13.94 €
1.22%	-38.51 €	-28.04 €	-18.70 €	-8.17 €	4.65 €	12.18 €	18.73 €
0.91%	-28.73 €	-19.80 €	-11.92 €	3.13 €	9.93 €	16.73 €	23.53 €
0.61%	-18.94 €	-10.67 €	0.99 €	7.82 €	14.66 €	21.49 €	28.32 €
0.30%	-9.15 €	-3.89 €	3.07 €	9.28 €	16.22 €	23.00 €	33.12 €

Exhibit 23. Sensitivity analysis considering the GDP effect

Discount Rate \ D&A Time Horizon	4	5	6	7	8	9	10
1.83%	-23.32 €	-11.24 €	-4.32 €	1.34 €	13.31 €	27.02 €	43.32 €
1.52%	-19.87 €	-8.74 €	3.32 €	14.18 €	25.87 €	38.08 €	57.41 €
1.22%	-15.64 €	0.02 €	13.32 €	27.40 €	40.12 €	53.43 €	71.50 €
0.91%	-9.71 €	4.54 €	18.34 €	32.13 €	46.48 €	61.01 €	85.60 €
0.61%	-4.50 €	7.99 €	25.62 €	42.03 €	57.94 €	73.77 €	99.69 €
0.30%	0.9 €	17.69 €	34.31 €	52.01 €	69.56 €	88.23 €	113.8 €

From these sensitivities analysis we can have a clear and broad overview of the outcomes of our model, applied to the Swedish National Health System. In particular, even without considering the GDP effect, we still reach the breakeven point near 9 years, considering the 30 years government bond as discount rate. Also, considering the same highest band of discount rate and considering the GDP effect, we reach the break-even between 6 and 7 years of amortisation.

Overall, with these sensitivity analyses, we are confirming the soundness of our models and of our findings, which are solids even considering higher discount rates – especially considering the overall conservative approach we use towards the majority of inputs.

SECTION IV: CONCLUSIONS

1. Outcomes Commentary

Throughout this thesis we analysed ATMPs, we studied the currently available ones, and we focused on the economic problem associated with their usage. In particular, we understood how, since they are extremely expensive, the various public National Health Systems may not afford to use them for all the total targetable population. As such we went through the broad set of theorised potential payment schemes, and we understood in-depth the functioning of the currently used payment-be-result scheme. Lastly, we proposed a new payment scheme, based on the accountability of ATMPs as intangible assets for the National Health Systems, and on the idea that these drugs have multiannual economic utility – especially when compared to traditional therapies for the same diseases and given their intrinsic characteristics (one-shot therapies).

On the other hand, we went in depth on the Italian National Health System, and we studied its history, the main legislation of it and its approach towards ATMPs.

Through the Italian case, we also wanted to show how the ATMP overall economic sustainability problem would enlarge in the following years if the overall population and the average life expectancy increased. As such, we made a regression demonstrating how there is a strong correlation between these two factors and the incidence, or total number of cases, of the main diseases currently targeted by ATMPs.

Always based on the Italian case, we wanted to prove how, through the innovative payment scheme we are proposing, ATMPs could become economically sustainable for the National Health Systems. To do so, we created a specific dataset – which has been extremely painful, considering the 'silos' budgeting of the Italian public health service and the general lack of data and literature – and through a tailor-made model (for the Italian national Health System) we compared the potential spending for ATMPs with the potential spending for traditional therapies.

Lastly, after we draw a strong factual parallelism between the Italian and Swedish National health Systems, we applied a similar empirical model to the Swedish National

Health System. The most painful parts have been: to understand whether the similarities and problems related to ATMPS between the two health systems were similar, to adapt the dataset to this new case study. As we expected, in both empirical applications, we proved how, with the currently used payment-by-result scheme, ATMPs are not economically sustainable. Additionally, as we moved forward with different scenarios, we included the potential macro-economic impact by considering the potential GDP produced by cured people, we empirically showed how ATMPs could not only become sustainable economically, but even profitable. In addition, to have a clear and broad overview of the results of our models, we conducted two sensitivity analysis that confirmed the soundness of the results of our empirical research.

We would like to underline, graphically, the main reason why the new proposed payment scheme is working. Clearly, by looking at exhibit 13 and 14, we see why, for the Italian National Health System would be convenient to consider the accounting of ATMPs as assets. Indeed – considering the situation of targeting all potential population in 10 years – in exhibit 13 we see that the traditional payment-by-result scheme would result in a concentration of costs in the first 10 years, while with the new proposed scheme, reflected in exhibit 14, costs would be better distributed among the next 20 years.

Clearly, we will not show these graphs for the Swedish case as we will get to a completely redundant and useless outcome, with the only difference being a smaller scale on the y-axes (due to the smaller size of the population).

Exhibit 24. Cost for the Italian National Health systems if targeting all currently potential population with ATMPs in the next 10 years, currently used payment-by-result scheme

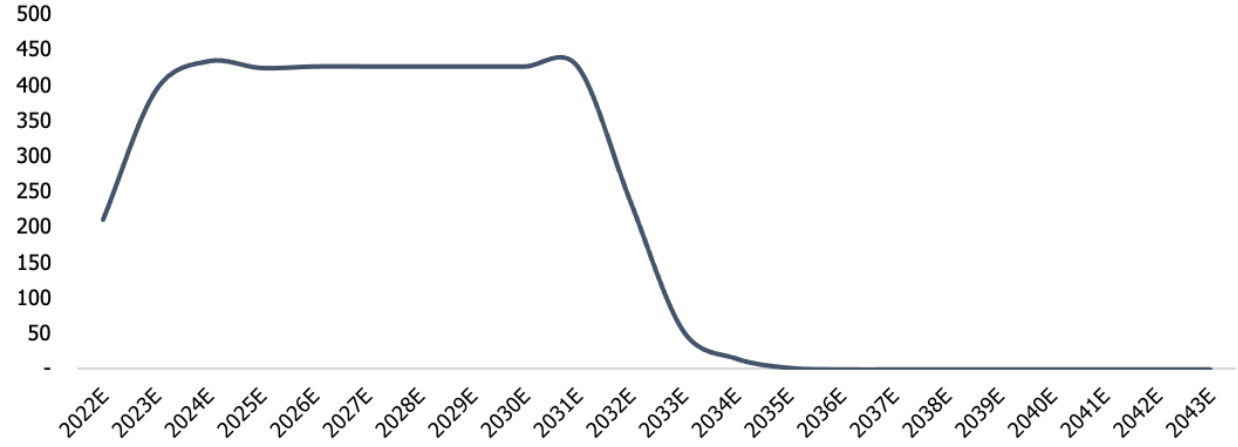
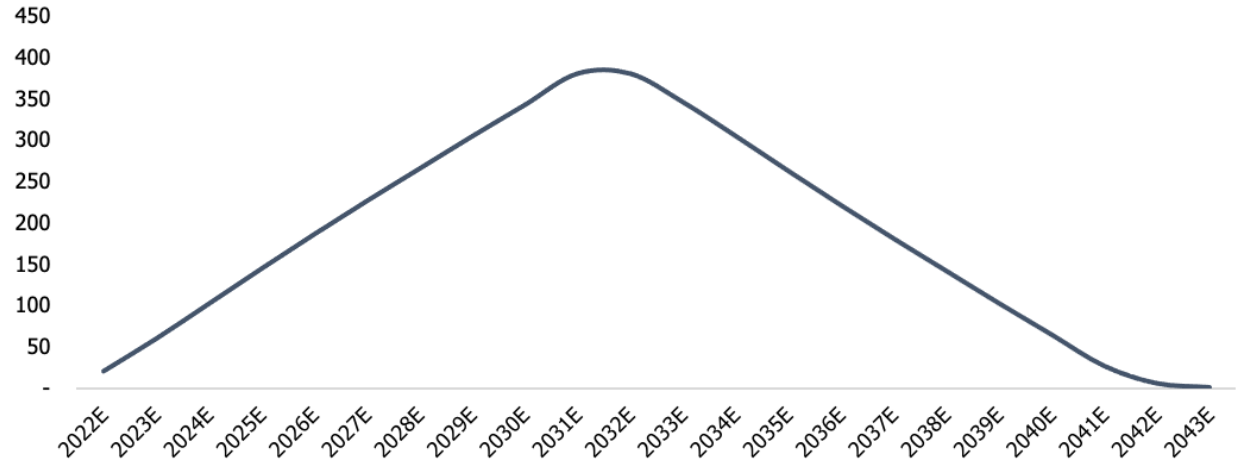


Exhibit 25. Cost for the Italian National Health systems if targeting all currently potential population with ATMPs in the next 10 years, new proposed payment scheme



2. Recommendations

Given our in-depth analysis, it is clear how from the medical and ethical point of views, ATMPs could really represent a ground-breaking technology (as defined by the European Legislation) for particularly rare and severe diseases. For this reason, we decided to propose a new payment scheme that could improve the economical sustainability of ATMPs, to be able to treat all targetable population through the public healthcare service. Through our proposal of considering ATMPs as intangible assets, with the possibility of amortising them throughout a specific time horizon, we have empirically proved the economic profitability of ATMPs, compared to traditional therapies, for the Italian and Swedish National Health Systems. For this reason, we would like to propose to the Italian and Swedish authorities to seriously think about a clear amendment to current regulations to give the possibility to consider these ground-breaking medicines as intangible assets – especially considering the greater number of ATMPs, the increase of the total population and of the average life expectancy age we expect; and the consequent increase in potential targetable population (and spending) by ATMPs. Based on our empirical research, we would propose to give the possibility to amortise these specific innovative medicines in a time horizon of 10 years – since it would be profitable to use ATMPs even considering 30 years government bonds as discount rate and without considering the GDP effect.

Obviously, it would be extremely interesting to conduct similar studies applied to other national health systems, to understand – especially throughout Europe – the different payment schemes that would grant economic sustainability in the adoption of ATMPs for each specific situation and to eventually legislate at a European level in terms of accountancy of these specific drugs. The more ATMPs would be adopted, the more people would be cured, the more research on the field will be conducted, the more economies of scale would increase, the more sustainable ATMPs would become even economically, the greater number of treated patients would be. A clear virtuous cycle,

triggered by a small change in regulation, from which all stakeholders (citizens, NHSs, pharmaceutical companies, others) would benefit.

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APPENDIX

Example of yearly cost for traditional treatments

Direct Costs of Diffuse Large B-cell Lymphoma (DLBCL + PMBCL) for the NHS

% Chance	Treatment / Average Direct Costs	Cost/year	Notes
	Average Direct Costs	**93467.425**	
100%	DLBCL	80271	CHOP-R + autologous transplantation + Ruxience + Rituximab
25%	PMBCL	52786	CHOP-R + autologous transplantation + trapianto autologico + Rituximab
	Life expetancy / cost for the SSN	4 years	
	Sources:		Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed https://fondazionematarelli.it/wp-content/uploads/2018/05/E_Oncologica1_2018_14.pdf

Direct Costs of Chondrial Injuries for the SSN

% Chance	Average Direct Costs		
		3200	
100%	Hyaluronic Acid Infiltration	1200	€100 per injection, 1 injection / month
40%	Prosthetic surgery	5000	
	Life expetancy / cost for the SSN	10	
	Sources:		https://www.humanitas-sanpiox.it/malattie/lesioni-della-cartilagine-o-lesioni-condrali/

Direct Costs of Multiple Myeloma for the SSN

% Chance	Treatment / Average Direct Costs	Cost/year	Notes
	Average Direct Costs	66900	
75%	Symptomatic patients - Chemotherapy	1629	
50%	Talidomide, lenalidomide o pomalidomide, e/o bortezomib, carfilzomib o ixazomib	50853	
	Talinomide - 39 per year	22281	
	Lenalidomide	175439	
	Bortezomib	72792	
	carfilzomib	75456	
	corticosteroidi	10000	
50%	Monoclonal antibodies, including elotuzumab and daratumumab	9000	
45%	Maintenance therapy with corticosteroids, thalidomide and/or lenalidomide and proteasome inh	50853	
20%	Autologous transplantation	5714	
35%	Radiotherapy	3429	
60%	Treatment of complications (anaemia, hypercalcaemia, kidney failure, infections and skeletal injuries, especially those associated with high risk of fracture)	3000	
	Life expetancy / cost for the SSN	7 years	Terminal ill
	Sources:		Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed Gazzetta Ufficiale Regione Piemonte

Direct Costs of Linfoma mantellare recidivante / refrattario for the SSN

% Chance	Average Direct Costs		
		48016.05	
100%	CHOP-R + autologous transplantation + Ruxience	48016	Mantle cell lymphoma, Ruxience - 12 flacons / year
	Life expetancy / cost for the SSN	4 years	
	Sources:		Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed http://www.malattiedelsangue.org/linfomi_non_hodgkin_aggressivi/ AIL Gazzetta Ufficiale

Direct Costs of Emofilia A for the SSN

% Chance	Treatment / Average Direct Costs	Cost/year	Notes
	Average Direct Costs	12692.1	
100%	VIII Factor - Klott	11578.5	Not always necessary, treatment between 10 and 20 times per year
25%	Transfusions	4454.4	
	Life expetancy / cost for the SSN	50	
	Sources:		Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed MSD Manuals Policlinico di Milano

Direct Costs of Glioblastoma for the SSN

% Chance	Average Direct Costs	
		12625
125%	Surgery	4000
125%	Radiotherapy	2400
125%	Chemiotherapy	1140
65%	Autologous transplantation	4000
20%	Palliative treatment	3000
	Life expetancy / cost for the SSN	10
	Sources:	Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed ISS Regione del Veneto

Direct Costs of β-talassemia for the SSN

	Treatment	Cost/year	Notes
% Chance	**Average Direct Costs**	**19754**	
	Transfusions	3526	Every 20 days - i.e. c. 19 per year, c. 400 per trasfusion
	Average chelation therapy Price per year	16228	
31%	Chelation therapy - Deferiprofene	7994	2 per day, 1000mg tablets - i.e. 730 per year, 50 tablets per blister, 15 per year
50%	Chelation therapy - Deferasirox	26281	3 per day, i..e 40 per year
19%	Chelation therapy - Deferoxamina	3178	2 per day, 500mg flacon - 730 per year, 10 flacons per confection, 73 per year
	Life expetancy	39 years	
	Sources:	Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed Report-Il-valore-per-la-persona-con-Beta-Talassemia-Major MedScape Gazzetta Ufficiale NCBI Mediately.co Il Sole 24 Ore http://www.quotidianosanita.it/cronache/articolo.php?articolo_id=3922

Direct Costs of Indolent non-Hodgkin's lymphoma (iNHL) for the SSN

	Treatment	Cost/year	Notes
% Chance	**Average Direct Costs**	**34497.753**	
44%	CHOP-R + radiotherapy + Ruxience	32643	Diffuse large B-cell lymphoma (DLBCL), 6 avg. cycles
40%	CHOP-R + radiotherapy + autologous transplantation if reminiscence + Ruxience	30896	Follicular lymphoma (LF)
15%	CHOP-R + autologous transplantation + Ruxience	49266	T-cell lymphomas (NHL-T), Ruxience - 12 vials/year
	Life expetancy / cost for the SSN	4 years	
	Sources:	Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed http://www.malattiedelsangue.org/linfomi_non_hodgkin_aggressivi/ AIL Gazzetta Ufficiale

Direct Costs of Haemophilia B for the SSN

% Chance	Average Direct Costs	
		33800
100%	Factor IX, 1 vial per week	33800
	Life expetancy / cost for the SSN	50
	Sources:	Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed MSD Manuals

Direct Costs of Distrofia di Duchenne for the SSN

% Chance	Average Direct Costs		
		55165.88	
50%	Steroids - Prednisone	169.46	25mg per day, 4.58 per 10, 37 blisters per year
50%	Steroids - Deflazacort	662.3	30mg per day, 17.90 per 10, 37 blisters per year
100%	Therapies	54750	150 per day
	Life expetancy / cost for the SSN	25	
	Sources:	Goldman Cecil Medicine, 20esima ed Oncologia. Principi e pratica. De Vita, Hellman 10ima ed Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed Goodman & Gilman. Le basi farmacologiche della terapia 13esima ed https://www.osservatoriomalattierare.it/malattie-rare/distrofia-muscolare-di-duchenne https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=IT&Expert=98896 guidafamiglie-parentprojectonlus https://www.mda.org/disease/duchenne-muscular-dystrophy

Direct Costs of Synovial sarcoma and Myxoid liposarcoma for the SSN

% Chance	Treatment	Cost/year	Notes
	Average Direct Costs	34747.7527	Similar Cure compared to lymphomas with R-CHOP
44%	CHOP-R + radiotherapy + Ruxience	32643	
40%	CHOP-R + radiotherapy + autologous transplantation if relapse + Ruxience if more aggressive	30896	
15%	CHOP-R + autologous transplantation + Ruxience	49266	
10%	Surgery	2500	
	Life expetancy / cost for the SSN	4	

Sources:

Goldman Cecil Medicine, 20esima ed
Oncologia. Principi e pratica. De Vita, Hellman 10ima ed
Robbins. Kumar & Klatt. Patologia generale e anatomia patologica. 9 ed
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